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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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December 8, 2011
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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MYRON L. WEISFELDT, M.D.	Temporary Voting Member
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RALPH BRINDIS, M.D.	Temporary Voting Member
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M E E T I N G

(8:00 a.m.)

DR. BORER: Good morning. It's approximately 8:00. I'd like to call this meeting of the Circulatory System Devices Panel to order.

I am Dr. Jeffrey Borer, the Chairperson of this Panel. I am the Professor and Chairman of the Department of Medicine and Chief of the Division of Cardiovascular Medicine at the State University of New York in New York City, and my expertise is in cardiology.

I note for the record 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.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the PMA P100045 for CardioMEMS CHAMPION HF Monitoring System for patients with New York Association Class III heart failure. The CardioMEMS HF Monitoring System is a permanently implantable pressure measurement system designed to provide daily pulmonary arterial pressure measurements including systolic, diastolic, and mean pulmonary artery pressures. These measurements are used to guide treatment of congestive heart failure.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please

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state your name, your area of expertise, your position and affiliation, and why don't we start to the right with Dr. Evans.

DR. EVANS: Scott Evans, Department of Biostatistics, Senior Research Scientist, Harvard University.

DR. FERGUSON: Mike Ferguson. I'm an interventional cardiologist and the Director of the Cath Lab at Walter Reed, Bethesda.

DR. WEISFELDT: I'm Myron Weisfeldt. I'm Chair of the Department of Medicine at Johns Hopkins. I have a long history of being interested in hemodynamics and cardiovascular disease.

DR. OHMAN: I'm Magnus Ohman from Duke in North Carolina, and I'm an interventional cardiologist, clinical trial specialist at Duke Clinical Research Institute, Professor of Medicine.

DR. SLOTWINER: David Slotwiner. I'm a clinical cardiac electrophysiologist at North Shore Hospital of Medicine in Long Island, New York.

MR. BARRETT: Good morning. I'm Burke Barrett. I'm the Vice President of Regulatory and Clinical Affairs at CardioFocus, and I'm the Industry Representative on this Panel.

MR. DUBBS: Good morning. Bob Dubbs. I am the Consumer Representative, and I am chairman of my own retirement committee.

MS. CURRIER: Good morning. I'm Judy Currier, and I'm the Patient Representative on this Panel. I have a background of math and

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systems analysis. Thank you.

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

DR. JEEVANANDAM: Valluvan Jeevanandam. I'm the Chief of Cardiac Surgery at University of Chicago, and I'm Surgical Director of the Hearth Failure and Transplant Program.

DR. BRINDIS: Ralph Brindis. I'm the Senior Advisor for Cardiovascular Disease at Northern California Kaiser Permanente, general cardiologist and recovering interventional cardiologist.

DR. MILAN: David Milan. I'm a cardiac electrophysiologist at Massachusetts General Hospital.

DR. CIGARROA: I'm Joaquin Cigarroa, the Clinical Chief of Cardiology at Oregon Health and Science University and an interventional cardiologist, clinical professor.

DR. LANGE: I'm Rick Lange, Vice Chairman of Medicine at University of Texas, San Antonio, and also an interventional cardiologist in the Twelve-Way Program.

LT RUSSELL: Lieutenant Avena Russell, Designated Federal Official for FDA.

DR. BORER: Thank you very much. Let me remind everyone, if you haven't already done so, please sign the attendance sheets that are on the tables near the doors through which you entered.

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Lieutenant Avena Russell, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

LT RUSSELL: Good morning, everyone, and welcome.

I will now read the Conflict of Interest Statement and the Deputization to Voting Member Statement.

The Food and Drug Administration is convening today's meeting of the Circulatory Systems 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 Rep, 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. Code 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.

The 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. Code 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 a particular

individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the Federal Food, Drug and Cosmetic 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 discussion 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. Code 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.

For today's agenda, the Panel will discuss, make recommendations, and vote on the information related to the premarket approval application for the CardioMEMS HF Pressure Measurement System sponsored by CardioMEMS, Inc. The CardioMEMS HF System is a permanently implanted pressure measurement system designed to provide daily pulmonary arterial pressure measurements including systolic, diastolic, and mean pulmonary artery pressure. These measurements are used to guide treatment of congestive heart failure.

Based on the agenda for today's meeting and all financial

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interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Mr. Burke T. Barrett is serving as the Industry Representative, acting on behalf of all-related industry, and is employed by CardioFocus, Inc.

We would like to remind members and consultants that if the discussions involve any other products and 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.

