

1 in the trial and the control group should also be
2 followed. But I think a control group for the
3 registry is really tough because the point of the
4 registry is you want all comers, and so some of those
5 people might not have exactly met the inclusion
6 criteria for the trial, and I mean as a statistician,
7 I think that would be really tough to try to then
8 compare them to a group that didn't get the device
9 because they're going to be different.

10 DR. MAISEL: Okay. John.

11 DR. SOMBERG: Well, a registry is never
12 perfect. You know, these postmarketing, and there's
13 going to be a lot of problems. Certainly it's not
14 the same as the randomized study where, you know,
15 they're equally balanced and that, but I think it's a
16 good idea to collect them. I mean one possibility of
17 a control group is patients who were offered the
18 procedure and decided to decline it for a host of
19 reasons. People could be in atrial fibrillation,
20 anticoagulation clinic. That can be followed as some
21 baseline. Just so that we don't have inordinate
22 differences and maybe, you know, I don't know, global
23 warming affected it or some other crazy thing.

24 And the last thing is it could be people
25 who were, you know, given the option of having the

1 device but somehow didn't meet all these criteria, et
2 cetera, and therefore decided for one reason or
3 another on this. So you have some comparability.
4 It's not meant to be -- I want to be very clear.
5 It's not meant to be a substitute for the initial,
6 you know, if they did this for the initial
7 application, it would be totally irrelevant, but it's
8 just some comparator to give you an idea because if
9 you don't have an idea, and all of a sudden you have
10 twice as many device embolizations and you have
11 nothing to compare it to, then you can't make any
12 risk-benefit decision, but if you see the stroke rate
13 of the people who were receiving Coumadin, keep
14 escalating as the Sponsor's clinician said it does,
15 that's reassuring, yeah, you have some more toxicity
16 for the device that's device specific, but you also
17 have toxicities from the alternative, and the FDA has
18 something to base a judgment on.

19 DR. MAISEL: So we've heard 2,000 patients
20 proposed. Anyone want to say more or less, or that's
21 about the right amount?

22 DR. KATO: Well, I don't think you can say
23 it's 2,000, Bill. I mean I think that, you know, you
24 can -- I think the consensus I've heard is that we
25 should put everybody into the registry. I mean

1 anybody who gets the device should be covered under
2 the registry.

3 DR. SOMBERG: Unless sales rocket --

4 DR. ZUCKERMAN: Okay. Let's take a time
5 out here. As Dr. Kato just said, we develop post-
6 approval studies that are hypothesis driven, but
7 we've heard the Panel say that it would be ideal if
8 it's a large registry, and frankly, given that our
9 usual goals are to show that acute procedural success
10 rates at new centers are acceptable and that there
11 isn't a difference between large volume sites and
12 small volume sites once they're adequately trained,
13 et cetera, the numbers usually become large norm.

14 If you can give us some of the key points
15 to investigate in this registry, then we can work out
16 the final numbers with the Sponsor.

17 DR. MAISEL: Well, I think we've heard some
18 of the endpoints that we're interested in knowing
19 about. The endpoints that are similar to the
20 clinical trial because we're interested in the
21 performance of the devices in the real world. So
22 John had mentioned issues related to stroke, death --

23 DR. SOMBERG: Bleeding.

24 DR. MAISEL: Embolization.

25 DR. ZUCKERMAN: Right. So you want to have

1 the acute procedural events captured and at what time
2 would you capture those chronic events, at one year
3 or --

4 DR. SOMBERG: Well, we said we want to go
5 for two years, specifically addressing the points --
6 you're the one who raised it earlier about is the
7 sample size inadequate at one year and two years. So
8 we really want to look at that. Now, you can make a
9 case about going out longer because these things are
10 going to be in for a long period of time, and that
11 would be something to consider, but we don't want to
12 be undue burdened as well. So I leave that to others
13 to balance.

14 DR. MAISEL: Fred.

15 DR. RESNIC: Yeah, I actually think Bram
16 probably said it all. You know, you can talk about
17 procedural rates and get some good information from a
18 registry. I don't think you're going to figure out
19 the answer to, you know, I don't think you're going
20 to sort of figure out the answer to a randomized
21 trial about, you know, whether it prevents, you know,
22 strokes or not. I do think you can get procedural
23 data, and I think that you can do that without
24 unreasonably burdening the manufacturer of this
25 thing, asking for huge numbers and amounts of data

1 that you're really not going to use very effectively.
2 So I would go for a lower rate and look at exactly
3 what you're talking about. How many times do you
4 really perforate the heart and so forth?

5 DR. MAISEL: Other comments? I think there
6 are issues that go beyond just the acute procedural
7 endpoints, including the application of this novel
8 therapy to a new population of patients, with new
9 procedures, and new physicians, and I personally
10 think it's critical that we carefully monitor the
11 rollout of the device to the community.

12 DR. DOMANSKI: I think there are huge
13 questions about it. I'm just not so sure a huge
14 registry is going to get, you know, get at them too
15 effectively.

