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

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November 20, 2008
8:00 a.m.

Holiday Inn
Gaithersburg, Maryland

PANEL MEMBERS:

JEFFERY BORER, M.D.	Chairperson
VALLUVAN JEEVANANDAM, M.D.	Voting Member
DAVID NAFTEL, Ph.D.	Voting Member
JUDAH WEINBERGER, M.D.	Voting Member
SETH BILAZARIAN, M.D.	Consultant
PAMELA E. KARASIK, M.D.	Consultant
PATRICIA KELLEY, M.D.	Consultant
DAVID SLOTWINER, M.D.	Consultant
JOHN C. SOMBERG, 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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HUGH CALKINS, M.D.

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M E E T I N G

(8:02 a.m.)

DR. BORER: I would like to call the Circulatory System Devices Panel to order.

I am Dr. Jeffery Borer, the Chairperson of the Panel. I am the Professor-in-Chief of the Division of Cardiovascular Medicine at State University of New York, Downstate Medical Center, and Director of the Cardiovascular Translational Research Institute as well at that Institution.

If you haven't already done so, please sign the attendance sheets that are on the tables next to the doors. If you want to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table.

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

For the record, note that the voting members present constitute a quorum as required by 21 C.F.R., Part 14. I'd also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

No one from the public or press is allowed

into the Panel area at any time during the breaks or during the conduct of this meeting.

In addition, please remember to put your cell phones on vibrate or silent or something because it would be good if they don't go off during the meeting.

Mr. Swink, the Executive Secretary for the Circulatory System Devices Panel will make some introductory remarks. Mr. Swink.

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

The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section

712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for that particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting,

expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of a premarket approval application sponsored by Biosense Webster, a Johnson & Johnson Company, for the NaviStar ThermoCool irrigated RF ablation catheter. This device, an open lumen, irrigated tip, steerable radiofrequency cardiac ablation catheter, is inserted through the venous circulation to the heart, across the intra-atrial septum to the left atrium to ablate cardiac tissue for the purposes of creating lines of block in the atria to eliminate conduction patterns that theoretically generate or allow propagation of electrical waves responsible for paroxysmal atrial fibrillation. This is a particular matters meeting during which specific matters related to this PMA will be discussed.

Based on the agenda for today's meeting and all financial interest reports by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during this meeting and will be

included as part of the official transcript.

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

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

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

Thank you.

I will now read the appointment of temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting on November 20, 2008.

Drs. Valluvan Jeevanandam, Patricia Kelley,

Seth Bilazarian, David Slotwiner, Pamela Karasik, John Somberg.

In addition, I appoint Jeffery S. Borer, M.D., to act as temporary Chair for the duration of this meeting.

For the record, these individuals are special Government employee who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This was signed by Daniel G. Schultz, M.D., Director for the Center of Devices and Radiological Health and dated November 14, 2008.

Before I turn the meeting back over to Dr. Borer, I have a few general announcements.

Transcripts of today's meeting will be available from Free State Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Presenters to the Panel who have already done so should provide FDA with a hard copy of their remarks, including overheads.

I would like to remind everyone that members of the public and the press are not permitted

around the Panel area, beyond the speaker's podium.

The press contact for today's meeting is Siobhan DeLancey and Scott McFarland.

I request that reporters wait to speak with FDA officials until after the Panel meeting.

Thank you.

DR. BORER: Good morning, everyone. At this meeting, the Panel will develop recommendations to the FDA, to the Food and Drug Administration, on the Premarket Approval Application, the PMA, P030031, Biosense Webster NaviStar ThermoCool irrigated radiofrequency, RF, ablation catheter.

Before we begin, however, I would like to ask our Panel members who are generously giving their time today, and other FDA staff seated at this table, to introduce themselves. As you do so, please state your name, your area of expertise, your position and your affiliation. Why don't we start with Mr. Halpin.

MR. HALPIN: Good morning. My name is Michael Halpin. I am the Industry Representative for today's Panel meeting. I'm the Vice President of Regulatory Affairs at Genzyme Corporation. Thank you.

DR. FLEMING: Good mooring. I'm Dr. Mike

Fleming. I'm the Consumer Representative on the Panel. My area of expertise is dental materials science.

DR. JEEVANANDAM: Good morning. My name is Valluvan Jeevanandam. I'm the Chief of Cardiac and Thoracic Surgery at the University of Chicago.

DR. KARASIK: I'm Pamela Karasik. I'm the Assistant Chief of Cardiology at the VA here in Washington, D.C., and I'm the Director of Clinical EP.

DR. SOMBERG: Good morning. I'm John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago, Illinois.

DR. NAFTEL: Good morning. I'm David Naftel. I'm a Professor of Surgery and Professor of Biostatistics at the University of Alabama at Birmingham, and my area of expertise is biostatistics.

DR. BORER: I'm Jeff Borer as I mentioned earlier.

DR. WEINBERGER: I'm Judah Weinberger. I'm an Associate Professor of Medicine and Pharmacology and interventional cardiologist at Columbia, New York.

DR. SLOTWINER: I'm David Slotwiner. I'm a

cardiac electrophysiologist practicing at Long Island Jewish Medical Center, Assistant Professor of Medicine, Albert Einstein College of Medicine.

DR. KELLEY: Good morning. Patricia Kelley. I'm a cardiac electrophysiologist at Montana Heart Center in Missoula, Montana.

DR. BILAZARIAN: I'm Seth Bilazarian. I'm a clinical and interventional cardiologist in private practice in Haverhill, Massachusetts.

DR. ZUCKERMAN: Brian Zuckerman, Director, FDA, Division of Cardiovascular Devices.

DR. BORER: Thank you very much.

We'll now proceed with the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and for decision making. To ensure this kind of transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship you may have with the

sponsor, its product, and if known, its direct competitors.

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

Does anyone wish to address the Panel at this time?

(No response.)

DR. BORER: There do not seem to be any. Do we have anybody listed?

MR. SWINK: No.

DR. BORER: Okay. We will then proceed with today's agenda. Please note there will be a second open public session in the afternoon if there are any comments to be made by anyone, any member of the public.

We'll begin with the sponsor presentation for the NaviStar ThermoCool Irrigated Radiofrequency

Ablation Catheter.

I'd like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel. That's true for the Sponsor as well. Once you give your presentation, any further comments really have to be made in the context of a request from the Panel or another specific opportunity in the program.

We'll then begin with the sponsor presentation.

DR. YAROSS: Thank you, Dr. Borer. Good morning. I'm Marcia Yaross, and I'm an employee of Biosense Webster. I thank the Panel and the FDA for the opportunity to present this morning on the clinical evidence in support of the safety and effectiveness of the ThermoCool catheter for radiofrequency ablation of systematic paroxysmal atrial fibrillation.

In this morning's presentation, I will briefly introduce you to the clinical trial with an overview of its history and design.

Dr. Donald Berry will then provide an overview of the Bayesian statistics at the FDA's request and then speak to the statistical rationale

for declaring early success following a planned interim analysis.

Dr. David Wilber, the study's primary investigator, will present the subject demographics and effectiveness results for the trial.

Dr. Waldo, who chaired the study's clinical events committee will present the safety data for this trial. I'll then conclude our presentation.

Atrial fibrillation is an important public health issue. AF represents the most prevalent arrhythmia encountered in clinical practice. Recent Miyasaka data estimate that between 2.3 and 5 million U.S. adults have atrial fibrillation. AF is a debilitating disease, particularly the symptomatic paroxysmal form.

Patients with atrial fibrillation are at increased risk of stroke, of heart failure, and other significant comorbidities. AF has also been found to be an independent marker of risk of death.

Patients with atrial fibrillation have a significantly reduced quality of life.

While pharmacological therapy is available, it has been proven to be ineffective in many AF patients, estimated up to 50 percent in some series.

Surgical techniques such as the Cox-Maze

procedure can be effective, but they are highly invasive with the associated morbidity and mortality one would expect from an open chest cardiovascular procedure.

In response to this need, radiofrequency catheter ablation has become increasingly important as a tool in the toolkit of electrophysiologists. RF ablation is today a standard of care for simple arrhythmias such as Wolff-Parkinson-White Syndrome, atrial flutters, and AV node reentry and tachycardias.

It's also increasingly being used for more complex arrhythmias. This has been recognized by a number of FDA approved indications for VT procedures.

Catheter ablation is also increasingly used for atrial fibrillation, which is the subject of this morning's discussion.

Catheter ablation was formally recognized in 2006 as a second line therapy for atrial fibrillation in the American College of Cardiology, AHA, ESC practice guidelines, and we'll discuss this some more this morning.

HRS and several European EP societies also affirmed the importance of ablation in treating AF in their expert consensus released in 2007. This

consensus statement identified catheter ablation as indicated for symptomatic AF where it is refractory or intolerant to at least one class I or class III antiarrhythmic drug. The task force also recognized in some rare circumstances ablation may be appropriate as first line therapy. The document also stated that it's appropriate for selected patients with heart failure and/or reduced ejection fraction.

Despite this growth of support of the recognition of the importance of AF, however, no ablation catheter is today approved for treatment of AF in the United States.

The ThermoCool catheters, which are the subject of this morning's discussion, are well established in the practice of electrophysiology. They have been used in nearly 40 countries across the world over the past decade. A quarter of a million catheters have been distributed worldwide since their initial introduction overseas, and about a quarter of that experience has been in the United States since they were first FDA approved for the treatment of atrial flutter in 2004.

A ThermoCool catheter is a steerable, multi-electrode, deflectable electrophysiology catheter with saline irrigation provided through six

ports in the tip. These ports irrigate and cool the catheter tip to maintain low temperature during RF application. This thereby reduces the risk of char or thrombus. There is a temperature sensor for feedback to assure that the irrigation is cooling the tip as intended. However, the catheters are intended for use in power control and not temperature control mode.

The NaviStar version used in this clinical trial also contains a location sensor for visualization with the CARTO electroanatomical mapping system.

ThermoCool catheters are today approved by the FDA for two indications: Type 1 atrial flutter as well as post-MI ventricular tachycardia. Please note that the atrial flutter indication applies to both the location sensor enabled NaviStar models as well as well as the Celsius catheters which lack such sensors. The VT indication is specific to the NaviStar Catheters.

We are now asking FDA to extend these indications to include treatment of symptomatic AF as detailed in your Panel packages.

The clinical study we're presenting to you was a randomized clinical trial. Randomization was 2

to 1 with more subjects randomized to the ThermoCool treatment arm. The population consisted of symptomatic paroxysmal patients refractory to at least one antiarrhythmic drug. The study was multi-centered, and the final protocol included planned interim analyses beginning with 150 subjects.

