

UNITED STATES OF AMERICA
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
 MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

+ + +

April 23, 2009
 8:30 a.m.

Hilton Washington DC North
 620 Perry Parkway
 Gaithersburg, MD 20877

PANEL MEMBERS:

WILLIAM MAISEL, M.D.	Chairperson
MICHAEL J. DOMANSKI, M.D.	Voting Member
JOANN LINDENFELD, M.D.	Voting Member
GARY M. ABRAMS, M.D.	Consultant
JEFFREY BRINKER, M.D.	Consultant
DAVID C. GOOD, M.D.	Consultant
ROBERT PETERS, M.D.	Consultant
NORMAN KATO, M.D.	Consultant
PATRICIA KELLY, M.D.	Consultant
SHERYL KELSEY, Ph.D.	Consultant
FREDRIC RESNIC, M.D.	Consultant
JOHN C. SOMBERG, M.D.	Consultant
THOMAS VASSILIADES, M.D.	Consultant
MICHAEL HALPIN	Industry Representative
MIKE FLEMING, D.D.S., P.A.	Consumer Representative
JAMES P. SWINK	Executive Secretary

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JIM BULLOCK, President and CEO, Atritech, Inc.
KENNETH HUBER, M.D.
SCOTT BROWN, Ph.D.
DAVID HOLMES, M.D.
VIVEK REDDY, M.D.

PUBLIC SPEAKER:

PETER HENMAN-LAUFER

INDEX

	PAGE
CALL TO ORDER - William Maisel, M.D.	5
PANEL INTRODUCTIONS	5
CONFLICT OF INTEREST STATEMENT - James P. Swink	8
TEMPORARY VOTING MEMBER STATEMENT - James P. Swink	11
GENERAL ANNOUNCEMENTS - James P. Swink	13
1st OPEN PUBLIC HEARING (No speakers)	13
SPONSOR PRESENTATION	
Introduction - Jim Bullock	15
Atrial Fibrillation, WATCHMAN® Technology and PROTECT AF Study - Kenneth Huber, M.D.	17
Statistical Overview - Scott Brown, Ph.D.	34
Efficacy Results - David Holmes, M.D.	45
Safety Results - Vivek Reddy, M.D.	61
Post-Approval Plans - Vivek Reddy, M.D.	79
Conclusions - David Holmes, M.D.	80
SPONSOR Q&A	82
FDA PRESENTATION	
Introduction and Preclinical Summary - Donna Buckley, M.D., M.S.	95
Statistical Summary - Xu (Sherry) Yan, Ph.D.	104
Clinical Summary - Julie Swain, M.D.	111
Post-Approval Studies Plan - Ellen Pinnow, M.S.	138
Questions - Donna Buckley, M.D., M.S.	145

INDEX

	PAGE
FDA Q&A	148
QUESTIONS FOR FDA AND SPONSOR	160
SPONSOR RESPONSE TO PANEL QUESTIONS	185
PANEL DELIBERATIONS	198
FDA QUESTIONS	
Question 1	207
Question 2	238
Question 3	261
Question 4	272
Question 5a and 5b	277
Question 5c	292
Question 5d	292
Question 6a and 6b	292
2nd OPEN PUBLIC HEARING	307
Peter Henman-Laufer	307
SUMMATION	
FDA (No comments)	309
Sponsor - Jim Bullock	309
COMMENTS FROM INDUSTRY REPRESENTATIVE - Michael Halpin	312
COMMENTS FROM CONSUMER REPRESENTATIVE - Mike Fleming, D.D.S., P.A.	312
PANEL VOTE	313
ADJOURNMENT	339

M E E T I N G

(8:00 a.m.)

1
2
3 DR. MAISEL: I would like to call this
4 meeting of the Circulatory System Devices Panel to
5 order.

6 I'm Dr. William Maisel and will be serving
7 as Chairperson for this Panel today. I'm a
8 cardiologist from Beth Israel Deaconess Medical
9 Center.

10 Today the Panel will be making a
11 recommendation to the Food and Drug Administration on
12 the Premarket Approval Application, P080022,
13 submitted by Atritech, Incorporated, for the WATCHMAN
14 Left Atrial Appendage Closure.

15 Before we get much further, I would like to
16 ask the Panel members to introduce themselves, and
17 I'll start on my left with Dr. Zuckerman, please.

18 DR. ZUCKERMAN: Good morning. Bram
19 Zuckerman, Director, FDA, Division of Cardiovascular
20 Devices.

21 DR. KELLY: Patricia Kelly. I'm a cardiac
22 electrophysiologist in Missoula, Montana.

23 DR. SOMBERG: John Somberg, a Professor of
24 Medicine in Pharmacology at Rush Medical Center in
25 Chicago.

1 DR. KELSEY: Sheryl Kelsey, University of
2 Pittsburgh. I'm a Professor of Epidemiology and a
3 statistician.

4 DR. VASSILIADES: Tom Vassiliades, cardiac
5 surgeon at Emory University.

6 DR. PETERS: Bob Peters, I'm a
7 cardiologist, University of Maryland, Baltimore.

8 DR. KATO: Norman Kato, cardiothoracic
9 surgery, Los Angeles, California, private practice.

10 DR. GOOD: David Good. I'm Chair of
11 Neurology at Penn State University. I'm a stroke
12 neurologist.

13 MR. SWINK: James Swink, Executive
14 Secretary for the Secretary of the Panel.

15 DR. LINDENFELD: JoAnn Lindenfeld,
16 cardiologist at the University of Colorado.

17 DR. ABRAMS: Gary Abrams, neurologist,
18 University of California San Francisco in the San
19 Francisco VA Medical Center.

20 DR. BRINKER: Jeff Brinker, interventional
21 cardiologist, Johns Hopkins.

22 DR. DOMANSKI: Mike Domanski. I'm a
23 cardiologist in the National Heart, Lung and Blood
24 Institute.

25 DR. RESNIC: Fred Resnic, interventional

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1 cardiologist, Brigham and Women's Hospital in Boston.

2 DR. FLEMING: Mike Fleming, Consumer
3 member.

4 MR. HALPIN: Mike Halpin. I'm the Industry
5 Rep, and I'm with Genzyme Corporation.

6 DR. MAISEL: Thank you. For the audience,
7 if you haven't already done so, please sign the
8 attendance sheets that are on the tables outside the
9 doors. If you wish to address this Panel during one
10 of the open sessions, please provide your name to
11 Ms. AnnMarie Williams who is out at the registration
12 table.

13 If you are presenting in any of the open
14 public sessions today and have not previously
15 provided an electronic copy of your presentation to
16 the FDA, please arrange to do so with Ms. Williams.

17 I note for the record that the voting
18 members present constitute a quorum as required by 21
19 C.F.R. Part 14. I would also like to add that the
20 Panel participants in the meeting today have received
21 training in FDA device law and regulations.

22 At this point, I'd like to turn it over to
23 Mr. Swink, the Executive Secretary for the
24 Circulatory System Devices Panel who will make some
25 introductory remarks.

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1 MR. SWINK: I will now read the Conflict of
2 Interest Statement.

3 The Food and Drug Administration is
4 convening today's meeting of the Circulatory System
5 Devices Panel of the Medical Devices Advisory
6 Committee under the authority of the Federal Advisory
7 Committee Act of 1972. With the exception of the
8 industry representative, all members and consultants
9 of the Panel are special government employees or
10 regular federal employees from other agencies and are
11 subject to federal conflict of interest laws and
12 regulations.

13 The following information on the status of
14 this Panel's compliance with federal ethics and
15 conflict of interest laws covered by, but not limited
16 to, those found at 18 U.S.C. Section 208 and Section
17 712 of the federal Food, Drug and Cosmetic Act are
18 being provided to participants in today's meeting and
19 to the public.

20 FDA has determined that members and
21 consultants of this Panel are in compliance with
22 federal ethics and conflict of interest laws. Under
23 18 U.S.C. Section 208, Congress has authorized FDA to
24 grant waivers to special government employees who
25 have potential financial conflicts when it is

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1 determined that the Agency's need for that particular
2 individual's services outweighs his or her potential
3 financial conflict of interest. Under Section 712 of
4 the FD&C Act, Congress has authorized FDA to grant
5 waivers to special government employees and regular
6 government employees with potential financial
7 conflicts when necessary to afford the Committee
8 essential expertise.

9 Related to the discussions of today's
10 meeting, members and consultants of this Panel who
11 are special government employees have been screened
12 for potential financial conflicts of interest of
13 their own as well as those imputed to them, including
14 those of their spouses or minor children and, for
15 purpose of 18 U.S.C. Section 208, their employers.
16 These interests may include investments; consulting;
17 expert witness testimony; contracts/grants/CRADAs;
18 teaching/speaking/writing; patents and royalties; and
19 primary employment.

20 Today's agenda involves a discussion of a
21 premarket approval application for the WATCHMAN Left
22 Atrial Appendage Closure Technology, sponsored by
23 Atritech, Incorporated. The WATCHMAN device, a
24 percutaneous placed permanent implant, is intended as
25 an alternative to warfarin therapy for patients with

1 nonvalvular atrial fibrillation. The WATCHMAN LAA
2 Closure Technology is designed to prevent
3 embolization of thrombi that may form in the left
4 atrial appendage thereby preventing the occurrence of
5 ischemic stroke and systematic thromboembolism. This
6 is a particular matters meeting during which specific
7 matters related to the PMA will be discussed.

8 Based on the agenda for today's meeting and
9 all financial interests reported by the Panel members
10 and consultants, a conflict of interest waiver has
11 been issued in accordance with 18 U.S.C. Section
12 208(b) (3) to Dr. Thomas Vassiliades.
13 Dr. Vassiliades' waiver involves his employer's
14 interest in the Sponsor study. His institute
15 received between \$20,000 and \$30,000 a year in
16 funding. Dr. Vassiliades has no personal involvement
17 in the study. This waiver allows this individual to
18 participate fully in today's deliberations. FDA's
19 reasons for issuing the waiver are described in the
20 waiver document which is posted on FDA's website at
21 www.fda.gov. Copies of the waiver may also be
22 obtained by submitting a written request to the
23 Agency's Freedom of Information Office, Room 6-30 of
24 the Parklawn Building. A copy of this statement will
25 be available for review at the registration table

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1 during this meeting and will be included as part of
2 the official transcripts.

3 Michael Halpin is serving as the industry
4 representative, acting on behalf of all related
5 industry, and is employed by Genzyme Corporation.

6 We would like to remind members and
7 consultants that if the discussions involve any other
8 products and firms not already on the agenda for
9 which the FDA participant has a personal or imputed
10 financial interest, the participants need to exclude
11 themselves from such involvement and their exclusion
12 will be noted for the record.

13 FDA encourages all other participants to
14 advise the Panel of any financial relationships that
15 they may have with any firms at issue. Thank you.

16 I will now read the appointment to
17 temporary voting member statement.

18 Pursuant to the authority granted under the
19 Medical Devices Advisory Committee Charter of the
20 Center for Devices and Radiological Health, dated
21 October 27, 1990, and as amended August 18, 2006, I
22 appoint Sheryl F. Kelsey, Ph.D., as a temporary
23 voting member of the Circulatory System Devices Panel
24 for the duration of this meeting on April 23, 2009.
25 For the record, Dr. Kelsey serves as a consultant to

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1 the Cardiovascular and Renal Drug Advisory Committee
2 of the Center for Drug Evaluation and Research. She
3 is a special government employee who has undergone
4 the customary conflict of interest review and has
5 reviewed the material to be considered at this
6 meeting. This is signed by Randall W. Lutter, Ph.D.,
7 Deputy Commissioner for Policy. I have one more to
8 go through. Just bear with me.

9 Pursuant to the authority granted under the
10 Medical Devices Advisory Committee Charter of the
11 Center for Devices and Radiological Health, dated
12 October 27, 1990, and as amended August 18, 2006, I
13 appoint the following individuals as voting members
14 of the Circulatory System Devices Panel for the
15 duration of this meeting on April 23, 2009:

16 Drs. Gary Abrams, David Good, John Somberg, Patricia
17 Kelly, Fredric Resnic, Norman Kato, Thomas
18 Vassiliades, Jeffrey Brinker and Robert Peters. For
19 the record, these individuals are special government
20 employees who have undergone the customary conflict
21 of interest review and have reviewed the material to
22 be considered at this meeting.

23 In addition, I appoint William H. Maisel,
24 M.D., to act as the temporary Chairperson for the
25 duration of this meeting. This was signed by Daniel

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1 G. Schultz, M.D., Director, Center for Devices and
2 Radiological Health, and dated April 14, 2009.

3 Before I turn the meeting back over to
4 Dr. Maisel, I'd like to make a few general
5 announcements.

6 Transcripts of today's meeting will be
7 available from Free State Reporting, Incorporated.
8 Information on purchasing videos of today's meeting
9 can be found on the table outside the meeting room.
10 Presenters to the Panel who have not already done so
11 should provide FDA with a hard copy of their remarks,
12 including overheads.

13 I would like to remind everyone that
14 members of the public and press are not permitted
15 around the Panel area beyond the speaker's podium.
16 The press contact for today's meeting is Siobhan
17 DeLancey. She's raising her hand in the back. I
18 request that reporters wait to speak to FDA officials
19 until after the Panel meeting. Thank you.

