

1 evaluation.

2 We examined the embracement of  
3 endovascular repair for abdominally aortic aneurysms  
4 as reported in the State of New York through the years  
5 to 2000 and 2002. We can see a fairly significant  
6 increase in the utilization of these procedures in 24  
7 to 60 hospitals. And even with a fairly large number  
8 of institutions performing this for the first time,  
9 there remains significant reductions in mortality from  
10 4 to 1 percent for endovascular procedures, suggesting  
11 that this technology can be translated.

12 The benefits of the TAG device as we have  
13 demonstrated are the significant reduction of major  
14 adverse events, hospital stay can be reduced and  
15 patients return to normal activity more quickly.  
16 There is also a significant improvement in aneurysm-  
17 related mortality and to date we have seen no evidence  
18 for aneurysm rupture in the late follow-up.

19 We should note, however, that although we  
20 have made comparisons to endovascular repair of  
21 abdominal aortic aneurysms, make no mistake the  
22 operative repair of thoracic aortic aneurysms is a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 more severe procedure and the incurred morbidity  
2 increases 2 to 3 fold. The incremental benefit  
3 afforded to these patients by repair, endovascular  
4 repair of these descending aneurysms is dramatic. We  
5 feel this device offers patients and their physicians  
6 an important therapeutic alternative.

7 Speaking as a surgeon, we need this device  
8 and our patients want it. Thank you.

9 MR. NILSON: Thank you, Dr. Mitchell. The  
10 sponsor is proposing the following post-market program  
11 to evaluate long-term performance of our patients  
12 enrolled under the pivotal confirmatory and treatment  
13 IDE studies, we will follow approximately 250 patients  
14 through five years. This includes approximately 100  
15 modified TAG device patients. A post-market study is  
16 being discussed at the Agency and could include up to  
17 100 patients and up to 25 centers. The purpose of  
18 this study is to evaluate the performance of the  
19 procedure in a wider community.

20 The indication we propose for your  
21 consideration is the following: The GORE TAG Thoracic  
22 Endoprosthesis is indicated for endovascular repair of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 aneurysms of the descending thoracic aorta. The  
2 presentation is concluded. Thank you very much for  
3 your attention.

4 Before we start the Q&A session, I would  
5 like to introduce a few potential respondents for the  
6 sponsor. Dr. John Matsumura, who is a Professor of  
7 Surgery at Northwestern University and an investigator  
8 in the Clinical Trial Program. Dr. Joel Verter, who  
9 is a biostatistician, and Mr. Lou Smith is a medical  
10 products technical leader for Gore and co-chairs the  
11 AAMI Vascular Prosthesis Committee. I will be the  
12 moderator for the sponsor during the Q&A session and  
13 we welcome your questions at this time.

14 ACTING CHAIR MAISEL: Thank you very much  
15 for a very thorough and eloquent presentation and I  
16 would like to open the session now to questions from  
17 the Panel, reminding the Panel that we will have ample  
18 time to discuss these issues further this afternoon.  
19 Dr. Normand?

20 DR. NORMAND: I just have some questions  
21 of clarification. Could you define for me what you  
22 mean by intent-to-treat failures? I'm not sure what

1 you mean by that.

2 MR. NILSON: The TAG 99-01 Study was an  
3 intent-to-treat study.

4 DR. NORMAND: Yes.

5 MR. NILSON: Which means any patient who  
6 has consented under either arm, even if they received  
7 the device, was still enrolled in that part of the  
8 trial.

9 DR. NORMAND: But it sounded like you said  
10 you accounted for attrition as well as intent-to-treat  
11 failures. So then the question is did you do an  
12 intent-to-treat analysis?

13 MR. NILSON: We included intent-to-treat  
14 failures in our worst case analysis.

15 DR. NORMAND: Okay. And then I just have  
16 two more quick clarifications. You had mentioned  
17 follow-up schedules like one month and 12 months.  
18 From what time point is that measured? From the time  
19 of the procedure?

20 MR. NILSON: From discharge.

21 DR. NORMAND: From discharge.

22 MR. NILSON: Yes.

1 DR. NORMAND: And was that just for the  
2 TAG patients?

3 MR. NILSON: I believe it was for both.

4 DR. NORMAND: So even for the surgical  
5 repair arm it was from discharge?

6 MR. NILSON: Yes, it was from discharge.

7 DR. NORMAND: Thank you.

8 ACTING CHAIR MAISEL: John?

9 DR. SOMBERG: A couple of questions. The  
10 first is for the confirmatory study, it's 30 days is  
11 the follow-up and I understand the rationale, but do  
12 you have additional follow-ups since the brief and  
13 what was presented, you know, probably put together  
14 information months ago? And I just wondered if  
15 there's additional information? Is there anything out  
16 of the ordinary in the follow-up of the confirmatory  
17 study?

18 MR. NILSON: We do have additional follow-  
19 up in preparation for our upcoming one-year follow-up.  
20 We have had one death and we have had one major  
21 device-related event, which was an aneurysm. And we  
22 have contacted 90 percent of the subjects who were

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 enrolled in the trial. So 46 of the 51 patients  
2 enrolled have been contacted post-30 days.

3 DR. SOMBERG: You also in a narrative  
4 discussion, in one of the cases that had a mortality,  
5 something called post-implant syndrome for TAG. I  
6 just wondered what that was. And that was not  
7 mentioned or categorized in any other areas. Is that  
8 a problem with the -- is there such a thing as a post-  
9 implant syndrome?

10 MR. NILSON: I would defer to Dr. Makaroun  
11 to give the clinical perspective on post-implant  
12 syndrome.

13 DR. MAKAROUN: Early in the experience  
14 with endovascular treatment of aneurysms of the  
15 abdominal aorta, post-implant syndrome of fever and  
16 prostration and various systemic symptoms was  
17 described. It actually was relatively frequent with  
18 the hand-made devices in a variety of settings and  
19 that's why it is included, essentially, with most of  
20 these trials and continued to be follow-up with the  
21 advent of the commercial available devices with  
22 sterilization of product. This implant syndrome has

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       been extremely rare, but it's customary to continue to  
2       include it as one of the possible adverse events.

3               DR. SOMBERG: I had one further.

4               ACTING CHAIR MAISEL: Dr. Johnston?

5               DR. JOHNSTON: Can you clarify in the  
6       censored data and in other parts of the submission, I  
7       could not get a sense of how many patients were  
8       actually lost to follow-up.

9               MR. NILSON: Dr. Verter will answer that.

10              DR. VERTER: My name is Joel Verter. I'm  
11       a statistical consultant along with other members of  
12       my group on this project. We have no equity interest  
13       in the company. Censoring is used in the sense of a  
14       statistical term. There are actually no patients that  
15       were really censored in the sense of not providing  
16       information. So, for example, in answer to previous  
17       questions, those patients who didn't have a 12 month  
18       visit when we did the one-year analysis, you get a  
19       worst case analysis and provided then, imputed to them  
20       an actual event.

21              If you're referring to the 03 Study,  
22       perhaps, in particular, where at the end of 30 days it

1 is indicated that 60 subjects are in the censored  
2 column, is that what you are referring to?

3 DR. JOHNSTON: No, I'm not. I'm referring  
4 to the fact that when I went through the individual  
5 data and I'm familiar with what censoring is, I could  
6 not anywhere determine whether 100 percent of the  
7 patients were, indeed, followed or whether X number  
8 were lost to follow-up and therefore not included.

9 DR. VERTER: Okay. In --

10 DR. JOHNSTON: I'm simply looking for the  
11 number of patients.

12 DR. VERTER: Right. There were a number  
13 of patients who withdrew from the study at various  
14 times.

15 DR. JOHNSTON: Correct. What were those  
16 numbers?

17 DR. VERTER: We have a -- please, show  
18 this slide. This slide describes the status of the  
19 subjects in the 99-01 Study through 24 months. For  
20 example, at one year, 73 percent of the TAG and 55  
21 percent of the total subjects had a follow-up visit,  
22 20 and 23 percent, respectively, had died, 6 and 7

1 percent, respectively, withdrew, and 1 to 14 percent  
2 missed the visit.

3 DR. JOHNSTON: So looking at the line of  
4 lost to follow-up and we're only looking at TAG, is  
5 that a cumulative number 3 plus 6 plus 9?

6 DR. VERTER: No, no. At one year, it was  
7 6 percent.

8 DR. JOHNSTON: I'm sorry. And so at two  
9 years 10 percent. Thank you.

10 DR. LINDENFELD: Could I just follow-up on  
11 that? Do you know the mortality for all the subjects  
12 at one year or are there some for whom you don't know  
13 mortality at one year?

14 DR. VERTER: The best estimate we have  
15 would be the Kaplan-Meier curve, which, of course,  
16 would censor those patients at their last known visit.  
17 So subject to withdrawing at three months, we would  
18 not know the mortality.

19 DR. LINDENFELD: Not. So we do not know.  
20 Okay. Maybe one of the presenters can clarify this  
21 for me. It was a very nice presentation. Thank you.  
22 The concurrent controls look very similar to the TAG

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 patients. But some were chosen for surgery and I just  
2 would like to get a little bit better sense of -- can  
3 you give me a little bit better sense about, you know,  
4 the patients wanted this device, the surgeons are very  
5 enthusiastic about it. That means there have to be  
6 some differences between the TAG patients and the  
7 surgical patients.

8 Can one of you give me a little bit of  
9 insight into what those differences were? How you  
10 chose those? I know some was the size of the neck and  
11 maybe you can comment on the fact of how having an  
12 inadequate neck for this device impacts complication  
13 rate. But just give me a sense of how the patients  
14 were put into these two categories.

15 MR. NILSON: Dr. Mitchell can give you a  
16 clinical perspective on that.

17 DR. MITCHELL: Thank you for that  
18 question. Patients came to surgical procedures by  
19 various routes. The primary route was some anatomical  
20 constraints not related necessarily to the aneurysm  
21 size, but inadequate length of aneurysm necks,  
22 although they still had to be able to have a clamp

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 applied or inadequate access vessels, that's  
2 predominant, that's a characteristic that doesn't have  
3 a cohort in the open repair.

4 Additionally, some patients didn't elect  
5 to have the procedure with endovascular repair because  
6 of the necessity for long-term follow-up and they  
7 might very well be living at very remote places from  
8 study sites and didn't want to return. So there were  
9 probably three incidents, three criteria that put  
10 people into the or out of a surgical group.

11 DR. LINDENFELD: Well, then can you  
12 comment for me the lack of an inadequate proximal  
13 neck, at least means that you are closer to the -- to  
14 some central vessels. And does that impact on the  
15 outcome of these patients, do you think? Is that a  
16 difference in these patients?

17 DR. MITCHELL: One of the criteria was  
18 still that they had to be an adequate neck to have a  
19 clamp safely placed by the judgment of the surgeon.  
20 So I think as long as you can clamp that neck, you  
21 have -- I think you still have comparable patients.

22 DR. LINDENFELD: Okay. And then in terms

1 of the access, you're talking about peripheral  
2 vascular disease.

3 DR. MITCHELL: Correct.

4 DR. LINDENFELD: And extensive peripheral  
5 vascular disease not allowing access, do you think  
6 that makes a difference in these groups of patients  
7 and their outcomes?

8 DR. MITCHELL: I think the surgical  
9 control group could have the same distal vascular  
10 disease, but it didn't exclude them from the operating  
11 procedure. So it's a requirement only for the TAG  
12 group. I don't think it makes the groups  
13 incomparable.

14 DR. LINDENFELD: Okay. I don't know if  
15 we'll go back this way. Tell me about also thrombus  
16 is not allowed in the aneurysm for the TAG group?  
17 Does that impact on your difference in mortality  
18 between the two groups?

19 DR. MITCHELL: Probably all these necks  
20 have some thrombus, but we thought that there couldn't  
21 be a good seal if there was extensive thrombus in the  
22 proximal neck, but probably that same extensive

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 thrombus would preclude clamping. So I suspect that  
2 had an equal effect on both groups.