The primary study goals were to demonstrate superior chronic effectiveness of the ThermoCool catheter versus antiarrhythmic drug treatment in the prevention of symptomatic AF recurrence. This was measured during a nine-month effectiveness window in each arm. The safety goal was to have an acceptable safety profile versus a prespecified performance goal.

Chronic effectiveness was evaluated during comparable nine-month evaluation periods. The ThermoCool group had a three-month blanking period during which repeat ablation could be performed up to 80 days. Freedom from symptomatic AF recurrence was then measured in accordance with protocol criteria from days 91 to 361.

The control group had a two week dosing window to titrate, the drug regimen to maximum effectiveness. Chronic success was then evaluated from days 15 to 285.

Freedom from symptomatic AF recurrence was monitored throughout the effectiveness evaluation period through regular transtelephonic ECG monitoring.

The primary safety endpoint was comprised of 18 serious adverse events occurring during the first 7 days after an ablation procedure, and this included new or prolonged hospitalization for any reason. The primary safety performance goal was prospectively established based on a literature review. Incidence of pulmonary vein stenosis was also deemed a primary safety measure, although no quantitative hypothesis was established.

The study enrolled patients who had been diagnosed with symptomatic AF and who had experienced at least three episodes in the proceeding six months. All had failed at least one antiarrhythmic drug. Either rate or rhythm control agents were considered AADs for study inclusion purposes.

Exclusion criteria were typical of paroxysmal atrial fibrillation trials with exclusion for amiodarone therapy in the six months prior to enrollment in accordance with the FDA guidance document.

I'd now like to take you through a number

of the key milestones in this study. Enrollment in this trial was extremely challenging with nearly a year elapsing between IDE approval and enrollment of the first subject. Only 10 additional subjects were enrolled in the next 12 months despite aggressive advertising and subject recruitment efforts.

Over the next year, we managed to get up to 53 total subjects with a combination of sites both inside and outside of the United States. We continue to add high volume ablation sites, and as you can see, the pace of enrollment increased substantially. Nonetheless, we were still looking at a prolonged time span to reach the original population of 230 subjects.

We therefore approached the FDA to discuss the use of a Bayesian statistical analysis approach to facilitate early completion of the trial should the results so warrant.

During this period of time, the FDA also convened a meeting of this Advisory Panel during which the barriers to enrollment in AF IDE studies were discussed in detail, and I note that a number of you were here for that Panel meeting which was 14 months ago today.

FDA approved our protocol amendment for a

Bayesian analysis plan in early September of 2007. This allowed us to conduct our first interim analysis in a prospective manner. This interim analysis was done independently by our outside statisticians, Berry and Associates. Based on this interim analysis of a December 2007 dataset, we were able to declare early success, and therefore subject enrollment was terminated in early October of 2007.

Our subject database was locked in June 2008, after thorough site monitoring, and so it's the June 2008 dataset that you will see for most of the analyses presented today.

To further illustrate the challenges to enrollment, about 5500 patients were screened in order to enroll 167 subjects in the trial. While the trial only enrolled 3 percent of total screened candidates over 3 years, about 1/3 of the subjects actually did meet inclusion criteria as shown in this graph presented at last year's September Panel meeting. You'll note that 62 percent were excluded by protocol requirements. There were others that were unable to return for personal reasons, refused randomization, et cetera.

Final enrollment was therefore comprised of 167 subjects at 19 centers. While the largest two

centers were outside the United States, no center exceeded 30 percent of the total population.

Poolability among the 19 centers is based on a common protocol, identical data collection instruments and rigorous monitoring proportional to the number of subjects enrolled at each site.

With that, I'd like to introduce Dr. Donald Berry. First, he will provide an overview of Bayesian statistics at the request of the FDA. He will then present the statistical analysis plan for the study as well as the interim analysis that provided the early stopping decision and declaration of success.

DR. BERRY: Thank you, Dr. Yaross. My name is Donald Berry. I'm a statistician at the M. D. Anderson Cancer Center and a member of Berry Consultants, a consultant to the company. Berry Consultants designed the Bayesian aspect of the ThermoCool trial and carried out the interim analysis.

I want to give you a primer on Bayesian methods. Dr. Laura Thompson of the FDA is going to give you the FDA perspective. I think these two presentations are supplementary and complementary. There's a bit of redundancy, but as usual, if you

hear something twice, it means it's important.

In 1997, the FDA Modernization Act used the term least burdensome. The Secretary shall consider in consultation with the applicant the least burdensome, appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval. The first Bayesian approval at CDRH was in 1997. Draft Guidance was presented in 2006.

This is the set of table of contents of the Draft Guidance and the website where it's available, and we chose the use of the least burdensome approach and its relationship to Bayesian statistics.

Current use of Bayesian adaptive designs at my home institution, M. D. Anderson Cancer Center, we've designed and have run or are running over 300 trials since I arrived there nine years ago. Many device companies are using the Bayesian approach. There have been over 20 PMAs and many 510(k)'s. In the last few years, virtually all of the top drug companies have been taking the Bayesian adaptive approach in at least some of their clinical trials and many biotechs.

Some of the Bayesian device applications that have been submitted and some approved by the FDA

are listed here.

Bayes' Rule is the basis of the Bayesian approach and many have been exposed to the use of Bayes' Rule. Many M.D.'s, for example, in the context of diagnoses, diagnostic tests, many are familiar with sensitivity of a diagnostic test. Specificity, positive predictive value.

The bottom formula here shows the relationship between sensitivity, the probability that a test is positive if an individual has a disease, and the positive predictive value. This is what we really want, what is the probability of the individual has the disease if he or she tests positive and what we have is sensitivity and specificity, not listed here.

This crazy looking means proportional. There's a constant that's not included here.

The relationship between the inverse relationship as given by Bayes' Rule, an aspect which is crucial, is the so-called prevalence of the disease, the proportion of individuals who have the disease among those in the population that we are testing.

Same relationship applies up here. This is called the likelihood function, the probability of

the data that you've observed given a hypothesis or the value of a parameter, an unknown parameter, and this is the posterior probability, the probability of the hypothesis given the data. The analog of the prevalence is the probability, the prior probability of the hypothesis, which is a fundamental part in the use of the Bayesian approach.

The Bayesian approach is a formalism for learning under uncertainty. Anything that's not known has a probability distribution that includes hypotheses and all hypotheses, parameter values, and future data. Hypothesis test is the posterior probability of no treatment effect. The analog of the confidence interval is an interval that contains the parameter with a particular posterior probability such as 95 percent.

The Bayesian approach is inherently synthetic. The probability of a hypothesis given data means probability of a hypothesis given everything that you know, which includes not only the study at hand but other studies that are going on or have been conducted.

Advantages of the Bayesian approach is naturally adaptive, and I want to focus a bit more on that. It leads to the ability to calculate

predictive probabilities. It uses early by-patient information and, for example, in the ThermoCool trial, we modeled the hazard as being potentially different than the early time periods, and you see that indeed in Dr. Wilber's presentation, that the failure rate vary over the course of time and remodeled that aspect uses historical data -- hierarchical modeling. That's an aspect that we, in fact, did not use in ThermoCool trial.

A Bayesian update, I want to take you through a very simple example. Suppose there are paired observations within each pair. One of the members gets a treatment and the other gets control. The probability that the treatment wins the pair is PS here, and the null hypothesis is that that probability is a half. If there's no difference between the two, half of the pairs would be won by T and half by C.

This is the first 17 observations in this particular example. The first pair was won by the treatment of success. The second pair won by the treatment again of success, then a failure of the first 10, you see there were 7 successes and 3 failures.

The Bayesian approach, as we said, starts

with a prior probability distribution, and this is a so-called non-informative prior or plat prior. It uses a minimal of historical information. It regards each value of P, the probability of success, as being as likely as every other value.

It also has the characteristic that it leads to at least approximately the same type of measures as the more standard, frequentist approach, such as the confidence interval is actually a Bayesian posterior probability interval.

After the first observation, which you remember was a success for the treatment, this distribution changes, and it changes by Bayes' Rule. The technical aspect is that you multiply by the likelihood the probability of what you actually observe. You observe the success, and so the probability changes by multiplying by the probability of success, which is P itself. After the next observation, there's another success, and you get P squared as the new posterior distribution. After the next, you multiply it by the probability of failure, which was the third observation. So you get P squared times 1 minus P.

The technical aspects are not too important here. What I'm interested in demonstrating is that

you can do this. You make an observation and you update what you know on the basis of that previous observation, and you can do that daily or monthly or periodically.

So just showing you after the next success, after the next success, another failure, it shifts a little bit to the left. After 10 observations, we're at this point here. This is final after the 10. It's the current distribution.

The other thing I want to show you is what happens tomorrow. So the next pair of observations will either give you a success in which case this moves up a little bit or failure in which case this moves down a little bit. The Bayesian approach is unique in allowing for the calculation of the probability of those two outcomes, and that is a well-known Laplace's rule of succession. In this instance, it says that the probability of its success is 8/12 or 2/3. The probability of a failure is 1/3.

Predicted probabilities are essential for monitoring trials. It's a critical component of experimental design and were a critical component in the ThermoCool trial, and I give a quote here from the famous Bayesian clinical trialist, we must ask, we must ask where we are and whether we are tending.

This is the current distribution after 17 observations and, you know, the most likely values are in the .7, .8 range. The Bayesian approach allows for calculating the probability of superiority, which means that the treatment success is bigger than a half, and that's the area under this posterior distribution which indicates again is .985.

Remember, we have 17 observations, 13 successes. If you say, well, how useful will it be to increase the sample size to go to the next 17 observations, let's say, this is the predictive probability distribution of the next 17. So ranging from 0 to 17, and it incorporates two types of uncertainty. One is the future, the variability, the sampling variability, but also the variability in P and the variability in P, what we know today is critical to incorporate into this distribution. If you didn't incorporate it, if you used what's called a binomial distribution, a typical coin tossing, with the most likely value of P, you'd get a distribution which is much more concentrated. Notice the tail of this distribution is greater than here and the same on this side. This is the correct distribution. This is artificially assuming that the variability is less than it truly is in the future observations.

So an instance of that is supposedly to calculate the probability of statistical significance. After the next 17 observations, that would require 10 of the 17 to be successes or 23 of the 34 observations, the actual probability is 88 percent. If you assume that you knew the value of P, which, of course, you don't, it's 96 percent. This artificially inflates what we know and actually explains some of the causes of failure of phase 3 trials in the drug world.