16 DR. MAISEL: Fred.

17 DR. RESNIC: I think it would be very
18 helpful to help answer some of the questions about
19 learning curve effects to incorporate into the
20 registry the sort of strict data collection about the
21 operator's, you know, previous experience with the
22 device, number of transseptals done before this
23 device, so that hopefully you will inform the
24 training over time to refine it so that the more
25 arbitrary recommendations that were made regarding

1 training could be informed as the registry
2 information becomes available to FDA.

3 I think it would be really helpful to
4 understand the diffusion of this technology, if it's
5 approved, to patient populations that haven't been
6 studied. I just think that that would greatly inform
7 your postmarket surveillance.

8 DR. MAISEL: David.

9 DR. GOOD: So the registry would take the
10 place of the proposed acute follow-up and be expanded
11 and in that we could look at other sites, too, and
12 new operators. You know, the acute study they
13 propose helps to look at that in a smaller scale, but
14 you're talking about expanding it basically.

15 DR. MAISEL: So I think to summarize the
16 Panel thoughts are we want to see two types of post-
17 approval studies. One is the long-term follow-up
18 with the cohort that's already been studied, and we
19 want all patients studied for five years. And then
20 the other would be a registry to look at acute
21 procedural complications at the time of implant and
22 also for them to be followed long-term, somewhere
23 around two years, and precise number to be determined
24 after a power calculation based on the endpoints that
25 the Panel has discussed.

1 DR. ZUCKERMAN: Good.

2 DR. MAISEL: So we're done talking about
3 the questions. We're going to move forward in the
4 following fashion. Because we have some Panel
5 members who need to leave, we're going to skip our
6 break, but if people need to get up and step out for
7 a minute or two, then feel free to do so.

8 We're going to move straight onto the open
9 public hearing followed by very brief, maximum five
10 minute FDA and Sponsor summations, and then a Panel
11 vote.

12 So at this point, we'll open the second
13 open public hearing or we'll open the public hearing
14 for the second time. We have one scheduled public
15 speaker, Mr. Peter Henman-Laufer, and I'll remind
16 Mr. Henman-Laufer to state your name and the nature
17 of any financial interest that you may have in this
18 or any other medical device company that's relevant
19 to today's proceedings.

20 MR. HENMAN-LAUFER: Good afternoon. My
21 name is Peter Henman-Laufer. I live in Los Angeles.
22 I'm 81 years old. I've had the device fitted some
23 two years ago. I've had a history of heart failure.
24 I've had a heart attack in '93. Some 25 percent of
25 my heart has been badly affected. So it's not

1 functional. I've had a monitor, not a monitor, a
2 pacemaker fitted, and was eventually placed on
3 Coumadin.

4 Coumadin is a very unpleasant drug. I
5 ended up being black and blue each time I bumped into
6 some furniture or the dog would play with me, my
7 arms, my legs were badly, badly affected, and it was
8 at the suggestion of my cardiologist that I spoke to
9 Dr. Doshi who at that time had been involved in the
10 experiments or the trials which they had with the
11 manufacturer and suggested that if I were to have the
12 device fitted, it could well end up that I would no
13 longer have to take the warfarin.

14 Accordingly, I went with Dr. Doshi to
15 Boston where I had the procedure, which was really no
16 big deal. It was painless. So some two months
17 later, I was taken off warfarin. I had the TEE
18 procedures to control it over the next 18 months.

19 Since then, I've had absolutely no problems
20 or complications, and I had peace of mind when I
21 heard that this may be one way of avoiding having a
22 stroke. This was something that I was prepared to do
23 at a time when I don't think many people had the
24 device. I have it, and I'm pleased that I did.

25 So if the Panel has any questions, I'll be

1 more than happy to answer them.

2 DR. MAISEL: We have a minute if anyone has
3 any questions.

4 Thank you very much for your trip here
5 today. I think the Panel really appreciates your
6 coming and telling us about your story. Thank you.

7 MR. HENMAN-LAUFER: Well, I'm pleased to
8 come, and if I can help other people who had similar
9 problems, that's the least I can do. Thank you for
10 having me.

11 DR. MAISEL: Thank you very much.

12 Is there anyone else that would like to
13 address the Panel in the public session at this time?

14 Seeing none, we will close the second open
15 public hearing.

16 I would invite the Sponsor to -- I guess
17 FDA goes first. Does the FDA have any final remarks
18 they would like to make?

19 DR. ZUCKERMAN: No.

20 DR. MAISEL: Does the Sponsor have any
21 final remarks that they would like to make?

22 MR. BULLOCK: Mr. Chairman, you are
23 familiar with this process. You are familiar with
24 this process around the table of asking incredibly
25 tough questions that have really aimed at the heart

1 of the matter, have identified specific bumps in the
2 process and nonbumps in the process. And so you need
3 to realize that while you're familiar with it, the
4 people in the audience, at least the presenters,
5 haven't been familiar with it, but it's an incredibly
6 impressive group of questions and group that you have
7 assembled. So it's a real privilege to have been
8 able to interact with you, and it really
9 substantiates the faith that we would have that the
10 process is a good one because the questions were very
11 tough, very demanding. That's the first piece of
12 information.