3 DR. LINDENFELD: Do we know that? I mean,  
4 I'm concerned, because doesn't thrombus predict  
5 enlargement of the aneurysm? At least in some  
6 literature it does. You know, there are some fairly  
7 major differences here that it's difficult to see in  
8 this list, but exist and, you know, just to get back  
9 to whether or not these were fairly comparable groups.

10 DR. MITCHELL: I'm not aware of thrombus  
11 in the aneurysm neck being a risk factor to  
12 enlargement or rupture.

13 DR. LINDENFELD: Okay. And then I guess  
14 what I would like to see maybe, Bill, let me know if  
15 we'll come back to this later, but can you see a list  
16 of why the surgical, at least the concurrent controls  
17 chose to have surgery or why they were eliminated from  
18 the TAG group? Can we just get a sense of that? I  
19 mean, I would like to know if it was for anatomical  
20 differences, for choice?

21 DR. NORMAND: Yes, I would like to know  
22 what percent were excluded from the TAG that were in

1 the concurrent.

2 DR. LINDENFELD: Right. Exactly.

3 DR. NORMAND: I mean, that's a really  
4 important number, in my mind.

5 DR. KRUCOFF: So while they are looking,  
6 can I just ask along this line one other just point of  
7 clarification? If you approached a patient who was in  
8 every other way a reasonable patient for the TAG  
9 device and the patient declined to participate in the  
10 study, were they considered and/or consented as a  
11 controlled patient?

12 MR. NILSON: If a patient was a candidate  
13 for the test arm, but chose not to be in the test arm?

14 DR. KRUCOFF: Right.

15 MR. NILSON: He could be enrolled in  
16 certain control arm.

17 DR. KRUCOFF: Okay. And so hopefully if  
18 we can get what John is asking for, there would be  
19 some population in your control arm who actually are  
20 anatomically truly comparable and just didn't want to  
21 participate in the treatment arm? Any idea how many  
22 such patients?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 MR. NILSON: We don't have that  
2 information. With regard to the subject screening,  
3 could you show the slide, please? This is the  
4 information we have for the pivotal study. This  
5 includes both arms of the study and this shows that 28  
6 percent or 90 subjects were rejected for either  
7 anatomical, including and excluding violations or  
8 insufficient screening documentations. We do not have  
9 a subset analysis of this information.

10 DR. NORMAND: Because it seems to me as  
11 you're saying, if you were to randomize, I guess, a  
12 certain percentage of your control group, it wouldn't  
13 be part of that study. And I just want to figure out,  
14 because in theory it doesn't make any sense to  
15 estimate an effect if you're not comparable. It would  
16 be really important to know that number.

17 ACTING CHAIR MAISEL: Dr. Edmunds?

18 DR. EDMUNDS: I would like to know,  
19 because I couldn't find it in the handout material,  
20 were the exclusion criteria applied to the study  
21 patients' neck by your cobbled, serial backward  
22 regression control group.

1 MR. NILSON: The inclusion and exclusion  
2 criteria were identical for both of the groups in  
3 question.

4 DR. EDMUNDS: So that none of the patient's  
5 had an emergency surgery or had a stroke or heart  
6 attack within six weeks of the procedure in the  
7 control group.

8 MR. NILSON: Prior to six weeks that was  
9 the exclusion criteria.

10 DR. EDMUNDS: Well, the exclusion criteria  
11 was within six weeks, not prior.

12 MR. NILSON: Within six weeks to  
13 enrollment into the study.

14 DR. EDMUNDS: Well, I mean, someone would  
15 be pretty insane to operate on somebody within six  
16 weeks.

17 MR. NILSON: We agree.

18 DR. EDMUNDS: The second thing I would  
19 like to ask is, don't extrapolate, do you have any  
20 histologic data of this device in a patient who died  
21 for whatever reason?

22 MR. NILSON: The sponsor has received

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 several explants throughout the course of the device.  
2 We have evaluated those explants for a number of  
3 attributes including histological evaluation and we do  
4 have histological results from patients.

5 DR. EDMUNDS: Do you have it for us today?

6 MR. NILSON: We do not have physical  
7 histological slides for you to view today.

8 DR. EDMUNDS: All right. The third thing  
9 and I hope -- I think Scott's presentation was cut a  
10 little bit, but I haven't seen any presentation of the  
11 deployment of the device.

12 MR. NILSON: During the device part of my  
13 presentation, I showed an animation which was a  
14 cartoon, for a lack of better words, to describe the  
15 deployment and then I actually showed an actual  
16 deployment that may have been difficult to see which  
17 is why we have the cartoon animation, because some of  
18 the radiographic images do not project very well.

19 DR. EDMUNDS: You don't have a video?

20 MR. NILSON: I will show you again. Would  
21 you like me to show you the cartoon or the actual  
22 video?

1 DR. EDMUNDS: Well, that's up to the  
2 Chairman.

3 ACTING CHAIR MAISEL: We already viewed  
4 the video. If you would like to view it again, why  
5 don't you pull that up and meanwhile, Mitch, why don't  
6 you ask your question?

7 DR. KRUCOFF: I'm sorry. Because you all  
8 have actually two control groups, I just want to make  
9 sure that I'm not getting confused. My understanding  
10 is there was one control group that was concomitant in  
11 time who were simply by and large not anatomically fit  
12 for the device, although as you've said if the patient  
13 chose not to have the device, they might end up in  
14 that group.

15 My understanding is the other control  
16 group was taken from participating centers, registries  
17 or whatever of previously operated patients, marched  
18 backward in time. Do you have a breakdown of that  
19 control group as to how many, in fact, might or would  
20 have been TAG candidates had the device been available  
21 or the study been enrolling, i.e., the comparability  
22 of that population to the actual TAG implant

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 population?

2 MR. NILSON: Baseline morphology was  
3 collected on both groups and Dr. Makaroun showed that  
4 they were very comparable in specific attributes like  
5 aneurysm diameter, which is a predictor of risk  
6 rupture. But I have the aneurysm morphology data for  
7 99-01.

8 DR. KRUCOFF: Okay. I don't want to drag  
9 this in the wrong direction. What I'm trying to ask  
10 is simply at the end of the day out of your backward  
11 in time control group, the patients identified within  
12 the participating sites before enrollment in this  
13 study had begun, how many of those patients in that  
14 control group would actually have been candidates in  
15 all features for enrollment if the trial had been  
16 running, at that time?

17 MR. NILSON: Dr. Makaroun?

18 DR. MAKAROUN: That's the same question.

19 DR. EDMUNDS: That's the same question I  
20 asked.

21 DR. KRUCOFF: I thought so too, but I just  
22 wanted to make sure we're talking about the same

1 enrollment.

2 DR. MAKAROUN: Unfortunately, this  
3 particular data set is not very complete, because of  
4 imaging of the patients that were involved  
5 historically, it was, obviously, not obtained  
6 prospectively and not all of it is available to  
7 analyze that those particular patients could have been  
8 or would not have been candidates for the TAG device.

9 ACTING CHAIR MAISEL: Thank you. Why  
10 don't you show the video one more time, so Dr. Edmunds  
11 can see that?

12 MR. NILSON: Could we show the live video  
13 not the animation?

14 DR. EDMUNDS: If you all have seen it,  
15 it's fine.

16 ACTING CHAIR MAISEL: Well, I would like  
17 you to see it as well.

18 DR. NORMAND: We want you to see it.

19 MR. NILSON: So the device is constrained  
20 on the delivery catheter in the upper portion of this  
21 video. This device -- this video will loop in  
22 sequence. You can see the device constraining there

1 to being deployed. This is real time, the actual  
2 deployment takes fractions of a second. Again, it's  
3 constrained, deployed.

4 ACTING CHAIR MAISEL: Thank you. I think  
5 at this point, I would like to take a break. We'll  
6 take a 10 minute break and regroup at 11:35.

7 (Whereupon, at 11:25 a.m. a recess until  
8 11:37 a.m.)

9 ACTING CHAIR MAISEL: At this point, I  
10 would like to invite the FDA to give their  
11 presentation and remind the Panel that it will have  
12 ample opportunity this afternoon to ask questions in  
13 more depth.

14 MS. ABEL: All right. Thank you for the  
15 opportunity to present the FDA perspective on this  
16 application that you are discussing today. I am  
17 Dorothy Abel. I am the primary lead reviewer on this  
18 application and, as with every PMA, we do have a  
19 review team most of which are listed here, and you  
20 will see that Matthew Krueger was my co-team leader.

21 And I wanted to mention that a lot of the  
22 folks that are on this team were also on the AAA

1 Endovascular Graft Teams that presented previously at  
2 this Panel, and many of the folks are here in the  
3 room, in case you have any specific questions with  
4 respect to their areas of expertise.

5 The proposed indication you have already  
6 seen is for treatment of endovascular repair of  
7 aneurysms of the descending thoracic aorta and this is  
8 the first endovascular graft for treatment of thoracic  
9 aneurysms considered for marketing approval by the  
10 FDA. The unique aspect of this PMA is the fact that  
11 we do have the two different device designs, and so I  
12 will spend some time discussing the modifications in  
13 the evaluation before I talk about the FDA review  
14 summary.

15 You have already heard about the clinical  
16 studies on this device. I did want to remind you that  
17 the evaluation of the original device design included  
18 the feasibility and the pivotal study with enrollment  
19 between February of '98 and May of '01.

20 After enrollment was complete in the 99-01  
21 Study, fractures were observed in the longitudinal  
22 spines, as you have already heard about, and those

**NEAL R. GROSS**  
COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 spines were intended to provide longitudinal stiffness  
2 during the deployment of the device. There were also  
3 a few fractures in the supporting wire frame in the  
4 region where the wires were not bonded to the  
5 underlying graft material, so in this area right here  
6 those stent portions were able to move more and there  
7 were some that had fractures.

8 This table is included in your Panel  
9 package. I just wanted to point out that there were  
10 four patients who had both spine and apex fractures,  
11 one patient who had an apex fracture and the rest, the  
12 39, were spine fractures and these are worldwide  
13 numbers.

14 The clinical sequelae associated with  
15 these spines were five cases worldwide of endoleak and  
16 one case of an enlarging aneurysm OUS. Despite these  
17 fractures, the clinical results of the original design  
18 in the pivotal study were favorable as compared to the  
19 surgical control. And as you have seen, there is a  
20 statistical improvement in the proportion of patients  
21 experiencing greater than one major adverse event  
22 through the one-year post-treatment.

1           The sponsor determined anyway that it was  
2           appropriate to redesign the device to minimize the  
3           potential for wire fractures, and they made the  
4           modifications with the intention of maintaining the  
5           clinical performance. There was no change in the  
6           fundamental design of the implant. Both versions were  
7           constructed of an expanded ePTFE tube, reinforced with  
8           ePTFE/FEP film with an external nitinol wire  
9           supporting structure bonded to the graft material with  
10          an external ePTFE/FEP bonding tape.

11           The differences between the designs, the  
12          original design had the longitudinal spines, which the  
13          company is referring to as deployment wires, and there  
14          was the unbonded portion of the wire frame that I  
15          mentioned, and that unbonded portion was intended to  
16          accommodate the spines. The modified design does not  
17          have the longitudinal spines and the wire frame is  
18          bonded in a uniform manner to the graft material.

19           There were graft material modifications to  
20          strengthen, to provide the longitudinal stiffness  
21          previously provided by the spine. The graft material  
22          strengthening was accomplished by replacing several

1 layers of the original reinforcing film with layers of  
2 an additional stronger, less permeable ePTFE/FEP film.

3 There were no new materials incorporated  
4 into the device. The result was an axially stiffer  
5 and less permeable graft material. The same material  
6 as was incorporated into the commercially available  
7 EXCLUDER Bifurcated Endoprosthesis that's intended to  
8 treat AAA devices was done.

9 For all device modifications, whether  
10 implemented before or after marketing of the device,  
11 FDA considers the potential impact of the changes on  
12 device function when identifying the testing needed to  
13 verify that the changes have not adversely affected  
14 device performance. So in other words, we look at a  
15 risk assessment to determine what additional  
16 information is necessary. For the GORE TAG Thoracic  
17 EXCLUDER Endoprosthesis, this consisted of the  
18 preclinical testing and the confirmatory clinical  
19 data.