The Bayesian approach is rather more conservative than this fixed P approach.

Important issues to discuss, the Bayesian approach must have something fundamental in clinical research as to have a prospective design and so even though the Bayesian approach is adaptive, uses information to possibly modify the trial design, that has to be specified completely up front in order to calculate operating characteristics like false positive rate, controlling type on error, and in the case at hand, require an agreement with the FDA as to that this was an appropriate design before anything happened.

Changing from frequentist to Bayes, this is something that's addressed in the Bayesian guidance,

the FDA Draft Guidance, and it's discouraged. In the instance of the ThermoCool trial, we discussed this with the FDA very early on, and they agreed that since most of the data was yet to accrue, they okayed the switch to the Bayesian approach.

Why do people do Bayesian things? The hook is smaller trials, and I say usually. Sometimes it's actually bigger. Sometimes you get to the end of the trial and you wished the trial were not over, and so you can build that in prospectively to allow for increasing the sample size. When I say you wish the trial weren't over, I don't mean that you haven't answered the question in the way that you want to. I mean that you are on the cusp. You don't know whether you have a device which is safe and effective.

That leads to more accurate conclusions and in many examples, and the thing that is so appealing to physicians of patients in cancer is potentially better treatment of patients in trials.

So now I'll turn to the ThermoCool AF trial. The amended design of the Bayesian sample size was prospective -- rate was controlled with planned interim analyses, the technical aspect of this, is that we simulated many, many trials under

many different scenarios, including the scenario where the device has no benefit in comparison to the control, AAD. The Bayesian adaptive sample size kept the maximum, the previous maximum of 230 but allowed for stopping on the basis of predictive probabilities when we get to 150. And as Dr. Yaross indicated, that occurred at the time that the FDA agreed to the Bayesian approach in September 2007. We performed the interim analysis, and it showed two things: one, that the accrual could stop, and the other was that the data were sufficiently compelling that, in fact, we could claim early success and submit an application.

So these were the results, and this is in contrast to it, not contrast to but anticipates the presentation of Dr. Wilber. These were the interim results, and he will be presenting you the final results or the current results, and his presentation is the right one in the sense that the Bayesian approach, even though it asks where we're going, when you eventually get there, what matters is what you have at the end of the day.

So there are 148 patients eligible for the interim analysis. The predictive probability of eventual success which was defined to be at the end

of the day, probability of superiority of at least .98, the probability of that had to be at least 90 percent in order to stop accrual. So we could stop accrual at the sample size, 150, if we had a predictive probability of success of at least 29, and if we had a predictive probability of success of at least 29.9, then we could declare a success at that time. We would, of course, continue to follow and the company did that.

The result of the interim analysis was a predictive probability of, in fact, greater than .999, and therefore early success was declared.

I'll now introduce Dr. David Wilber who will give you the present results of the trial.

DR. WILBER: Good morning. My name is Dave Wilber. I'm Director of Cardiology at Loyola University Medical Center. I'm the primary investigator for the study, and I'm a consultant for Biosense Webster. What I'll be presenting are the final results of the study and demographics as a follow-up in June of 2008.

Overall, there were 167 patients who met the study criteria, were consented and randomized, 106 in the ThermoCool group and 61 in the antiarrhythmic drug group.

There were seven patients that were excluded from the study. Five of these were because of withdrawal of consent after randomization. One patient who was assigned to ablation, the insurance company didn't approve the ablation procedure and reimbursement for it, and so that patient was not in the study. And then one patient was found subsequently not to meet the enrollment criteria and was excluded.

One additional subject in the antiarrhythmic drug group actually underwent initial treatment with the assigned drug and then decided to withdraw consent for follow-up.

So the final cohort is 103 in the ablation group, 56 in the drug group, for a total of 159 patients who comprised the effectiveness analysis cohort.

These are the demographics. The two groups were well matched in terms of gender and age. Approximately a third of the patients enrolled were female, and the mean age was approximately 56 years.

Patients in this trial were highly symptomatic, and there was a mean of approximately 63 episodes of symptomatic afib that were reported in the 6 months prior to randomization, and these were

equally distributed between the two groups.

This slide demonstrates the cardiac comorbidities at baseline in the two treatment groups, red being antiarrhythmic drugs, blue being ThermoCool. As you can see, there were no significant differences between these two groups. Approximately half of the group had hypertension. Approximately 15 percent structural heart disease. These are very typical comorbidities in a population of patients with paroxysmal atrial fibrillation.

This slide summarizes prior antiarrhythmic drug experience before randomization. There was an average of 2.2 antiarrhythmic drugs failed, and you can see there's no difference between the ThermoCool and antiarrhythmic drug group. This included a mean of 1.5 class I or III antiarrhythmic drugs and a mean of 1.3 class II or IV antiarrhythmic drugs.

Patients who were assigned to antiarrhythmic therapy received a new, not previously administered class I or III drug. The minimum recommended dosing was based on the ACC, AHA, ESC guidelines published in 2001. These were all drugs that were approved at that time of study onset for treatment of atrial fibrillation, and they included sotalol, dofetilide, flecainide, propafenone and

quinidine.

The prescribed antiarrhythmic drug was adjusted in dose for maximum efficacy during the 14-day dosing period, and then the antiarrhythmic drug and dose were fixed at day 15 and remained on the same drug and dose for the chronic follow-up. Amiodarone therapy was not an option by protocol definition.

In the ablation group, it was required that all patients have circumferential isolation of the pulmonary veins and that there be electrophysiologic confirmation of entrance block into the pulmonary veins as the acute procedural endpoint.

CARTO electroanatomical mapping was used in all patients.

At the discretion of the investigator, and depending on the outcome of the procedure after pulmonary vein isolation, patients could undergo isolation of the superior vena cava if that was an initiator of atrial fibrillation. They could undergo ablation of non-PV -- that initiated atrial fibrillation. They could undergo left atrial linear lesions if atrial fibrillation could be induced after pulmonary vein isolation. They could undergo a left inferior pulmonary vein to mitral isthmus line if

left atrial flutter was induced. And finally, they could undergo cavotricuspid isthmus ablation if isthmus-dependent right atrial flutter was induced.

This slide addresses the time from randomization to initial treatment in each group. In the ablation group, a mean of 28 days and a mean of 43 days between randomization and treatment with catheter ablation. This largely reflected the issues with simply getting patients on the schedule and having the procedure performed.

In the drug group, there was a mean of 10 days and a mean of 16 days from randomization to the initiation of antiarrhythmic drug therapy. While there was a slightly longer delay in initiating treatment in the ablation group, given that atrial fibrillation is in general a progressive disease, we feel that it is unlikely that this biased the outcome in favor of the ablation group.

This slide summarizes acute effectiveness outcome for the protocol definition. 103 patients underwent the ablation procedure, and entrance block was confirmed in all 103 patients. However, 2 patients underwent a second ablation procedure between day 80 and 90 of the blanking period. That was outside the protocol-defined window. That

resulted in an acute effectiveness success of 101 of 103 patients or 98 percent.

Chronic success in the ThermoCool group was defined by protocol as freedom from the following: documented symptomatic afib recurrence during the follow-up period; freedom from acute procedural failure, irrespective of afib recurrence, and that included failure to confirm entrance block into the targeted pulmonary veins; EP afib ablation procedure after 80 days; and freedom from protocol adjudicated antiarrhythmic drug failure, again irrespective of afib recurrence. And these drugs included class I and III antiarrhythmic drugs but also beta blockers, calcium channel blockers, digitalis, ARBs and ACE inhibitors.

In the drug group, chronic success was defined by protocol as freedom from the following: documented symptomatic afib recurrence during the efficacy evaluation period; protocol adjudicated antiarrhythmic drug failure defined similarly to that in the ablation group; and also safety failure which required discontinuation of the assigned antiarrhythmic drug during the efficacy evaluation.

A standardized transtelephonic monitoring protocol was followed within both groups. Subjects

were instructed to transmit once a week for the initial eight weeks and monthly for the remaining seven months. They were also instructed to transmit during any cardiac symptoms. These recordings were initially reviewed by two laboratory technicians that provided the initial interpretation and then finally all recordings were reviewed by an independent cardiologist who was blinded and adjudicated the final outcome of the recording.

This slide summarizes the compliance to the standard TTM protocol in both treatment groups. As you can see, there was high compliance over time. This was very similar between both treatment groups and the average was 89 percent compliance with the prespecified time periods for transmission of data.

Bayesian analysis was then used to examine the significance of the treatment differences in the two groups, and the critical results of this analysis are the predicted probability of study success for 230 patients and the posterior probability of superiority for the ThermoCool group. The posterior probability that the ThermoCool group was superior to the antiarrhythmic group is essentially 1. The probability of success for a subject in the ThermoCool group is 62.7 plus or minus 4.8 percent,

and the probability of success for a subject in antiarrhythmic drug group is 17.2 plus or minus 4.9 percent.

This slide graphically illustrates that outcome and shows the distribution of probability for the antiarrhythmic drug and ThermoCool group, and as you can see, there's overlap in the probability distribution between those two groups.

This slide demonstrates the Kaplan-Meier curve of time to first chronic failure, protocol defined, by randomization group. At the end of follow-up, 64 percent of ThermoCool ablation patients and only 16 percent of antiarrhythmic drug patients were free of any chronic failure as defined by the protocol.

These circles in the graph represent the 14 censored ThermoCool subjects who at the time of the June database had not yet completed follow-up.

This slide summarizes again the chronic effectiveness failures in the ThermoCool group. Twenty-four patients failed because of recurrent symptomatic atrial fibrillation or 23 percent of the ablation group. The remaining failures were not due to symptomatic atrial fibrillation recurrence but were due to protocol differences, the first one being

2 patients who had a re-ablation within 80 to 90 days, and 10 patients who had protocol adjudicated antiarrhythmic failures, again not due to recurrence but because of the initiation, in a small number of patients, a class I or III antiarrhythmic drug, but in the majority because of a new beta blocker, calcium channel blocker, ACE inhibitor or ARB.

Similarly, in the chronic effectiveness failures, there were 47 failures in the antiarrhythmic drug group or 71 percent of the control subjects; 40 of these were due to symptomatic afib recurrence. In 7 patients, there was no symptomatic recurrence, but all 7 failed due to intolerance or serious adverse events related to the prescribed antiarrhythmic drug.