13 The second piece of information is to say
14 that I have worked with a lot of companies in the
15 past, and this is an extraordinarily interesting
16 company. They are committed to making this work and
17 they are looking forward, hopefully, to working
18 closely with you, with the Agency, in terms of making
19 this the very best product, the very best rollout,
20 the very most important product for a very large
21 number of patients, and making sure that the
22 indications are just right, that the training is just
23 right, that the postmarket surveillance is just
24 right, so that everybody, most of all our patients,
25 benefit from it.

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1 The third thing is to thank you for the
2 chance to present this data on 800 of our patients
3 from 59 centers and a whole bunch of implanting
4 physicians, and us to present this data to you.

5 We are committed as investigators to make
6 sure that this rolls out well. We are as concerned
7 as you about some of that early safety issue in terms
8 of the strokes at the time of the procedure. We
9 noticed that there was clearly a learning curve that
10 they got better. In the CAP registry, the incidence
11 of ischemic strokes the day of the event was zero in
12 the next 88 patients and in the next 120 patients.

13 The incidence of pericardial effusion had
14 plummeted from sort of 5.5 percent down to 1.1
15 percent. We are committed to working with you to
16 make sure that the rollout of this is associated with
17 that improved procedural outcome because that
18 improved procedural outcome makes the long-term
19 outcome even look better and better in terms of
20 efficacy without any early safety bumps.

21 And so I would just thank you for the
22 chance to have presented the data. Thank you for the
23 chance for participating with you in evaluating this
24 data. Thank you for your careful review of it and
25 the chance to hopefully move forward to identify that

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1 magic partnership between patients and families and
2 society and regulatory agencies and physicians to
3 make this real. Thank you.

4 DR. MAISEL: Thank you. Before we proceed
5 to the vote, I just wanted to ask our industry
6 representative and our consumer representative if
7 they have any observations or comments they would
8 like to make. Why don't we start with Mr. Halpin.

9 MR. HALPIN: I just wanted to thank both
10 the FDA and the Sponsor for giving excellent
11 presentations and having a good discussion. I think
12 this was a very good review of the data, and I think
13 I'd like to comment that the study appears to have
14 been very well done and has met its primary endpoint,
15 and with that, I think I'm done.

16 DR. MAISEL: Thank you. Dr. Fleming.

17 DR. FLEMING: Well, I think what we've seen
18 here is literally a breakthrough technology for
19 persons who suffer from this oftentimes disabling
20 condition, and I trust that I will not advance into
21 further disability and perhaps this device would be
22 of some use to someone like myself in the future.

23 I think the study is well done. I
24 especially appreciate your explaining things so
25 thoroughly to us in an understandable manner and look

1 forward to the vote of the Panel.

2 DR. MAISEL: Okay. We are now ready to
3 vote on the Panel's recommendation to the FDA for
4 this PMA.

5 Mr. Swink will now read the Panel
6 recommendation options for premarket approval
7 applications. Mr. Swink.

8 MR. SWINK: The Medical Device Amendments
9 to the Federal Food, Drug and Cosmetic Act, as
10 amended by the Safe Medical Devices Act of 1990,
11 allows the Food and Drug Administration to obtain a
12 recommendation from an expert advisory panel on
13 designated medical device premarket approval
14 applications that are filed with the Agency. The PMA
15 must stand on its own merits, and your recommendation
16 must be supported by safety and effectiveness data in
17 the application or by applicable, publicly available
18 information.

19 The definitions of safety, effectiveness,
20 and valid scientific evidence are as follows:

21 Safety as defined in 21 C.F.R. Section
22 860.7(d)(1) - There is a reasonable assurance that a
23 device is safe when it can be determined, based upon
24 valid scientific evidence, that the probable benefits
25 to health from use of the device for its intended

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1 uses and conditions of use, when accompanied by
2 adequate directions and warnings against unsafe use,
3 outweigh any probable risks.

4 Effectiveness as defined in 21 C.F.R.
5 Section 860.7(e)(1) - There is reasonable assurance
6 that a device is effective when it can be determined,
7 based upon valid scientific evidence, that in a
8 significant portion of the target population, the use
9 of the device for its intended uses and conditions of
10 use, when accompanied by adequate directions for use
11 and warnings against unsafe use, will provide
12 clinically significant results.

13 Valid scientific evidence as defined in 21
14 C.F.R. Section 806.7(c)(2) is evidence from well-
15 controlled investigations, partially controlled
16 studies, studies and objective trials without matched
17 controls, well-documented case histories conducted by
18 qualified experts, and reports of significant human
19 experience with a marketed device from which it can
20 fairly and responsibly be concluded by qualified
21 experts that there is reasonable assurance of safety
22 and effectiveness of a device under its conditions of
23 use. Isolated case reports, random experience,
24 reports lacking sufficient details to permit
25 scientific evaluation, and unsubstantiated opinions

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1 are not regarded as valid scientific evidence to show
2 safety or effectiveness.

3 Your recommendation options for the vote
4 are as follows:

5 1. APPROVAL - If there are no conditions
6 attached.

7 2. APPROVABLE with conditions - The Panel
8 may recommend that the PMA be found approvable
9 subject to specified conditions, such as physician or
10 patient education, labeling changes, or a further
11 analysis of existing data. Prior to voting, all of
12 the conditions should be discussed by the Panel.