20 Finally, as a courtesy to those around you,
21 please silence your electronic devices if you've not
22 already done so.

23 DR. MAISEL: Thank you, Mr. Swink. We will
24 now proceed with the Open Public Hearing portion of
25 the meeting.

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1 Both the Food and Drug Administration and
2 the public believe in a transparent process for
3 information gathering and decision-making. To ensure
4 such transparency at the Open Public Hearing Session
5 of the Advisory Committee meeting, FDA believes it is
6 important to understand the context of any
7 individual's presentation. For this reason, FDA
8 encourages you, the open public hearing or industry
9 speaker, at the beginning of your written or oral
10 statement, to advise the Committee of any financial
11 relationship that you may have with the Sponsor, its
12 product and, if known, its direct competitors.

13 For example, this financial information may
14 include the Sponsor's payment of your travel,
15 lodging, or other expenses in connection with your
16 attendance at this meeting. Likewise, FDA encourages
17 you at the beginning of the statement to advise the
18 Committee if you do not have any such financial
19 relationships. If you choose not to address the
20 issue of financial relationships at the beginning of
21 your statement, it will not preclude you from
22 speaking.

23 Is there anyone who wishes to address the
24 Panel at this time?

25 Seeing none, we will close the Open Public

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1 Hearing session of the meeting and move on.

2 At this point, I would ask the audience
3 again to silence your beepers and cell phones if you
4 haven't already done so and remind people to speak
5 clearly into the microphone. I would like to invite
6 the Sponsor to make their presentation, and you will
7 have 90 minutes to do so.

8 MR. BULLOCK: Thank you, Dr. Maisel. My
9 name is Jim Bullock. I'm the President and Chief
10 Executive Officer of Atritech. Good morning.

11 First of all, I'd like to thank the FDA for
12 their guidance during this process. I'd also like to
13 recognize and thank the 60 centers that were involved
14 for the PROTECT AF trial who diligently worked over
15 the 3 1/2 years during the PROTECT AF trial.

16 The company was incorporated in 1999 for
17 the sole purpose of developing the WATCHMAN for LAA
18 Closure. Our facilities where we design and
19 manufacture the WATCHMAN device are in Plymouth,
20 Minnesota, and we currently have 40 employees.

21 To give you a context of our pilot study,
22 it was initiated in 2002 and was closed in 2005 with
23 about 66 patients implanted. About 50 of those
24 patients are out over 4 years now, and the WATCHMAN
25 was approved for CE Mark in 2005.

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1 Following the results of the pilot study,
2 the PROTECT AF trial commenced in February of 2005
3 and was closed in June of 2008, some 40 months and
4 over 800 patients.

5 The continued access registry for the
6 PROTECT AF trial is ongoing. We currently have 120
7 patients in that registry.

8 The WATCHMAN LAA Closure Technology is
9 designed as a alternative to long-term warfarin
10 therapy. The product has gone through extensive
11 bench testing to prove reliability and verify its
12 specifications. It was tested, nearly 100 animals,
13 to prove safety and demonstrate technical
14 performance. The cycle testing, over 400 million
15 cycles, which is equivalent to about 10 years, was
16 completed and passed as was all biocompatibility
17 testing which completely passed all ISO standard
18 testing.

19 I won't go through these, but on Monday,
20 our company submitted the final open issues which you
21 can see here, on FDA questions, mainly centering
22 around biocompatibility and other kinds of testing.

23 So I have the pleasure of introducing the
24 speakers today who were very much involved in the
25 PROTECT AF study, starting with Dr. Ken Huber from

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1 St. Luke's in Kansas City. He's an interventional
2 cardiologist. He'll introduce atrial fibrillation
3 and the challenge of managing patients with current
4 methodologies as well as describe the PROTECT AF
5 trial.

6 Dr. Scott Brown, who I say is frequently
7 Bayesian, will talk about our statistical overview.

8 Dr. Holmes from the Mayo Clinic will talk
9 about the efficacy results followed by safety results
10 with Dr. Vivek Reddy, an electrophysiologist from the
11 University of Miami, and then Vivek will also talk
12 about post-approval plans, and then Dr. David Holmes
13 from the Mayo Clinic will offer conclusions.

14 So with that, I'd like to start out by
15 introducing Ken Huber to open up the PROTECT AF
16 study.

17 DR. HUBER: Thank you very much. Again, my
18 name is Ken Huber. I'm an interventional
19 cardiologist and the Executive Medical Director of
20 the St. Luke's Mid America Heart Institute in Kansas
21 City, Missouri. I have no financial equity in the
22 company. They did pay for my travel and time here
23 today.

24 I am an investigator of the trial. I
25 enrolled 34 patients in the PROTECT AF trial and have

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1 subsequently enrolled six patients in the CAP
2 registry.

3 What I'd like to do during my portion of
4 this discussion this morning is again to review the
5 current state, if you will, of stroke prevention and
6 patients with atrial fibrillation, and I'm going to
7 discuss the WATCHMAN Technology and describe the
8 procedure a little bit for everybody and then finish
9 with a trial overview and design.

10 We all know that atrial fibrillation is a
11 common problem, and it's estimated that as many as
12 eight million patients in the United States of
13 America will have atrial fibrillation by the year
14 2020. And, indeed for those of us that are over the
15 age of 40 in this room today, there's about a 1 in 4
16 chance that we will have atrial fibrillation. And
17 the significance of these millions of patients with
18 atrial fibrillation is that they are indeed at risk
19 of having a stroke.

20 There are about 800,000 strokes in the U.S.
21 per year, and about 15 to 20 percent of those are
22 related to atrial fibrillation. So that then
23 translates into about a 5 to 6 percent annual risk of
24 stroke, and so of those 800,000 strokes per year in
25 the U.S., about 100,000 of them can be attributed to

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1 atrial fibrillation.

2 And as the clinicians in the room know,
3 that there's probably nothing that creates a higher
4 level of angst in patients than the concern about the
5 disability or mortality related to a stroke. And in
6 that regard, you can see on this slide here the
7 functional impact of AF-related strokes can be
8 profound. It causes and can cause significant
9 disability in many patients, and the 30-day mortality
10 rates are substantial. For all AF-related strokes,
11 off of treatment, the mortality rate is as high as 24
12 percent. And it's important to also note that in the
13 smaller subset of hemorrhagic strokes, the mortality
14 rate at 30 days can be 44 percent and at 1 year, 60
15 percent.

16 So what then is the basic pathophysiologic
17 process that results in this risk of having a stroke,
18 and I think you can see very nicely here in this
19 slide, it's related to thrombus formation in the left
20 atrial appendage. This is related to insufficient
21 contraction of left atrial appendage, stagnant blood
22 flow with the potential for thrombus formation.

23 And so you can imagine looking at this
24 picture that if this large thrombosis dislodges and
25 goes to the brain, it can cause the substantial

1 disability and mortality that we just reviewed in the
2 last side.

3 Now, why is it the left atrial appendage
4 that's the culprit? Well, theoretically clot can
5 form in other parts of the left atrium, but the
6 studies, the TEE studies that have looked and
7 evaluated patients with atrial fibrillation around
8 the time of stroke show that about 90 percent of the
9 time, if thrombus can be detected in the left atrium,
10 it's detected in the left atrial appendage. So we
11 really believe that this is the primary
12 pathophysiologic process that we're dealing with.

13 So what then is the current state, if you
14 will, of stroke prevention in a patient with atrial
15 fibrillation? Well, it's basically systemic medical
16 therapies, anticoagulants, i.e., warfarin and
17 antiplatelet agents, that are aimed at reducing this
18 risk of thrombus formation in the left atrial
19 appendage. And it's important to note that all
20 strategies do indeed work to a certain degree, but
21 warfarin is clearly the gold standard and the
22 cornerstone of therapy.

23 In a very eloquent network meta-analysis
24 from Cooper, et al., published in the Archives of
25 Internal Medicine in 2006, they reviewed 19 different

1 randomized clinical trials, 9 different treatment
2 strategies in over 17,000 patients, and they
3 concluded that warfarin was about 30 to 40 percent
4 better than aspirin and about 60 to 70 percent better
5 than no treatment at all.

6 But, although the benefit is recognized, it
7 comes with a risk, and again this is very nicely
8 displayed here, and in this network meta-analysis,
9 assuming 51 ischemic strokes per 1,000 patient-years,
10 off of treatment, off of any treatment, aspirin would
11 be expected to prevent about 16 of those 51 strokes
12 but at the expense of 6 major or fatal bleeds. The
13 adjusted standard dose warfarin is better. It would
14 be expected to prevent 28 or about 65 percent of
15 those 51 ischemic strokes but at a higher expense of
16 11 major or fatal bleeds.

17 And so it's always a balance between
18 benefit and a risk and, because of that, help
19 patients and physicians kind of ferret through this
20 risk to benefit ratio, multiple evidence-based risk
21 models have been developed. The one that's displayed
22 here is the CHADS₂ Score. It's perhaps the best
23 validated risk thought model. It looks at clinical
24 criteria that you can see here, and basically you can
25 get a score of 0 to 6.

1 The current ACC/AHA guidelines published
2 most recently in 2006 indicate that patients with a
3 CHADS score of 0 should receive aspirin, with a CHADS
4 score of 1 should be either on an aspirin or
5 warfarin, up to the discretion of the physician, and
6 patients with a CHADS score of greater than one
7 should be on warfarin.

8 That said, I think it's important to point
9 out to the Panel that these risk models are basically
10 very rough guides at best, and many clinicians
11 believe that they tend to, and the CHADS score in
12 particular, underestimate the severity of risk.

13 So we've learned that warfarin works, but
14 all of us know that there are significant issues
15 related to warfarin, and it's just a really, really
16 difficult drug to use. And this list here covers
17 many of those issues. First of all, it's a very
18 narrow therapeutic window. The target INR is between
19 2 and 3, and it's really difficult to keep the INR
20 between 2 and 3, and I'm going to show you some data
21 in that regard.

22 The drug has a very long half-life, and
23 that can be problematic especially in patients that
24 require cessation of warfarin therapy, for instance,
25 for an interventional procedure or an invasive

1 procedure of some kind.

2 Many of these patients have comorbidities
3 and concomitant diseases that require dual
4 antiplatelet therapy, patients with acute coronary
5 syndromes, recent stenting, where the indication for
6 dual antiplatelet therapy can be as long as months or
7 even a year or perhaps even indefinitely in some
8 patients. And, if those patients also have atrial
9 fibrillation and need to be on warfarin, that's a big
10 deal because then they're confronted with the triple
11 therapy issue which dramatically increases the risk
12 of bleeding.

13 Many of these patients have
14 contraindications and the bleeding risks are
15 substantial, and the difficulty with the bleeding
16 risk is that it's really difficult to basically
17 determine those bleeding risks for any specific
18 patient.

19 This is data looking at INR control. It's
20 very difficult. About 50 to 60 percent of the time
21 is the best that we can do. About 20 to 30 percent
22 of the time, INRs typically are subtherapeutic and 10
23 to 15 percent of the time, they're supertherapeutic,
24 and the implication for this are profound because if
25 the INRs are greater than 3, it dramatically

1 increases the risk of bleeding, and if they're even
2 just a little bit less than 2, it substantially
3 reduces the benefit of the drug.

4 Of course, the big issue related to
5 warfarin is the bleeding risk. There are about
6 10,000 patients annually that have hemorrhagic
7 infarcts related to anticoagulant therapy.

8 The bleeding risks are all over the map.
9 When one looks at the literature, it can be 1
10 percent, 2, 3, they can be as high as 5 percent, and
11 certain subsets can be as high as 13 percent, for
12 instance, in warfarin-naïve patients and elderly
13 patients. And, again, the difficulty with assessing
14 the risk of bleeding is that unlike the risk of
15 stroke where there are a lot of different models to
16 help us, try to guide us through, who's at risk for a
17 stroke, there are no really good validated bleeding
18 risk models. So this is a bit of a difficult issue.

19 That said, the FDA has recognized a black
20 box warning because of the bleeding complications
21 related to warfarin, and this was issued in 2006.

22 And, lastly, again because of warfarin
23 limitations, many patients don't get the therapy that
24 they should be on. This is data looking at patients
25 that don't have contraindications. They actually

1 have no contraindications to warfarin therapy, and
2 they are eligible for it and they should be on it,
3 but only about half of patients are on the therapy.
4 And why is that? It's not because we don't believe
5 that the therapy reduces the risk of stroke. It's, I
6 think, largely because of the risk of bleeding and
7 the hassle of warfarin.

8 So I'd like to then turn our attention to
9 what we believe is an alternative to warfarin therapy
10 for stroke prevention in patients with atrial
11 fibrillation, and here you see it in this picture.
12 It's the WATCHMAN device.

13 The technology consists of the device
14 itself. You can see here in this picture, this is a
15 self-expanding nitinol cage with fixation barbs. It
16 has a polyester cover on the atrial side to promote
17 endothelialization. The device is preloaded in a
18 delivery system. It comes in five different devices,
19 and then the device is delivered into the left atrial
20 appendage through this WATCHMAN Access System which
21 is basically a 14 French sheath.

22 The procedure goes something like this.
23 After a transseptal puncture is performed, this 14
24 French access sheath is placed in the left atrial
25 appendage. We use transesophageal echocardiography

1 and fluoroscopy to pick the right size of the device,
2 and once that device has been chosen, we put it into
3 the left atrial appendage as depicted here.