Several additional considerations we should review. In the ThermoCool group, 50 percent of the patients underwent PV isolation alone. In the remaining patients, other procedures more than one in a single subject included cavotricuspid isthmus ablation for flutter, 34 percent, superior vena cava isolation in 16, other focal drivers in 17 percent, a mitral isthmus line in 21 percent, and other left atrial lines in 20 percent.

As allowed by the protocol, 13 subjects or

12 percent underwent a second procedure within the first 80 days of the blanking period. The protocol did allow for the use of previously failed antiarrhythmic drugs during follow-up, but this was limited to only 7 percent of subjects classified as success during the 6 months of follow-up.

In the antiarrhythmic drug group, the vast majority of patients were treated with either flecainide or propafenone. Sotalol and dofetilide accounted for the remaining patients in terms of their assigned treatment drug.

As allowed by protocol, 64 percent of the antiarrhythmic drug group ultimately had an ablation procedure after symptomatic recurrence and classification as a treatment failure.

To better characterize the effectiveness results, we conducted several post-hoc Kaplan-Meier analyses. These included freedom from symptomatic atrial fibrillation recurrence and freedom from any atrial fibrillation recurrence, either symptomatic or asymptomatic.

This slide demonstrates a Kaplan-Meier curve of time to first symptomatic afib recurrence. As you can see, there's a dramatic difference between the two groups. At the end of the follow-up period,

75 percent of the ThermoCool ablation patients, and only 21 percent of the antiarrhythmic drug patients, were free of any symptomatic atrial fibrillation recurrence.

Similarly, for total AF recurrence, including both symptomatic and asymptomatic events, at the end of the treatment period or rather at the end of the follow-up period, 72 percent of the patients in the ThermoCool group and only 21 percent of patients in the antiarrhythmic drug group were free of any recurrence of atrial fibrillation.

Eleven of the antiarrhythmic drug subjects were prescribed the same or a higher dose of a previously failed antiarrhythmic drug. We did perform sensitivity analysis removing these 11 subjects from the antiarrhythmic drug control group, and the results were consistent with the primary analysis to continue to show the superiority for the ThermoCool group at the highly significant P value.

In addition, four antiarrhythmic drug subjects received less than the protocol recommended antiarrhythmic dosage. That included one subject that was also in the above group. When Bayesian multiple -- analysis was conducted for these 14 subjects receiving less than the protocol specified

minimum antiarrhythmic dosage, superiority was still demonstrated.

We also analyzed effectiveness outcomes by site and region, and this included OUS 1 versus remaining sites and non-US versus US sites.

This slide is a Kaplan-Meier curve of time to chronic failure per protocol at OUS site 1. There were no protocol chronic failures and there were, and this was the recurrence in the antiarrhythmic drug group. This is the comparison of that one. This is the comparison in excluding that site. Even in this group of patients, there remained a significant difference between the ThermoCool and antiarrhythmic drug treated patients although the less, a somewhat smaller magnitude.

But there's several potential reasons why there were some differences between that site and the remaining sites. First of all, this was one of the highest volume AF ablation centers worldwide. It's had access to the ThermoCool catheter since 1999, whereas many of the, particularly in the United States, the first experience with the catheter was at the onset of the clinical trial since the catheter has not been available commercially released until two years ago.

There were minor differences in baseline demographics in favor of the OUS site 1 in that there were smaller atrial size, less hypertension, and somewhat younger subjects.

There were also differences in procedures between the OUS site 1 and the remaining sites. Cavo-tricuspid isthmus ablation was performed more often, 23 out of 31 compared to 13 out of 72. In addition, at OUS site 1, left atrial linear lesions were performed more frequently, 20 of 31 at OUS 1 versus 9 of 72 at the remaining sites.

In the patients assigned to ablation, there were four early recurrences at OUS site 1, and all of these patients went re-ablation within 80 days. In contrast, there were only 9 re-ablations within the protocol specified period in all of the remaining sites. So the OUS 1 was very good at getting their patients back and having them re-ablated within the protocol if they had an early recurrence.

And finally, there were some differences in medical management. One of them was that since it was possible to continue a previously failed antiarrhythmic drug post-ablation, this was done somewhat more often at this site. However, there were typically continued for only three to six

months, and as we had stated earlier, only a small number of patients remained on these drugs at the end of follow-up.

And probably and very important as we point out in subsequent analyses, this site was very good at strict protocol compliance so that non-compliance with other drugs, not necessarily antiarrhythmic drugs, but beta blockers, calcium channel blockers and ARBs that were the source of protocol adjudicated failures in U.S. and other non-OUS 1 sites, never occurred at this particular site. So for the primary effectiveness criterion, this made a substantial impact on differences and outcome.

To examine this further, a Bayesian analysis was conducted excluding subjects from OUS 1. The resulting posterior mean probability of success in all of the remaining sites, again excluding OUS 1, was a 46 percent chronic success in the ThermoCool group versus the 20 percent success in the antiarrhythmic drug group, and the posterior probability that the ThermoCool group is superior to the antiarrhythmic drug group remains very high at 0.9975.

Finally, there were a variety of sensitivity analyses conducted, varying strengths of

borrowing of OUS 1 and remaining OUS site data. Even if one heavily discounts the OUS 1 and remaining OUS sites, the result is still very compelling. For example, if one borrows only 20 percent or discounts by 80 percent, the OUS 1 data and remaining OUS sites, the probability of superiority remains at 0.991.

This impact, I think, is made more clear by additional effectiveness outcomes that excluded OUS 1. If we look at time to symptomatic afib recurrence on the Kaplan-Meier curve, and time to any observed AF recurrence in the bottom curve, again these are from all of the remaining centers excluding OUS 1. There was still a highly meaningful and strong difference between the two groups. At the end of the follow-up period, 64 percent of the ThermoCool group and 26 percent of the antiarrhythmic drug group remained free of symptomatic atrial fibrillation. And for any recurrence of atrial fibrillation, 60 percent of the ThermoCool and 26 percent of the antiarrhythmic drug patients remained free.

So again, this particularly suggests that many of the differences in protocol defined success versus the actual recurrence of atrial fibrillation involved these differences in the use of non-

antiarrhythmic drugs such as beta blockers, calcium channel blockers, and ARBs in sites other than OUS 1.

Finally we looked at the outcome of the United States population alone. This is the Kaplan-Meier curve from time of first chronic failure per protocol at U.S. sites. There remains a difference between the ThermoCool group and the antiarrhythmic drug group of almost twofold, 44 percent of the patients in the ThermoCool group, 18 percent in the antiarrhythmic drug group, remained free of chronic failure as defined by the protocol.

But if you look again at the curves of time to symptomatic afib recurrence, and any observed afib recurrence, there remain very clinically meaningful differences between the two groups. At the end of the follow-up period, 61 percent of the ThermoCool patients and only 28 percent of the antiarrhythmic drug treated patients were free of symptomatic atrial fibrillation recurrence. Similar results for any observed afib recurrence.

We also looked at quality of life, and quality of life was significantly improved in the ThermoCool ablation patients. Quality of life was assessed at baseline and at three, six, and nine months of the follow-up period. Both the SF-36 and

the atrial fibrillation symptom frequency and severity checklist were used.

This slide demonstrates that SF-36 results. This is the mental component on the top and the physical component on the bottom. Baseline values for both groups were similar and below the population norm of 50, and this implies that, in fact, this was a significantly symptomatic group at the onset. The scores were similar for both the ThermoCool and antiarrhythmic drug groups.

Those patients in the antiarrhythmic drug group who subsequently underwent ablation were excluded from the then subsequent quality of life analyses. Overall for the SF-36, a three to five unit change is considered clinically significant and meaningful, and as you can see, in both of sets scales, mental and physical, there was a five to eight point difference improvement in quality of life that was maintained over the trial for both scales and again, very little improvement, really change in the quality of life for patients in the antiarrhythmic drug group.

Similar results were seen for the symptom checklist outcomes, both in terms of symptom frequency and symptom severity. In this case,

there's a decrease in score. That correlates with a decrease in symptoms. There was a greater than 50 percent decrease in symptom frequency and severity scores from baseline in the ablation group at all timeframes.

However, there was very little change in the antiarrhythmic drug group, the only exception being toward the end of the trial, symptomatic severity in the remaining patients that had not yet undergone ablation was somewhat less, and they think simply reflects the fact that most of the patients with severe symptoms in the antiarrhythmic drug group by that time had elected to have a catheter ablation procedure performed.

In terms of the relevance of this trial to heart failure, only New York Heart Association Class 1 and 2 subjects were eligible for study inclusion. There were five subjects, three in the ThermoCool arm and two in the antiarrhythmic drug arm, that were enrolled with a history of hear failure at baseline. There were no heart failure related primary adverse events reported in any of the three ThermoCool subjects. However, the safety and effectiveness inference based on these small numbers I think is extremely difficult to make.

There are, however, some data outside of the trial, relating to both catheter ablation and the use of the ThermoCool catheter in heart failure patients. The safety of the ThermoCool catheter has been adequately characterized in the VT population by a previous PMA, and in that PMA more than 56 percent of patients that were enrolled and treated with the ablation catheter had heart failure.

Finally, there is data not relating specifically to this catheter, that restoration of sinus rhythm by ablation in subjects with heart failure and afib significantly improves cardiac function, symptoms, exercise capacity and quality of life with a low complication rate.

We did look at the small subgroup of patients who were enrolled based on the failure of only a class II or IV antiarrhythmic drug. So only 16 percent of all enrolled subjects, 20 were in the ThermoCool group, 7 in the antiarrhythmic drug group. These were the protocol defined chronic effectiveness. As you can see here, because these numbers are very small, I think it's difficult to make inferences about the impact of this particular subset of patients on chronic effectiveness.

We feel that the results of this trial are

generalizable to the U.S. population. There were 15 U.S. sites that contributed to the study population. The statistical results of the trail were insensitive to the exclusion of OUS 1 and to discounting of all OUS sites. Analysis of time to symptomatic afib recurrence and time of any observed afib recurrence, demonstrates substantial -- effects in the U.S. population alone.

And finally while amiodarone in this study was excluded by protocol, it is considered an unacceptable option by many patients and practitioners for paroxysmal atrial fibrillation due to potential long-term side effects.

In this study, electroanatomical mapping was incorporated as part of the ablation procedure. However, alternative mapping guides for AF ablation including fluoroscopy, intra-cardiac, echocardiological, and circulatory mapping catheters, and these have been documented in the literature. We feel that this study does not address whether electroanatomical mapping is superior to these alternative approaches.