I will now read the appointment to 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 Systems Devices Panel for the duration of this meeting on December 8, 2011:

Drs. Scott Evans, Myron L. Weisfeldt, Richard A. Lange, Michael Ferguson, David Milan, Joaquin Cigarroa, Ralph Brindis.

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

In addition, I appoint Dr. Jeffrey Borer to act as Temporary Chairperson for the duration of this meeting.

This has been signed by Dr. Jeffrey Shuren, Director for Center for Devices and Radiological Health on November 28, 2011.

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

The transcripts of today's meeting will be available from Free State Court Reporting, Inc., telephone number (410) 974-0947. Information on purchasing videos of today's meeting can be found on the FDA meeting registration desk.

The press contact for today's meeting is Karen Riley.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. James Clark at the registration desk.

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In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and any other electronic devices at this time. Thank you very much. Dr. Borer.

DR. BORER: Thank you very much, Lieutenant Russell.

I'd like to remind the public as we now proceed to the Sponsor's presentation that while public observers are invited to be present at this meeting and it is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor's presentation will be allotted 90 minutes and will be introduced by Jay Yadav, Dr. Jay Yadav, founder and CEO of CardioMEMS.

Dr. Yadav.

DR. YADAV: Good morning. Thank you, Mr. Chairman.

On behalf of the people of CardioMEMS, it's my pleasure to speak with you this morning. I want to thank you, the Panel members and the Agency, for giving us a chance to present our work over the last decade with you today.

Our goal today is to demonstrate the safety and efficacy of the CardioMEMS CHAMPION Heart Failure Monitoring System. We are all aware of the burden of heart failure both on patients, their families, as well as the healthcare system. CardioMEMS is founded on the premise that having chronic ambulatory PA pressure information could allow more effective heart failure

management leading to fewer hospitalizations.

To do this, we developed a very novel and elegant wireless, batteryless sensor technology, and then implemented it in a randomized trial called the CHAMPION Trial in NYHA Class III patients who had been hospitalized at least once in the previous year and demonstrated that hospitalizations could be reduced. The trial met all primary safety and efficacy endpoints as well as the secondary efficacy endpoints.

I'll tell you a little bit about CardioMEMS. I started CardioMEMS in 2001 with Dr. Mark Allen, who is a Professor of Electrical Engineering at Georgia Tech.

The need for CardioMEMS was really dictated by my own practice. When I was attending in the CCU, we would have many heart failure admissions, typically driven by hemodynamic decompensation that we would manage using right heart cath information. It seemed logical to wonder if having this type of information routinely might allow the prevention of decompensation and the hospitalizations we were treating at that time.

We wanted to develop an elegant, small sensor technology. So I sought out Dr. Mark Allen who is head of the MEMS Program at Georgia Tech, microelectromechanical systems, which is a way to combine mechanical and electrical components in a single chip, and it's commonly used in consumer applications such as projectors, automobiles.

Working together, we developed this novel technology.

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Because it truly is novel for medical device applications, it took several years to perfect the technology. The original sensor was utilized in the aortic aneurysm application both AAA and thoracic, and we have 8,000 patients in the U.S. with the sensor with an excellent safety record.

We reduced the size of the sensor for the second generation AAA device, and that sensor is the same as the heart failure sensor that you see today, and I believe we have passed out some of these sensors for you to look at and touch.

We also have received CE mark for the heart failure sensor.

The system is comprised of three components, the sensor which is mounted on a simple over-the-wire delivery system, electronics that the patient uses at home to take readings from the sensor and transmit them to our secure websites, and then a HIPAA-compliant interface that the healthcare providers log onto and can review the information as well as get alerts from this information.

The sensor itself is interesting and very elegant. It was developed by Dr. Allen's team on a DARPA grant to develop sensors for the combustion chamber of military jet engines. In this environment, it's not possible to have either wire connections or batteries. So they created something which seems contradictory, which is a wireless, batteryless device.

The sensor conceptually is quite simple. It's a capacitor in association with an injector coil making a resonant LC circuit. As the pressure

changes, the capacitor changes which changes the frequency. The sensor is very precise, measuring single nanometer changes in these membranes.

The second piece is the wireless communication and energy transfer. This is based on the work of Dr. Neil Gershenfeld at the MIT Media Lab where he developed passive wireless sensors, which is a very energy-efficient way to power and receive information from devices. So think of it as if you had a cell phone without a battery where the cell phone tower not only provides information, but also energizes your cell phone.