20 The mechanical and preclinical in vivo  
21 testing that we agreed or required from the risk  
22 assessment addressed the potential for changes in this

1 list of attributes, including deployment accuracy,  
2 conformity to the vessel wall, migration resistance,  
3 durability, etcetera. The evaluation included a  
4 comparison to the original device design, and the  
5 modified device performed as well or better than the  
6 original device, including long-term implant  
7 durability testing. We also agreed that a clinical  
8 evaluation would be appropriate to confirm the  
9 favorable results of the preclinical testing.

10 I wanted to emphasize that although I have  
11 spent a little bit of time talking about  
12 modifications, that the primary data set for this PMA  
13 is the clinical data for the original device design  
14 out to one year. There is also five-year data for the  
15 feasibility study from the original device design and  
16 24 month data provided for the pivotal study.  
17 Evidence to support approval of the current device  
18 designs includes preclinical testing on the modified  
19 device, as compared to the original device, and the  
20 confirmatory clinical data.

21 I will now speak to the review summary,  
22 although I will not be covering the clinical review as

1 that will be discussed by Dr. Farb and Mr. Kamer.

2 The draft summary of safety and  
3 effectiveness data in the Panel package includes  
4 summaries of the preclinical test data provided in the  
5 PMA. A review of the biocompatibility, in vivo animal  
6 studies, manufacturing and sterilization information,  
7 including packaging and shelf life, have been  
8 completed and there are no outstanding issues  
9 regarding these parts of the PMA.

10 I want to talk a little bit more about the  
11 bench testing aspect of our review. A complete  
12 battery of testing results was provided for the  
13 modified design of the device and, as the sponsor  
14 mentioned, the testing platform was based on the ISO  
15 Standard for Endovascular Prosthesis. In addition,  
16 there was testing to further evaluate the performance  
17 of the device under conditions simulated in the  
18 clinical environment.

19 In all preclinical testing, the modified  
20 device performed as well or better than the original  
21 device, including long-term implant durability  
22 testing. And I just wanted to note that all of the

1 preclinical testing was repeated for the final device  
2 design, so that we aren't counting on any of the  
3 testing of the original design for our consideration  
4 of the safety and effectiveness of the device.

5 Bench testing review observations. The  
6 testing was comprehensive and the results acceptable.  
7 There was some clarification requested and provided on  
8 the corrosion properties of the metallic components of  
9 the implant, but there are no outstanding concerns  
10 regarding the bench testing for this device.

11 You may be wondering why we don't have  
12 outstanding concerns with respect to device integrity,  
13 because the second study that was conducted is a 30  
14 day study, which was not designed to evaluate device  
15 integrity. The thoracic endovascular grafts are  
16 subject to conditions that may result in the loss of  
17 device integrity, such as structural failures, as you  
18 saw with the original studies.

19 Depending on the location and type of the  
20 breach of integrity, there may or may not be an  
21 immediate or eventual clinical consequence. This was  
22 demonstrated by the information from the original

1 design of the GORE TAG Thoracic Endoprosthesis. The  
2 fractures were associated with a relatively low rate  
3 of clinical sequelae, although there was a high rate  
4 of structural failures.

5 The results of the clinical study for the  
6 original design were favorable as compared to the  
7 surgical control. The parts of the original device  
8 that were prone to breaking, that is the longitudinal  
9 spines, were removed in a redesign of the product.

10 So as far as our assessment of the  
11 integrity for this device, the implant durability  
12 testing showed that the modified device was superior  
13 to the original design. All of the parameters  
14 measured were comparable or improved for the modified  
15 device. There is a risk of wire fractures in the  
16 modified device, though none have been observed in the  
17 clinical use of this device within the limited  
18 duration of follow-up.

19 Despite this, the clinical results for the  
20 original design of the device demonstrate that  
21 fractures are rarely associated with clinical  
22 sequelae, and that is why we believe that adequate

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 information has been provided to assess safety and  
2 effectiveness with respect to the structural integrity  
3 of the device.

4 Additional considerations we would like to  
5 present for the Panel are the training for this  
6 product. The proposed training program is predicated  
7 on the training program utilized for the GORE EXCLUDER  
8 Bifurcated Endoprosthesis for treatment of AAA and the  
9 European release of the TAG device. The program  
10 includes a tiered approach based on prior endovascular  
11 experience.

12 The most intensive training will be  
13 provided to clinicians with experience using AAA  
14 endovascular grafts, but not thoracic endovascular  
15 grafts. The training program includes a Gore-  
16 sponsored training course, additional TAG case viewing  
17 and Gore-supervised training cases.

18 What we would like the Panel to consider  
19 is that this is the first thoracic endovascular graft  
20 that may be approved in the U.S., and the adequacy of  
21 the proposed physician training plan, as described in  
22 the Panel pack, should be discussed.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           The sponsor already described the post-  
2 approval study plan and we just wanted to mention that  
3 the study to assess the performance of the device when  
4 used to treat other etiologies, such as dissections,  
5 transections, penetrating ulcers in addition to  
6 aneurysms in patients at high risk of morbidity and  
7 mortality associated with surgical repair is planned  
8 to begin in the near future, and that would be an  
9 aspect of post-market evaluation that we would be  
10 interested in making sure it covers the fact that the  
11 device can be used in different etiologies.

12           The sponsor is going to continue to follow  
13 the other patients up to five years in accordance with  
14 the original IDE protocols, and you have heard that  
15 they are also working with us to determine whether an  
16 additional 100 patient study would be appropriate.

17           So the post approval study considerations  
18 is that the plan includes a collection of longer term  
19 clinical data. The numbers of patients to be followed  
20 should be discussed. The plan does not include  
21 enrollment of new patients. It didn't before, we just  
22 started talking about it, and so the need for real-

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 world data should also be discussed.

2 In summary, the clinical results were  
3 favorable for the original TAG design despite the wire  
4 fractures. In addition, the Circulatory System  
5 Devices Advisory Panel has recommended approval of  
6 endovascular AAA devices with wire breaks. However,  
7 the sponsor elected to modify the device to minimize  
8 the risk of fractures.

9 A 30 day confirmatory study was determined  
10 to be appropriate, because the risk analysis  
11 demonstrated that the modifications should only affect  
12 device delivery and not long-term efficacy. The  
13 results of preclinical testing were favorable, and the  
14 majority of the device-related events occurred within  
15 the first 30 days in the pivotal study.

16 Finally, the confirmatory study results  
17 for the modified device design satisfactorily  
18 addressed the device deployability and the short-term  
19 risk potentially associated with the design changes.  
20 With that, I will turn over the podium to Dr. Andrew  
21 Farb who will be covering the clinical aspects of our  
22 review.

1 DR. FARB: Thank you, Dorothy. I am  
2 Andrew Farb. I am the lead clinical reviewer and,  
3 like other speakers, I am going to make reference to  
4 the original TAG device, as well as the modified TAG  
5 device, the original being the other one above with  
6 the longitudinal spine and the spine removed in the  
7 modified device.

8 Here is a summary table of the various  
9 clinical studies that have been discussed and are also  
10 available in the Panel pack. I'm going to speak  
11 briefly about the feasibility study, but spend most of  
12 my remarks concentrated on the pivotal and  
13 confirmatory studies. Please, understand that some of  
14 the data that you are going to hear you have heard  
15 already this morning. I'm going to try to call out  
16 those data, which we feel are most important.

17 The feasibility study achieved initial  
18 clinical experience with the device. It was a single  
19 arm study of 28 patients using the original device  
20 with the longitudinal spine, and the purpose of the  
21 study was to establish preliminary device safety and  
22 to justify and aid in the design of the longer pivotal

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 study. And at this point, this feasibility study  
2 provides five-year follow-up data to explore the  
3 durability of this treatment.

4 There were 28 patients that received the  
5 device. There were no endoprosthesis deployment  
6 failures and no procedural deaths. Through one-year  
7 post-treatment, 57 percent had at least one major  
8 adverse event, but I would like to emphasize the low  
9 event rate of clinically important events such as  
10 paraplegia, stroke, renal failure and myocardial  
11 infarction.

12 Looking long-term from the feasibility  
13 study, no adverse events were reported during the  
14 second and fifth years of the follow-up period and one  
15 adverse event was reported for each the third and  
16 fourth years in the follow-up period.

17 And now through a five year, 60 months,  
18 follow-up in 11 patients, there have been no aneurysm  
19 ruptures, no endoprostheses migrations.  
20 Endoprostheses fractures have been observed in nine  
21 subjects, endoleaks in six, aneurysm enlargement in  
22 five and of that group, two of the patients required

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 intervention, one, a revision and, one, a convergence  
2 into an open surgical procedure.

3 With these data, the pivotal study was  
4 designed and implemented. It is a non-blinded, non-  
5 randomized control study using the original device  
6 design. And as you have already heard, 140 patients  
7 were in the GORE TAG group to be compared with a  
8 surgical control group consisting itself of two  
9 groups, a historical control group working  
10 retrospectively from the clinical centers enrolled in  
11 the trial and a concurrent surgical control group.

12 This was a multicenter study that was  
13 performed in the United States at seven clinical  
14 sites. Subjects were evaluated for adverse events and  
15 device-related events that occurred through the  
16 hospital discharge and these patients had follow-up  
17 visits at 30 days and six months post-treatment and  
18 annually thereafter. As you have already heard, these  
19 patients will continue to be treated, continue to be  
20 followed, for five years.

21 The GORE TAG subjects had chest X-rays  
22 performed at 6, 12 and 24 months with CT scans in

1 these patients performed at 1, 6, 12 and 24 months.  
2 There were 140 patients in the GORE TAG group compared  
3 to 94 surgical controls.

4 All baseline demographic and clinical  
5 characteristics were similar between treatment groups,  
6 except for a higher prevalence of symptomatic  
7 aneurysms in the surgical control groups versus the  
8 GORE TAG group. Pretreatment aneurysm diameters were  
9 similar between the GORE TAG group and the control  
10 group.

11 The primary safety endpoint was the  
12 proportion of subjects who experienced greater than  
13 one major adverse event through one-year post-  
14 treatment, and I would like to just call out the  
15 alternative hypothesis at the last bullet, and that is  
16 the proportion of subjects who experience at least one  
17 major adverse event through one-year post-treatment  
18 would be less in the TAG group than in the control  
19 group.

20 Major adverse events were categorized as  
21 either major and minor and that has been covered  
22 previously, and so I will move on to the actual

1 events. And the safety endpoint was the proportion of  
2 subjects who had had any of these following events  
3 during the follow-up period.

4 Looking at results. Safety. The  
5 proportion of patients with at least one major adverse  
6 event for the GORE TAG group was 42 percent versus 77  
7 percent for the surgical controls, and with these data  
8 one can reject the null hypothesis with a p-value of  
9 less than 0.001. Looking at a worst case scenario, 10  
10 GORE TAG patients had no 12 month visit.

11 Assuming that all of these 10 patients  
12 experienced at least one major adverse event through  
13 one-year post-treatment, the estimated one-year major  
14 event incidence increased from 42 percent to 49  
15 percent. With these data, the significance level for  
16 the comparison to the surgical control group did  
17 remain significant at less than 0.001.

18 This table emphasizes the important,  
19 clinically relevant safety outcomes and for bleeding  
20 complications, pulmonary complications, renal, wound  
21 and especially neurologic complications, the Gore  
22 group had a lower incidence of events. Not

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 unexpectedly, vascular complications were increased in  
2 the GORE TAG group versus the control group. Kaplan-  
3 Meier estimates showed importantly that out to two  
4 years, the freedom from major adverse events was  
5 superior in the GORE TAG group versus the surgical  
6 control group.

7 Moving next to mortality. There was no  
8 between group differences in all-cause mortality  
9 between the device treated patients who had a  
10 mortality of 24 percent through two years versus the  
11 control group, which had a mortality of 26 percent.