So we conclude that the superiority for ThermoCool ablation versus antiarrhythmic drug therapy is demonstrated in achieving the primary

effectiveness endpoint. This was a randomized control trial. There was a conservative effectiveness endpoint definition that included the addition of other non-antiarrhythmic drugs for example. There was excellent transtelephonic monitoring and compliance and rigorous adjudication of these outcomes. The statistical conclusions were robust to some protocol deviations, and the directionality of treatment was robust across many subsets and many different analyses.

We also feel that there were clinical meetings that treatment effects in favor of the ThermoCool arm, in terms of other secondary endpoints including freedom from symptomatic afib or any observed afib recurrence and in quality of life. Thank you.

I'd like to now introduce Dr. Al Waldo who will present the results of the safety analysis.

DR. WALDO: I'm Al Waldo, a Professor of Medicine at Case Western Reserve University and I'm a consultant for Biosense Webster.

So we start now with the primarily safety analysis and the primary safety endpoint for this study was to find as the incidence of early onset, that is within seven days of the ablation procedure,

primary adverse events included in this long list which I think you will see in your handout.

This looks at the accountability for primary safety analysis, that is all subjects undergoing ablation. So in the ThermoCool group there were 106 patients, 3 of whom were excluded. That meant the overall safety cohort was 103. So the primary safety cohort in this group was 103 patients. In the antiarrhythmic drug group, that is the control group, there were 61 patients, 4 of whom were excluded, leaving 57, and the overall safety cohort. One subject was then discounted, 20 subjects did not undergo ablation. In other words, the remaining patients crossed over to the ablation arm. So there were 36 of them. So we get the final number of 139 patients.

Now, this looks at the primary safety endpoint. That is the early onset, within 7 days, and you can see that of the 139 patients, there were 15 subjects who had 16 events. So the percent was 10.8 percent with primary events which made the 95 percent upper confidence bound of 16.1 percent which missed by .1 percent of the primary adverse event performance goal of 16 percent.

But this breaks down what the nature of the

adverse events were. This list is actually a decreasing instance of severity beginning with death, atrioesophageal fistula, et cetera, and you'll notice that there are no events until we get to one pulmonary edema, one pericarditis, seven hospitalizations, one pericardial effusion, and five vascular access complications. So the great majority, that is seven hospitalizations and five vascular access complications made up the most of what this was about. The vascular access complications, of course, are something that can be seen in any kind of catheterization.

And this further breaks down the primary safety events for seven days. And of all of these events, we either satisfactorily resolved or improved. So that was pulmonary edema, pericarditis, eight hospitalizations in seven patients, one pericardial effusion and five vascular access complications, and just to again give you some perspective, for instance, the pericardial effusion patient was asymptomatic. It was picked up on the mandated echocardiogram later on, and that was completely resolved.

This looks at the hospitalizations in detail. In an extended study, one subject for

decrease in hemoglobin level, one subject for hematuria related to traumatic Foley catheter insertion, one subject for atrial flutter. Regarding readmission during the first week, three subjects developed an atrial fibrillation recurrence. One subject for pneumonia and one subject for shortness of breath. These two patients were the same.

So again I think you'll find that when you look at these events, they were really a clinically acceptable category.

So if we look at the primary adverse events by causality. There were 15 subjects, 16 events, only 1 was possibly device-related. This was a patient who developed heart failure two days out after going home for two days, and this was successfully resolved. There were nine procedure-related, and there were five that were unrelated to device or procedure.

Now, very important is to look at what happens in pulmonary vein stenosis. Pulmonary vein stenosis was defined in this study as 70 percent or greater reduction in the diameter of the pulmonary vein compared to baseline. The study cohort included all subjects undergoing an ablation procedure with follow-up CT or MRA. So it included ThermoCool

patients and also the antiarrhythmic drug patients who crossed over.

This looks at the instance of pulmonary vein stenosis that is greater than 70 percent or greater from the baseline in any targeted vein per subject. You notice there were none. So pulmonary vein stenosis at three months, none. In the ThermoCool group, pulmonary vein stenosis at 12 months, there were none, and the same for those who crossed over, none at 3 months and none at 12 months. So of the 82 patients at 3 months and no pulmonary vein stenosis clinically, and of the 29 patients at 12 month period with no pulmonary vein stenosis.

This slides look at the pulmonary vein diameter changes at these 3 and 12 month by pulmonary vein. So we're looking here at the total number of pulmonary veins that were examined, and you can see that some of them decreased and some of them increased. The histograms in yellow are those that were looked at 3 months into the bio CT or MRA, and the green were those who were looked at in 12 months. So you can see most of the patients were in the mild category with a decrease, in fact, the vast majority were either 20 percent to less. The remainder were the 50 percent at 3 months. At 12 months, there was

one patient whose diameter had decreased by 51.9 percent. And interestingly enough, some of these veins increased in size, again some 20 percent and some a little more than 20 percent. And really what I think this reflects is two things. Just look at this. It looks like a normal bell-shaped curve suggesting normal variability. The other thing is that when you make atria remodel and you shorten, which will decrease some of the diameter, and also there's variability from time to time, the diameter of these veins are physiologic dependent depending on your HO volume and what stage during filling or contraction, et cetera. So I think basically the important thing is to look at this. There were no patients who had over seventy percent, and not even close.

Now, this looks at the secondary safety analysis. So Biosense Webster developed a hierarchical classification of adverse events based on two categories of level of severity. Category one was adverse events that resulted in permanent injury or impairment, including death, cerebral vascular accident, myocardial infarction, pulmonary vein stenosis, diaphragmatic paralysis, or atrioesophageal fistula. Category two was a long list of temporary

or reversible causes.

So when we look at this thing, if we look at the secondary safety endpoint, that is early onset of serious adverse events within 90 days of initial treatment, there were no category one events in either the ThermoCool group or in the antiarrhythmic drug group. There were 19 events of category two in the ThermoCool group which was 18.4 percent of the cohort, and 20 events or 35.1 percent of the cohort in the antiarrhythmic drug group, so it was basically twice as many in the antiarrhythmic drug group or if you will, half as many in the ThermoCool group with a P value of .0221.

Now, here we look at the secondary safety analysis of the late onset of serious adverse events, that is beyond 90 days of initial treatment, and here in the ThermoCool group there was one death. This death occurred 284 days after the ablation. It was a gentleman who had a known history of coronary artery disease. He had chest pain at night, went to bed with the chest pain, and unhappily never woke up.

Then if we look at the category two, there were 7.8 percent in the ThermoCool group with 14 percent in the antiarrhythmic group and the category other that is these are some events that were not on

that list that I just showed you before. So we looked at the total. The incidence was 10.7 percent with the ThermoCool and 15.8 percent of the antiarrhythmic drug group. Again, the ThermoCool group did better considerably.

So we conclude then that there is an excellent safety profile from the ThermoCool atrial fibrillation catheter ablation patients. The primary adverse event incidence, the performance goal was 16 percent. The observed missed it by .1 percent. There was one possibly device-related event. There were no deaths, myocardial infarctions, strokes, cerebral vascular accidents, heart block, atrial perforation or the like within seven days. There is no clinically significant pulmonary vein stenosis.

Regarding the early onset serious adverse events, there was a lower incidence in the ThermoCool group of 18.4 percent compared to the antiarrhythmic drug group of 35.1 percent. Late onset serious adverse events, again a lower incidence in the ThermoCool group of 10.7 percent compared to the antiarrhythmic drug group of 15.8 percent.

So now I'm pleased to turn the podium back to Dr. Yaross.

DR. YAROSS: Thank you, Dr. Waldo. To wrap

up, we have presented valid scientific evidence as defined in FDA regulations for your consideration today.

The NaviStar AF study had randomized control design. The Bayesian analytical approach was used to permit efficient study completion following the challenges to enrollment that I described to you earlier.

The ThermoCool AF study was rigorously conducted. We had excellent TTM adjudication, and it was a thoroughly vetted dataset.

The sponsor continuously monitored the sites throughout the trial, and in addition, we had underwent FDA fire research monitoring audits of the two highest enrolling sites and at the sponsor.

There were no Form 483 inspectional observations at those sites, and thus this corroborates the validity of the dataset.

This therefore likely represents the most rigorously and thoroughly vetted AF ablation dataset to date.

The results therefore demonstrate the safety and effectiveness of the ThermoCool catheter for the treatment of AF. The primary trial objectives I outlined earlier were met. We have

shown the superior chronic effectiveness of the ThermoCool catheter ablation versus antiarrhythmic drug treatment by a rigorous protocol definition.

While we acknowledge on the safety side that we missed the other confidence limit at the safety endpoint by 0.1 percent, based on the lack of severe events, we also submit that this provides an acceptable safety profile as Dr. Waldo has outlined.

We have also shown to you additional important results for the ThermoCool ablation subjects. They, versus the AAD control subjects, were more likely to be free of any observed atrial fibrillation occurrence. They had improved quality of life and have fewer severe side effects. In fact, the secondary, the prespecified analysis that we provided, we had hypothesized non-inferiority for that analysis and, in fact, the results show superiority.

We'd also like to point out that both genders were well represented in the ThermoCool AF trial. Women represented one-third of the population, and logistic analysis showed that gender was not a predictor of product success outcome or primary adverse events in this study. We therefore conclude that the product is effective and safe in

both men and women.

Biosense Webster believes that the results of this trial should be incorporated with the ThermoCool catheter instructions for use. Public interest is best served by rapidly communicating the results of this trial so that information on AF ablation risks and benefits are communicated in an AF approved package insert with the device label.

Currently we, as a company, are unable to train physicians specifically on atrial fibrillation treatment. Given the growing performance of AF ablation off-label in the community, it is in the public interest for us to be able to conduct formal training on safe and efficient use of this catheter in the AF population.

Biosense Webster is committed to a formal training program. We currently require clinical training prior to first shipment of the catheter to a hospital, and we will commit to training on atrial fibrillation as well as part of this program post-approval.

As I showed you earlier, the current approved indications for use are Type 1 atrial flutter and recurrent drug and device refractory VT in the post-MI population.

Our proposed change to this indication produced is simply to add drug refractory, symptomatic paroxysmal atrial fibrillation. Draft information for use is in your handout.

We have also agreed to conduct a post-approval study to confirm that the results of the study may be generalized in a postmarket setting. In the study, we also propose to look at long-term safety and effectiveness.

Our proposal currently under review by the FDA includes 5 year follow-up and at least 50 percent more investigational sites within the United States to demonstrate that atrial fibrillation ablation with the ThermoCool catheter is safe and effective in other sites in addition to those in the clinical trial.