13 3. NOT APPROVABLE - The Panel may
14 recommend that the PMA is not approvable if:

15 - the data do not provide a reasonable
16 assurance that the device is safe or

17 - the data do not provide a reasonable
18 assurance that the device is effective under the
19 conditions of use prescribed, recommended, or
20 suggested in the proposed labeling.

21 Following the vote, the Chair will ask each
22 Panel member to present a brief statement outlining
23 the reasons for his or her vote.

24 Thank you.

25 DR. MAISEL: So for those of you who want

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1 to follow along, we have a nice little chart in our
2 packet that will help you with the voting options,
3 and just as a reminder, if we end up with approvable
4 with conditions, we vote on each individual condition
5 and then we vote at the end. We don't vote on the
6 whole thing until the very end, until all the
7 conditions are outlined.

8 So at this point, I am willing to entertain
9 any motions. Dr. Somberg.

10 DR. SOMBERG: I move that we vote for
11 approval with conditions of --

12 DR. MAISEL: No, stop. We'll do conditions
13 after. So --

14 DR. SOMBERG: It was a proposal.

15 DR. MAISEL: We don't list the conditions
16 yet. Your motion is for approvable with conditions.
17 And is there a second?

18 DR. RESNIC: Second.

19 DR. MAISEL: Dr. Resnic has seconded it.

20 So now does anyone want to discuss the
21 issue of approvable with conditions, or we can
22 entertain some conditions? Would anyone like to
23 propose a condition? Dr. Somberg.

24 DR. SOMBERG: The first condition I would
25 propose is that the indications be the indications

1 that we have discussed and reached a fair consensus
2 on and not the indication as initially presented.

3 DR. MAISEL: So the condition on the table
4 is that the indications stated be changed to read as
5 we had previously discussed during the indications
6 section. So that is incorporating the issues of
7 noninferior to warfarin and the endpoints that we
8 discussed, that specific thing that we put up on the
9 screen.

10 So is there a second for that condition,
11 that the indications statement be changed to what we
12 discussed earlier?

13 DR. ABRAMS: Second.

14 DR. MAISEL: Dr. Abrams has seconded it.
15 Any discussion about that or are we ready for a vote
16 on that issue? Any more discussion?

17 So by a show of hands, all those in favor
18 of the condition that the indications statement be
19 changed to our prior discussion, raise your hand, and
20 keep them up please.

21 So we have Dr. Kelly, Dr. Somberg,
22 Dr. Kelsey, Dr. Peters, Dr. Kato, Dr. Good,
23 Dr. Lindenfeld, Dr. Abrams, Dr. Brinker,
24 Dr. Domanski, and Dr. Resnic in favor.

25 All those opposed? Dr. Vassiliades.

1 So that condition passes.

2 Any other conditions that we would like to
3 entertain? Dr. Somberg.

4 DR. SOMBERG: That we require a
5 postmarketing registry as discussed with the similar
6 endpoints as the index protocol and with a power to
7 be approximately the size of 2,000 patients for at
8 least two years of follow-up with control population
9 to be viewed as well, the ratio and the exact power
10 to be determined.

11 DR. MAISEL: It's your condition. Would
12 you like to incorporate the other post-approval study
13 into that condition at the same time?

14 DR. SOMBERG: I would be glad to. I think
15 the follow-up should be encouraged or completed in
16 this trial, the index trial for the approval, and
17 that the proposed -- well, I'm not sure about the
18 second one. Those are the two things that I want to
19 incorporate in this additional condition.

20 DR. MAISEL: So I don't want to put words
21 in your mouth. So both studies, the post-approval
22 registry and follow-up of the cohort or not the
23 follow-up.

24 DR. SOMBERG: Yes, yes, yes. What I'm
25 saying is there is also a small study where they

1 would initiate new centers and follow that, and I'm
2 not sure that would be needed if you had the large
3 registry.

4 DR. MAISEL: Okay. So let me try to
5 restate your condition, and you tell me if I got it
6 right.

7 So there's a condition on the table, a
8 condition of approval that there be a post-approval
9 registry of device recipients to monitor the longer
10 term and real world performance as well as the key
11 procedural outcomes, that's somewhere around 2,000
12 patients in two years. We'll defer to the FDA
13 regarding the precise number, and also that the
14 original cohort be followed for five years, both arms
15 of the original cohort be followed for five years.

16 So do we hear a second for that condition?

17 DR. GOOD: Second.

18 DR. MAISEL: Dr. Good has seconded that.

19 Any discussion?

20 Vote. Please raise your hands if you are
21 in favor of that second condition of two post-
22 approval studies as described.

23 So we have yes from everyone.

24 Any other conditions? Dr. Resnic.

25 DR. RESNIC: The condition is that the

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1 physician specific training be in accordance with the
2 consensus recommendation of the Panel earlier, which
3 was to include levels of both didactic and practical
4 device training, imaging training, certification and
5 proctoring that we had described.

6 DR. MAISEL: Do I hear a second for a
7 physician certification program?

8 DR. SOMBERG: I second it.

9 DR. MAISEL: Dr. Somberg has seconded it.
10 Any other discussion?

11 DR. SOMBERG: Very quickly.

12 DR. MAISEL: I'm sorry.

13 DR. SOMBERG: Just very quickly. I just
14 want to say I'm not sure about the echocardiography
15 aspect of it because people doing routine
16 cardiography, I think that might be sufficient. So
17 I'm not sure what additional "certification" one
18 would have beyond being a competent cardiographer.