4 Prior to release of the device from the
5 cable, there are certain release criteria that had to
6 be met. These include position, to make sure that
7 the device wasn't too distal or too proximal, and if
8 the position wasn't great, one is able to partially
9 or completely retrieve the device. The device had to
10 be the right size, so that it's not too big or too
11 small. The device had to be stable and, in fact, the
12 protocol required a tug on the device to make sure
13 that the fixation barbs were in place, to make sure
14 that the device wouldn't come out.

15 And lastly, sealed, to make sure that there
16 was no flow around the device, and once those release
17 criteria were met, the device is released from the
18 cable and left behind, and what one sees
19 pathologically then in both the animal models and the
20 human pathologic models is very beautiful smooth
21 endothelialization across the device in most patients
22 and completed obliteration and occlusion of the left
23 atrial appendage.

24 So, then, as we then turn our attention to
25 getting into the trial, the PROTECT AF trial, I think

1 it's worthwhile to note that the original indications
2 for use for the device are that it's basically a
3 local therapy, which is the device for a local
4 problem, which is thrombus formation of the left
5 atrial appendage. And in that spirit, the WATCHMAN
6 Left Atrial Appendage Closure Technology was designed
7 to prevent embolization of thrombi that may form in
8 that left atrial appendage, thereby preventing
9 occurrence of ischemic stroke and system
10 embolization.

11 So let's then turn our attention to the
12 trial. This is a prospective, randomized trial of
13 the WATCHMAN device versus warfarin therapy. It's a
14 2:1 allocation device to control. A large number of
15 patients were enrolled, 800, 93 were roll-in and 707
16 were then randomized, 59 enrolling centers in both
17 the U.S. and Europe, and the follow-up requirements
18 were TEEs at 45 days, 6 months, and 1 years to see
19 how the device was evolving, clinical follow-up
20 biannually up to 5 years, and INR monitoring every 2
21 weeks for 6 months and monthly thereafter.

22 The follow-up was excellent with 439
23 patients followed for 1 years and 156 for 2 years.
24 The mean follow-up in the 900 patient-year cohort was
25 16 months.

1 The primary efficacy endpoint using the
2 noninferiority hypothesis was all stroke, both
3 ischemic or hemorrhagic, cardiovascular and
4 unexplained death, and systemic thromboembolism. If
5 a patient experiences a stroke followed by death, the
6 primary endpoint was the stroke, and it's important
7 to point out that the significant safety events,
8 those being hemorrhagic stroke and device related
9 stroke, are a part of this primary efficacy endpoint.

10 The primary safety endpoint did not have a
11 prespecified hypothesis in large part because those
12 important safety events were also folded into the
13 efficacy primary endpoint. But we did follow the
14 significant safety events. These were considered to
15 be life-threatening by the independent CEC, and these
16 included device embolization, significant pericardial
17 effusions requiring intervention, cranial and GI
18 bleeding and, in fact, any bleeding that would
19 require significant transfusion.

20 The safety endpoint emphasis was
21 periprocedural events that one would expect
22 potentially with an interventional procedure, and
23 then long-term bleeding or device embolization
24 events.

25 The key inclusion criteria were very broad.

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1 So basically all comers, documented atrial
2 fibrillation, either persistent, permanent, or
3 paroxysmal. Patients had to be eligible for long-
4 term warfarin therapy and have no other indications
5 that would require long-term warfarin therapy. And
6 in my practice, and in the 34 patients that I
7 enrolled in the trial, all of them were already
8 taking warfarin or were felt by the physicians to
9 require warfarin for stroke prevention. The
10 calculated CHADS score had to be greater than or
11 equal to 1.

12 The key exclusion criteria, there's a lot
13 of them there, and basically those are related to
14 nonatrial fibrillation issues that have the potential
15 to cause stroke.

16 This is the enrollment summary. 707
17 patients were randomized, 463 to the device group and
18 244 to the warfarin group. Of those 463, 449
19 actually had an implant attempted, and of those 449
20 attempted implants, 408 were successful. That then
21 results in an 88 percent success rate for
22 implantation in the WATCHMAN.

23 The baseline demographics were similar in
24 both treatment groups. It includes age, gender, and
25 race. The left atrial appendage characteristics were

1 similar in both groups, and it included the number of
2 left atrial lobes, included the length of the left
3 atrial appendage as well as the ostium of the left
4 atrial appendage.

5 The baseline risk factors are seen in this
6 table here. Again no statistically significant
7 differences between the groups. You can see the
8 distribution of CHADS score here, and this is fairly
9 traditional for a trial such as this with most of the
10 patients in the CHADS₁ and CHADS₂ territories.
11 Again, I would emphasize that the majority of these
12 patients were already determined to require warfarin
13 for stroke prevention long-term. Many of them were
14 recruited in anticoagulation clinics and, in fact, in
15 both of those arms, the average duration of warfarin
16 therapy prior to randomization was two years. The
17 atrial fibrillation patterns were identical in both
18 arms, and the injection fractions were similar.

19 The average number of patients enrolled per
20 site was 14. This included both interventional
21 cardiologists and electrophysiologists, and the top
22 enrolling site was 9.3 percent of the patients.

23 This then is the patient study timeline.
24 Following randomization, there was a brief period
25 ranging from 1 to 14 days, but really it usually was

1 just a matter of minutes to hours, if patients were
2 randomized in the cath lab. The device was
3 implanted.

4 Following device implantation, patients
5 were required to be on warfarin for 45 days, and then
6 they came back for a TEE, and if everything looked
7 good, the clinician decided whether or not to stop
8 warfarin.

9 If the warfarin was stopped, then per
10 protocol, the patients were asked to be on dual
11 antiplatelet therapy for six months. And, the reason
12 for this was basically because we all know that if we
13 put something on the left side of the heart, that in
14 and of itself can be thrombogenic, and oftentimes
15 dual antiplatelet therapy is indicated. And so it
16 would be reasonable to continue these patients for
17 six months on dual antiplatelet therapy after
18 warfarin cessation, hopefully giving the chance for
19 the device to completely endothelialize.

20 Seventy-six percent of the randomized
21 patients were discontinued warfarin at 45 days, and
22 87 percent of the implanted patients discontinued
23 warfarin at 45 days. And, by 24 months, 94 percent
24 of patients were off of warfarin.

25 Now, that said, there were some patients

1 where warfarin was reinitiated after it was initially
2 discontinued. That occurred in about 8 percent of
3 patients and was for a variety of different reasons,
4 primarily related to physician discretion or some
5 interventional device or something that happened to
6 the patient.

7 There were protocol requirements as I
8 mentioned in the timeline for medications, and this
9 table below shows the distribution of medication
10 therapy depending on which group you were in, and you
11 can see that this basically would match what one
12 would expect from the protocol-driven initiative
13 where about 19 percent of the time, the patients with
14 the WATCHMAN device were on warfarin, and that was
15 usually the 45-day period. And then about 51 percent
16 of their total duration of follow-up, they were on
17 Plavix and 91 percent of the time on aspirin, and for
18 the control group, 87 percent were on warfarin and 16
19 percent on Plavix and 54 percent on aspirin.

20 The total INR measurements in the trial
21 were as follows: 55 were within therapeutic range
22 consistent with clinical practice and, indeed, most
23 patients did have INRs outside of the recommended
24 range at least once during the study, but this is
25 typical for trials that we see using warfarin.

1 Thirty-four percent of control patients, it's also
2 important to note, at some point in time did
3 interrupt their warfarin therapy, and again, this is
4 typically related to some intervention of some
5 procedure or some bleeding that occurred.

6 When one looks at time in therapeutic
7 range, it's also consistent with recent clinical
8 trials, and here you can see that for the PROTECT AF
9 trial, the time in therapeutic range was about 65
10 percent, and that's about as good as it gets.

11 So, in conclusion, then, we have learned
12 that atrial fibrillation is a growing clinical
13 problem and introduces a substantial risk of stroke.
14 Warfarin is clearly the cornerstone of therapy but is
15 not well tolerated in all patients and is not used in
16 many others.

17 The PROTECT AF trial evaluated the WATCHMAN
18 compared with warfarin in nonvalvular AF patients.
19 The WATCHMAN and control groups were similar in
20 demographics and risk factors. The INR data confirms
21 clinical compliance levels similar to that reported
22 in clinical practice. Eighty-seven percent of the
23 WATCHMAN patients discontinued warfarin at 45 days,
24 and that's why they wanted to be part of the trial,
25 and 93 percent of those patients stopped warfarin at

1 six months.

2 So those would begin to tell the story and
3 describe the story. You're going to see this again
4 from the other presenters. We're going to build a
5 story of benefit versus risk, traditional therapy of
6 warfarin versus the WATCHMAN device, and based on
7 this presentation, I think we all agree that warfarin
8 works, reduces thromboembolic stroke reduction by 60
9 to 70 percent compared to placebo.

10 That said, there's a substantial risk to
11 warfarin. Long-term bleeding risk can be up to 5
12 percent per year, and the rates increase with age and
13 can have serious complications.

14 So what I'd like to do is turn the podium
15 over to Scott Brown who is going to talk a little bit
16 about some of the statistical analysis issues, and
17 then Drs. Holmes and Reddy will fill in the blanks,
18 if you will, to further discuss in much greater
19 detail what we believe is the benefit of the WATCHMAN
20 device versus the serious complications and risks
21 that are potentially related as well to the WATCHMAN
22 device. Thank you very much for your attention.

23 DR. BROWN: Thank you, Dr. Huber. Good
24 morning. My name is Scott Brown. I am a
25 biostatistical consult to Atritech. My time and my

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1 travel have been compensated. I have no financial
2 interest or equity position in the company, and the
3 reason I'm here this morning is to talk for a few
4 minutes about the statistical aspects of the PROTECT
5 AF trial, and that will lead into Dr. Reddy and
6 Dr. Holmes discussing the study's efficacy and safety
7 findings.

8 Now, PROTECT AF was designed and analyzed
9 under a Bayesian approach, and the FDA had released a
10 set of draft guidance of this study. The results
11 we'll discuss here today are consistent with that
12 guidance.

13 Under the Bayesian paradigm, what we do is
14 we combine the concept of a prior distribution with
15 data observed during the course of a study to produce
16 a variety of metrics we can then evaluate to declare
17 study success, failure, to evaluate various effects.
18 These are things like posterior probabilities for a
19 very statistical hypotheses and credible intervals
20 which are the Bayesian analog of confidence
21 intervals.

22 Now, as I just mentioned, the Bayesian
23 method explicitly permits the introduction and
24 inclusion of prior data and prior information. In
25 this particular trial, that was not done in the sense

1 that this analysis we're going to discuss today is
2 not the pooling of multiple trials. It's not the
3 borrowing of strength across different
4 investigations. It's not designed to permit, say, an
5 analytical correction mid-trial. This is simply a
6 Bayesian analysis of a single trial.

7 The Bayesian way of saying that is that we
8 have used a noninformative prior distribution and
9 that sort of Bayesian analysis produces inference and
10 results that are similar to traditional non-Bayesian
11 or Frequentist analyses.

12 As Dr. Huber mentioned, this is a
13 noninferiority design, in terms of the primary
14 efficacy endpoint, and as he, of course, mentioned,
15 warfarin has been shown to be effective in preventing
16 stroke. So from a statistical design standpoint, a
17 randomized superiority trial against a placebo or
18 perhaps a sham control would not have been ethical.

19 Therefore, from a statistical standpoint,
20 our objective particularly with respect to the
21 primary efficacy endpoint is to determine whether the
22 WATCHMAN device is at least as good as long-term
23 warfarin within a predefined region of
24 noninferiority.

25 Now, as a noninferiority trial, it was

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1 necessary to pre-specify a noninferiority margin or
2 delta. Again, from a design standpoint, one thing
3 this does is helps to establish the sample size for
4 the trial relative to the desired power, and it does
5 based on a combination of clinical and statistical
6 judgment as well as practicality.

7 For the PROTECT AF trial, the statistical
8 objective was to demonstrate that the event rate
9 ratio, that is to say, the ratio of primary efficacy
10 event rates, comparing WATCHMAN to control, to show
11 that that ratio was statistically less than 2, and
12 when we go to evaluate the primary efficacy endpoint,
13 the actual noninferiority margin consistent with the
14 data is represented by the upper 97.5 percent
15 credible limit, and we'll show some of that data
16 later on. This number may, of course, be much less
17 than the design value of 2.

18 And just a couple of more things. For
19 those that are familiar with noninferiority testing,
20 I just want to reemphasize that the requirement for
21 this ratio of 2 is a statistical one relating to
22 credible intervals. In particular, it was not
23 permissible for the actual observed event rate to be
24 twice as high in treatment as in control. In fact,
25 under the design of the study, it was required for a

1 relatively similar rate of events and treatment and
2 in control to meet noninferiority.

3 And so in our presentation, we'll be
4 focusing on relative risks on credible intervals and
5 on posterior probabilities dealing with these
6 hypotheses.

7 All right. This slide depicts for
8 illustrative purposes some hypothetical outcomes we
9 might have seen along with declarations and
10 statistical success or failure. And what we have
11 here is a graphical format where we display some
12 example of credible intervals relative to the
13 superiority and noninferiority definitions used in
14 this trial.