The device takes 2,000 readings per second creating a very high fidelity waveform as you see here. The patient takes an 18 second reading to make sure there's several respiratory cycles in the reading. Because the sensor is part of the vessel and because the information is turned into an electronic signal immediately at the sensor location, we do not see the undershoot and overshoot phenomena that we're all used to seeing with fluid-filled catheters.

From the very beginning, one of my concerns as a interventional cardiologist was patient safety. Having put many things in blood vessels over the last 20 years, this is a primary concern, and that's why we made the sensor so small and used MEMS technology. It is 1.5 mm across. The loops that you see are Nitinol and 10 mm across. So they're the same diameter as the Swan balloon. Therefore, the sensor gets implanted in a vessel much larger than itself, taking up less than 10% of the cross-sectional

area, and ensuring excellent flow and preventing vessel thrombosis.

Please also notice the loops come out at 90 degree angles, which this forces the sensor body up against the vessel wall encouraging rapid endothelialization and in many animal studies, by 30 days, it is fully endothelialized.

The sensor is attached to an over-the-wire delivery system. Wires loop through the sensor loops and retain it. The blue cap that you see is a release mechanism. It fits through an 11 French sheath and goes over an 018 wire.

This short video demonstrates the implant procedure. It starts with a right heart catheterization through the femoral vein. Once the Swan is in the appropriate position, the balloon is wedged, a hand injection selected pulmonary angiogram is performed to define the distal anatomy. Then a wire is passed through the Swan, and the balloon is deflated and it is removed. Then the over-the-wire delivery system is passed over that. The tether wire is released. The Nitinol loops pop open. Typically there's a bifurcation immediately distal of that. The loops are too big to go through that, and the sensor stops. It is a passive retention mechanism without causing vessel trauma. At this point, the sensor is calibrated to Swan readings. The entire sensor implant is very fast, adding only a few minutes to the right heart cath procedure.

The patient at home takes readings in a recumbent position in

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the morning at the same time every day. The information is transmitted via either a landline or a cellular connection to our servers where it is accessible to the healthcare providers that may receive alerts also automatically.

Now, one of our main concerns aside from patient safety was to make sure that not only did we make healthcare more effective in heart failure patients, but also more efficient. We're all busy in cardiology, and we did not want to add burden to the healthcare provider. We interviewed many clinical cardiologists and heart failure specialists as well as many heart failure nurses, had multiple focus groups to look at human use factors, and we designed this database and website to meet their needs. It is very intuitive, very visual, very trend based.

On the Y axis you are seeing the pulmonary artery pressures. The red line is the systolic pulmonary artery pressure. The blue line is the mean, and the green is diastolic. On the X axis you see time. You scroll across this, the individual measurements pop up in those little boxes, and the individual tracing actually can come up also in case you wanted the details of that particular transmission. There are customizable alerts that the healthcare provider can set, defining when they would get an automatic alert, either to their e-mail or to their BlackBerry or iPhone.

We also have present with us today members of our Clinical Events Committee. Dr. Miller was the Chairman of our Clinical Events Committee and Dr. Levy was a member of it. We also had members for a

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Steering Committee, Dr. Bourge as well as statistical and clinical consultants, Dr. Ogenstad or Dr. Kubo.

After myself, Dr. Stevenson will present on the ambulatory filling pressures and heart failure decompensation, followed by Dr. Adamson discussing the clinical trial design. Dr. Abraham will present the results. Dr. Holcomb will speak on statistical considerations, and Dr. Cowart will speak on regulatory aspects and medical management. And then I will conclude with comments on post-approval studies, training, and commercial support.

Thank you very much, Mr. Chairman. Dr. Stevenson.

DR. STEVENSON: Thank you very much. I'm Lynne Warner Stevenson. I'm the Director of the Cardiomyopathy and Heart Failure Program at Brigham and Women's Hospital in Boston. I have no financial relationship with CardioMEMS or any industry. I'm paying my own expenses for this event because I wouldn't miss it.

Together with some other people in this room, I've been taking care of patients with advanced heart failure for over 25 years, and we're still not able to figure out what's happening to them when they're out of the hospital.

Our children have technology to keep in touch with what they care about, and now it's our turn.

I believe that we now have an ambulatory pressure-based strategy that will help us to manage our patients out of the hospital living

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their lives and will help us keep them out of the hospital living their lives.

We've seen remarkable progress in preventing progression of mild to moderate heart failure and in treating end stage heart failure.

However, once patients have progressed to require hospitalization for heart failure, the prognosis remains discouraging because we've not been able to keep those patients out of the hospital.