We look forward to the Panel's input on the design of this study later today.

In closing, we conclude that we have met the statutory burden for premarket approval. We have provided a clinical study that meets the highest tier of the criteria for valid scientific evidence as outlined in Federal Regulations, and this is a randomized control trial.

The probable benefits from AF ablation with

the ThermoCool catheter have been proven. The probable risks when used as directed are clinically acceptable in symptomatic paroxysmal AF population.

Biosense Webster therefore respectfully requests that the Panel recommend this application for approval.

With that, I thank the Panel for its attention and the FDA for a very -- review.

DR. BORER: Thank you very much, Dr. Yaross and colleagues, for a very effective and efficient presentation.

I'm going to ask the Panel if anyone on the Panel has any questions, but I'd like to set some ground rules if I may.

At this point, I'd like to limit the questions to clarifications of the data. We're going to have the opportunity to ask questions of the Panel again later, and we're going to hear a FDA presentation, and I think that some of the questions that we might be asking going beyond clarification of the data might best be handled when we discuss the questions after you've heard everything.

In addition, we've heard a wonderful presentation by Dr. Berry about the statistics, and I'm sure that for us as cardiovascular investigators

and people focused on cardiovascular diseases in some but not all cases sitting around the table, the Bayesian approach is not one that we're very much accustomed to in clinical trials, although it's commonly used in oncologic trials. We're going to hear from Laura Thompson of the FDA about this as well, and I would suggest that we hold the questions about statistics until after we've heard the FDA presentation, and then Dr. Berry will be welcome to come up and answer some of the questions as well, even though it doesn't say that on the program.

And finally, please wait until the Chair recognizes you before asking a question so that we can maintain some order. I promise, we'll sit here all night if we have to, to get all the questions answered that anyone may have.

Having said all those things, I see Dr. Somberg's hand up already. So, Dr. Somberg.

DR. SOMBERG: Well, number one, I promise you we won't have to be here all night because I'm not going to be here.

Number two, congratulations to the company. It's a very nice study, and it certainly sets an example for many other device companies.

I have a couple of very small questions

about the data, that you present so much of it, therefore there's always some little tidbits here and there that I don't understand, and maybe you've said this.

But number one, the people who received the ThermoCool versus the antiarrhythmic drugs, the patients in the ThermoCool group were continued on drugs that were previously considered ineffective. Then it was said that at the end of the follow-up period, most of these people were off of it. Can you be a little bit more specific? How many people were off of it? And what is the -- and what I'm trying to drive at is, is this an ablation without drugs at the end or is it an ablation that the clinician should be encouraged to continue antiarrhythmic therapy? I think that's an important implication. So if you could be a little bit more specific, I'd appreciate it.

DR. YAROSS: I'll be happy to -- actually, I'll ask Dr. Wilber to respond to your question.

DR. WILBER: In general, when patients were allowed to have previously ineffective antiarrhythmic drugs, they were most often stopped at the end of the blanking period. However, they were allowed to continue by protocol through the chronic efficacy

period. However, this was largely at the first three months of the chronic efficacy evaluation period, and at six months and nine months of the chronic efficacy period, only seven percent of those successes were on antiarrhythmic drugs. So the protocol did not specify when they were stopped, but by the last two follow-ups at six and nine months, only seven percent.

DR. SOMBERG: That's very helpful. Maybe you should stay there for a minute because I think you're going to be asked to stand up again unless you want the exercise and all that.

There were patients who were initially or discontinued or considered inappropriate because you said beta blockers, calcium channel blocker, ACE inhibitors were added to that. Is there any information in the materials that was added because of arrhythmia or instability, et cetera, or was that for other things like blood pressure and what have you?

And the other question that sort of ties in with that is that there's been recently a lot of reports with statins being useful. Is there any imbalance in the statin use between the two populations?

DR. WILBER: With respect to your first question, investigators were asked as to the reason why a patient was prescribed with a specific drug if it was changed. There were times when a specific classification wasn't made. So the assumption was always by default that it was then used potentially as a antiarrhythmic drug. So the protocol by default took a very strict definition of changes in drug therapy, and as we pointed out, this tended to be more typical of U.S. sites than non-U.S. sites.

With regard to your second question about the statins, I don't have that information at this time.

DR. SOMBERG: And my last quick question, I guess to you, Dr. Wilber, there were 14 subjects I understand that were not, and this doesn't seem -- when the FDA's review, which we'll hear and then your presentation, which didn't seem to fit together the number of people who were excluded or lost to follow-up for some reason or not in the group. Was there 14 of the people, I don't know the exact number offhand, but of the people on the ThermoCool study, was there that number lost to follow-up?

DR. WILBER: It's not lost to follow-up. Let's bring up the Kaplan-Meier curve if we can for

the first chronic efficacy evaluation by protocol.

There were 14 patients that as of June had not yet completed their follow-up. So they weren't lost to follow-up. They were followed until the time of -- that's when the dataset was sealed or the last update. So we have no further data. They were censored at that time, and you can actually see very specifically when those times were, and that's what these circles are. It represents those -- these are the times the patients were followed up until.

So as with any other Kaplan-Meier curve, they're censored when follow-up is done. So the follow-up is not complete in 14 of those patients, and this data represents what was available when we submitted the data in June.

DR. SOMBERG: Can you comment on, you know, updating us on that? I mean that is a number of people.

DR. ZUCKERMAN: Dr. Somberg, perhaps as Dr. Borer said, Dr. Thompson will get into the predictive modeling of how you account for those 14 patients, and then the question and answer will be richer.

DR. SOMBERG: Okay.

DR. ZUCKERMAN: So we'll cover that.

DR. SOMBERG: I'll ask the question again later. That's what I've been told.

DR. BORER: Okay. Dr. Kelley.

DR. KELLEY: I have two questions for Dr. Wilber. One's simple, and I think I know the answer but just to clarify. On slide 61, you talked about freedom from symptomatic AF recurrence, and then any AF recurrence, and I'm assuming that's any documented on the --

DR. WILBER: Any observed afib recurrence using the scheduled transmissions during which the patient was not necessarily, in fact, usually was not symptomatic.

DR. KELLEY: Okay. And then the second question is the rationale where to -- for the inclusion in the study that patients had to have had three episodes in six months, only one of which was documented. The others it seems like less than 30 seconds of symptoms would be counted in the absence of documentation. But afterwards, it had to be documented. What was the rationale for that difference?

DR. WILBER: I think that the protocol which is there needed to be electrocardiographic documentation of the episode in at least one of the

three episodes that they had, part of that is simply the issues about enrollment. If you, and for folks who see atrial fibrillation patients, it's often very hard to get that documentation. This is the protocol as it was adjudicated when it was worked out with the FDA, that at least one of them had to be documented by atrial fibrillation. Otherwise, the collection of data would have been much more difficult in terms of finding patients suitable for enrollment, and I think that was one of our barriers.

DR. KELLEY: So post-ablation, suppose they had the same symptoms 30 seconds of what was called afib before but didn't have their monitor with them. It was still counted as atrial fibrillation or no?

DR. WILBER: If they had symptoms without an electrocardiographic definition, they would not -- there would be no way to count it as afib because we wouldn't know that, although I think much of that information would be picked up in the quality of life if there were patients who had continued symptomatic afib but didn't use their monitor during that recording, but it wouldn't capture all.

DR. KELLEY: Okay. Thank you.

DR. BORER: Dr. Slotwiner.

DR. SLOTWINER: Okay. Thanks. I just

wanted to clarify the catheter used. The ThermoCool technology from what I've seen is incorporated into five different catheters that are manufactured, unidirectional, bidirectional, with and without nav and the remote magnetic steering. But all these patients who underwent ablation had the unidirectional navigation capable catheter used?

DR. YAROSS: That's correct. The clinical trial was conducted using the NaviStar ThermoCool catheter, the original, not the bidirectional model.

DR. SLOTWINER: But the request for approval is for all five of the flavors, correct?

DR. YAROSS: That's correct.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: I have a simple question. Your transtelephonic monitoring, was that via an implanted device that was capturing everything and then downloaded, or was this something that the patient wore just when they were transmitting or when they were symptomatic?

DR. YAROSS: It's an external device. Dr. Wilber, do you want to comment any further? It was an external device that they applied, you know, that they used at the time of transmission.

DR. JEEVANANDAM: So if somebody had afib

that wasn't asymptomatic a week before they transmitted, it would not be picked up.

DR. YAROSS: They transmitted weekly during the first two months of the effectiveness evaluation period, monthly thereafter, but they did scheduled transmissions plus were instructed to transmit at any time they had cardiac symptoms.

DR. JEEVANANDAM: So within that week, if they didn't have symptoms but they were in afib, you wouldn't pick it up. You'd only pick it up when they actually transmitted?

DR. YAROSS: That's correct. The prospective endpoint was symptomatic paroxysmal recurrence.

DR. BORER: I have a series of questions but will interrupt them as people come up with others. First of all, I didn't understand from protocol, the presentation, how anticoagulants were managed. It appeared that people who got the ThermoCool therapy were on anticoagulation generally for a period of a couple of months afterwards. It wasn't clear what the AAD, the people on AAD were getting, and that might have some impact on the AEs that were or weren't recorded. There may be some difference of opinion about how anticoagulants should

be used, but I'd like to know how they were used.

DR. YAROSS: I'll ask Dr. Wilber to respond to that question.

DR. WILBER: So all anticoagulation therapy was recommended in the ablation group for a minimum of the three months after the procedure. If patients had continuing atrial fibrillation, it would be continued thereafter. If they did not have atrial fibrillation in follow-up, it was possible and generally with a low CHADS score to allow discontinuation of anticoagulation in a limited number of patients. Immediately after the ablation, patients were treated with anticoagulation obviously until the NR reached two or three.

For the control group, it was recommended that patients be on oral anticoagulation in general throughout the course of the study.

DR. BORER: Okay. But some were and some weren't, I assume. Was there any relation to outcome of anticoagulation or it just didn't show anything?

DR. WILBER: We do not have any data to suggest that any of the outcome were related to, and since there were, in the sense of thromboembolic events, it was a small study. There weren't thromboembolic events --

DR. BORER: Or bleeding.

DR. WILBER: -- or significant bleeding.

DR. BORER: Judah.

DR. WEINBERGER: Yeah, I just want to ask at this point, there seems to be this issue about the intensity of AF monitoring. Since you're only looking for symptomatic AF, and you're not particularly interested in asymptomatic AF, I mean that's not a piece of data that you capture, unless it happens to be there during the transtelephonic transmission. Nevertheless, you allow discontinuation of anticoagulation if there's no symptomatic AF. So were there any Holters that were mandated during this time?