15 The X-axis displays the relative risk
16 comparing WATCHMAN to control. Now, you see the two
17 vertical lines on the left here. This left most
18 vertical line represents equal risk or equal event
19 rates between WATCHMAN and control. To the left of
20 that region would therefore be superiority of the
21 WATCHMAN device. On the right side, the vertical
22 line is the noninferiority definition of two times
23 relative risk. Everything to the left of that line
24 represents noninferiority.

25 So the examples that we have here at the

1 top is an unsuccessful finding, although the actual
2 event rate, the relative risk is just under 2. The
3 credible interval extends outside of 2, and therefore
4 this is a failure of noninferiority because the
5 entire credible interval does not lie within the
6 noninferiority bound.

7 The middle example is noninferiority
8 because the entire interval lies within the
9 predefined noninferiority margin and, of course, the
10 bottom example is superiority, the entire credible
11 interval lies to the left of the equal risk margin
12 denoting superiority.

13 Now, just a moment to talk about the model
14 itself. The PROTECT AF primary efficacy endpoint
15 evaluation looked at the rate of primary efficacy
16 endpoint events per patient year comparing the
17 WATCHMAN arm to the control arm. And at the bottom
18 there, you see that we maintain traditional type I
19 error rates of 5 percent in traditional power of 80
20 percent.

21 The most important thing on this slide, I
22 think, is the results of these statistical analyses.
23 All of these Bayesian models we're going to talk
24 about for the efficacy endpoint are adjusted for
25 differences in baseline CHADS score.

1 As Dr. Huber showed in his presentation,
2 there are no statistically significant differences at
3 baseline. However, nonetheless, this analysis
4 controls for any numerical or qualitative differences
5 irrespective of statistical significance, and this
6 was the prespecified stratification for the primary
7 endpoint.

8 Now, this was a sequential analysis along
9 with the Bayesian design. Under this particular
10 analysis, we were to analyze the data at specific
11 time points. The first formal statistical analysis
12 of the data was to occur at 600 patient-years and
13 then another formal analysis every subsequent 150
14 patient-years. There was an additional requirement,
15 the Agency requested, that at least 300 patients have
16 reached their 1-year follow-up and at least 100
17 patients reached their 2-year follow-up prior to any
18 formal statistical analysis.

19 The trial was designed to continue accruing
20 patient-years up to a potential maximum of 1500 but,
21 in fact, noninferiority of the primary efficacy
22 endpoint was met at the first formal statistical look
23 at 600 patient-years. That was conducted on a
24 database frozen in June 2008.

25 Additionally, we have the 900 patient-year

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1 dataset to discuss here today, and that dataset was
2 frozen in December of 2008.

3 All right. A little about some of the
4 analytical cohorts we're going to look at today. Of
5 course, the primary analysis of all endpoints was
6 intent-to-treat, but there were other analytical
7 cohorts defined to answer questions of potential
8 clinical interests. One of them was the prespecified
9 protocol analysis which assesses only those patients
10 who were successfully treated with their randomized
11 therapy. What that means is that for patients
12 randomized to WATCHMAN, this evaluates only those
13 patients who actually received the device and
14 discontinued warfarin, and in that event, time 0 for
15 event analyses is the date of warfarin
16 discontinuation.

17 In the control group, this analysis counts
18 those patients who were taking warfarin at baseline
19 or at least by 45 days post-randomization. And the
20 clinical purpose is to help isolate the device effect
21 independent of drug effects.

22 The learning curve is something that
23 Dr. Reddy's going to talk about in much greater
24 length. This again was a prespecified analysis, in
25 the statistical analysis plan, designed primarily to

1 evaluate a potential learning curve in the WATCHMAN
2 patients, and the way this worked was to look at the
3 entire cohort of patients and evaluate the first
4 three enrolled at a site versus all remaining
5 patients, and the objective again was to establish
6 the potential existence of learning particularly in
7 safety.

8 I'll add one other thing. In the Panel
9 pack, we discuss a post-procedure analysis that was
10 also part of our discussion of the study endpoints.
11 We are going to focus today on the intent-to-treat
12 and the protocol analyses.

13 I now get the opportunity to preview the
14 results of the primary efficacy endpoint. Dr. Holmes
15 is going to talk about this at much greater length,
16 but what you see on the screen here is the intent-to-
17 treat analysis of the 900 patient-year cohort.

18 Now, you recall that this is a
19 noninferiority design. The study was designed with
20 the expectation that the rate of events in WATCHMAN
21 and control would be similar. What we observed, in
22 fact, was that the rate of primary efficacy endpoint
23 events in WATCHMAN was 3.4 events per 100 patient-
24 years versus a control rate of 5 events per 100
25 patient-years for a relative risk of .68 in the

1 direction favoring the WATCHMAN group.

2 Now, as this is a Bayesian analysis, one of
3 the nice things about Bayesian methodology is that we
4 can use vocabulary that sort of naturally expresses
5 the concept of probability instead of perhaps talking
6 about confidence the way a Frequentist analysis does.

7 What this slide shows us is that the
8 probability, given the data observed in this study,
9 the probability that the noninferiority hypothesis is
10 true, under the Bayesian paradigm, that probability
11 is 99.8 percent. We compare that to the 97.5 percent
12 criteria which was prespecified in the protocol, and
13 these two numbers collectively tell us again that the
14 primary efficacy endpoint, noninferiority hypothesis
15 was successful.

16 Additionally, we see under the Bayesian
17 posterior probability an 83.7 percent chance based
18 upon these data that the WATCHMAN is superior to
19 control in terms of the primary efficacy endpoints.

20 Here we have the primary endpoint displayed
21 a little differently, in a graphical fashion,
22 relative to the noninferiority and superiority
23 definitions that we discussed a little bit earlier.
24 Looking at our schematic, this is the same thing from
25 the hypothetical examples a few minutes ago, just

1 with the real data.

2 Once again, we display the relative risk of
3 .68. So roughly a 1/3 reduction in efficacy events
4 in the WATCHMAN group relative to control, and here
5 displayed we have the upper credible bound of 1.41.
6 So that vertical line there of 1.41 represents the
7 97.5 percent credible limit on the relative risk.
8 That number is substantially less than the designed
9 number of 2 for noninferiority. Once again, this is
10 a different way of showing the same thing, that the
11 noninferiority hypothesis was met for the primary
12 efficacy endpoints.

13 Now, the model assumption used for the
14 primary efficacy endpoint, as all statistical models
15 do, it is subject to certain assumptions, notably an
16 assumption of constancy of event rates across time.
17 It was recognized early on that such assumptions are
18 not always true and may not, in fact, hold in any
19 given circumstance. So for that reason, several
20 prespecified sensitivity analyses were performed
21 alongside the primary endpoint.

22 On this slide, the top row is the primary
23 Bayesian model that we just showed a moment ago with
24 the corresponding relative risk and the credible
25 interval. The next four rows are all sensitivity

1 analyses that remove one or more of the model
2 assumptions. A couple of them are proportional
3 hazards models which assume only proportional hazards
4 and not constancy of event rate. The bottom two are
5 piecewise models to deal with the constancy
6 assumption.

7 The important thing here to note is that
8 all of these analyses are similar to one another in
9 that all of them have a risk ratio or hazard ratio
10 favoring treatment over control. In every case, the
11 upper bound of the credible intervals are similar,
12 and in all cases, the credible intervals are well
13 below 2, which was the definition of noninferiority
14 for this trial.

15 And that completes the statistical portion.
16 I would like to now introduce Dr. David Holmes who's
17 going to talk about the PROTECT AF efficacy results.

18 DR. HOLMES: Good morning. It's a pleasure
19 to be here. I'm David Holmes from Rochester,
20 Minnesota. Mayo Clinic has the potential to earn
21 royalties from Atritech as a result of this.

22 As I listened to Scott, I am made aware of
23 the fact that I am neither a minister, like Bayes
24 was, nor am I Presbyterian, like Bayes was. So I
25 have much to learn in terms of the statistical

1 methodology that he has talked with you about. He
2 has teased you about some of the results. I am now
3 going to fill out a more full detail, fill out the
4 pages dealing with the efficacy results of this
5 important trial, PROTECT AF.

6 We have heard the primary efficacy endpoint
7 was a composite. It was a composite of all stroke,
8 both ischemic or hemorrhagic. We have also heard
9 that not all stroke is the same. Hemorrhagic stroke
10 has a much worse prognosis. Forty-four percent of
11 the people are dead, at least in Ken Huber's
12 information, rather than the group of people who have
13 ischemic stroke.

14 The second part of that was cardiovascular
15 and unexplained death. We need to remember that the
16 CEC adjudicated those. There is a saying that all
17 deaths are sudden. One moment you are alive and the
18 next you're dead. Well, the CEC indeed tried to
19 adjudicate those deaths that were related to the
20 procedure.

21 And then, finally, the third component will
22 be systemic thromboembolism.

23 This is a complex study because efficacy
24 endpoints and safety endpoints were sometimes
25 potentially the same, and the FDA really was very,

1 very helpful in our discussions with the FDA, and
2 they identified as you can see on the bottom in the
3 executive summary, that the primary efficacy endpoint
4 captures events that would also be considered
5 significant safety events, stroke, death, and
6 systemic embolization. And so this Venn diagram
7 shows you that overlap between safety events and
8 efficacy events, and that's terribly important to
9 remember because you will hear about both of those.
10 I will talk about efficacy. Dr. Reddy will talk
11 about safety.

12 The bottom line of this, if we were to look
13 at intent-to-treat, the primary efficacy result, if
14 you bring along a new technology as an alternative to
15 warfarin in a group of patients with nonvalvular
16 atrial fibrillation at risk for stroke, this is that
17 primary efficacy result. You can see the cohort at
18 600 patient-years and at 900 patient-years. You can
19 see the rate, the absolute rate with WATCHMAN was 3.4
20 and with control was 5.0. The relative risk was .68,
21 and you've heard from Scott about the posterior
22 probabilities. And we know that if we were to look
23 at the boundary for noninferiority, there is the
24 chance 99.8 percent that this device was noninferior
25 to warfarin.

1 Of interest, there's an 84 percent chance
2 that this device was superior, actually superior to
3 warfarin. It wasn't tested at this point in time.
4 It didn't meet that criteria, but 99.8 percent of the
5 time we can be certain that this device is
6 noninferior to warfarin. And, indeed, there's a 32
7 percent lower relative risk in the WATCHMAN group
8 using the primary efficacy results. That is the
9 bottom line.

10 Let's fall to the bottom line though and
11 say, give us more information. Give us more details.
12 Let's talk about events. Events occurred in both
13 groups. They occurred differently in both groups,
14 but they did occur. Let's look at the timing of
15 events. That's important as we deal with a procedure
16 that has some potential for events and a drug which
17 has potential for events later on once you start the
18 drug.

19 This is the information on the timing of
20 events broken down by WATCHMAN and control. On or
21 before the day of the procedure, we can see that
22 WATCHMAN had more events. No question about that.
23 It is an invasive procedure.

24 Let's look at day 1 to 45. After day 45,
25 you can see the frequency of events in the primary

1 efficacy event rate with the control group increased
2 from 0.8 within the first 45 days to 5.7 after 45
3 days.

4 If you were to go to the bottom line of
5 this, the rate per 100 patient-years is again 3.4
6 versus 5.0. And so the rate of events after 45 days
7 in the WATCHMAN group is still lower than the control
8 group. Even with those periprocedural events,
9 invasive events, there's no question about that, the
10 rate in the WATCHMAN group is still 32 percent less
11 than in the control group.

12 Let's talk about specific events. We have
13 talked about the temporal profile. Let's talk about
14 specific events. What are those things that could
15 happen during the procedure that would be efficacy
16 events?

17 Well, perhaps ischemic stroke, maybe that
18 would be the result of air embolism. These are big
19 devices. You could potentially get air embolism.
20 This is the data on day 1 to 45 and after 45 in terms
21 of the specific primary efficacy events. Ischemic
22 stroke is more frequent, six of those patients.
23 Hemorrhagic stroke occurred in one patient in the
24 WATCHMAN group. That one patient occurred during the
25 time that they were on warfarin, during the first 45

1 days. They had received the device, they had
2 received warfarin, and they had a hemorrhagic stroke
3 and died.

4 After day 45, you can see that there are
5 not hemorrhagic strokes because warfarin has been
6 discontinued. Contrast that with the five
7 hemorrhagic strokes, two percent, which were seen
8 with the control group and had major adverse events
9 associated with it.

10 If we were to then say, let's examine the
11 first element of the composite endpoint, let's look
12 at all stroke, intent-to-treat, we again have 600
13 patient-years and 900 patient-years. The intent-to-
14 treat rate has decreased from 3.4 to 2.6. Relate
15 that to 3.5 in the control group and the relative
16 risk is .74, and you can see the posterior
17 probability is 99.8. The bottom line then would be
18 26 percent lower relative risk in the WATCHMAN group
19 for all strokes, including the periprocedural
20 strokes.

21 Let's then talk about the specifics of the
22 stroke. Let's talk about the ischemic strokes. We
23 have talked about the fact that ischemic strokes in
24 general lead to less disability. Ken Huber talked
25 about that. In the ischemic stroke WATCHMAN group,

1 we know that there was one pre-procedural event that
2 resulted in mortality. That patient suffered the
3 stroke prior to implant. There were five procedural
4 events and three were related to air embolism.
5 Dr. Reddy will talk about that at length in the
6 safety presentation. But that is the data.