19 DR. RESNIC: I think it's just in terms of
20 whatever the nuances of understanding flow around
21 this device, which is not a typical finding for
22 people who aren't familiar with it.

23 DR. MAISEL: So the --

24 DR. BRINKER: I think that one of the key
25 elements was an electrocardiographer and not a

1 technologist be present at the implantation.

2 DR. MAISEL: Once again.

3 DR. BRINKER: I think that one of the
4 issues I had was that at the time of the implantation
5 be that it's an echo guided, if you will, procedure,
6 that it be an echocardiographer, not just a
7 technologist present.

8 DR. MAISEL: So the condition that's on the
9 table and that has been seconded is a condition for a
10 physician certification program as we discussed
11 earlier, which includes didactic training, imaging
12 training, training in patient selection, device
13 selection, complication management, proctoring, et
14 cetera, as discussed earlier. Any further discussion
15 before a vote on that?

16 Okay. By a show of hands, all those in
17 favor of that condition, please raise your hand.

18 Also unanimous.

19 Any other conditions that people would like
20 to propose? Dr. Somberg.

21 DR. SOMBERG: And this might be more
22 controversial. I think the study should be
23 undertaken, and if it is being undertaken abroad, it
24 should be presented to the FDA as well of patients
25 who were not on Coumadin therapy similar to the index

1 protocol here but that they do not require Coumadin
2 therapy.

3 DR. MAISEL: Okay. Before we go on with
4 that, I'm going to ask for some assistance from
5 Dr. Zuckerman.

6 Dr. Zuckerman, does this Panel have the
7 authority to demand an abroad indication or study for
8 the device?

9 DR. ZUCKERMAN: No. I think the Agency and
10 Sponsor have heard that another very important IDE
11 study, a separate IDE study, would be the one that
12 Dr. Somberg just mentioned, but it's really not part
13 of this voting procedure right now.

14 DR. SOMBERG: I withdraw it.

15 DR. MAISEL: Okay. The condition has been
16 withdrawn. Any other conditions that people would
17 like to propose?

18 Before you go, I just had one thought that
19 I meant to mention earlier but I did not. Is there
20 any concern about this procedure being performed at
21 places that do not have cardiac surgery? We want to
22 make some statement that the procedure can only be
23 done at a place where cardiac surgery is present.
24 There's a 22.5 percent pericardial effusion. Just
25 asking for discussion.

1 DR. DOMANSKI: I think that deserves maybe
2 a little of discussion. Now, we don't have things
3 like atrial fib ablation that early on had a
4 significant complication rate. Was there a mandate
5 for cardiac surgical support? Not that I know of,
6 but I believe angioplasty and stent did.

7 DR. BRINKER: Yeah, angioplasty does
8 because with an artery going down, you need a cardiac
9 surgeon. With a pericardial effusion, you don't need
10 a cardiac surgeon. A thoracic surgeon, which is
11 usually available, could do what would be necessary
12 if a simple drain didn't.

13 So there are reasons for me to support
14 this, that your motion --

15 DR. MAISEL: I can't make a motion.

16 DR. BRINKER: -- but your thought, but I
17 think it needs some discussion before we should vote.
18 I think there are a lot of pros and cons. The pros
19 would be that you were at a place that has all of the
20 facilities necessary should something more than a
21 pericardial perforation occur, including embolization
22 of the device or what have you. You're apt to have a
23 lot more support, better echocardiography support. I
24 think the whole thing would be better.

25 I would perhaps consider making a

1 recommendation that it's preferable to do this in a
2 facility with availability of cardiac surgery, but
3 I'm not sure I'd make it an absolute condition.

4 DR. MAISEL: Mike.

5 DR. DOMANSKI: I think we're, while I
6 suspect Jeff's probably right, I think we're drilling
7 down too far in terms of telling people what to do
8 with this thing.

9 DR. MAISEL: Okay.

10 UNIDENTIFIED SPEAKER: Is your concern
11 about the effusion?

12 DR. MAISEL: Twofold. One is the fact that
13 some patients needed surgical intervention, urgent
14 surgical intervention at the time of their procedure
15 placement was one thought. And two is I thought it
16 would control the rollout of the device to centers
17 that have more expertise, but I'm going to defer to
18 the Panel's judgment. Dr. Somberg, did you have
19 another conditions?

20 DR. SOMBERG: Well, it's either a new
21 condition or I may have omitted. Did we talk about
22 the CHADS score? Was that in one of the prior
23 things? Because we had discussed that, that we
24 recommend that there be -- I'll put it this way. I
25 recommend that I think it was condition 2 where we

1 added a registry, that we encourage that the CHADS
2 scores 2 and higher be enriched in the population, or
3 the population be enriched by having a substantial
4 number of higher than CHADS score 1 patients.