DR. WILBER: Just to correct one statement, in general, in accordance with the current guidelines we would not recommend discontinuation of antiarrhythmic therapy unless patients have a low CHADS score.

DR. WEINBERGER: I said anticoagulation.

DR. WILBER: Anticoagulation, I'm sorry. So that presumably to some extent is independent of the occurrence of atrial fibrillation. Your second question.

DR. WEINBERGER: They both tied into

intensity of monitoring.

DR. WILBER: And I think the other question is that it's always problematic to decide how much monitoring you need to do to pick up asymptomatic atrial fibrillation and there's probably -- and there are some data to suggest that if you monitored them forever during the entire trial, you would obviously pick up more than taking 15 isolated times, and at some point you have to make a decision about what's practical. For this study, the decision was 15 time points. I would agree with you that that certainly doesn't capture all potentially asymptomatic episodes.

DR. BORER: Dr. Kelley.

DR. KELLEY: Still for Dr. Wilber. This is about the antiarrhythmic drug issue. Certainly the difference between OUS 1 and the other sites is pretty dramatic and one of the theories is that those patients were on -- drugs. Also if you look at the difference between the results of the patients who had just failed class II and IV drugs versus the other patients, those patients had more afib, and one wonders if it's because by protocol they couldn't be on another antiarrhythmic drug. So I wondered if there were any analyses looking at results by

patients on antiarrhythmic drugs versus not.

DR. WILBER: Is the question that you're asking about the chronic effectiveness evaluation.

DR. KELLEY: For chronic efficacy.

DR. WILBER: Yeah. For patients who were on anti -- again, because there were so few patients on antiarrhythmic drug therapy that were successes at the end of the trial that, in fact, most patients who were on any antiarrhythmic drugs that had not failed, in other words, had not had a recurrence, were really only on them for the first three or four months of the chronic efficacy evaluation.

DR. KELLEY: But not at OUS 1.

DR. WILBER: Even at OUS 1, yes, that includes OUS 1. So in general, U.S. sites tended to have no antiarrhythmic therapy at all, even a failed drug, whereas OUS 1 did use the protocol that allowed one for the first three or four months of the chronic efficacy period, and then tended to stop it. And there are only seven percent of those for the six and nine-month follow-up.

So in a preliminary analysis of just looking at who was and who wasn't, there's no impact on outcome. We did not sort of do some time dependent modeling to account for the fact that the

drugs were withdrawn during that, and that is an analysis that could be done.

DR. KELLEY: In other words, did we see the failure when those drugs were withdrawn or --

DR. WILBER: No, no. In other words, they didn't suddenly pop up a month after that drug was stopped. So the ultimate impact of doing that I think is still a question that's unknown, and is it about remodeling? Is the remodeling more than three months? Is the remodeling less than three months? As you know, clinically there's still a debate about that in terms of when does the benefit of healing end, and so I'm not sure that you can say much of anything except there's no obvious signal that the continued use of a prior failure antiarrhythmic drug had an impact on chronic success.

DR. KELLEY: Okay. Thank you.

DR. BORER: Let me follow-up on that with a question about the amiodarone. I understand the protocol, but you had one patient, I believe that it was a patient in OUS 1, who had an initial ablation, a recurrence, was given intravenous amiodarone, converted, I think it was intravenous, converted, and then had a second ablation about two months later which was within the protocol and then was fine. It

sounds as if there may be some inconsistency in the application of the amiodarone rule, or maybe I don't understand the amiodarone rule. Was this patient continued in this study after the amiodarone was given? How was that handled? And were other patients given amiodarone for recurrences?

DR. WILBER: That was the only patient that received intravenous amiodarone. Because it was an intravenous administration, was short-lived, and there are quite a bit of data that much of the efficacy of acute amiodarone intravenously may have more to do with not as class III but its class I effects, and it's unlikely that that single dose, that it persisted two months later to have an impact on the trial, so that that patient was continued in the group and that it was not considered a failure because this was all in the blanking period. That patient did not receive chronic amiodarone therapy, and there are no patients that for purposes of chronic success had received amiodarone. There was some amiodarone use after patients had recurrences and had met the failure criteria.

DR. BORER: Yes. Dr. Fleming.

DR. FLEMING: I wanted to follow-up on Dr. Somberg's question. What's not clear to me from

reading this is whether the established protocol post-ablation is to put all your patients on antiarrhythmic drugs. Some centers do, some don't. So I think it's a legitimate question from a consumer's point of view, and I would also tell the Panel that I have PAF. So I'm very interested in not taking those drugs. And as a matter of fact, I would not take them if offered. So what I'm asking you is what is the general sense of antiarrhythmic drugs. I think that was part of what Dr. Somberg was asking earlier, and it's a legitimate question.

DR. WILBER: It's absolutely a legitimate question. I'm not sure that the data from this study can address that in that they're not, similar to the specific ablation set that was done, there wasn't a mandated criteria that you either must do this or must do that for antiarrhythmic drugs. So leeway allowed the investigator, and as one might expect, there were differences in practices across group. I'm not sure that even in the larger world of afib ablation there's currently agreement among all investigators on how this is handled, and so I wish I would provide that result. We can't do it from this study, but one thing we did try to assure is that the use of those drugs didn't somehow have an impact on

the endpoint, which for that I'm satisfied they don't, but whether or not it's a benefit otherwise, unfortunately and where there are solid data, people feel very passionately on different sides of the issue about whether they should or shouldn't have it after three months. Probably the most common practice is that the drugs are stopped within three months, certainly within the U.S. That is not necessarily a European practice.

DR. BORER: John.

DR. SOMBERG: Yeah, this is to Dr. Waldo. I'm going to give you a break for a minute, but I didn't want to leave Professor Waldo who has come this far without a question. I think it was very nice to break it up into category 1 and category 2 safety actions, and it's really testimony to the device that it didn't have category 1 or the drugs for that matter.

But, you know, then you went on to compare category 2 effects between the drug and the ThermoCool, and it favors the ThermoCool. But isn't one of the criteria prolonged QT and the drugs prolong the QT. So the type 3 drugs are acting as part of the efficacy by -- in the QT, but that's considered a safety problem. Did you -- I mean what

is prolonged QT? Did it have to be more than 5 -- 40 milliseconds or something? And if you leave out the QT, was that the driver of the difference between ThermoCool and the drug?

DR. WALDO: No, it was not. First, most of the patients were on class Ic drugs. So the class III drugs were really not very, very important in the trial. None of the patients had a prolonged QT interval. There's no -- or nothing even close. So it really wasn't an issue.

DR. SOMBERG: Okay. And then the other question I would have is do you have any comment on why most, you know, it just struck me as interesting that they would use mostly Ic's, like -- and do you think that is routine practice not to use the sotalol and dofetilide?

DR. WALDO: Well, dofetilide, as you know does not have an indication for paroxysmal atrial fibrillation, and as you also probably know, Pfizer did six different trials trying to see if dofetilide would be effective in paroxysmal atrial fib, but it didn't show that. There's not a lot of data about sotalol in paroxysmal atrial fibrillation, but the class Ic's have that indication. Not only that, remember the patient population, the mean age was

about 55, 56, and young patients and they didn't have underlying structural heart disease for the most part. So I think it was very appropriate, very understandable as far as I could see.

DR. BORER: Dr. Karasik.

DR. KARASIK: This is question is probably best for Dr. Wilber, but perhaps you can address it. So we weren't allowed to use amiodarone. You weren't allowed to use amiodarone in this particular protocol, but I'm wondering what percentage of the patients had actually been exposed to amiodarone prior to the six-month exclusionary procedure? If patients had failed that drug in the past, it would suggest that it was unlikely that any other drug would be effective. So was there potentially a bias there?

DR. YAROSS: The protocol was only specific to the six months prior to enrollment. I'll have our team check and see if we have that information and provide that to you a little bit later.

DR. BORER: Okay. A couple of more -- oh, Dr. Weinberger.

DR. WEINBERGER: This is for Dr. Wilber. The OUS site number 1 did a lot better than everybody else as you pointed out, and you presented several

hypotheses as to why that could be, including previous experience with a catheter or previous AF ablation experience. And I was wondering whether or not you tested those hypotheses against the rest of the group. In other words, did people improve, did outcomes improve as more experience was garnered with the NaviStar catheter?

DR. WILBER: It's an excellent question, and it was an analysis we hoped to do, and the reason why we couldn't do it is that for most of those centers, there weren't enough volume that we could rely on their self-reported afib volume. The problem is since it's not verifiable and you'd have no hard data, I'm not sure of the value of the observation. So the question you raise is an important one, but within the context of the study, we couldn't answer it.

DR. WEINBERGER: And then one thing I'll ask you, Dr. Waldo listed as possible hypothesis for why there was some pulmonary vein shrinkage as improvement and shrinkage of the left atrial size, and I wondered whether, although this wasn't presented, whether the echocardiographic information in fact showed return of left atrial function in these patients. Did they all have LA function and

shrinkage of the LA size?

DR. WILBER: We have not yet finalized the analysis of that data. So I don't have that specifically at this time.

DR. YAROSS: I can go back and answer the previous question on amiodarone use. In the ThermoCool group, there were seven subjects who had had prior exposure to amiodarone, and in the control group there were six subjects. So 6.7 percent and 10.2 percent, and there was no significant difference between those two values.

DR. KARASIK: Thank you.

DR. BORER: I'd like to ask something about the protocol itself in the pre-randomization period and actually after randomization. You allowed a 14-day dosing interval in the AAD group. At the end of the day, the results are what they are, and I have no major concern about this, but is it reasonable to allow such a relatively short period to add multiple drugs together and titrate them, et cetera, et cetera? I mean what was the basis for selecting 14 days?

DR. YAROSS: I'll have Dr. Wilber return to the podium.

DR. WILBER: The protocol was designed as a

single drug. So a possible alternative might have been to have had multiple drugs in which case a longer window might have been appropriate, but the design of the study was to compare ablation to a single antiarrhythmic drug, and if that drug didn't work out in the two week dosing period, then it was a failure.

DR. BORER: Okay. As a follow-up to that, everyone had to have three episodes of atrial fibrillation prior to entry, and I understand that you were not capturing data on these because you couldn't. It would be retrospective. However, maybe you have some information.

Do you have any idea how long these episodes lasted and how they were aborted? This would be anecdotal, but I'd be interested to know.