7 Let's look at the subsequent ischemic
8 strokes and let's look at the outcome of the sub-
9 ischemic strokes. We can see the outcome on the
10 right is no deficit and no deficit. The litany goes
11 on. In general, these strokes are less severe,
12 resulting in less increase in morbidity associated
13 with ischemic strokes. That is the WATCHMAN group.

14 How about the control group? How did they
15 fair? We know that warfarin is not perfect.
16 Warfarin still can be complicated by an ischemic
17 stroke. It doesn't work all the time. This is the
18 data on ischemic strokes and warfarin. We can see
19 that one required speech therapy, no deficit, no
20 deficit, one died, but in general, they didn't die.
21 They had minor disability, less major disability, if
22 they had an ischemic stroke, and it occurred in both
23 limbs, more frequently periprocedurally related in
24 the group of patients treated with WATCHMAN.

25 The other side of the stroke coin is the

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1 worst side. If you had to choose which kind of
2 stroke you would have, you would choose none. If
3 your second choice is you're going to have one, which
4 one do you want? You do not want an hemorrhagic
5 stroke.

6 This is the data on hemorrhagic stroke. In
7 the WATCHMAN group, as I have mentioned, there was
8 one. It occurred at day 15 while the patient was on
9 warfarin. You might define that double jeopardy.
10 The patient was treated with warfarin. That was the
11 protocol. That was the IDE protocol. They were
12 treated with warfarin as well as the device. They
13 had a hemorrhagic stroke and they died. After that,
14 there were no further hemorrhagic strokes. No
15 further hemorrhagic strokes with the device group
16 because after that they stopped the warfarin in the
17 device group.

18 In the control group, we can see the
19 hemorrhagic strokes during follow-up, and these are
20 awful strokes. Death, death, death, can't walk,
21 can't talk, feeding tube, death. Hemorrhagic stroke
22 is an awful thing, and indeed in this study, there
23 was a statistically significant difference in
24 hemorrhage stroke which was less with the device than
25 with the control group.

1 If we were to sum up the data on stroke,
2 intent-to-treat all stroke, ischemic or hemorrhagic,
3 all stroke here and ischemic stroke and hemorrhagic
4 stroke, we can see the marked difference in WATCHMAN,
5 .2 percent versus 1.3 percent. All stroke was .3
6 versus 1.6, and we would summarize and say that after
7 day 0, WATCHMAN ischemic stroke rate was 1.7 versus
8 2. That excludes the periprocedural events, air
9 embolism, that is true. We can work on that.

10 Hemorrhagic strokes, the big ones, had
11 higher mortalities, and hemorrhagic strokes were
12 significantly less in the WATCHMAN group than in
13 control.

14 Let's talk about the second part. We
15 talked about stroke. Let's talk about mortality. We
16 will again remember that all deaths are sudden. The
17 patient is alive one moment and dead the next. These
18 were all CEC adjudicated. If you would look at the
19 death events, they were efficacy events. Not safety
20 events, efficacy events, and Vivek will talk about
21 those. There were three efficacy events in the
22 WATCHMAN group and five in the control group. The
23 relative risk was .30, .30 in favor of the WATCHMAN
24 device.

25 The final piece of that triad is systemic

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1 thromboembolism. You might not expect that with
2 Coumadin or with warfarin. You might have expected
3 that potentially with a device, and it was seen on
4 two different occasions. One was funduscopy
5 evaluation. There was a retinal artery occlusion, an
6 embolism into the arterials of the eye, and the other
7 was a hemiretinal arterial occlusion. One resolved
8 the next day and one resolved later. That was the
9 information on system thromboembolism.

10 We then have talked about intent-to-treat.
11 We've talked about stroke. We have talked about
12 mortality. We have talked about systemic
13 thromboembolism. One of the issues is that this
14 device is brought along as an alternative to
15 warfarin. So you would like to know how this device
16 behaves when there is no longer warfarin there. This
17 was a prespecified subset. That is true. This
18 prespecified subset was per-protocol. So at day 45,
19 those patients, about 85 percent, could stop
20 warfarin. What happens to those patients?

21 Well, granted they are on aspirin and
22 Plavix, and we'll talk about that. But what happens
23 at day 45 when they stop warfarin. Is there an
24 uptick in events? Contrast that with a group of
25 patients who continue with warfarin forever and ever

1 and ever. What do we know about that?

2 We know this, that that allows us to access
3 and evaluate those patients who were successfully
4 treated with the randomized therapy because it
5 includes only those patients who received the
6 assigned therapy, WATCHMAN, received the device and
7 discontinued the Coumadin. Warfarin control group
8 continued to take the warfarin, and then it helps to
9 isolate the sole device effectiveness. That's a
10 terribly important prespecified analysis.

11 This is what we found after we stopped the
12 warfarin in the one group, the device group, and
13 continued the warfarin in the other group. We can
14 look at 600 patient-years and 900 patient-years.
15 With WATCHMAN, it's 2.1, and controlled, it's 4.7.
16 The relative risk is .44. The posterior probability
17 is 99.9 percent that it is noninferior, and the
18 posterior probability in terms of superiority is 97
19 percent because there was a 56 percent lower relative
20 risk in the WATCHMAN group once they stopped the
21 Coumadin. That is sole device.

22 What could we say about fatal stroke? We
23 talked about the fact that hemorrhagic strokes were
24 typically more fatal. How about fatal stroke? This
25 is the same data intent-to-treat and per-protocol

1 after they get off of the warfarin. You would be
2 able to predict this result. The WATCHMAN group had
3 a lower relative risk of stroke and fatal stroke.

4 It becomes even more significant after the
5 procedural risk and the 45-day warfarin regimen is
6 passed. You'll remember that there was not a single
7 hemorrhagic stroke after warfarin was discontinued,
8 and there weren't any fatal strokes in the WATCHMAN
9 group after that time.

10 The next question that you should raise and
11 has been raised is the issue of belt and suspenders,
12 double protection. Or is that double jeopardy?

13 If you were to say during the first 45 days
14 all of these patients who received the device had
15 Coumadin, too, and that helped them out,
16 alternatively, you could say during that first 45
17 days, they got Coumadin and the device. So they had
18 double jeopardy. They had the procedural
19 complications and the potential bleeding into their
20 head from warfarin.

21 This looks at double protection or double
22 jeopardy. So what we did was we then isolated those
23 patients and identified those patients who made it
24 through the procedure fine and then followed them to
25 45 days and then stopped their warfarin.

1 Prior to warfarin discontinuation, this is
2 after the procedure is finished, the rate of events
3 was 4.6 percent. When they stopped the warfarin, it
4 dropped dramatically to 2.1. So this was not belt
5 and suspenders, double protection. This was indeed
6 double jeopardy. Patients paid the price for double
7 jeopardy.

8 Is that going to be important in the
9 future? Is it necessary? Study is underway in the
10 European Union to evaluate implantation without that
11 45-day warfarin requirement.

12 This is a complex slide. It's a complex
13 group of patients who are very familiar with multiple
14 medications with polypharmacy. We took this approach
15 for the device group to mandate the use of warfarin,
16 clopidogrel, and aspirin. It was a conservative
17 approach. It was along the lines of the fact that we
18 have put in PFO devices for a long time, and after we
19 put in a PFO device, we use Coumadin for a while and
20 we use aspirin and Plavix for a while. We use that
21 to make sure that the device fully endothelializes,
22 as Ken Huber showed, and so this was IDE-approved
23 protocol that was mandated. And those requirements
24 reflected how we would use the device in clinical
25 practice. And clinical practice, again if we put in

1 a PFO device, we would say, well, we're going to give
2 you Coumadin for a while and then aspirin and Plavix.
3 You might say, well, maybe it's the aspirin and
4 Plavix after you stop the Coumadin that prevents
5 events. That's a good question.

6 It has been answered by the ACTIVE-W trial,
7 you will remember that was published in Lancet. The
8 ACTIVE-W trial evaluated 6,700 patients who were at
9 risk for stroke with atrial fibrillation. They
10 studied aspirin and clopidogrel versus warfarin, and
11 they found that aspirin and clopidogrel was inferior
12 to warfarin for preventing stroke.

13 By virtue of that fact, we can be certain
14 that indeed that event after we stop the warfarin is
15 not related to aspirin and Plavix. It hasn't worked
16 at any other time. It is not as good as warfarin.
17 There is not an increased uptick of events after you
18 stop the warfarin. That is not because of aspirin --
19 it's because the device works equivalently. It is
20 noninferior to warfarin. Antiplatelet effects would
21 not be expected to explain that effect.

22 Here we have the Kaplan-Meier, well-known
23 Kaplan-Meier estimates. You're familiar with that.
24 We can see the event free survival on the top, and
25 the dotted line is WATCHMAN, and the control group is

1 solid. As we look at these curves, we can see that
2 over the course of time, other than this blip here
3 that is seen, they do not begin to converge again.
4 There is not a late catch-up event. It's terribly
5 important as we think about longer and longer term
6 follow-up of these patients.

7 On the bottom, we have the absolute event
8 rates at 1 year, at 2 year, and at 3 year for
9 WATCHMAN and control. These patients will not live
10 forever. Most of us don't. As we look at WATCHMAN
11 and control, we can see that the event rates climb,
12 but let's look at 2-year event rates. It's 6.5
13 versus 9.7 in warfarin. 6.5 versus 9.7. That's
14 about a 30 percent reduction, and that is very, very
15 close to the 32 percent reduction we saw in primary
16 efficacy endpoints with the WATCHMAN device as
17 compared to control warfarin.

18 As I begin to summarize, I am led back to
19 this slide, that you have seen before. The design
20 included a specific boundary of two times for
21 noninferiority. We need to focus on the absolute as
22 well as the relative risk. This is the relative risk
23 of events, and here we have the relative risk of the
24 events was .68. It's again .32, 32 percent reduction
25 in events with the WATCHMAN device. The upper

1 confidence interval, confidence boundary, was 1.41,
2 much less than noninferiority of the two. That's the
3 actual relative data.

4 For those of you that are used to looking
5 at absolutes data, we can see this on the next slide.
6 This is the absolute difference. The absolute
7 difference is -1.6. And remember, the WATCHMAN was
8 3.4 in terms of primary efficacy. Control was 5.0.
9 And now the upper bound is even less. It's a 1.3.
10 And that really is the bottom line. That confidence
11 interval upper boundary is 1.3, but the absolute
12 difference is -1.6, a 30 percent reduction in primary
13 efficacy events with WATCHMAN compared with warfarin.

14 And so I would fill in this next part of
15 the quadrangle that you've already seen. Ken Huber
16 talked about benefit and risk with warfarin. I will
17 close with the benefit of WATCHMAN.

18 This device, if you were to look at primary
19 efficacy, it met noninferiority boundaries with a 32
20 percent reduction compared to warfarin, using intent-
21 to-treat. If you were to say there's a double
22 jeopardy issue with warfarin, and that is true, there
23 seems to be, if we eliminate that, after 45 days,
24 they get off of Coumadin, that double jeopardy goes
25 away. Then using that analysis, the efficacy looks

1 even better with a 56 percent reduction in events
2 with the WATCHMAN device as compared to control
3 warfarin.

4 With those efficacy results, I will turn
5 you over to Vivek Reddy to talk about some of the
6 safety issues.

7 DR. REDDY: Thank you very much, David. So
8 my name is Vivek Reddy. I'm an electrophysiologist,
9 and before I get started, I just need to disclose two
10 important points. One is that I am an investigator
11 in the study, and the second is that my time has been
12 compensated and my lodging and travel to this meeting
13 has been compensated by the company.

14 So my charge is to discuss the safety
15 results of the study, and before getting started, I
16 would like to make some general observations or
17 suggestions.

18 First, as with any device versus drug
19 comparison, I think we have to balance the higher up-
20 front, acute risk of complications associated with
21 this procedure, as with any procedure, with the
22 numerically lower, of a continual risk of
23 complications that are often associated with drug
24 use.

25 Now, how do you compare these? How do you

1 compare two different types of constellations of
2 complications? Well, certainly the simplest and
3 easiest parameter to look at is the composite event
4 rate, and that is actually the first parameter that I
5 will be discussing. But I think we also have to
6 consider the functional impact of this heterogeneous
7 group of complications, and indeed, the grossest
8 measure of that would be all-cause mortality, which
9 I'll talk to or speak to later in the presentation.

10 I think we also have to consider the time
11 course of these events. As you know oftentimes in
12 these studies, the device related safety events
13 oftentimes occur very early in the course of the
14 study.

15 Why is this important? Well, we want to
16 get some idea of what happens after the study ends,
17 that is, in the drug group, one could expect that
18 whatever safety events occur will continue to occur
19 over the course of the patient's lifetime. And we
20 want to try to understand in the device group, what
21 percent of those safety complications are up front
22 and what percent of those may continue to accrue over
23 the patient's lifetime.

24 I think it's also important because
25 oftentimes these device-related or procedure-related

1 events are oftentimes amenable to training and
2 education and experience by the operator.