12 However, the company then chose to look at  
13 aneurysm-related mortality defined as death prior to  
14 hospital discharge, death within 30 days of the  
15 primary procedure or within 30 days of any secondary  
16 procedure to treat the original aneurysm or death due  
17 to aneurysm rupture. And here, aneurysm-related  
18 mortality was lower in the TAG group versus the  
19 control group through two years. Further, there were  
20 no device-related deaths noted through two years.

21 The efficacy endpoint was the proportion  
22 of subjects treated with the GORE TAG Endoprosthesis

1 who are free from a major device-related event through  
2 the 12 month follow-up visit, and this efficacy  
3 endpoint was a composite of the proportion of subjects  
4 free from the complications listed below including  
5 aneurysm enlargement, rupture, deployment failure,  
6 branch vessel occlusion and lumen obstruction.

7 In designing the efficacy endpoints,  
8 several considerations were made. FDA and the sponsor  
9 agreed to an analysis plan where the device would need  
10 to show superior safety since the efficacy of the GORE  
11 TAG prosthesis was expected to be less than that of  
12 surgical repair with the efficacy of open surgical  
13 repair assumed to be 100 percent. A point estimate of  
14 80 percent was judged to be a reasonable efficacy  
15 outcome for endovascular treatment in this study.

16 Looking at the outcome, freedom from a  
17 major device-related event for the GORE TAG group was  
18 94 percent. For this 94 percent, eight subjects or 6  
19 percent experienced at least one major device-related  
20 event through the 12 month follow-up visit with 75  
21 percent of those events occurring within 30 days. And  
22 with those data, one can reject the null hypothesis

1 with a significant p-value.

2           Once again, during a worst case scenario,  
3 10 patients who had no follow-up visit and assume all  
4 those 10 patients experienced a major device-related  
5 event, now the estimate of the probability of not  
6 having a major device event decreases from 94 percent  
7 to 87 percent but, once again, still able to reject  
8 the null hypothesis that  $p$  equals 0.02.

9           A little difficult to see, but here are  
10 the clinically relevant device-related events in these  
11 eight patients, four endoleaks, zero aneurysm  
12 ruptures, two treatment-related device events, one  
13 unplanned occlusion of a branch vessel, one prosthesis  
14 migration and three aneurysm enlargements. If you  
15 look to the right, you can see that from 12 months to  
16 24 months, there was only one additional device-  
17 related event and that is an aneurysm enlargement seen  
18 below right.

19           Secondary endpoints, as you have heard,  
20 were procedural blood loss, length of ICU and hospital  
21 stay and the time to return to normal activities. And  
22 as you have already heard, there was a decrease in the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 immediate length of ICU and hospital stay, as well as  
2 less blood loss and a quicker return to normal  
3 activities in the GORE TAG Endoprosthesis group.

4 The imaging core laboratory observed 19  
5 patients with prostheses material failures and that is  
6 all wire fractures through 24 months. To date, one  
7 adverse event has been associated with breaks in the  
8 spine wires and that is a Type III endoleak requiring  
9 implantation of an additional GORE TAG Endoprosthesis.

10 As also you have heard, the device has  
11 been modified to minimize the risk of fractures  
12 through the elimination of the longitudinal spine.  
13 Uniform bonding has been added to the stent structure  
14 to aid in deployability.

15 The rationale for the 30 day confirmatory  
16 study, that's TAG 03-03, for the modified device  
17 design was based on a risk analysis demonstrated that  
18 only device delivery and not long-term efficacy would  
19 be affected by the modifications. The modified device  
20 performed as well or better than the original device  
21 in preclinical bench testing. The majority of device-  
22 related events occurred within the first 30 days in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the pivotal study.

2           So this led to the confirmatory study,  
3 which was a non-blinded, non-randomized prospective  
4 single arm study using the modified device design.  
5 This was performed in 51 patients and the controls  
6 were the surgical controls in the original pivotal  
7 study, 99-01. The study was performed at 11 sites in  
8 the United States. It had the same inclusion and  
9 exclusion criteria, the same screening assessments,  
10 core laboratories and study data collection as the  
11 pivotal study.

12           There were 51 patients who were similar in  
13 age to the 94 surgical controls, as well as the 140  
14 TAG patients in Study 99-01, the pivotal study, and  
15 baseline critical characteristics were generally  
16 similar among the various arms of the study, except  
17 for a higher incidence of cancer in one of the groups.

18           Further, the aorta and aneurysm  
19 measurements for the confirmatory patients, the 03-03  
20 TAG subjects, did not differ from the pivotal study  
21 TAG patients with respect to aortic diameters,  
22 proximal and distal to the aneurysm, the aneurysm

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 diameter itself and aneurysm length.

2 The safety endpoint was the proportion of  
3 subjects who experienced at least one major adverse  
4 event through 30 days post-treatment, and the  
5 important alternative hypothesis was the proportion of  
6 subjects who experienced at least one MAE through 30  
7 days post-treatment would be less in the TAG subjects  
8 than in the surgical controls.

9 For the outcome, the proportion of  
10 patients with at least one major adverse event in the  
11 prosthesis group was 12 percent versus 70 percent for  
12 the surgical control group. We can reject the null  
13 hypothesis with a p less than 001 and doing a worst  
14 case scenario of the two patients who had no 30 day  
15 follow-up visit, the MAE incidence increases from 12  
16 percent to 16 percent, which remains statistically  
17 significant.

18 And here are the clinically important  
19 outcomes and you can see for bleeding, pulmonary,  
20 cardiac, renal, wound and neurologic complications, a  
21 lower incidence of the major adverse events in the  
22 endoprosthesis group versus the surgical controls.

1 None of the 51 patients died during the first 30 days  
2 versus 6 percent in the surgical group, and there have  
3 been no aneurysm ruptures reported with the modified  
4 TAG device.

5 For efficacy, this was defined as the  
6 proportion of subjects treated with the modified  
7 device who were free from a major device-related event  
8 through the 30 day follow-up visit and, as you have  
9 heard, no subjects in the device group experienced at  
10 least one major device-related event through 30 days.  
11 That corresponds to a 95 percent confidence interval  
12 of .9321.00.

13 There were two patients, as mentioned, who  
14 did not have a follow-up visit and if we take a worst  
15 case scenario and assume those patients did have a  
16 major device-related event, the confidence interval  
17 changes from 0.93 to 0.87 as a lower bound. There  
18 were no deployment-related adverse events and six  
19 patients had minor endoleaks.

20 The same secondary endpoints were looked  
21 at in the confirmatory study and, once again, the mean  
22 length of ICU stay, hospital stay, blood loss and time

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to return to normal activities were superior in the  
2 endoprosthesis group versus the surgical controls. To  
3 date, no wire fractures have been observed in the  
4 modified device.

5 Additional clinical data is and will be  
6 available, the out-of-U.S. Gore registry of 114  
7 subjects, and there are three sponsor-investigator  
8 IDEs, two of which include patients of high surgical  
9 risk and one study is a study of patients with  
10 thoracic aortic emergencies.

11 And just to give you an appreciation of  
12 the different etiologies of the thoracic diseases that  
13 will be available from these studies, you can see that  
14 in the Sponsor-Investigator Study I and II and the  
15 European Registry, just over 50 percent of these  
16 patients will be treated for thoracic aneurysms with  
17 a smaller percentage of patients for the various other  
18 aortic pathologies listed.

19 So in conclusion, from the studies  
20 presented, all pre-specified safety and effectiveness  
21 hypotheses were met. Spine wire fractures in the  
22 original device design occurred, but were rarely

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 associated with clinical sequelae. Device  
2 modifications, specifically removal of the spine  
3 wires, did not compromise device deployment or safety  
4 and efficacy through a 30 day endpoint.

5 There have been no aneurysm ruptures  
6 reported for patients treated with either of the TAG  
7 devices, and the reported product results are  
8 acceptable. With that, I will close and turn this  
9 over to Mr. Kamer.

10 MR. KAMER: Good afternoon. I'm Gary  
11 Kamer. I'm the statistician who reviewed this for the  
12 FDA, this submission. First I want to look at the  
13 statistical considerations. These are general, a very  
14 large overview. One has to do with the clinical study  
15 design that was non-randomized, and also the  
16 effectiveness of the endovascular repair is assessed  
17 somewhat differently from that of the surgical control  
18 in that the surgical control is assumed pretty much to  
19 be at 100 percent.

20 Secondly, two primary studies were  
21 performed, TAG 99-01 and 03-03, both with  
22 complimentary objectives showing that the device, the

1 current device works. Another issue was hypothesis  
2 formulation. We'll discuss that a little bit more  
3 later. And then finally, safety and effectiveness  
4 conclusions, what can be said when we're finished with  
5 the study.

6 Now, turning to TAG 99-01, it's a non-  
7 blinded, non-randomized control study using the  
8 original device design. There were 140 GORE TAG  
9 subjects and then there were two groups that you heard  
10 already, of open surgical control patients, some  
11 historical controls and some concurrent, and there  
12 were 17 clinical sites.

13 Now, turning back to non-randomized  
14 studies, although this applies to both the 99-01 and  
15 03-03 studies, I can introduce, I think, at this point  
16 the issues of selection bias and comparability  
17 considerations. First of all, selection bias may  
18 present itself as an observed baseline comparability  
19 issue. Physical adjustment techniques do exist for  
20 this type of a bias, dealing with this type of  
21 covariates.

22 Secondly, treatment arm imbalances in

1 unobserved or unmeasured baseline variables cannot be  
2 adjusted via statistical techniques. So that remains.  
3 Thirdly, bias may also express itself in the exclusion  
4 of various types of patients or assignment decisions  
5 being based on unobserved criteria. Again, adjustment  
6 techniques, statistical techniques are not cable of  
7 adjusting for those.

8 Finally, treatment comparison may be  
9 improved via covariate adjustment or propensity score  
10 analysis. These are two of the statistical techniques  
11 that do exist for making adjustments in those things  
12 that can be adjusted for.

13 Now, going back to TAG 99-01, we're  
14 looking at the comparability of the treatment groups.  
15 The comparison of baseline covariates between TAG  
16 subjects and the surgical control groups appear to be  
17 reasonably well-matched. Covariate analysis pretty  
18 much have held that. And now, I'm going a little bit  
19 more into the propensity score analysis, which is one  
20 we want to stress in this case.

21 Propensity score analysis provides a post-  
22 randomization via calculation of each patient's

1 probability of having been assigned to the treatment.  
2 All observed covariates should be or may be considered  
3 in propensity score analysis. It eliminates the  
4 issues of over-fitting or at least it mentions the  
5 issues of over-fitting of the model as common in  
6 covariate adjustment approach.

7 It emphasizes overall patient condition  
8 relevant to outcome. I think it does this more so  
9 than the covariate approach. Still, it cannot adjust  
10 for unobserved baseline errors. Propensity score  
11 analysis results showed the reasonable baseline  
12 covariate balance between the original TAG device arm  
13 and the surgery arm for the safety comparison.  
14 Propensity score analysis is used only for the  
15 evaluation of comparability of the treatment groups  
16 and not for the adjustment result p-values and  
17 estimates. This is speaking now of the analysis that  
18 we received.

19 Finally, model and results are still being  
20 evaluated by FDA due to recent receipt of the data.  
21 We actually received the raw data for analysis  
22 purposes on January 7, so we've had less than a week

1 to look at them, at this point. The safety  
2 hypothesis, the null hypothesis was that the  
3 proportion of subjects who experienced at least one  
4 major event, adverse event through one-year post-  
5 treatment was equal to the control subjects and the  
6 TAG -- was equal between the control subjects and the  
7 TAG subjects.

8 The alternative is that the proportion of  
9 subjects or patients who experienced at least one  
10 major event, adverse event through one-year post-  
11 treatment was less for the TAG subjects than the  
12 controls. The effectiveness hypothesis was a  
13 different TAG sort, in that it was just showing simply  
14 the proportion of subjects free from any major device-  
15 related event through 12 months would be less than .8  
16 or 80 percent. The alternative is that it would be  
17 greater. And I think also the sponsor also presented  
18 a cognizable approach to that also showing the same  
19 thing.