We believe that we could improve the outlook for these patients by focusing on ambulatory filling pressures as a key to heart failure decompensation. The relationship between filling pressures and stroke volume is complex, with cardiac output strongly dependent on the adequacy of filling pressures in the normal heart and on moderately elevated filling pressures in the stiff heart of acute ischemia.

In chronic heart failure, maladaptive reflexes drive filling pressures much farther up, far past the optimal level. As the ventricle enlarges and mitral regurgitation develops during chronic remodeling, the relationship changes such that the best stroke volume and cardiac output are achieved at filling pressures that are closer to the normal range. At these levels, wall tension, myocardial oxygen consumption, and coronary perfusion are more favorable, and there's less stroke volume lost backwards to dysfunctional mitral regurgitation that develops from ventricular distension.

Most heart failure prognostic factors are determined by cardiac filling pressures. In addition to dominating the picture of hospitalization,

elevated filling pressures are tightly linked to disease progression and prognosis as shown in the spectrum of prognostic factors that all relate back to filling pressures.

It's the symptoms of elevated filling pressures that define Class IV, a robust predictor of bad outcome. Signs of elevated filling pressures each have been shown to predict poor outcome as does increasing diuretic requirement.

Multiple factors affect the biomarkers and the echo patterns which are well shown to predict outcome, and changes in these parameters are strongly related to changing filling pressures.

Among the hemodynamic measurements, pressures are the strongest predictors of outcome once heart failure is advanced. This is that from the ESCAPE Trial, a therapy tailored to relieve congestion in the hospital, showing that the most important hemodynamic predictors for events were the pressures in the pulmonary artery and the systemic blood pressure, not the cardiac index.

We know that hospitalizations represent not only distress and cost, but are also associated with increasing mortality as shown here in a study of over 14,000 patients. Each hospitalization increases the likelihood of death within the next two years in the first in the blue line, to the fourth in green line on the top.

With all the clinical and laboratory prognostic markers we have,

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why can't we monitor patients well enough to intervene and prevent these hospitalizations?

Well, if we could examine and test these patients every day, most re-hospitalizations probably could be prevented, but we can't. Most days we don't see these patients anywhere.

What is the best surveillance for patients at home? I used to be one of the most ardent advocates for the daily weight drill, two pounds in two days, you double the diuretic, and we thought the weights worked because changes in weight reflect changes in fluid when we see them in the hospital over a short time and during the follow-up early the first few days after discharge. Weight-guided management is better than nothing. So we thought it was good enough, and when monitoring the weights didn't work at home, we blamed the patients or we gave them scales with bigger numbers or scales that talked.

But we learned a lot from the early hemodynamic results of the COMPASS Trial. We saw that overall weights didn't change in most people prior to events. This is because the scales can't tell the difference between fluid and fat. Fluid retention often leads to gut congestion that decreases appetite, causes early fullness. So the real weight falls, but this weight loss masks the fluid retention.

On the other hand, looking over this population from the trial of ambulatory pressure monitoring, we could see that right ventricular

pressures consistently went up prior to hospitalizations. This figure doesn't show ideal examples. It shows all the patients in the COMPASS Trial prior to hospitalizations. You can see that the filling pressures rise slowly before events, about 21 days before events for patients with low ejection fraction heart failure shown here in blue. It also goes up for patients with preserved ejection fraction.

Previously we thought these events were usually flash pulmonary edema from sudden changes, but this shows that the changes are gradual for almost as long in the high ejection fraction patients as in the low ejection fraction patients.

The strategy in the previous COMPASS Trial was designed to catch these peaks of pressure and intervene in time to avert an event, but we didn't appreciate the pressure levels where these patients were living. As you can see in this arrow on the left, the average daily PA diastolic pressures were in the range of 28 to 30 mm. From this experience, we learned about the relationship of the risk of events to the median daily filling pressure, excluding the pressures around the events themselves.

You can see that the higher the chronic pressures, the higher the risk of an event. So a patient living at a high pressure all the time is at highest risk for that increment of pressure that leads to an event.

We learned from this relationship that the target is not in the mid 20's where we once aimed but down here around 18 millimeters.

It's long been known that congestion is the most limiting and crippling symptom of advanced heart failure. Then we learned that when you relieve congestion, cardiac output is not only adequate but actually optimized. So relief of congestion treats the symptoms but also treats the disease by improving many of the factors that lead to poor prognosis. However, once out of the hospital, symptoms and weights do not provide a reliable early warning system, and we miss the chance to preserve the success of the hospitalization.