3 And, finally, I want to present some of
4 that data. What is the evidence that we see in the
5 study that there is experience-related improvement in
6 the outcome of the procedure from a safety
7 perspective?

8 So Scott and others have already spoken
9 about the primary safety endpoint. Please note that
10 there is no predetermined hypothesis for this
11 particular endpoint.

12 This prespecified composite endpoint is
13 comprised of life-threatening events as determined by
14 the independent Clinical Events Committee after their
15 review of the source documents.

16 Now, at this point, I want to point out
17 that all the data that I'll be presenting in this
18 presentation has been independently adjudicated by
19 the Clinical Events Committee. There will be no
20 reinterpretation of these outcomes by either myself
21 or any of the other presenters in our presentation.

22 Now, CEC did have a former charter prior to
23 initiating the study. In addition, there were
24 decision guidelines that were developed during their
25 initial meetings prior to adjudicating the first

1 event.

2 Now, what are these life-threatening
3 events? Well, they focused on the one hand on
4 procedural-related events, whether they be device
5 embolization or traumatic bleeding events such are
6 pericardial effusion.

7 On the other hand, they focused on bleeding
8 events such as bleeding related to Coumadin, for
9 example, in the drug arm or Coumadin or antiplatelet
10 agents in the device arm. And these would be such as
11 cranial bleeding, gastrointestinal bleeding requiring
12 transfusion, or any bleeding related to the device or
13 procedure necessitating the operation or transfusion
14 of two units of packed red blood cells.

15 Now, you've already seen this Venn diagram.
16 I want to show this again to point out again that
17 there are several safety events that account in the
18 efficacy endpoint. Remember that the efficacy
19 endpoint is comprised of stroke, systemic
20 embolization, and cardiovascular unexplained death,
21 but if we parse this stroke further, you see that
22 they are a procedural-related stroke, which in
23 addition to being counted in the efficacy endpoint is
24 also counted in the safety endpoint.

25 In addition, hemorrhagic stroke is also

1 counted in the safety endpoint since this is bleeding
2 related to anticoagulation.

3 I think this is important because as
4 pointed out in the FDA Executive Summary, even though
5 there's no predetermined safety hypothesis, since
6 safety and effectiveness are captured in the primary
7 efficacy endpoint, a separate powered hypothesis for
8 the safety endpoint was not deemed essential.

9 I also want to show this because what you
10 notice here in the efficacy endpoint is
11 cardiovascular or unexplained death, but nowhere in
12 this Venn diagram do you see all-cause mortality.
13 All-cause mortality, while it was a secondary
14 endpoint, is not captured in either the efficacy
15 endpoint or the safety endpoint, and I will speak to
16 that separately in just a few slides.

17 So let's get to the primary safety
18 endpoint. As you see here, there's 600 year patient
19 data, the 900 year patient data. If you look at the
20 WATCHMAN group, the composite safety endpoint is 11.6
21 percent. It's 11.6 per 100 patient-years versus 4.1
22 percent of the control group to give a relative risk
23 of 2.85, and you see the confidence intervals.

24 In the 900 patient-year data, you can see
25 the relative risk decreased to 2. Now, why did that

1 happen? Well, the event rate in the control group
2 certainly stayed the same, 4.1, 4.2, but in the
3 WATCHMAN group, it decreased from 11.6 to 8.7.

4 Now, how can that happen? How can you have
5 a decrease in the safety event rate? Well, the
6 reason is that this 8.7 is not percent of total
7 number of patients. All the data being presented at
8 least in this slide is per 100 patient-years. So
9 this statistical peculiarity is because of this
10 slide, which you see on this Kaplan-Meier curve, the
11 dotted line represents the device safety events, and
12 the solid line represents the safety events in the
13 Coumadin group in which you notice, in the Coumadin
14 group there's a continual low level increase in the
15 event rate.

16 However, in the device group, you see this
17 very high event rate in the first couple of days of
18 the procedure, and then after that, it sort of levels
19 off.

20 Let's look at the timing of these events in
21 a little bit more detail. Again, we arbitrarily
22 broke these up into the upfront and the continuous
23 risk. So those events that occurred either on the
24 day of the procedure or the first week of the
25 procedure versus those that occurred thereafter. And

1 if you notice, on the day of the procedure, 27 of the
2 48 events occurred, 7 in the first week of the
3 procedure. So fully 70 percent of the safety events
4 occurred within the first week of the procedure.
5 Beyond that point, the event rate is 3.2 percent in
6 the WATCHMAN group and 5.4 percent in the control
7 group and numerically a little bit lower in the
8 device group.

9 Let's look at these upfront and continuous
10 risk a little bit further. If you look just at the
11 upfront risk, these again are risks that occurred
12 arbitrarily that we defined as within the first week
13 of the procedure. Well, the majority of these 34
14 events were pericardial effusions. You can see that
15 21 or about 2/3 of the events were pericardial
16 effusions. There are also five ischemic strokes to
17 which I'll speak in more detail as well as a device
18 embolism and bleeding.

19 If you look beyond this point, you see one
20 pericardial effusion, so one -- pericardial effusion,
21 two device embolisms, and then we start getting to
22 those risks that occurred in both groups, the
23 hemorrhagic strokes as well as bleeding.

24 So let's just talk about these various
25 safety events. Device embolization is certainly one

1 that we have to talk in details. In this study,
2 there were a total of three device embolizations.
3 The first occurred during the procedure itself, was
4 recognized during the procedure itself, and the
5 patient eventually underwent an operation to remove
6 the device. The other two occurred sometime between
7 the implant and the 45-day TEE when it was
8 identified, and those other two patients, the device
9 embolization was asymptomatic. Of those other two
10 patients, one of them underwent percutaneous vascular
11 removal. The other patient refused to have the
12 device removed. The device was left in place for
13 approximately two years at which time the device was
14 eventually removed surgically.

15 Now, I want to talk about the rest of these
16 safety events, the major bleeding, the stroke events,
17 and the pericardial effusions in the upcoming slides.
18 I'm also going to talk about device thrombus and all-
19 cause mortality. These were not primary safety
20 events as defined by the study. I think all of us
21 are interested in knowing about device thrombus since
22 this is a cardiovascular device and device thrombus
23 certainly can occur and, of course, we'll talk about
24 all-cause mortality.

25 So if we look at the major bleeding events,

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1 in the control group, there were seven, which
2 translates to 2.9 percent. In the WATCHMAN group,
3 there were 15, remember twice as many patients. That
4 translates to 3.2 percent. Four of those bleeding
5 events were related directly to the procedure, five
6 of those occurred while the patients were still
7 taking warfarin, that is, prior to discontinuation of
8 warfarin, and the remaining occurred while the
9 patients were taking double platelet agents, aspirin
10 and Plavix.

11 Please note that this is a continuous risk
12 that was observed throughout follow-up and there were
13 similar rates in both groups.

14 What about the stroke events? Well,
15 Dr. Holmes already spoke to the hemorrhagic strokes.
16 Remember in the control group, there were six events,
17 four of which resulted in death, the other two in
18 long-term disability. In the WATCHMAN group, there
19 was one event that occurred prior to discontinuation
20 of warfarin.

21 But I also want to talk about the ischemic
22 strokes. Again, as defined by this protocol,
23 procedural-related ischemic strokes were counted also
24 in the safety endpoint, and there were a total of
25 five such events. Three of them were clearly related

1 to air embolism. The other two, although we can't
2 prove this, were likely related to sheath-related
3 thrombus. Now, this is a 12 French sheath. It has
4 at least 10 to 15 ccs of dead space. So it's really
5 important to continuously flush the sheath and
6 evacuate any potential air thrombus that's in this,
7 and I'm going to speak a little bit more to that.

8 What is the functional consequences of
9 these strokes? Well, the extended hospitalization by
10 the mean is seven days, and as I'm going to show you
11 in the next slide, two patients have died.

12 Here are the five patients with the
13 strokes. The first three patients ultimately there
14 was not deficit or minimal permanent deficit, but
15 these last two patients did have significant deficit,
16 and both patients did become nursing home bound.

17 The first patient eventually died about
18 eight to nine months later, the second patient about
19 two months later. And I should note that both of
20 these patients, the Clinical Events Committee
21 independently adjudicated these events as not having
22 been related to the device or the procedure.

23 Having said that, please note that both of
24 these events, regardless of what you believe what the
25 causality of the mortality to the device, both of

1 these patients are captured in both the efficacy
2 endpoint and the safety endpoint, the efficacy
3 endpoint because these patients had strokes. So they
4 are actually captured in that particular endpoint.

5 It's also important to note that both of
6 these patients are captured, both of these
7 mortalities is captured in the all-cause mortality
8 endpoint which I'm going to show you in just a few
9 slides.

10 Okay. Pericardial effusions. This is
11 certainly important. This represented the largest
12 fraction of safety events in this particular study.
13 There were a total of 32 effusions that were
14 considered greater than what was seen at baseline.
15 Of these, 10 had no -- significance. It didn't
16 require treatment. So I'm going to focus on these 22
17 effusions that actually were serious, resulting --
18 and required drainage.

19 Of these 22 effusions, 15 were drained
20 percutaneously. This extended the hospital by an
21 average of 6 days, and you see the range of
22 hospitalizations, 0 to 17. The remaining seven
23 patients required surgical intervention, and that
24 extended the hospitalization an average of, I think
25 these numbers are transposed, but I think this is 6

1 days, and you see the range here of 4 to 26. Of
2 importance, all these pericardial effusions resolved,
3 that is they did not reaccumulate after treatment,
4 and none of them resulted in death or permanent
5 disability.

6 What's the cause of these pericardial
7 effusions? Well, when we did a root cause analysis,
8 in seven of these, there was no definitive cause. In
9 the remaining, I think what's important is only two
10 of them were related to transseptal puncture itself,
11 the remaining to various other aspects of the device,
12 using a device to gain access to the left atrial
13 appendage, manipulating the delivery system,
14 protruding the delivery system from the access
15 sheath, or doing the actual deployment process
16 itself.

17 Now, I also want to talk about the device
18 thrombus. Again, remember, this was not a primary
19 safety endpoint. There were a total of 12 patients
20 who had device thrombus in the randomized phase of
21 this study, as adjudicated by the Clinical Events
22 Committee. Eleven of these twelve were treated with
23 warfarin readministration. All of these patients,
24 eventually the device thrombus resolved. And I
25 should note, one of these 12 patients did experience

1 an ischemic strike, and presumably that was related
2 to the device thrombus, and this was, of course,
3 captured in both the efficacy and the safety
4 endpoint.

5 Now, this is the all-cause mortality data,
6 and I just want to again note, this is the first time
7 we're showing all-cause mortality data. And what you
8 see here even at the 600 patient-year time point, the
9 relative risk is .69, and you'll see the confidence
10 interval, the upper bound of 1.66, with a
11 noninferiority of 99.1 percent. At the 900 patient-
12 year, again the relative risk is .61. That means
13 that at least numerically, 39 percent lower relative
14 risk in the WATCHMAN group compared to the warfarin
15 group, and you see the upper confidence bound.
16 Again, the noninferiority is 99.9 percent of
17 noninferiority.

18 If you look at these various deaths, this
19 table, the first two rows represent cardiovascular
20 unexplained death. These are the two rows that were
21 already captured in the efficacy endpoint. The third
22 row are stroke complications that ultimately resulted
23 in death. Now, these events were captured in the
24 efficacy endpoint but as stroke as opposed to death.
25 And the last two, you see the cancer deaths and

1 deaths for other reasons. Again, the all-cause
2 mortality, 3.7 percent of WATCHMAN versus 6.1 percent
3 of the control group.

4 So if we look at a synopsis of these safety
5 events, please note that the majority of these safety
6 events in the WATCHMAN group were periprocedural,
7 which we believe is important because they typically
8 then occur under the direct physician's care. And
9 indeed, pericardial effusions, which did comprise a
10 large proportion of these safety events, did not
11 cause death or long-term disability.

12 Now, I also want to speak to one of the
13 prespecified analyses that was performed in this
14 study, and this was to look at the safety event rate
15 after the date of the procedure. So if you take out
16 all those events that occurred on the day of the
17 procedure, and what you see is a 3.9 percent event
18 rate versus a 4.2 percent of the control group, the
19 relative risk of close to 1.

20 Now, why am I showing this data? Well,
21 certainly we have to assess this data on intent-to-
22 treat. There's no doubt. But as a clinician who is
23 going to be implanting these devices, I want to be
24 able to tell my patients or I want to be able to know
25 for myself what do I expect from my safety event rate

1 once I get past my learning curve? That is, once I'm
2 technically proficient, what can I expect? And I
3 think this is reasonable data that speaks to that.

4 Now, what's the reality? I mean can we
5 actually achieve technical improvement in our ability
6 to place this device? Well, there were certainly
7 improvements made over the course of this study, and
8 I just summarize them here. Investigators certainly
9 shared knowledge, and these included conferences and
10 meetings. There were training improvements,
11 particularly the roll-in phase of the new centers.
12 There were procedural improvements, including
13 anticoagulant change such as standardizing heparin
14 dosing, another SAFE program which is a procedural
15 improvement, and technical improvements in the sheath
16 as well as a short implant than the initial implant
17 to accommodate more anatomical variations.