20 Safety and effectiveness conclusions for  
21 TAG 99-01, the first 12 month major adverse event  
22 rates for the original TAG device were statistically

1 lower than that for surgery. Secondly, dealing with  
2 the effectiveness, the effectiveness rate of the  
3 original TAG device was greater than 80 percent. And  
4 then finally, what happened, which wasn't anticipated  
5 at the time, was the discovery that there were  
6 fractures resulted in major redesign of the original  
7 TAG device, which lead to the next study TAG 03-03.

8           Once again, it was a non-blinded and non-  
9 randomized study using the modified device designs you  
10 saw earlier. 51 TAG subjects, the safety control was  
11 going to be the surgical control enrolled in the TAG  
12 99-01 Study. There were 11 clinical sites all in the  
13 U.S. for this study. The same inclusion/exclusion  
14 criteria, screening assessments, CEC scores, etcetera  
15 were used in the TAG 99-01 Study.

16           Now, dealing with the comparability of  
17 recruitment groups in TAG 03-03, the same  
18 comparability and selection bias considerations as  
19 existed for 99-01. The comparison of baseline  
20 covariates between the TAG 03-03 subjects and the  
21 surgical controls were pretty much well-matched again.  
22 The covariate analysis again showed that the groups

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 were reasonably well-matched. There wasn't anything  
2 indicated.

3 Now, turning again to the propensity score  
4 analysis, we have a chart or picture which basically  
5 is a box plot and without going into any great detail,  
6 what you're looking for on there is we could have done  
7 one of any three that they presented analyses. We  
8 chose the one that probably looks the worst for the  
9 showing similarity between the patients or the  
10 populations or the randomization, fairness of the  
11 randomization. But this one still is not really bad,  
12 because what you're looking for is an overlap of the  
13 two boxes that you see. And as you notice, there is  
14 substantial overlap in this.

15 This was for the TAG 03-03 device versus  
16 the surgical control from TAG 99-01. And going  
17 further with the results, they do show the reasonable  
18 balance between a TAG device arm and the surgical  
19 control arm. And that's for the safety comparison.  
20 Propensity score analysis only used for the evaluation  
21 comparability to treatment groups again and not for  
22 the adjustment results. In other words, no p-values

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 no confidence intervals were adjusted in the analysis.

2 Looking now, turning to the safety  
3 hypothesis for TAG 03-03, the modified device, the  
4 safety null hypothesis was the proportion of subjects  
5 who experienced at least one major adverse event  
6 through 30 days post-treatment was equal in the  
7 control subjects and the TAG subjects. The  
8 alternative is that the proportion through experience  
9 rarely one major adverse event through 30 days was  
10 less in the TAG subjects than in the control patients,  
11 an improvement.

12 Safety outcomes for that study, the  
13 proportion of patients with at least one major adverse  
14 event per TAG device was 12 percent versus 70 percent  
15 for the surgical control group of 30 days. Therefore,  
16 the null hypothesis was rejected at the .001 level.  
17 Secondly, you have 2 or 4 percent of the TAG subjects  
18 who had no 30 day follow-up, that's been mentioned  
19 before. Now, assuming that both of these patients  
20 experienced the major adverse through 30 days post-  
21 treatment, the estimated 30 day adverse, major adverse  
22 event incidence increases from 12 percent to 16

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 percent. Again, compared to the control, that is  
2 still significant. So it does not change the result.

3 Effectiveness endpoint, TAG 03-03, the  
4 proportion of subjects treated with the TAG modified  
5 device design who were free from a major device-  
6 related event, two 30 day post-follow-up visit. On  
7 the day it was presented descriptively both by the  
8 sponsor and by us, primarily because the original  
9 hypothesis was not appropriately stated to be tested  
10 and then used as a claim. No subjects experienced  
11 even one major -- greater than one -- even one major  
12 adverse-related event to 30 day follow-up visit for  
13 the device.

14 They gave a 95 percent confidence interval  
15 from 93 percent to 100 percent. But you did have, as  
16 we mentioned earlier, two subjects who had no 30 day  
17 follow-up. Assuming that both patients experienced a  
18 major device-related event, then the 95 percent  
19 confidence interval for the proportion of patients  
20 free from a device event is 87 percent to  
21 approximately 100 percent. So 87 percent is the lower  
22 confidence interval.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           Looking further at effectiveness for that,  
2           for the TAG 03-03 Study, 2 out of 51 patients were not  
3           evaluated 30 days and what I'm going to do is show the  
4           -- what would happen if one or two of these patients  
5           had now been evaluated or had experienced at least one  
6           major adverse, a device-related adverse event. And  
7           that's just an extension of what you had before. As  
8           you see, at 2, the 86 or 87 percent to almost 100 and  
9           zero which was observed, you realize that the adverse  
10          event-free rate would be no lower than 93 percent  
11          based on the confidence interval.

12                 So you can look at that. And, basically,  
13          what happens is you are dropping about 3 percent every  
14          time you add one other patient on. That's not only to  
15          show that these were missing, it's also to show  
16          somewhat sensitivity or volatility for so few  
17          patients. Volatility results. The limitations of  
18          effectiveness analysis for TAG 03-03, the 03-03  
19          hypothesis was not formulated so as to statistically  
20          establish effectiveness in the modified TAG device, so  
21          nothing can be a first statistic concerning the  
22          effectiveness of the modified TAG device relevant to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the original device.

2 The modified device effectiveness,  
3 therefore, is limited to the point estimate and  
4 confidence interval for that device. All right. Our  
5 closing, looking at the statistic prospective on this  
6 overall. We have non-randomization in TAG in both  
7 studies and it was appropriately addressed in the  
8 submission and the subsequent analysis. Safety  
9 hypothesis of both devices were met. Effectiveness  
10 assessment of TAG 99-01 was addressed in that also.  
11 The effectiveness assessment of the TAG 03-03, the  
12 modified device, is limited by the absence of an  
13 appropriately defined hypothesis comparing the two TAG  
14 treatment groups. Thank you.

15 ACTING CHAIR MAISEL: Thank you very much.  
16 At this point, I'll open the discussion to the Panel  
17 Members to ask questions of the FDA and I'll take the  
18 liberty of asking the first question for Dorothy or  
19 whoever wants to answer it.

20 I had a question about the structural  
21 integrity of the device, the modified device, in  
22 particular, and TAG 99-01 could be the poster child

**NEAL R. GROSS**  
COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 for why we need clinical studies and why preclinical  
2 testing is not in and of itself sufficient. They did  
3 all the appropriate testing, all the required testing,  
4 yet it wasn't until after the device was implanted  
5 that we detected these fractures.

6 While they developed a preclinical test  
7 that was able to identify the problem, there is now a  
8 new device which I would consider substantially  
9 modified from the original, and I'm concerned that  
10 preclinical testing might not identify all the  
11 potential problems with that device. And so I wonder  
12 if you just might address the guidelines for testing  
13 of endovascular stents, how they came about and how  
14 confident you are that all the long-term structural  
15 abnormalities can be identified by the preclinical  
16 testing?

17 MS. ABEL: I think, first of all, there  
18 are different reasons for doing preclinical testing.  
19 And certainly, one is to try to predict a longer term  
20 clinical performance. But also it's to compare device  
21 designs as we have here. Initially, when these parts  
22 were developed, both the thoracic and the AAA

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 endovascular grafts, there were no standards or  
2 guidances that were applicable specifically to these  
3 devices.

4           So the stent guidances and the vascular  
5 graft guidances were used by the manufacturers who did  
6 their analysis to try to determine the appropriate  
7 testing. Each individual manufacturer came up with  
8 their own testing strategy, they conducted their test,  
9 they justified their results, and that's really all we  
10 had to go on. Since then, we have had quite a bit of  
11 advancement in the area of evaluation of endovascular  
12 grafts.

13           First of all, we have written a standard,  
14 the ISO standard for endovascular prosthesis and that  
15 covers both AAA and thoracic endovascular grafts as  
16 well as some other implant locations, and that  
17 standard is based on a risk assessment. So you look  
18 at what sort of characteristics does the product need  
19 in order to be able to perform appropriately  
20 clinically? And so let's say you have to be able to  
21 deliver the implant. And so what testing do you need  
22 to do in order to determine whether or not you can

1 actually do that?

2           So I think we have come a long way with  
3 respect to the testing in general. I think the  
4 company has also come a long way even beyond the  
5 standard, because after they saw the failures, they  
6 were able to further advance the testing to  
7 incorporate what they had learned about the clinical  
8 environment. And that's one of the limitations we've  
9 had from the beginning with these devices is trying to  
10 figure out even if you know the type of testing that's  
11 applicable, how do you determine the parameters of  
12 test? What sort of stresses are these devices subject  
13 to in the in vivo environment?

14           And what the sponsor did was try to  
15 incorporate those sorts of things with some additional  
16 testing and also within their existing testing so that  
17 they do have more realistic testing. I don't think we  
18 can ever be certain that a device is not going to have  
19 failures, even if we looked at it in the preclinical  
20 setting. But what we can look at is we know the  
21 benchmark for the current design. We've modified that  
22 design and so now you are comparing to the current

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 design, and in this case it was as good or better in  
2 all the aspects. So we're talking about specifically  
3 durability.

4 The other thing is that there certainly is  
5 the potential for an occasional wire fracture and  
6 we've seen that with the AAA devices, but also what  
7 we've seen is that there has not been clinical  
8 sequelae associated with the majority of those  
9 fractures. So we can't guarantee that there won't be  
10 any fractures with this device, but we feel that even  
11 if there are fractures, the potential of having  
12 clinical sequelae associated with those are fairly  
13 low. Does that help?

14 ACTING CHAIR MAISEL: Yes, it does very  
15 much. Thank you. Judah?

16 DR. WEINBERGER: This is a question  
17 regarding the composite endpoint but consists of about  
18 three dozen different adverse events. We've been  
19 educated in the coronary world to accept composite  
20 endpoints like major adverse cardiac events which are  
21 hard composite endpoints or fairly hard anyway. When  
22 I look at the list of composite endpoints that were

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 thrown in to define a major adverse event, there are  
2 things in here that are rather soft and that are  
3 certainly dependent on other adverse events.

4 So for instance, angina, many of these  
5 patients had angina pre-op. They were Class II or  
6 Class III angina pre-op and pre-procedure. They then  
7 went on to have a procedure and certainly in the  
8 operative group would be expected to have more blood  
9 loss. And seeing more angina post-op is sort of a  
10 secondary effective that's more or less expected. So  
11 I'm troubled a little bit by seeing composite  
12 endpoints that are this large and this complex and you  
13 can't tease out the objective components that are  
14 really independent in trying to assess is this truly--  
15 do we see a safety benefit?

16 So that if I could pull out prospectively,  
17 ideally, those hard endpoints that are clinically  
18 relevant, make sure the patients don't go home with  
19 stroke, paraplegia, a new change in ejection fraction  
20 or, you know, new QAs, I mean, really hard endpoints  
21 that would help a lot. What I see when I see the  
22 large composite endpoint like this is you can shove a

1 lot of stuff under the rug with soft endpoints,  
2 especially since you are very well-aware of what the  
3 treatments of the patients have been exposed to are.

4 MS. ABEL: I'll let Dr. Farb answer that  
5 question. Though I just want to emphasize that we did  
6 present the results for those various endpoints  
7 separately also. And the reason that we do end up  
8 with these composite endpoints is so that we can  
9 design a study that's a reasonable size that can be  
10 conducted in a reasonable time frame.

11 DR. WEINBERGER: But we're giving equal  
12 weight to endpoints of varying degrees of hardness.  
13 So death counts the same thing as an angina episode or  
14 a bump in creatinine or a transfusion.

15 MS. ABEL: Well, that's why we have the  
16 differentiation between the major adverse events and  
17 the minor adverse events in an attempt to address that  
18 to some extent.

19 DR. FARB: I think your point is very  
20 well-taken in presentation and try to call out those,  
21 the sort of the meat of those endpoints that we are  
22 really interested in, and that is things like

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 paraplegia, respiratory failure, certainly death,  
2 myocardial infarction and there are some statistical  
3 implications of doing multiple testing and I can defer  
4 to my statistical colleagues for that.