5 DR. MAISEL: A registry?

6 DR. SOMBERG: Yeah.

7 DR. MAISEL: Okay. So why don't offline,
8 you can convey your help with the FDA in forming --

9 DR. SOMBERG: I think that's more than
10 just, you know, a side by consult. Maybe I should
11 have included it in my earlier proposal, but I think
12 that it's most important that it's just not an
13 iteration of this particular, where a third of the
14 patients are CHADS₁ where they could be treated with
15 aspirin, that it should be CHADS₂ and higher.

16 DR. MAISEL: Okay. Well, I think certainly
17 the registry components we discussed earlier will be
18 incorporated, but we either need a second or a
19 withdraw of your motion. So does anyone want to
20 second that motion?

21 Okay. No second. Any other conditions?

22 DR. ABRAMS: Are you going to make that
23 motion about the cardiac surgery?

24 DR. MAISEL: I cannot make a motion. I was
25 bringing it up for discussion.

1 DR. ABRAMS: I think the issue about, we
2 didn't discuss about the issue of slowing or
3 controlling the rollout of it, I think from my point
4 of view, is a good idea. I mean I know it may not be
5 the direct reason for asking for a cardiac surgeon,
6 but I think if we add some safety and with control of
7 the rollout. So I'll make a motion.

8 DR. MAISEL: Okay. So we have a motion
9 that the device implant be limited to facilities that
10 have cardiac surgery on site or urgently available?

11 DR. ABRAMS: Urgently available.

12 DR. MAISEL: Okay. Do I hear a second on
13 that motion?

14 DR. BRINKER: I'll second it.

15 DR. MAISEL: Dr. Brinker has seconded it.
16 Any further discussion?

17 Vote. So all those in favor of having
18 urgent cardiac surgery available at the time of
19 device implantation, raise your hand please.

20 So I'm going to tell you the nos are
21 Dr. Somberg, Dr. Kelsey, and Dr. Domanski. The other
22 are yeses. So that motion passes 9 to 3.

23 Any other conditions of approval?

24 Dr. Resnic.

25 DR. RESNIC: Sorry. It was in our

1 discussions regarding questions we had. I had raised
2 the question of whether some commentary in the
3 labeling could include the comment that alternative
4 therapies are available for CHADS₁ patients so that
5 the implication of the labeling doesn't imply that
6 patients need only be treated with the two
7 alternatives considered here.

8 DR. MAISEL: So historically, the labeling
9 discussions get incorporated by the FDA into the
10 label with discussion. I think if the Panel felt
11 extremely strongly about one particular issue, we can
12 do that. Is that an accurate thing, Dr. Zuckerman?
13 Or do you --

14 DR. ZUCKERMAN: That's correct. We review
15 the transcript very carefully. So we're not going to
16 forget that comment.

17 DR. RESNIC: Withdrawn.

18 DR. MAISEL: Any other conditions of
19 approval?

20 So at this point we have a motion on the
21 table of approvable with conditions. The conditions,
22 there are four of them. One is that the indication
23 statement be modified in the way in which we have
24 advised. Two is that there be post-approval studies,
25 a registry and a long-term follow-up of the initial

1 patient cohort. Three is that there be a physician's
2 certification program. And four is that the
3 procedure be performed only at sites with cardiac
4 surgery urgently available.

5 Are there any other conditions or
6 discussion? Dr. Good.

7 DR. GOOD: I have some discussion. I don't
8 want to make it a condition yet. But that some of
9 the device concerns raised by the FDA be properly
10 addressed or approved by the FDA that have already
11 been proposed by the Sponsor, but that might be --
12 Dr. Zuckerman.

13 DR. MAISEL: Do we need to specifically put
14 a condition that the postmarket issues that you have
15 that they've submitted data on that you haven't had a
16 chance to review yet be a condition of approval, or
17 is that self-evident?

18 DR. ZUCKERMAN: Well, we routinely look at
19 the whole package post this Panel meeting. So it's
20 part of what we do.

21 DR. GOOD: Okay.

22 DR. MAISEL: Any other conditions? We have
23 a motion on the table, approvable with conditions,
24 indications statement, post-approval registry and
25 study, physician's certification, and cardiac surgery

1 urgently available. Any further discussion before
2 the vote?

3 So we're going to go around the table, not
4 just do a show of hands. So your vote is yes,
5 approved with the conditions.

6 It has been moved and seconded that the
7 Atritech PMA Application P080022 for the WATCHMAN
8 Left Atrial Appendage Occluder be found approvable
9 with the four conditions I outlined. We will now
10 vote on the main motion.

11 I guess we can do it with a show of hands.
12 Please indicate if you concur with the recommendation
13 that the above-named PMA be found approvable with
14 conditions, with the four conditions being the ones I
15 mentioned, indication statement, post-approval
16 studies, physician's certification program, and
17 cardiac surgery urgently available. So if you agree
18 with that, raise your hand.

19 So I'm going to go around the table. We
20 have yeses from Dr. Resnic, Dr. Brinker, Dr. Abrams,
21 Dr. Kato, Dr. Peters, Dr. Kelsey, and Dr. Somberg.
22 That is seven.

23 Please raise your hand if you are opposed
24 to that motion.

25 We have Dr. Domanski, Dr. Lindenfeld,

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1 Dr. Good, and Dr. Vassiliades and Dr. Kelly.