18 And we can assess how this actually had an
19 impact, and here are the two different types of
20 assessments: the site-level learning that is for any
21 individual center or investigator, how did they
22 improve? So we compared the early patients, that is
23 the first three device implants they placed versus
24 all subsequent implants, as well as trial-level
25 learning, that is, if you look at the first third of

1 the patients that were on the study compared to the
2 second third and compared to the third third, and
3 here's the data.

4 If you look at the early versus late
5 patients, what you see, and again this is on a per
6 center basis, what you see is improvements in
7 procedure time, improvements in the success of
8 implantation, and importantly on the safety side, you
9 see an improvement in the overall safety event rate
10 from 8 percent to 5 percent as well as in the serious
11 pericardial effusion rate within seven days from 6
12 percent down to 4 percent.

13 Now, before I talk about the trial-level
14 learning, I just want to point out the CAP registry
15 which was introduced earlier. Please remember this
16 is a nonrandomized registry, a nonrandomized registry
17 that commenced at the end of the PROTECT AF
18 randomized registry. This has the same assessment
19 intervals and follow-up schedule. This included 16
20 PROTECT AF sites, and I'm going to show data that
21 included 88 patients, though as you've heard earlier,
22 there are now a total of 120 patients that have been
23 enrolled in this particular registry.

24 So let's look at this data.

25 DR. MAISEL: Dr. Reddy, just a 10-minute

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1 warning. You have 10 minutes left, okay.

2 DR. REDDY: Okay. So let's just look at
3 this data. What you see here on these different
4 bars, the first, second, and third represent the
5 different tertiles, and the last represents the CAP
6 registry. Look at the procedure time, going from
7 initially 70 now in the CAP registry to under an hour
8 at 48 minutes. Implant success, initially 86
9 percent, now up to 95 percent of procedural success.

10 On the safety side, I think this is pretty
11 striking. We went from 9 to 4, 4, and finally down
12 to 1 percent. In actuality, now that we're 120
13 patients, it's less than one percent. And serious
14 pericardial effusion, less than 1 percent of the CAP
15 registry. And even in the randomized study,
16 significant improvements.

17 I'm also showing this. This is procedure-
18 related strokes. So those air embolism, clot
19 embolism, whatever that are associated with the
20 procedure, and notice again the tertiles, the event
21 rate, and finally the CAP registry with over 100
22 patients implanted, there's not been a single air or
23 clot embolism. I think this is very important
24 because certainly it's important to the safety event
25 endpoint, but this also speaks to what our potential

1 efficacy endpoint, because remember these strokes
2 were also counted in the efficacy endpoint.

3 Very quickly, let me just look at the
4 improvement in warfarin discontinuation at 45 days.
5 In the early, it was 80 percent and now 98 percent,
6 at least in the CAP registry, 98 percent of the
7 patients were able to successfully discontinue
8 warfarin.

9 So let me conclude with this section. The
10 warfarin patients experienced twice as many events,
11 primarily periprocedural events in the control group.
12 And please remember when you assess this that there
13 were a total of 59 implanting sites with more
14 investigators since there was more than one
15 investigator per site, and with increased experience,
16 there were positive trends in the safety, both in
17 terms of overall safety events as well as serious
18 pericardial effusions, from 7 percent down to less
19 than 1 percent.

20 What's the clinical impact of this? There
21 was no death or disability of the pericardial
22 effusions, the largest component of the safety event,
23 and importantly, all-cause mortality was numerically
24 39 percent lower than the WATCHMAN group.

25 So when we look at this quadrangle, in this

1 risk, we have a short-term safety signal that we have
2 to acknowledge and deal with, 7.3 percent rate.
3 Importantly, the rates have decreased, and it's
4 particularly encouraging what we see in the CAP
5 registry, and overall one could argue that these are
6 less serious outcomes. Pericardial effusion can be
7 dealt with. A stroke is much more difficult to deal
8 with.

9 Just a few points in terms of post-approval
10 plans. There is a plan to actually have a training
11 program, including pre-study, case review, case
12 observation at sites that are already implanting the
13 device. There's a formal training simulation as well
14 as case coverage during the initial implants.

15 There's a plan for two post-approval
16 studies. One is an acute study which will involve a
17 total of 300 subjects and up to 40 centers of which
18 10 of those centers will be centers who have never
19 implanted a device.

20 And the goal of this study is to understand
21 what the safety event rate is based on all the
22 improvements that have been made.

23 And, finally, there's a long-term study
24 that's planned to continue follow-up on those 485
25 subjects who are currently enrolled in the randomized

1 phase, the device phase of the PROTECT AF study.

2 Thank you very much, and I'll turn the mic
3 over to Dr. Holmes who will conclude.

4 DR. HOLMES: You are tired. The time's
5 about to go off and the hook comes, and so I'm going
6 to move right along here.

7 We need to think about the issues in terms
8 of patients and families and society. Those are
9 really the three important issues to deal with.

10 The first thing we can say is that long-
11 term warfarin for treatment of patients with atrial
12 fibrillation has been found effective. We all know
13 that. There are considerable risks and difficulties
14 maintaining patients in therapeutic range, the
15 trouble with hemorrhage and hemorrhagic stroke, a
16 huge problem.

17 The second is that the PROTECT AF trial
18 evaluated the WATCHMAN device, a device, a single
19 study, prospective, large, randomized study of about
20 800 patients to evaluate a device approach with early
21 warfarin versus a Coumadin approach. We can say from
22 the patient and their family standpoint, how often
23 can you get off of warfarin. We can say in this
24 study, 86 percent of the WATCHMAN patients
25 successfully implanted were able to discontinue

1 warfarin, and they did not pay a price for that.
2 There was no uptick in events. That's the first
3 important piece of information; you can get off of
4 warfarin, and most patients are wild about that, and
5 their families even more wild.

6 The second piece of information from the
7 patient and family standpoint is to say that we have
8 seen that there are some safety issues. The safety
9 issues are much better. Any invasive procedure has
10 potential complications, but Dr. Reddy has talked
11 about the training experience and the evolution of
12 our experience and the CAP registry which documents
13 the procedural safety rates are down to 1 percent and
14 serious pericardial effusion rates are down to 1
15 percent but that all-cause mortality is still 39
16 percent lower with the WATCHMAN group. From the
17 patients' and their families' standpoint, that's a
18 terribly important finding.

19 Finally, we could say that from the
20 standpoint of society as well as patients and their
21 families, the efficacy events are 32 percent fewer in
22 the WATCHMAN group. This trial met noninferiority.
23 It is noninferior to warfarin. Irrespective, it is
24 noninferior. There is not an uptick in events after
25 we stop warfarin. This is as good as warfarin.

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1 Strokes are 22 percent fewer in the WATCHMAN group.
2 There are some periprocedural events, that is true.
3 We can decrease those. That is true after day 0, the
4 WATCHMAN ischemic stroke rate is a little bit less
5 than in the control group. The risk of death is
6 markedly increased with hemorrhagic strokes and
7 statistically significant. There are fewer
8 hemorrhagic strokes in the WATCHMAN group.

9 Finally, from the societal standpoint, if
10 we were to look at the data, if we were to project
11 out, what does this mean for society as a whole,
12 potentially there are 26,000 strokes which could be
13 prevented per year with the WATCHMAN device, 26,000
14 strokes, leading us to this final conclusion from our
15 standpoint, from the Sponsor's standpoint.

16 The PROTECT AF data with this specific
17 device provides reasonable assurance of the safety
18 and the effectiveness of the WATCHMAN Left Atrial
19 Appendage Closure Technology, which is intended and
20 was intended to begin with in this trial, and is now
21 still intended, as an alternative to warfarin therapy
22 for patients with nonvalvular atrial fibrillation.

23 Thank you.

24 DR. MAISEL: Thank you very much for a very
25 thorough and provocative presentation. We're going

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1 to open up to the Panel for questions, and I'll
2 remind the Panel, our main deliberations will happen
3 after the FDA presentation and after lunch when we've
4 been presented all the data. I'd like you to limit
5 your questions now to just burning issues that you
6 want to address the Sponsor with. Dr. Kelly.

7 DR. KELLY: I think my biggest question is
8 the, and I think Dr. Holmes can speak to this, the
9 risk of hemorrhagic stroke in the control group which
10 is considerably higher than that in other trials.
11 You mentioned the ACTIVE-W trial and in the Coumadin
12 patients there, the risk of hemorrhagic stroke was
13 less than .1. I'm just wondering if you have any
14 insight as to why the hemorrhagic stroke risk is so
15 high in this control group?

16 DR. HOLMES: Sure. That's a great
17 question. I guess there are several different pieces
18 of information that can be brought to bear upon that.
19 The first, the majority of these patients had had
20 something about them that the clinicians taking care
21 of them thought that they were clearly at increased
22 risk for stroke because they came out of prothrombin
23 clinics.

24 DR. KELLY: Although their CHADS score was
25 almost identical at ACTIVE-A and ACTIVE-W.

1 DR. HOLMES: I agree entirely with that.
2 There was something about these people that they had
3 been on Coumadin for two years, in patients. At
4 least in our practices, when we think that they are
5 super low risk, they may be given aspirin. There was
6 something about these patients that made the
7 clinician be concerned about that, and I think that's
8 an unmeasurable variable that is true, but I think
9 this is part of the judgment taking part of the
10 practice that these patients were felt to be at risk,
11 and I think that's the reason for that.

12 DR. MAISEL: Dr. Somberg and then Dr. Good.

13 DR. SOMBERG: Once again, Dr. Holmes, don't
14 leave the microphone because you're the one who
15 discussed this slide 64 please and, you know, the
16 ones leading up to it. From my understanding, I just
17 want to make sure that per-protocol analysis includes
18 those patients that received the device but did not
19 stay on Coumadin or did not have Coumadin added once
20 they came off the Coumadin. Is it both or is it just
21 the former?

22 DR. HOLMES: Seven percent of the patients
23 had Coumadin added back on in the warfarin group. We
24 have seen that on the previous slide. The per-
25 protocol are patients who did not have.

1 DR. SOMBERG: So these patients are not on
2 Coumadin after the 45 days --

3 DR. HOLMES: Correct.

4 DR. SOMBERG: -- and they're compared to
5 the control group.

6 DR. HOLMES: Correct.

7 DR. SOMBERG: So that's about 22 or
8 whatever the number. It's the 13 percent that
9 continue plus the 8 percent who had to have it
10 reinitiated.

11 DR. HOLMES: Correct.

12 DR. SOMBERG: Okay. Thank you.

13 DR. MAISEL: Dr. Good.

14 DR. GOOD: One follow-up comment about the
15 hemorrhagic strokes in the control group. I know
16 that all of the events were adjudicated, but the
17 third one actually is trauma. It isn't really a
18 hemorrhagic stroke. The patient had a skull
19 fracture, and certainly that would be a safety event,
20 but I don't know that it should be classified as a
21 hemorrhagic stroke, and I noticed a couple of others
22 are subdural hematomas and that's how you want to
23 classify those, but certainly one was trauma I would
24 say. Just a comment.

25 DR. MAISEL: Dr. Abrams.

1 DR. ABRAMS: I'd just like to follow-up on
2 that because I think there would be a lot of question
3 where five out of these six hemorrhagic strokes are
4 actually considered "strokes." I think you could
5 argue that these are serious events but only one of
6 them actually looks like a stroke. The other ones
7 may very well be related to trauma or either overt
8 trauma, invert trauma, but certainly not the kind of
9 stroke that one would expect in association with
10 atrial fibrillation.

11 So these seem to me like they are adverse
12 events, but I'm not quite sure how they were decided
13 to be counted as hemorrhagic strokes.

14 DR. MAISEL: And if I may generalize the
15 question because it relates to a question I had, were
16 there predefined definitions that were written
17 regarding each of these events that the Clinical
18 Events Committee was defining, and if so, to my
19 knowledge, the Panel has not been provided with any
20 of those definitions. So if you have them, it would
21 be useful if after a break or after lunch you can get
22 those to us. You can answer Dr. Abrams question.

23 MR. LEW: Brian Lew. I was the head of the
24 CEC for this committee. I'm a private practicing
25 cardiologist in Minneapolis. I have no financial

1 interest with the company. They have compensated me
2 for my time and travel.

3 We looked at all the source documents as
4 best we can, and all these documents, if you've been
5 involved with these studies, some of them are good,
6 some of them are bad. We try to adjudicate the
7 events, and for the traumatic strokes, that's one of
8 the risks that you have with Coumadin, and you can
9 argue about it, and I accept that, but my other
10 members of the committee adjudicated and tried to be
11 very consistent in the way we adjudicated these
12 events.

13 DR. MAISEL: Thank you. Tom.

14 DR. VASSILIADES: I have --

15 DR. REDDY: Can I just add to that previous
16 statement? Just two other points. I think
17 reasonable people can argue about how these should be
18 adjudicated, but I just want to point out two things.

19 First, those cranial bleeding events would
20 be considered safety events regardless of what
21 happened. The second, regardless of the causality,
22 et cetera, the pathophysiology, I think it should be
23 noted they obviously result in significant either
24 disability or, in several of those cases, death. I
25 just want to point that out.