5 In their data analysis, while we don't  
6 have significant levels that are valid for each  
7 individual important endpoints that we're both sort of  
8 concentrating on, there are confidence intervals  
9 presented. And when the confidence intervals do not  
10 include zero, then we have some basis for saying that  
11 we think that there is a meaningful difference between  
12 the two groups.

13 DR. LINDENFELD: If I could just add to  
14 that comment? I think the concern about soft  
15 endpoints is not just soft endpoints. But the  
16 surgical patients were monitored for soft endpoints  
17 for a much longer period of time. So if we consider  
18 reversible angina without an MI or a lot of non-  
19 sustained V-tach, the surgical group is monitored for  
20 three days in the ICU and we're going to see every one  
21 of those, whereas we're going to see none of them or  
22 very few of them after the first day in the device

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 group.

2 And I think that's another really  
3 important part of those kinds of soft endpoints. The  
4 observation period is enormously different between  
5 these two groups and I'm concerned about that as --  
6 we'll come back later to the definition of some of  
7 these.

8 ACTING CHAIR MAISEL: Dr. Krucoff?

9 DR. KRUCOFF: Are you going to sit down,  
10 Andrew? Doctor, I'll let you pick the responder. I  
11 have, actually, these are somewhat statistically or  
12 random questions, although the interpretations may --  
13 you might be the right person at the mike.

14 Gary in his presentation said several  
15 times that there is no statistical method that can  
16 address for unobserved baseline variables. And it's  
17 impressive to me that we have a control group, some of  
18 whom are anatomically individuals who might have been  
19 appropriate for the TAG device, but were done before  
20 the study started or declined or whatever and others  
21 who were not. Now, your conclusion in a propensity  
22 analysis is that these populations are comparable.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           So is your real conclusion that these  
2           anatomic variations are meaningless?

3           DR. FARB: I don't know if we know that  
4           answer. There are a few anatomical differences that  
5           were present between the two groups. And they did do  
6           an analysis between the two control groups showing  
7           that the covariates were similar between those groups,  
8           independent of the comparison between the control and  
9           the TAG endoprosthesis. Propensity score, again,  
10          I'll, you know, defer to Gary, does help us in being  
11          able to conclude that the two groups were reasonably  
12          comparable in terms of the observed covariates.

13          DR. NORMAND: If I can interject?

14          DR. KRUCOFF: Okay. The observed --

15          DR. NORMAND: Weren't they missing more  
16          for the control group, some of that information, that  
17          would permit that comparison of what Mitch is asking?

18          DR. FARB: Right.

19          DR. NORMAND: So it was differentially  
20          missing in the control group?

21          DR. FARB: Yes, I think that's the  
22          limitation of using the retrospective surgical

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 controls as alluded to that you don't have the  
2 opportunity to have the imaging, for example, in all  
3 those patients. That's right. That is the  
4 limitation.

5 DR. EDMUNDS: Do you really have enough  
6 numbers for propensity, Mitch?

7 DR. FARB: Gary?

8 MR. KAMER: I didn't hear the question.

9 DR. FARB: The question is do you have  
10 adequate numbers to do propensity or not?

11 MR. KAMER: Yes, I believe we do. It is  
12 getting a little small when you get down to 51  
13 patients, with missing data and everything, but you  
14 can. I think it is possible to do. You end up doing  
15 probably instead doing deciles, you're going to do  
16 tertiles, you know, just three levels for matching,  
17 which makes it a little broad. Then adjustment may be  
18 an issue also. But it's much harder with 51 patients  
19 than it is when you're looking at the original 99-01,  
20 which has a larger number of patients.

21 DR. NORMAND: But you --

22 DR. KRUCOFF: So, Gary, did I miss it?

1 Are you -- the covariates that I saw are almost  
2 exclusively demographic and/or clinical. Do you have  
3 anatomic characteristics in there somewhere?

4 MR. KAMER: I think the sponsor can --  
5 we've had about five days to look at it and actually  
6 nobody in this group has looked at it extensively on  
7 the team right here.

8 DR. KRUCOFF: My understanding from --

9 MR. KAMER: But let me ask.

10 DR. KRUCOFF: -- the related question  
11 earlier, from a clarification point of view, is that  
12 these data do not exist.

13 ACTING CHAIR MAISEL: So why don't we ask  
14 this?

15 MR. KAMER: Okay. Then it would not be  
16 included in the model that doesn't exist, if they  
17 don't exist.

18 DR. KRUCOFF: Yes.

19 MR. KAMER: That would be the situation.

20 DR. KRUCOFF: Okay. Because the implicit  
21 conclusion that these are comparable populations only  
22 reaches to demographics and clinical studies, right?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 MR. KAMER: Well, it only reaches those  
2 observed or recorded covariates, right.

3 DR. KRUCOFF: All right. So while I've  
4 got you, let me ask one last point of clarification  
5 that's probably fully unfair, because you haven't had  
6 these data long. But we were shown a slide in the  
7 sponsor's presentation that is a comparison of freedom  
8 from MAEs through 30 days.

9 MR. KAMER: Yes.

10 DR. KRUCOFF: It's plotted as a survival  
11 curve.

12 MR. KAMER: Yes.

13 DR. KRUCOFF: That includes the control  
14 population, the pivotal study and the confirmatory  
15 study.

16 MR. KAMER: Right.

17 DR. KRUCOFF: Okay. So my understanding  
18 of the pivotal study and the confirmatory study is  
19 they used the same enrollment criteria and they  
20 gathered the same data.

21 MR. KAMER: That's what I understand.

22 DR. KRUCOFF: Okay.

1 MR. KAMER: Yes.

2 DR. KRUCOFF: And, at least as I look at  
3 this graft, it looks to me like the confirmatory study  
4 population behaves significantly differently or at  
5 least differently.

6 MR. KAMER: Yes.

7 DR. KRUCOFF: Enough to raise a question  
8 of are we capturing or are we missing something here  
9 that's actually even capable of defining different  
10 outcomes in the populations treated with the device?

11 MR. KAMER: Yes, there may be. Again,  
12 we're dealing very -- we're at the very beginning of  
13 analyzing several different components, one of which  
14 would be, of course, the treatment patients in 99-01  
15 and 03-03. There are some indications that that may  
16 be a more diverse comparison than some of the other  
17 ones we have looked at to this point. But is it  
18 diverse enough to cause a problem, to cause the  
19 difference? I couldn't say at this time. But there  
20 does appear to be some more difference between that  
21 than you would find say between the original, the 99-  
22 01 control and surgical groups.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. KRUCOFF: Okay.

2 MR. KAMER: Control surgical and treatment  
3 groups, there seems to be a little more difference in  
4 those.

5 DR. KRUCOFF: I guess what I'm trying to  
6 get at, Gary, is do you think that we are  
7 characterizing, even with propensity scores,  
8 similarities between these populations that are  
9 totally independent of whether or not or how the  
10 device behaves?

11 MR. KAMER: Similar?

12 DR. KRUCOFF: Well, we're calling these  
13 populations the same.

14 MR. KAMER: Right.

15 DR. KRUCOFF: Based on demographic and  
16 clinical descriptors that you have data for to model  
17 propensity profiles.

18 MR. KAMER: Yes.

19 DR. KRUCOFF: That may, in fact, be  
20 leaving out what actually makes these populations  
21 different or not.

22 MR. KAMER: Well, that's the argument for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 randomization all the time. When you randomize, you  
2 balance, at least in theory you balance, and hopefully  
3 you do.

4 DR. KRUCOFF: I'm just asking whether you  
5 think you have enough data in these data?

6 MR. KAMER: Observed and unobserved, and  
7 I agree with that. So I think it could be. Yes, of  
8 course, they could be left out, yes.

9 DR. KRUCOFF: Do you think you have enough  
10 data in these data sets to call these populations  
11 comparable for the purposes of this assessment?

12 MR. KAMER: I've heard it said before that  
13 the -- by a clinical trial expert who had a lot more  
14 experience than I had, it is actually designed to run,  
15 that you only account for about 25 percent when you do  
16 go back and adjust these covariate adjustment  
17 procedures or apparently propensity score analysis  
18 type procedures. So you can't account for all of  
19 them. You just start gathering, maybe it's a grant in  
20 a person's eye that makes one person be assigned a  
21 certain way or it's just really the only way to do it  
22 to feel comfortable that you have done it is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 randomization.

2 But these methods try to bring a non-  
3 randomized study back towards a randomized study with  
4 what information you have. Are they perfect? No.

5 DR. NORMAND: If I could interject for a  
6 second? It sounds to me, I mean, we already know  
7 already you can't adjust for what you didn't collect.

8 MR. KAMER: Right.

9 DR. NORMAND: And so we're concerned about  
10 the selection bias based on the unobservables. But I  
11 don't know if this is what you're getting at, but I  
12 think a secondary concern, not necessarily in the  
13 importance, is that for the data that are collected,  
14 you're missing data and you're missing data much more  
15 in the control group. So even if you believe they  
16 were comparable, which we don't have the data for, I  
17 guess my question would be adjusting for what you had  
18 knowing that, at least based on my read of this, that  
19 you have differential missing-ness for the control  
20 group versus the treated group.

21 Do you feel that you had enough or  
22 sufficient information, because now there's a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 selection bias on missingness, to look at the  
2 comparability of even the observed people?

3 MR. KAMER: Again, I think that's always  
4 a trouble within the study we run into. And quite  
5 often we do find that the treatment groups differ as  
6 far as missing data, follow-up, etcetera, in general.  
7 And the answer, I think, would be it's a problem. Do  
8 we have enough? I think it's way too early, after six  
9 days of looking at data.

10 DR. NORMAND: Sure.

11 MR. KAMER: To say yes or no to that.

12 ACTING CHAIR MAISEL: Dr. Somberg, did you  
13 have a question?

14 DR. SOMBERG: Yes, I think there's an  
15 important thread here that we've had in this question  
16 period and I agree with Dr. Weinberger that there are  
17 so many different endpoints in these composites, some  
18 of which are significant, some of which are less. So,  
19 therefore, I move to the mortality. With that said,  
20 I would like you to look at page 10 of my briefing  
21 book from the FDA's material here, the second  
22 paragraph. It goes on to state that even really the

1 mortality endpoint, and I think the TAG 01 pivotal  
2 study is what we should focus on, because that's going  
3 to be the major -- have the major number of patients,  
4 the longest follow-up and really is what is pivotal  
5 for the, by its definition, approval of this device.

6 And it says there is a very major  
7 difference between the New York Heart Association and  
8 the symptomatology of the aneurysms, but at least half  
9 in the control group, half of the data is missing.  
10 You can't replace missing data. But my specific  
11 question, after all those statements, is was there any  
12 attempt made to adjust for the difference in severity  
13 Class III versus Class II, which has an impact on  
14 outcome for the data we have to try to account for  
15 that or has that not been done? Because I didn't see  
16 that in the sponsor's presentation and I didn't see it  
17 in the follow-up materials from the FDA.

18 MS. ABEL: I really think that that would  
19 be most appropriately addressed by the sponsor. I  
20 think there are several of these questions that would  
21 be most appropriately addressed by the sponsor. I  
22 think they have the clinical expertise to discuss what

1 effect potential differences in anatomy would have on  
2 the two treatment groups. And I also think that they  
3 know better in terms of what they were using NYHA data  
4 for and how much of this information they have been  
5 able to obtain and what additional analysis they have  
6 done. That we have presented what we have seen.

7 ACTING CHAIR MAISEL: So we can address  
8 those questions to the sponsor after lunch. But just  
9 to directly address the FDA. So in your analysis, was  
10 New York Heart Association adjusted for in the  
11 propensity score analysis?

12 MR. KAMER: We took a look at that, at  
13 those. We noticed there was a large discrepancy in  
14 missing data between the two groups, treatment groups.  
15 And really a little surprised that that wasn't  
16 collected, whereby it's a very important normally  
17 covariate. However, upon using the data that were  
18 provided, we really found that it was not correlated  
19 to outcome as much as we had thought.

20 DR. NORMAND: Is that complete case then?  
21 You did a complete case analysis? How did you do it  
22 for those? How did you include it for those that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 didn't have it measured in the propensity score  
2 analysis?