2 That's seven in favor and five opposed.

3 The motion passes.

4 The recommendation from this Panel is
5 approval with conditions.

6 Is there anyone abstaining? That was the
7 right number of votes. So I don't think so.

8 So it is recommended from the Panel to the
9 FDA that the Atritech PMA Application P080022 for the
10 WATCHMAN Left Atrial Appendage Occluder is approved
11 with the previous voted upon conditions.

12 And now we're going to go around, and I
13 want to hear from each Panel member what you voted
14 and why you voted, and we'll start with Dr. Kelly.

15 DR. KELLY: Well, I voted not to approve it
16 at this time mainly because of safety concerns. I'm
17 certainly hopeful that once more data comes in, it
18 will be, but right now I still have some safety
19 concerns.

20 DR. MAISEL: Dr. Somberg.

21 DR. SOMBERG: I voted in favor because I
22 thought the Sponsor had shown that both in the
23 intent-to-treat analysis and the on-protocol
24 analysis, that the device was comparable, and that's
25 the language we inserted for the indications

1 comparable to long-term warfarin therapy. I think it
2 was a very nicely executed study. I think there was
3 some flaws in that patients could be continued on
4 Coumadin at the discretion, or placed back on it, of
5 the investigator, but I was heartened that that went
6 even further in the direction of favoring the device.

7 I think the points that were made about the
8 severity of hemorrhagic stroke are certainly correct,
9 and if this can possibly alleviate it.

10 There certainly is a lot of doubt about the
11 data because it's a small study, but it's larger than
12 we see in many devices, and I think with our mandated
13 additional follow-up both in registry and in the
14 application protocol to be continued for five years,
15 we will obtain that additional data. So I think we
16 are in as strong a position as I've seen with many
17 devices that even have broader applications than
18 this.

19 DR. MAISEL: Dr. Kelsey.

20 DR. KELSEY: I voted yes based on the data
21 that reviewed today and listening to the discussion
22 around the table.

23 DR. MAISEL: Dr. Vassiliades.

24 DR. VASSILIADES: I voted against.

25 Although the statistical analysis supports the

1 approval, I thought there were too many confounding
2 variables such as antiplatelet therapy to approve
3 based on clinical grounds. Two-thirds of the
4 patients were CHADS₁ or CHADS₂, and that gives me
5 concern about using the device in the general
6 population.

7 And then finally I thought that the data at
8 two to three years was so miniscule and that
9 implanting a device in the left atrium needed a
10 longer follow-up for me to feel comfortable to
11 approve it.

12 DR. MAISEL: Dr. Peters.

13 DR. PETERS: I voted to approve. The
14 number of events were relatively small in both
15 groups. I think this is, you know, a fairly --
16 thing. I share a lot of concerns. I don't think
17 doing another study, a bigger study would get over
18 those concerns. The problems that the investigators
19 ran into, such as drop in, drop out, and platelets is
20 going to continue because that's what clinical
21 practice is like. So I don't think we're going to
22 get any closer, and I'm convinced that the
23 contingencies that we've added have addressed the
24 concerns that all of us have sufficiently.

25 DR. MAISEL: Dr. Kato.

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1 DR. KATO: I voted yes, but with a lot of
2 trepidation. I still am very, very concerned about
3 the small sample size despite the fact that it
4 reached noninferiority. I still am wondering whether
5 the scientific evidence will come down saying that
6 atrial fibrillation that causes strokes may or may
7 not be treated by this device.

8 On the other hand, I would like to see more
9 expansion and more patients enrolled in this just to
10 see what the answer is.

11 So I hope that with the conditions of
12 approval, namely certification, very careful on-site
13 training, registry, et cetera, will provide some
14 important clinical equipoise to a massive rollout of
15 this device because I think that in less experienced
16 hands, this could be a real problem.

17 DR. MAISEL: Dr. Good.

18 DR. GOOD: I voted against. This is a
19 difficult study. My concerns were some of those that
20 were voiced by my colleagues. The relatively small
21 number of subjects, the confounding variables, the
22 relatively small number of outcome measures that were
23 recorded. I still have some concern about the rather
24 high number of intracerebral bleeds in this
25 particular cohort and why that would be. So those

1 are my major concerns.

2 I'm concerned about the long-term
3 durability of the device and how safe it is long-
4 term, and I would like to see a longer-term study.

5 I am reassured by the improvement in the
6 safety indicators through the course of the study,
7 which initially I was concerned about but are
8 improving. I think that's positive.

9 I will say that the contingencies that were
10 added make me feel better about going ahead, but I
11 still felt compelled to vote against.

12 DR. MAISEL: JoAnn.

13 DR. LINDENFELD: I voted against. I was
14 right on the fence, but I'm still swayed by the very
15 small number of events, the difference here. The
16 higher than expected incidence of intracranial
17 hemorrhage. It is a randomized trial, and I
18 understand that, but this was a substantially higher
19 incidence of intracranial hemorrhage than one would
20 expect to see in a study of this type.

21 In the first year, there was no difference
22 of anything. The device was worse in the primary
23 efficacy endpoint. It was only between year one and
24 year two that it was better, and we have really no
25 data after year two.