1 DR. MAISEL: Tom.

2 DR. VASSILIADES: I have four fairly brief
3 questions. One is can you tell us a little bit more
4 about the seven patients who had surgical
5 interventions for serious effusions? Number two,
6 when a thrombus was discovered at TEE, where was it
7 typically located relative to the device? Question
8 three, when the device was inserted and flow was
9 still seen around the device, how is that typically
10 handled? Were you able to retrieve it and put a
11 larger device in, or how does that usually work? And
12 then the last question is, what were the technical
13 requirements of the investigators? Were those
14 investigators selected based on their ability to
15 perform a septal puncture approach ahead of time, or
16 did you also have investigators that had to learn
17 that in addition to inserting the device?

18 DR. REDDY: Okay. I'm glad I wrote these
19 down. So the first one was pericardial effusions,
20 surgical interventions. Three of those seven
21 patients -- I take that back. Four of those seven
22 patients had a percutaneous attempt first and
23 presumably failed and then underwent the surgery.
24 The other patients went straight to surgery. I
25 should note --

1 DR. VASSILIADES: Surgery meaning what?
2 Sternotomy or --

3 DR. REDDY: Surgical pericardial window.
4 If you're asking how many of those underwent full
5 sternotomy versus pericardial window, I'll have to --
6 we have that data. I can come back to you with that.

7 DR. VASSILIADES: Okay.

8 DR. REDDY: I can just say anecdotally that
9 I'm of the feeling that most of these cases can be
10 dealt with percutaneously. I mean our experience is
11 that oftentimes the bleeding continues, but you just
12 keep drawing back, and eventually after you reverse
13 the heparin, it eventually stops. But anyway, that's
14 anecdotal.

15 The second question was -- I can't read my
16 writing.

17 DR. VASSILIADES: Thrombus.

18 DR. REDDY: Oh, the thrombus, right. So
19 the majority of the time, in fact, all of the time
20 except for one case, the thrombus was associated with
21 the face of the device itself typical to what one may
22 see with atrial septal defect closure devices, et
23 cetera. So it was seen on the face of the device
24 itself.

25 The third was about flow. It's a great

1 question. When we implant the device, we start off
2 with what we guess is the right size of the device.
3 Remember, it was presented earlier that there's six
4 different sizes. Sometimes we guess wrong, in which
5 case we can take the device and take it back into the
6 sheath. So until we actually decide that we have a
7 good occlusion of the left atrial appendage, we do
8 not have to release a device. The only time that
9 we're past the point of no return is after we made
10 all our assessments and then we unscrew it and then
11 it's fully released.

12 Then your last question was the tech
13 requirements of the investigators. I think this is a
14 really important point. Remember again, there are 59
15 centers, more than that many number of investigators.
16 The only real requirement was that there were
17 interventional cardiologists or electrophysiologists
18 who knew how to do a transseptal puncture. I think
19 that's important. When you assess this, remember,
20 there is no predicate procedure for this device.
21 This is not an ablation study where we've already
22 been doing ablations or stent trial or whatever. We
23 don't really go into the appendage normally. So I
24 think when you consider that, I think it's reasonable
25 to consider that given that only requirement of

1 having been able to do a transseptal puncture and
2 given no other predicate experience for this kind of
3 a procedure, I think it's important to recognize the
4 safety event rate did come down in the study itself.

5 DR. MAISEL: Thank you. Dr. Domanski.

6 DR. DOMANSKI: Yeah, I want to focus the
7 attention of the Committee anyway, on the notion --
8 on this business of hemorrhagic stroke versus not.
9 Hemorrhagic stroke, not, you know, general safety
10 endpoint is actually part of the endpoint of this
11 trial. I want to underscore Dr. Abrams' comment
12 because if you take the position that the hemorrhagic
13 strokes are not well adjudicated or not appropriately
14 adjudicated, then all of the arithmetic in this trial
15 result changes substantially. So as we go through
16 the day, I would like us to focus on whether or not
17 we believe that because if we don't believe that, we
18 don't believe their numbers on the endpoint.

19 DR. MAISEL: JoAnn.

20 DR. LINDENFELD: I know there are data for
21 TEEs at six months and one year. We haven't seen
22 those, and I don't need them now, but I'd like to see
23 data on those later. And then also why the seven
24 percent of patients were restarted on warfarin, and
25 when you show us the TEE data at six months and a

1 year, I'd like to know how many of the total number
2 of patients in the study actually had those
3 completed.

4 DR. MAISEL: Dr. Kelsey.

5 DR. KELSEY: I have some questions on the
6 Bayesian analysis, but let me save those until after
7 the FDA presentation. The reason that we're always a
8 little cautious about the per-protocol analysis is
9 because the people who don't follow the protocol are
10 not like the ones who do and because you're no longer
11 protected by randomization.

12 I wonder how the patients who did follow
13 the protocol may differ from the ones who didn't, and
14 in particular, are those -- how about the timing of
15 the study? Were the protocol patients more likely to
16 be towards the end of the recruitment period?

17 DR. MAISEL: If you'd prefer to address
18 that after --

19 UNIDENTIFIED SPEAKER: We can address that,
20 we can get --

21 DR. MAISEL: Okay. Yeah. We'll get that
22 later. I have a question regarding the device
23 itself, and I'm wondering if you could provide us a
24 little bit of an overview of the device iterations
25 that occur during the trial, the reasons for those

1 device iterations, and clarify exactly what device is
2 on the table that we're being asked to approve
3 because there was some mention in the FDA review that
4 parts of the device, such as the delivery system, had
5 not actually been used in humans. So please clarify
6 that.

7 DR. REDDY: Sure. The device itself,
8 remember that there are two devices. There's what
9 we'll call the regular device, which has the same
10 width and length, and then there's a short device
11 which is 20 percent shorter for every size than the
12 width. Those two devices were used almost
13 equivalently over the course of the study, so meaning
14 that approximately 50 percent of the device of the
15 patients received the short device and approximately
16 50 percent received the larger device in the study
17 itself. And, by the way, there was no difference in
18 the efficacy of the safety endpoints with either of
19 those devices.

20 There were earlier generations of the
21 device that were in the feasibility study, which we
22 have not spoken to at all up to this point, that were
23 not evaluated in this particular study.

24 There was certainly fine element testing
25 and bench testing on both of these devices that were

1 used in the study, including stress and multiple
2 cycles of compression, et cetera. There was in the
3 short device, in the first couple of devices, there
4 was a fracture that was noted on one of the barbs,
5 and this is in the very initial experience with the
6 short device. After that, there was a modification
7 made in the angle of the barbs of the short device.
8 So the majority of the patients that have received a
9 short device in this particular study, as well as in
10 the follow-up CAP registry, have received this second
11 generation short device. There have been no barb
12 fractures either in the animal testing or in the
13 clinical experience with this short device with
14 modification.

15 In terms of the delivery sheath, the
16 delivery sheath that you're referring to I believe is
17 a delivery -- there's a minor modification made in
18 the delivery sheath compared to the sheath that was
19 used in the study. The modification was a change in
20 the caliber of the sheath itself to make it a little
21 bit more narrow along the proximal segment of the
22 sheath, the middle and proximal segment. The reason
23 for that was to decrease the amount of dead space in
24 the sheath. But you are correct in stating that that
25 particular delivery sheath has not been used in any

1 of the patients in this particular study.

2 DR. MAISEL: Okay. Thanks for that
3 clarification. At this point, we're going to take a
4 15-minute break. We will return to hear the FDA
5 presentation.

6 (Off the record.)

7 (On the record.)

8 DR. MAISEL: Welcome back. At this point,
9 I'd like to invite the FDA to give their
10 presentation.

11 DR. BUCKLEY: Good morning. Thank you for
12 coming today. I'm Donna Buckley. I'm the lead
13 reviewer and engineer for the Atritech PMA.

14 Numerous FDA physicians and scientists
15 participated in the review of this application, a few
16 of whom will be part of FDA's presentation this
17 morning.

18 First, I'd like to provide some brief
19 introductory remarks, then a summary of the
20 preclinical data. I'll then introduce the clinical
21 trial design. Then I'll be followed by Dr. Sherry
22 Yan, a statistician from the Office of Surveillance
23 and Biometrics. Dr. Yan will be followed by
24 Dr. Julie Swain, cardiovascular surgeon and
25 consultant to FDA's Division of Cardiovascular

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1 Devices, who will provide the clinical summary.
2 She'll be followed by Ms. Ellen Pinnow from the
3 Office of Surveillance and Biometrics, Epidemiology
4 group, who will provide a summary of the post-market
5 approval study. I'll then conclude with some
6 questions that we'll ask you to address this
7 afternoon in your discussions.

8 Okay. So first the introduction and
9 preclinical summary.

10 As you know, Atritech has provided a PMA to
11 FDA to request marketing approval for the WATCHMAN
12 device, and the intended patient population are those
13 patients with paroxysmal persistent or permanent
14 nonvalvular atrial fibrillation, and the problem with
15 these patients is that they have an estimated 3 to 5
16 percent per year stroke risk, due in part or in full
17 to presumed thromboembolism from the left atrial
18 appendage. Currently these patients are maintained
19 on medical therapy.

20 A risk stratification scheme is often used
21 to guide treatment. One such scheme is the CHADS₂
22 Score, which was used in the PROTECT AF trial, and
23 the mainstay of therapy is usually warfarin. As an
24 alternative, the WATCHMAN device is a permanent
25 cardiac implant placed in the left atrial appendage

1 to trap thrombi from embolizing that may form there.

2 The requested indications for use of the
3 WATCHMAN device are that it is intended as an
4 alternative to warfarin therapy for patients with
5 nonvalvular atrial fibrillation, and it's designed to
6 prevent embolization of thrombi that may form in the
7 left atrial appendage, thereby preventing the
8 occurrence of ischemic stroke and systemic
9 thromboembolism.

10 There are no similar devices on the U.S.
11 market with the same indication or functions. So
12 this is considered a first of a kind PMA. The PMA
13 was originally submitted to FDA in August 2008 based
14 on a planned interim analysis at 600 patient-years.

15 FDA did grant the application expedited
16 review status, given that it was intended to treat a
17 life-threatening disease and had the potential to
18 offer breakthrough technology. FDA issued a major
19 deficiency letter to the Sponsor in November 2008,
20 and the Sponsor responded to the clinical and
21 statistical issues in that letter in January 2009.

22 Evaluation of the response to the
23 preclinical issues is pending as Mr. Bullock had
24 mentioned. The Sponsor just submitted a response to
25 FDA two days ago to those issues. So we have not

1 reviewed that yet.

2 In the interim, since the original
3 submission in August 2008, the Sponsor did update
4 their clinical report to include 900 patient-year
5 data and submitted that approximately seven weeks ago
6 in early March, and that's just the primary dataset
7 in FDA's discussion this morning.

8 As the Sponsor included in their
9 presentation, the WATCHMAN system is comprised of the
10 permanent implant component referred to as the
11 WATCHMAN device, and also includes the delivery
12 system access sheath and optional obturator.

13 The WATCHMAN device is available in five
14 device sizes, corresponding to the diameter of the
15 device, and specified echocardiographic and
16 fluoroscopic criteria are used to guide device
17 selection. The majority of devices used in the
18 PROTECT AF trial were the three smaller device sizes.

19 The WATCHMAN implant component proposed for
20 marketing was studied in the PROTECT AF trial.
21 However, there were some modifications made to the
22 device during the course of the clinical trial. As
23 Dr. Reddy mentioned, the short implant was
24 introduced. Shortly after the introduction of the
25 short implant, however, there were two devices noted

1 to have fractured barbs. So the short implant was
2 redesigned and reintroduced into trial, and the final
3 device version was used in over 50 percent of the
4 patients in the PROTECT AF trial.

5 The delivery system, access system, and
6 obturator proposed for marketing were not the version
7 studied in the PROTECT AF trial. There were some
8 modifications where FDA questioned the clinical
9 impact of these changes on the performance of the
10 device, and an evaluation of the response is pending
11 as we received the submission a couple of days ago.

12 So the outstanding preclinical issues
13 relate to the different device generations, which
14 device sizes were chosen for testing. There was a
15 case of entanglement during deployment, and there
16 were also some questions and clarifications regarding
17 the MR testing, particulate testing, and
18 biocompatibility and sterility testing.

19 With regard to the mechanical performance
20 of the device during the PROTECT AF trial, the
21 majority of devices were placed successfully, 58
22 percent, on the initial attempt. However, there were
23 42 percent of placement attempts that required at
24 least one recapture with 4 percent of the cases
25 requiring over 4 recaptures before adequate

1 positioning.

2 Of note is the incidence of recaptures
3 isn't reflected in the 91 percent implant procedure
4 success rate. However, there was demonstrated trial-
5 level and site-level learning with regard to device
6 recaptures. In particular, the average device
7 recaptures in the first half of the study decreased
8 in the second half of the study, and the average
9 number of recaptures decreased with increased number
10 of implants at each site where specifically there was
11 a lower recapture rate when the site had experienced
12 with 4 or more cases compared to those sites who had
13 experienced with 3 or less cases.

14 There were 24 device malfunctions in 23
15 patients. Most of these included difficulty
16 positioning the sheath, advancement of the device
17 through the sheath, or device release. There were
18 other problems with the valve kink, dilator
19 malfunction, and a few other minor device
20 malfunctions, and again, there were those couple barb
21 fractures with the original short implant, and after
22 redesign, there were no known future events.

23 So, in conclusion, no malfunctions reported
24 are known to be directly related to any clinical
25 adverse events.