3 MR. KAMER: Was that imputed? It was  
4 imputed. Okay. It was imputed also. I know most of  
5 the analysis we have performed have been using  
6 imputations.

7 DR. NORMAND: So you imputed the New York  
8 Heart score for those that were missing the data?

9 MR. KAMER: Yes. Again, this is  
10 preliminary, but we were -- but it was not then one of  
11 those covariates that would have been related to  
12 outcome and therefore was not different. I don't  
13 believe it was different. Well, it was somewhat  
14 different, but it was not included, I don't believe,  
15 in any of the other analysis.

16 DR. NORMAND: So you just used mean  
17 imputation for everybody? I'll stop.

18 ACTING CHAIR MAISEL: I mean, the bottom  
19 line is that there is a lot of data missing from the  
20 control group that we can never get back and we can do  
21 all kinds of analyses, but we just don't know what we  
22 don't know.

1 DR. LINDENFELD: I just have a specific  
2 question maybe for Bram or for some of the FDA  
3 representatives. It seems to me that not only are we  
4 missing data, but I'm not certain that we have  
5 collected the data that indicates the risks to the  
6 patients adequately. Just looking back before I came,  
7 there was a recent review of 1,100 patients with  
8 thoracoabdominal aneurysms and the four biggest risk  
9 factors for mortality were creatinine, which we don't  
10 have in here, age, which we do, symptoms, which were  
11 clearly worse in the surgical group, and the Crawford  
12 type of aneurysm, which we don't have.

13 So those in a multi-variate analysis were  
14 the top four. We have one not different, one very  
15 different and two we don't have. This would be an  
16 opportunity to look back at the SVS database and let  
17 them also tell us what are the top risks and do we  
18 have enough of that data to be sure that we can  
19 compare these groups? I mean, what are their risks as  
20 well? But I'm concerned that we're just missing a lot  
21 of baseline data which we can't correct for, because,  
22 as was said, we can't correct for data that we don't

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 even have.

2 ACTING CHAIR MAISEL: Do you have any more  
3 specific questions for the FDA? Dr. Bridges and then  
4 Dr. Edmunds.

5 DR. BRIDGES: I have a question that also  
6 relates to Dr. Weinberger's point about the question  
7 about endoleaks. There is a significant incidence of  
8 minor endoleaks or minor adverse events that are  
9 endoleaks. It was 12 percent in the TAG 03-03 and 14  
10 percent, approximately, in the TAG 99-01. And in  
11 terms of major adverse events related to endoleaks, it  
12 was only 3 percent. And the definitions of those two  
13 are somewhat soft, i.e., a minor endoleak is one  
14 that's being followed serially that doesn't require  
15 intervention. Whereas, a major endoleak is one that  
16 does require intervention.

17 So, first of all, I would expect that  
18 there should be an incidence of minor endoleaks that  
19 become converted to major endoleaks at some point, and  
20 I'm not sure looking through the data that I see  
21 evidence that that happens. And secondly, the issue  
22 of whether an intervention is required or not is also,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 you know, somewhat subject to observer, interobserver  
2 differences. Do you have any comment on that? Is  
3 that an issue? And what's the fate of all those 14  
4 percent of patients that have minor endoleaks? Have  
5 those -- maybe someone could comment on that.

6 ACTING CHAIR MAISEL: That seems like a  
7 more appropriate question for the sponsor. Maybe you  
8 can work on getting that. Do you have that  
9 information available, at this time, regarding the  
10 endoleaks? Why don't you step up and just answer his  
11 question, please?

12 MR. NILSON: The definition of major and  
13 minor was determined by the Sacks criteria as you've  
14 already alluded. I would like to point out that we  
15 have not seen any ruptures in either of the arms. I  
16 will bring up Dr. Makaroun to give the clinical  
17 perspective on major versus minor endoleaks.

18 DR. MAKAROUN: Forgive me if I ask you to  
19 go back and give me the multiple questions.

20 DR. BRIDGES: Yes, sorry.

21 DR. MAKAROUN: If I remember your question  
22 correctly, one of them related to whether some minor

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 endoleaks can turn into a major endoleak in the  
2 further follow-up.

3 DR. BRIDGES: Right.

4 DR. MAKAROUN: Obviously, by the  
5 definition that is used, an endoleak that does not --  
6 let's say for two years and is classified as minor and  
7 is treated in the third year becomes major, but  
8 typically that essential endoleak becomes classified  
9 as major. The majority of endoleaks that you saw  
10 reported there are through a particular period. And  
11 at any time an endoleak was observed even if it went  
12 away, it gets reported in that percentage that you are  
13 seeing. Actually, the number of endoleaks that are  
14 still there and observed is much fewer than the number  
15 of endoleaks that are reported in this data. I can  
16 probably show you this.

17 ACTING CHAIR MAISEL: Were there any minor  
18 endoleaks that became major?

19 DR. MAKAROUN: One that retroactively  
20 became major. It was -- it was during year three.

21 ACTING CHAIR MAISEL: Okay. Maybe we can  
22 do this a little more in depth after lunch. And, Dr.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Edmunds, if you could ask your final question and then  
2 we'll take a break.

3 DR. EDMUNDS: Has the FDA seen any  
4 histologic data about this endoprosthesis or any  
5 endoprosthesis?

6 MS. ABEL: We have not seen histological  
7 data for this particular endoprosthesis. We have seen  
8 it on other devices. We have seen it for the AAA  
9 device, from Gore and other AAA devices.

10 DR. EDMUNDS: How does it heal?

11 MS. ABEL: I'm really not qualified to  
12 answer that question and I don't think you've looked  
13 at the -- I would ask that the sponsor be able to  
14 address that question. I'm sorry.

15 ACTING CHAIR MAISEL: At this point, why  
16 don't we take a break and we can explore those and  
17 other issues after lunch. We will resume at 1:45.

18 (Whereupon, the hearing was recessed at  
19 12:45 p.m. to reconvene at 1:46 p.m. this same day.)

20

21

22

1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 1:46 p.m.

3 ACTING CHAIR MAISEL: If everyone could,  
4 please, take their seat, we can begin. Please, be  
5 seated, so we can begin the afternoon session. I  
6 would like to start with our lead reviewers doing  
7 their reviews and questioning the sponsor, and we will  
8 begin with Dr. Edmunds. Actually, you can do it from  
9 your seat. That's okay.

10 DR. EDMUNDS: My review of this very  
11 thick, heavy, repetitious package can be consolidated  
12 down to, first, I don't think there is any material  
13 difference made with the modification. I think the  
14 modification is an improvement and I see no downside,  
15 and I did notice that when you bend it, holding the  
16 two ends like the curve of the aortic arch that is not  
17 involved in this protocol, there is no compromise of  
18 the lumen whatsoever.

19 I also think that the safety and the  
20 efficacy of the device is demonstrated. However, I  
21 must say that I think the statistical control group is  
22 a joke.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           ACTING CHAIR MAISEL: Do you have any  
2 questions for the sponsor at this point?

3           DR. EDMUNDS: Well, I would really like to  
4 see some histologic data, but there is none here, so  
5 I don't think that needs to be brought up again.

6           ACTING CHAIR MAISEL: Okay. Thank you.  
7 Dr. Yancy?

8           DR. YANCY: Thank you, Bill. I apologize  
9 that I didn't hear the sponsor's presentation. Flight  
10 delays weren't avoidable. But nevertheless, I have  
11 reviewed the supplied PowerPoint file and gone through  
12 the same continued information, as so described.

13           I think it has already been identified  
14 what disease process it is that we are concerned  
15 about, and that is a fairly significant expression of  
16 peripheral atherosclerotic disease with significant  
17 morbidity and mortality. And as a cardiovascular  
18 specialist, I certainly have a great amount of respect  
19 for this disease, because I recognize how commonly it  
20 is companioned with significant coronary disease, thus  
21 increasing perioperative risk, so that a percutaneous  
22 treatment strategy, one that would minimize the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 morbidity and mortality of the given procedure would,  
2 in fact, be a significant advance.

3 So one looks at this platform from a  
4 clinician's perspective with hopes that the technology  
5 is at the point where it can be embraced and move  
6 forward in a reasonable way. Reviewing the  
7 technology, there are some immediate concerns that  
8 come to mind and, in reviewing the entire packet,  
9 there are more significant concerns that come to mind.  
10 Specifically, I will start with the last comment made.

11 There is, in fact, reference in our packet  
12 of animal data from which there are necropsy findings  
13 that simply give us global statements that the host  
14 response was normal and that the histology was  
15 unremarkable. In my judgment, that is insufficient  
16 information and it would be helpful to know what the  
17 integrity of the endothelialization is of the device,  
18 if that indeed is what occurs, and what the kind of  
19 scarring process might happen to be. So there are  
20 some qualitative references to that, but I agree that  
21 I think it would be helpful to have better  
22 information.

1           As I have gone through and looked at the  
2 three different trials starting with the feasibility  
3 study, I view that as a pilot study utilizing only 28  
4 patients, a fairly reasonable 30-day mortality rate of  
5 3.6 percent, but I remark that the one-year mortality  
6 rate was 21 percent. Now, that's only five patients  
7 but, nevertheless, that is of concern.

8           As well, the major adverse event rate in  
9 the feasibility study was 57 percent. The more  
10 worrisome events didn't occur, but I make the point of  
11 the 57 percent, because the statistical estimates for  
12 the pivotal trial were based on a 50 percent reduction  
13 of the major adverse event rate, so it would almost  
14 seem as if the suggestion is that for the surgical  
15 cohort, 100 percent of the patients would end up with  
16 a major adverse event.

17           It was interesting that the questions of  
18 lead fracture or wire fracture were identified during  
19 the feasibility study, and I find it somewhat curious  
20 that the adjustment in the technology was not made at  
21 that point, but rather was made after the pivotal  
22 study.

1 I think, as has been suggested earlier,  
2 that the pivotal study is the most significant  
3 database to look at, because it does, in fact, have a  
4 pretence of a comparative population. I say pretence,  
5 because I am very concerned that this was a non-  
6 randomized experience, and I am even more concerned  
7 that the control group or the reference population was  
8 quite heterogenous.

9 Approximately, half of the control group  
10 were consecutive retrospective cases that perhaps may  
11 have been candidates for the device or not, and then  
12 44 percent were prospectively enrolled cases. But I  
13 am even more concerned about the prospectively  
14 enrolled cases, because in the text of the information  
15 provided by the sponsor, it's indicated that the main  
16 reason that those individuals were treated in the  
17 surgical cohort is that they failed the screen for the  
18 EXCLUDER with the most likely reason for failure being  
19 an inappropriate, unacceptable anatomical substrate.

20 Now, Mitch was getting at this earlier,  
21 and I fully support the direction of his questions.  
22 It is indicated in the table that the incidence of

1 symptomatic aneurysms was 21 percent in the device  
2 group, 38 percent in the surgical group. That is a  
3 difference of nearly 100 percent, and I cannot  
4 appreciate how we could say the groups are similar  
5 when the anatomical substrate, that upon which the  
6 surgical methodology is based, appears to be so  
7 strikingly different at least in a qualitative way.

8           What further raises my concern is that not  
9 only is the anatomy more likely to be problematic in  
10 the surgical group, but the distribution of the NYHA  
11 class, even though data points were missing, was  
12 clearly disparate with more Class II individuals in  
13 the device group and more Class III individuals in the  
14 control group.

15           Thus, if you take those two observations,  
16 it seems to me that the surgical group or the control  
17 group was actually a higher risk group, and so when  
18 one compares an appearance of safety and a reduction  
19 of major adverse events with the device against what  
20 appears to be a higher risk group, I think that, to a  
21 certain extent, disqualifies the statements that based  
22 on those comparators, that the group treated with the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 device was, in fact, treated with a platform that was  
2 felt to be safe.

3 It is admitted that this statistical  
4 analysis does, in fact, demonstrate with reasonable  
5 power that the relative risk reduction of events was  
6 quite impressive, but that was a 14 day, 61 percent  
7 relative risk reduction. By two years, it was 37  
8 percent and one wonders about the durability of the  
9 device and whether or not the difference between major  
10 adverse event rates would be neutralized with longer  
11 follow-up.