DR. WILBER: We did not collect specific data on the duration of those episodes. So I could only sort of extrapolate from our own experience in the trial in those patients, but typically since the protocol definition would allow up to 30 days, the vast majority of patients had symptoms from hours to a day or two in duration and very rarely beyond that.

DR. BORER: And how were these episodes aborted generally?

DR. WILBER: Generally spontaneously. In fact, it would be rare. There was an occasional patient that we all see that after two hours of atrial fibrillation comes to the emergency room and insists on being cardioverted, but in general, most of these patients, since they've been long-time atrial fibrillation patients, know if they wait it out, their episode will stop and typically don't come to the emergency room.

DR. BORER: Okay. Also just for clarification, Dr. Waldo, you referred to the pulmonary edema, the one patient who had pulmonary edema, as having had a device-related complication.

DR. WALDO: Possibly device-related.

DR. BORER: My recollection of that case is that the three and a half liters of fluid were given to the patient during the procedure. I would have thought that one would consider that procedure-related rather than device-related, but can you just, how would it? Why was it classified as device-related?

DR. WALDO: Well, it was possibly device-related because it happened so late. The patient was discharged, don't forget, and came back, but that's the reason we called it possibly device-related

because the ThermoCool injects saline as part of its mechanism, and that could be an issue.

DR. BORER: So the injection of saline is automatic. It's not --

DR. WALDO: It's part and parcel of the procedure. And David could talk about it better than I could.

DR. BORER: But is the saline injected automatically or is it a decision by the operator to --

DR. WALDO: No, the amount of saline injected can be controlled, and there are recommendations for that in the protocol.

DR. BORER: Okay. It's not a big deal obviously. I just wanted to clarify it for myself.

DR. WILBER: The flow rate of the saline from the tip is dependent on the power, and there's certain recommendations. If the power is 30 watts or lower, it's 17 ccs per minute, and if it's greater than 30 watts, it's generally 33 ccs per minute. So that can be quite a bit of fluid over the course of a long ablation.

MS. YAROSS: Dr. Borer, if I can, I'd also like to just go back to a previous question. We were asked about the duration of the AF episodes. There

was a baseline Holter, and in the ThermoCool group, the mean AF duration in a 24-hour Holter was 8.3 hours, and this was versus the AAD group, which was 10.9. So we did have patients with significant duration.

DR. BORER: Dr. Somberg.

DR. SOMBERG: The blanking period was 90 days for the ThermoCool, but you only have 14 days for the drug. Was an analysis looked at if you -- if you looked at 90 days for both was -- if the drug had prolonged time for action and then took that period and, you know, made 90 days for the drug comparable to 90 days for that, would there be any change? You didn't do that analysis. Okay.

DR. WILBER: That specific analysis was not done, although because all of the drugs that we used had a half-life of hours, as opposed to days, at least from the standpoint of achieving adequate efficacy, the 14-ay window should have been adequate. Obviously if amiodarone had been one of the drugs, then the trial design might have needed to be different than it was.

DR. BORER: Dr. Weinberger.

DR. WEINBERGER: I'm sorry to go back to OUS 1. It's just such a striking outcome. There was

reference made by somebody that maybe the patients were a little less -- had somewhat smaller atria, maybe the patients were a little bit younger, maybe there was a little bit less hypertension, and I'm wondering whether or not in that particular group of patients who are younger and healthier, AF is frequently triggered by another supraventricular tachycardia. And the ablation of a bypass tract might be sufficient to inhibit subsequent events of atrial fibrillation. So my question was whether specifically at other sites, there was a search for other initiators of atrial fibrillation at the time of electrophysiological study?

DR. WILBER: All patients had atrial pacing as part of their evaluation procedure, and so it would be -- they have no data from any of the sites that we did collect data on other arrhythmias that the patients had and whether any other arrhythmias were ablated. None of them had, other than flutter, there weren't other arrhythmias documented other than triggering afib is another possible one or atrial --

DR. BORER: I'd like to ask again only for clarification because this is, you know, it's not nitpicking. I just want to know the answer. You used a SF-36 to assess quality of life. I'm a strong

proponent of assessing disease burden as QOL. So I like that you did that.

However, has the SF-36 ever been formally validated for arrhythmias?

DR. YAROSS: I'd like to ask Dr. Matthew Reynolds to come and address this issue please.

DR. REYNOLDS: Thanks. I'm Dr. Matthew Reynolds, an electrophysiologist from Boston, the Director of the Economics and Quality of Life Assessment group with the Harvard Clinical Research Institute and a consultant to the company.

Thanks for your question. To my knowledge, the SF-36 instrument, which, as you know, is a generic quality of life tool, has not been specifically validated in terms of a validation study in AF population. It has, however, very commonly been used in previous AF studies, including NIH funded studies and other antiarrhythmic drug studies.

DR. BORER: Okay.

DR. REYNOLDS: So there's a good body of experience with it in AF populations. In terms of a specific validation, the answer is no.

DR. BORER: And that's probably good enough but, you know, these days with several formal statistical tests used to validate QOL instruments, I

would have liked to have known, but you've answered the question. It really hasn't been.

Are there any other issues around the table?

(No response.)

DR. BORER: I have a couple of more if you'll just bear with me for a second.

On slide CP76, it says no HF-related primarily AEs reported in any of the three ThermoCool subjects. These were the patients who had heart failure, rather mild, at inclusion. So that did not include the one person who developed heart failure because that person presumably didn't have any symptoms before. Is that right?

DR. YAROSS: That's our understanding, yes.

DR. BORER: Okay. That's fine. That's great. Let me just see. Finally, the difference between OUS 1 and other centers, which is going to be I think an important topic for future discussion, the difference seemed to me to be in the effectiveness of ThermoCool which may have been due to any number of factors, all of which you mentioned. There was also a difference in the effectiveness of drugs. As I recall, for the OUS 1, at the end of the day, there was 11 percent effectiveness, and for everybody else,

17 percent. It doesn't seem like a big difference to me. But I wonder if you did some formal statistical assessment to see if it was likely that the difference was significant, you know, if there was an interaction by sight on the AAD side?

DR. YAROSS: I'll ask Dr. Berry to speak to the statistical analyses.

DR. BERRY: We can provide a formal answer after lunch but --

DR. BORER: Okay.

DR. BERRY: -- but in my quick and dirty assessment of those numbers, is it's not statistically different.

DR. BORER: Okay. If you want to check and tell us after lunch, that's fine, but that was my impression.

Now, the issue of mapping, I infer from the data that we were sent that every site mapped every patient. Is that right or wrong.

DR. YAROSS: The trial did call for CARTO mapping in all cases, yes.

DR. BORER: And it was done.

DR. YAROSS: Yes.

DR. BORER: Okay. So the OUS 1 success could not possibly have been related to the fact that

they mapped and maybe not everybody else did. Okay. That's good.

Are there any other non-statistical questions from the Panel?

(No response.)

DR. BORER: If not, I want to thank you very much. If we're allowed to, Mr. Swink, you'll have to tell me, if we're allowed to, can we take the break now instead of waiting until 10:30?

MR. SWINK: Absolutely.

DR. BORER: Okay. You know, at Government meetings, you have to be sure you're allowed to do things. Okay. We will take a 15-minute break and then we'll go onto the FDA presentation.

(Off the record.)

(On the record.)

DR. BORER: We will now have the FDA presentation. And according to my slide here, this will begin with Dr. Benjamin Eloff of the Division of Cardiovascular Devices.

DR. ELOFF: Good morning. My name is Ben Eloff. On behalf of the FDA review team, I would like to extend my thanks to the distinguished members of this Panel for their participation today.

I'm serving as the leader of the review

team for the application being discussed today from Biosense Webster, to indicate the NaviStar ThermoCool catheter for radiofrequency ablation of symptomatic paroxysmal atrial fibrillation. This application is a Panel-Track supplement to the original PMA Number P030031.

The FDA review team consists of Randall Brockman, a clinical officer; Laura Thompson, who reviewed the statistical aspects of this application; Ellen Pinnow, a postmarket epidemiologist; Martin Hamilton, from our Division of Bioresearch Monitoring; and myself, a biomedical engineer and lead reviewer.

This device has a regulatory history dating back to December 2003 when FDA approved the original IDE study to investigate the use of the NaviStar ThermoCool catheter in the treatment of symptomatic paroxysmal atrial fibrillation or AF.

Subsequently, in 2004, FDA approved the NaviStar and Celsius ThermoCool catheters for treatment of type I atrial flutter.

In August 2006, FDA approved another PMA for the NaviStar variant of the ThermoCool family only, for the treatment of recurrent drug/device refractory sustained monomorphic ventricular

tachycardia due to prior myocardial infarction in adults.

The sponsor notified FDA in October 2007, that they had completed an interim analysis and met criteria for closure of the atrial fibrillation study to enrollment.

In August of this year, the sponsor submitted the present Panel-Track PMA supplement to add an indication for treatment of drug-refractory symptomatic paroxysmal AF to the approved indications for the ThermoCool family.

FDA granted this application expedited status based on the novelty of the device to address a serious unmet public health need.

The existing indications for the ThermoCool family of devices are as follows: All variants are approved for the treatment of type 1 atrial flutter. The NaviStar variants are approved for the treatment of recurrent drug device refractory sustained monomorphic ventricular tachycardia due to prior MI in adults.

For all variants of the device, the sponsor has proposed the new indication of treatment of drug-refractory symptomatic paroxysmal atrial fibrillation, which is the primary point of

discussion today.

The ThermoCool family of devices have in common that they are deflectable catheters capable of performing electrophysiologic mapping and ablation procedures. A maximum of 50 watts of radiofrequency ablation energy is delivered through a 3.5 millimeter tip electrode that is actively cooled by an open loop irrigation system.

The ThermoCool family of devices consists of five distinct variants. The NaviStar ThermoCool, the EZ Steer ThermoCool Nav, NaviStar ThermoCool RMT, Celsius ThermoCool and EZ Steer ThermoCool.

The NaviStar ThermoCool, the EZ Steer ThermoCool Nav, and NaviStar ThermoCool RMT are approved for both treatment of atrial flutter and ventricular tachycardia, as opposed to the Celsius and EZ Steer ThermoCool catheters which are approved for atrial flutter only.

This distinction is due to the presence of a location sensor in the navigational variants which allows for generation of advanced electroanatomic maps of the heart which aid the physician in diagnosing arrhythmias and identifying specific sites for placing ablation lesions. This technology is independent of the deflection mechanism which include