1 So those are the things that swayed me to
2 vote no.

3 DR. MAISEL: Dr. Abrams.

4 DR. ABRAMS: Yes. I voted yes. It was
5 kind of a tepid yes. I'm not convinced about the
6 noninferiority, although I sit on the fence with
7 that, but I was swayed by the safety issues. I think
8 those late intracranial hemorrhages were due to the
9 falls and other kinds of things that could happen in
10 this age group. I think once the early morbidity
11 from this gets worked out, as people get experience
12 with it, I think it offers an option to people who
13 have to stay on this drug for many, many years, and
14 they could do it more safely perhaps with the device.

15 DR. MAISEL: Jeff.

16 DR. BRINKER: I think pretty much the same.
17 I think the opportunity to avoid heparin, a drug
18 which is relatively hard to titrate. It has a 65
19 percent optimal dosing experience in those patients
20 who have to take it over the remainder of their life,
21 offers the possibility that there will be a way out
22 of that.

23 Second of all, from a practical point of
24 view, the device occludes most of the, even if it's
25 not totally occlusive, it occludes most of the atrial

1 appendage, and it's a big clot that gets people most
2 in trouble, and even if there's a little at the
3 orifice, there may be less of a sequela.

4 Certainly the risk of Coumadin is high, and
5 it's especially high in the elder population who
6 fall, who have more fragile blood supply to their
7 brain, and it's a lifelong, once they start it,
8 issue.

9 So I'm comfortable that this is the right
10 thing to do, and I anticipate that the information
11 that we're asking from the Sponsor, post-approval
12 studies will be helpful in furthering that
13 encouragement that I see already.

14 DR. MAISEL: Mike.

15 DR. DOMANSKI: Well, I voted against. I
16 thought several things. First of all, the ischemic
17 strokes are, if anything, increased with the use of
18 this device, in a setting where ascertainment was
19 suboptimal. The high rate of hemorrhagic
20 cerebrovascular accidents could probably be lessened
21 by simply more attention to follow-up of the patients
22 rather than putting a device in. The numbers in the
23 trial, if anything, were tiny. I mean the events
24 you're talking about are six versus one for
25 hemorrhagic CVA, which is an awfully small number of

1 events to base approval of a high complication rate
2 device on. I think there were lots of complications.
3 I don't think they're minor at all.

4 So, you know, I really think it's a mistake
5 for the FDA to approve this device.

6 DR. MAISEL: Dr. Resnic.

7 DR. RESNIC: I voted in favor of the
8 approval with the I think stringent conditions that
9 were recommended, recognizing and accepting a lot of
10 the concerns of everyone on the Panel.

11 However, I think that we were really asked
12 to compare a reasonably well thought out and well
13 executed pivotal trial for a device in comparison in
14 a noninferiority manner with a really poor and narrow
15 therapeutic window standard of care medication.

16 And I think that the evidence from the
17 intention-to-treat analysis does support
18 noninferiority and that my greatest concerns are
19 regarding safety but not the safety endpoints in the
20 trial, but the safety of unanticipated outcomes from
21 inadequately trained centers or providers or late
22 complications that we may not be aware of but I think
23 that Dr. Somberg's recommendations regarding the
24 post-approval study refinement and the training
25 recommendations that we included in our conditions

1 address those concerns.

2 DR. MAISEL: Dr. Fleming, your thoughts.

3 DR. FLEMING: I'm definitely in agreement
4 with those who approved the device. I think, as I
5 said earlier, it's a novel device but one which has a
6 lot of promise.

7 DR. MAISEL: Mr. Halpin.

8 MR. HALPIN: I am also in agreement with
9 the folks who voted for approval.

10 DR. MAISEL: So I didn't have the
11 opportunity to officially vote, but I have to say,
12 and maybe it's just PTSD, but we sat in this very
13 room to talk about drug-eluting stents about two and
14 a half years ago, and three of the issues that led us
15 to that point are present here today.

16 One of them is the potential for a really
17 huge number of patients to get this device very
18 quickly. Two is lack of clarification regarding low
19 rate but important safety events. And the third
20 component for the drug-eluting stent issue was the
21 lack of adequate postmarket data in a timely fashion
22 to a certain degree, particularly some of the
23 registry data.

24 So I think the lessons from that are one,
25 you know, it may sound like a great idea to rollout

1 the device really quickly to as many patients as
2 possible, but I hope the Sponsor will be very careful
3 about where the device goes.

4 Number two is the postmarket study I think
5 is crucial and needs to be started in a very timely
6 fashion upon device approval and hopefully will
7 include enough patients quickly enough to give us
8 some measure of confidence in how the device is
9 performing.

10 Any comments from the Sponsor before we
11 conclude our meeting today? Any final word?

12 Okay. FDA have any final statements or
13 comments?

14 DR. ZUCKERMAN: I want to thank the Panel
15 for doing an extremely good job today. This was a
16 challenging device and the information that we got
17 was extremely worthwhile.

18 DR. MAISEL: Thank you very much. I'd like
19 to thank the Panel members for their thoughtful
20 commentary, and our meeting is adjourned.

21 (Whereupon, the meeting was concluded.)

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C E R T I F I C A T E

This is to certify that the attached proceedings
in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

April 23, 2009

Gaithersburg, Maryland

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