12 I am especially concerned looking at the  
13 pivotal trial that the issues that I, as a  
14 cardiovascular specialist, would be concerned about,  
15 specifically mortality in cardiac events, were totally  
16 unaffected by the use of what, at face value, appeared  
17 to be a lower risk platform. There was no difference  
18 in mortality probably related to the sample size,  
19 admittedly, and there was no difference in cardiac  
20 events.

21 And given the very high event rate of this  
22 group, the sample size should have been enough to

1 detect a difference in cardiac events. And so that,  
2 in my judgment, means that we would have to look at  
3 other components of the major adverse event category  
4 that would have to be quite robust to overcome a lack  
5 of difference in those major outcomes.

6 Admittedly, there was a difference in the  
7 incidence of paraplegia, which is a large risk for  
8 this kind of surgery, but I don't think it reaches the  
9 bar and I would embrace what Dr. Weinberger said, that  
10 when you have this kind of surfeit of variables that  
11 are in your major adverse event category and you have  
12 a composite that is so broad, I think that greatly  
13 dilutes the implication of any single component of  
14 that composite. And certainly from cardiovascular  
15 clinical trials, we're very reluctant to do studies  
16 with a large number of composite endpoints, because it  
17 can disqualify our study design.

18 The confirmatory study is also one that I  
19 have great concern about, because if it represents the  
20 iteration of the platform that has been improved, that  
21 is to say that the wire has been removed and there is  
22 still longitudinal integrity through other

1 manipulations in the engineering, then we would be  
2 going forward to market with an n of 51 observations  
3 in an uncontrolled observational experience that could  
4 not qualify as a study.

5 And basing that as our means of saying  
6 that this is reasonable, I believe that the reference  
7 to a control group in the confirmatory study is  
8 inadequate. I say that, because that control group is  
9 the historical control group from the pivotal trial,  
10 which I already believe is problematic, because it's  
11 heterogenous and it is, in my judgment, clinically  
12 different from the group upon which there was an  
13 intervention.

14 I note that there is a statement that over  
15 2,000 such devices are commercially deployed in  
16 European countries. It may be inappropriate for us to  
17 see those data, but I would be curious to know what  
18 the market experience has been like in those European  
19 applications.

20 There are statements in the manual about  
21 the intent for a post-market analysis plan. I am  
22 troubled by the sponsor's design of an apparent

1 registry. The total number of subjects engaged in  
2 that registry would be 250, the majority of which are  
3 individuals that are already in the stated clinical  
4 trials.

5 I think that one of the areas of great  
6 concern is in the perioperative experience, and to  
7 miss that opportunity in the registry would be  
8 problematic. Clearly, we need long-term data, but I  
9 don't think this registry would suffice and that would  
10 need to be strongly revisited.

11 There also are statements that the sponsor  
12 has suggested about the training of future implanters,  
13 and it strikes me that it is largely a technical plan  
14 and doesn't really capture the nature of the illness.  
15 And given what I believe are differences in the  
16 populations that were identified and cited in these  
17 experiences, I believe that that needs to be a part of  
18 any educational format.

19 So if I summarize my observations, these  
20 are the things that I would say are concerns for me.  
21 The total number of individuals evaluated in the three  
22 submitted trials is only 313. Given the sponsor's own

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 data to suggest there are 15,000 new cases annually  
2 and another 5,000 procedures done per year, I don't  
3 see how we can likely move forward with data on only  
4 51 patients using the most reasonable platform that is  
5 available.

6 I am also concerned that we don't have a  
7 good handle on major adverse events, because we have  
8 been so global in the inclusion. There are more than  
9 three dozen or actually over 40 major adverse events  
10 and they are of varying severity, and I don't believe  
11 that that's a reasonable way to look at those.

12 I think that we have to respect the fact  
13 that the possibility exists, at least from a clinical  
14 perspective, that dissimilar patient populations were  
15 studied in the pivotal trial and so, in my judgment,  
16 disqualifies the comparisons.

17 Finally, I believe that the plans to move  
18 forward are compromised. We have not yet dealt with  
19 one of the major issues that concern me going through  
20 the data, and that is that there are inherent risks  
21 associated with this procedure, particularly at the  
22 vascular level.

**NEAL R. GROSS**  
COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           There is a statement in the FDA memo tab,  
2           page 10, that TAG subjects experience more vascular  
3           complications than control subjects, 18 percent versus  
4           6 percent. That is a threefold increase, and the  
5           majority of those vascular complications were vascular  
6           trauma. And in the sponsor's supplied information,  
7           the comparison chart of the size of the aneurysm  
8           compared to the size of the introducer sheath to  
9           deploy the device suggests sizes as large as 20-24  
10          French.

11                   And for those of us that have been in the  
12          invasive suite, it may not intimidate a surgeon, but  
13          it certainly intimidates me. Balloon pumps usually go  
14          through 9.5 or 10 French. So I am concerned about  
15          taking people with overtly diseased blood vessels with  
16          a large atherosclerotic burden and applying such  
17          technology. So I think that that is a problematic  
18          issue. Thus, I have great concerns about the data  
19          that are presented to us.

20                   ACTING CHAIR MAISEL: Thank you very much,  
21          Dr. Yancy. Did you have any specific questions that  
22          you wanted to ask the sponsor? You mentioned some

**NEAL R. GROSS**  
COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 outside of U.S. experience that they had mentioned or  
2 other specific questions?

3 DR. YANCY: I really just wanted to make  
4 comments. I don't know that there are any answers to  
5 questions that would change the perspective that I  
6 have.

7 ACTING CHAIR MAISEL: Very well. So why  
8 don't we go ahead and proceed with additional  
9 questions and comments from the Panel Members and  
10 we'll start with Dr. Weinberger, please.

11 DR. WEINBERGER: I only have a couple of  
12 questions by way of clarification. We were presented  
13 and a couple of slides highlighted groups of outcomes  
14 in terms of safety. I think Dr. Makaroun presented a  
15 couple of slides where you showed us what the risks  
16 were for the TAG versus the surgical groups broken  
17 down in categories, respiratory, renal, etcetera,  
18 where you had red highlights. Did any of those reach  
19 statistical significance?

20 DR. MAKAROUN: A confidence interval was  
21 constructed for every single one of them, except for  
22 the one I specifically mentioned did not reach

1 statistical significance, which was the cardiac. All  
2 the others highlighted in red did and they were all in  
3 favor of the TAG control group, except for the  
4 vascular complication, which was in favor of the  
5 surgical control group and that also, the 95 percent  
6 confidence interval of the risk factor, did not cross  
7 zero, so it was significant.

8 DR. WEINBERGER: And in those patients who  
9 underwent surgical conversion at some point during  
10 their course, was the implant actually removed? Was  
11 the device removed?

12 DR. MAKAROUN: There was one conversion  
13 and that happened in month three. The particular  
14 patient was suspected to have an infection and that  
15 prosthesis was removed.

16 DR. WEINBERGER: And getting to what Dr.  
17 Edmunds has been asking about, was there any analysis  
18 done of that device?

19 DR. MAKAROUN: I will let the sponsor  
20 answer this, but typically after three months we would  
21 not expect a whole lot of changes.

22 DR. WEINBERGER: It's too early?

1 DR. MAKAROUN: Excuse me?

2 DR. WEINBERGER: It's too early in the  
3 course?

4 DR. MAKAROUN: Too early.

5 MR. NILSON: All devices that were  
6 explanted were not returned to Gore. In fact, we only  
7 received three U.S. devices that have been explanted  
8 over the course of all the pivotals and confirmatory  
9 and feasibility studies.

10 DR. WEINBERGER: Okay. And then I hate to  
11 harp on this control group issue, but it seems to me  
12 that there is a very distinct imbalance not just in  
13 terms of anatomy, but also in terms of the clinical  
14 setting. There were a much larger number of patients  
15 who are having symptoms, unstable symptoms, in the  
16 control group of impending aneurysm rupture. Is that  
17 the case?

18 MR. NILSON: Dr. Makaroun will address  
19 symptomatic versus non-symptomatic aneurysms.

20 DR. MAKAROUN: We actually feel that the  
21 control group was very well-balanced. In terms of the  
22 symptom, which is the only variable that was

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 statistically significant between the two groups, I  
2 would like to preface by saying that all patients with  
3 ruptures were excluded from this trial and all  
4 patients with mycotic aneurysms were excluded from  
5 this trial.

6 The symptoms are not strictly pain  
7 symptoms. Some of them were pain, but some of them  
8 were also related to local pressure on phrenic nerve  
9 or on the trachea or on the esophagus, so some of them  
10 did not carry any of the characteristics that you may  
11 associate with the higher risk type of category that  
12 we discussed. Can you, please, show us the slide?

13 A subgroup analysis was actually performed  
14 for the symptomatic aneurysms, and on the left hand  
15 side you can see the classification between  
16 symptomatic and non-symptomatic aneurysm with the  
17 major adverse event rate through one year listed for  
18 both the TAG and the surgical controls, and you can  
19 see that the therapeutic benefit of the TAG over the  
20 surgical control is actually evident for the  
21 symptomatic aneurysm alone and for the asymptomatic  
22 aneurysms alone.

1                   It's also of note that the major adverse  
2                   event rate for symptomatic versus non-symptomatic is  
3                   essentially the same whether the patient was treated  
4                   by the TAG or by the surgical control. In addition,  
5                   a Cox Regression Analysis Model that was performed did  
6                   not show that symptomatic aneurysm was predictive of  
7                   any major adverse events.

8                   DR. WEINBERGER: That's it.

9                   ACTING CHAIR MAISEL: Thank you. Dr.  
10                  Johnston?

11                  DR. JOHNSTON: I recognize the difficulty  
12                  of developing a clinically safe and effective  
13                  treatment for this very complex and important problem.  
14                  I would like to ignore the comparative data for a  
15                  moment and go to the complications, and I would like  
16                  to start with the minor complications.

17                  I understand the definition of minor  
18                  complications, but I am not sure how fair some of the  
19                  definitions might be and I can cite the examples if  
20                  you want, Table 62, defining renal insufficiency as  
21                  minor. Most clinicians, no matter how that occurred,  
22                  would not feel that was minor.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Prosthesis thrombosis in Table 21 does not  
2 strike me as a minor complication. Late nerve injury  
3 does not strike me as minor. Table 27 listing  
4 prosthesis migration, prosthesis failure, is that  
5 minor? And one of the late endoleaks. And then  
6 further, there was one late case of paraplegia listed  
7 as minor, late.

8 I wonder if you can address the reasons  
9 why these complications might be listed as minor  
10 complications, because I am going to then come back to  
11 the major complications in trying to understand the  
12 true impact of this prosthesis.

13 MR. NILSON: Can you show the major/minor  
14 definition from the main presentation?

15 DR. JOHNSTON: I understand the  
16 major/minor definition. I'm trying to understand how,  
17 in these individual numbers that are in the tables,  
18 they could be listed as minor.

19 MR. NILSON: Dr. Makaroun will address the  
20 clinical relevance of the major versus minor  
21 definition.

22 DR. MAKAROUN: You listed several

1 descriptive terms for the type of complication. We  
2 did discuss initially why some of them were classified  
3 as major, some of them were classified as minor. The  
4 type of the complication did not determine whether  
5 something was classified as major or minor, but the  
6 severity of the complication and its clinical  
7 importance.

8           You went through some examples. I'm  
9 blocking on the several that you had the chance to  
10 mention, one of them --

11           DR. JOHNSTON: For example, page 63, Table  
12 21, prosthesis thrombosis.

13           DR. MAKAROUN: That particular event was  
14 a layering of thrombus on the inside of the prosthesis  
15 that did not affect the lumen and nothing was done  
16 about it, so it was classified as minor.

17           DR. JOHNSTON: Right.

18           DR. MAKAROUN: There are certain other --

19           DR. JOHNSTON: Prosthesis migration, page  
20 72, Table 27, prosthesis migration.

21           DR. MAKAROUN: Again, the definition of  
22 migration was movement of more than 1 centimeter from