Seeing congestion is necessary for relieving congestion. The events are associated with increased pressures that rise slowly over time. We know that heart failure with preserved ejection fraction shows the same trend making relief of congestion the first intervention that works for all heart failure.

We know from other intervention studies that the signal we measure has to allow a response cycle quick enough and tight enough to intervene again if necessary to avert an event.

Since earlier work, we learned the lesson that we need to reduce not just the peaks but also the plateau of pressures to maintain the stability.

Exciting also is the possibility that compensation will be more stable when we can also act in the other direction when we see filling pressures get too low so we can raise the valleys. This should help preserve

renal function and diuretic response over time.

We've learned that it's not enough to treat heart failure in the hospital, send patients home on recommended therapies, and hope everything will stay the same. We know that some patients on recommended therapies will actually improve over time and need lower diuretic doses while others will have episodes of fluid retention when they need more diuretics but not for long.

We know that ACE inhibitors and beta blockers can be slowly up-titrated over time if we keep the patient from being either too wet or too dry.

Now that we know how to follow pressures in patients at home, we can welcome change, respond to change, and help to change outcomes through truly centered care for heart failure.

And now I'd like to introduce Dr. Phil Adamson. This has been a long journey for many of us, and he's one of the people who's taught us so many things along the way and made the journey better. Phil.

DR. ADAMSON: Thank you, Dr. Stevenson. Ladies and gentlemen, thank you for serving on this Panel and for providing the opportunity to elaborate with you the trial design of the CHAMPION Trial.

My name is Phil Adamson. I'm a heart failure cardiologist from Oklahoma City, and I am the Director of the Oklahoma Foundation for Cardiovascular Research. I also serve as an Adjunct Associate Professor of

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Physiology at the University of Oklahoma Health Sciences Center.

Dr. William Abraham and I are the national co-principal investigators of the CHAMPION Trial.

I am a paid consultant for the trial Sponsor, but I do not have equity interest in the company or technology.

My discussion today will cover the study rationale, objectives, design, endpoints, and the clinical management strategy employed in the trial's protocol. Finally, I will discuss the conduct of the clinical trial.

The CHAMPION Trial objective is to determine if heart failure management based on pulmonary artery pressure reduces hospitalizations. The key to adequate scientific evaluation of this hypothesis goes well beyond whether the CHAMPION sensor correctly measures pressures, but relies on clinical use of the pressures in management of the patients in the trial.

The rationale for the CHAMPION Trial really starts with unmet clinical needs. Over the past 20 years, we've seen a dramatic, nearly 50% reduction in coronary mortality, and this is the result of the cardiology community's focuses on advancements in the treatment of acute coronary syndromes. During this time, we've also seen great advancements in chronic heart failure management, neurohormonal blockade with drugs such as ACE inhibitors, beta blockers and aldosterone antagonists, and devices such as ICDs and biventricular pacemakers have significantly improved long-term prognosis and survival.

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Despite these major breakthroughs, we've seen the number of hospitalizations for heart failure triple over the same period of time. Our success in focusing on mortality modifying interventions, both for acute coronary syndromes and chronic heart failure, has created a growing population of patients who survive and are at risk for hospitalization.

So now our clinical focus must shift from acute interventional care with emphasis on mortality reduction to apply the same level of innovation to chronic disease management with a focus on preventing hospitalizations.

The community has recognized the importance of preventing hospitalizations. Researchers have tested multiple clinical strategies involving well over 8,000 patients. Now, this list is not a comprehensive review but just lists several trials attempting to reduce hospitalizations in heart failure patients. These studies included frequent evaluation of signs and symptoms, telemonitoring of weights and blood pressures, remote monitoring of device-based diagnostics, as well as frequent biomarker assessments. To date, these trials have been inconsistent at best. Most had no impact on heart failure hospitalizations. In fact, the largest prospective multicenter trials investigating telemonitoring strategies were negative.

Let's look a little bit closer at the interventional telemonitoring strategies tested in clinical trials. Close telephone-based monitoring of symptoms and weights in three prospective clinical trials, involving over 2,700

heart failure patients, failed to reduce hospitalizations compared to standard care. These trials had such high level involvement of national study personnel that the Tele-HF principal, Dr. Chaudhry, said after the trial was published that, "We couldn't have been more involved in patient management. We went out and visited them. We had ongoing support 24 hours a day. We solved problems in the patient self-reports, for example, worrying about eating a smoked turkey sandwich or not taking medications." It seems that even having study investigators so closely involved in patient care that they knew what the patients had for lunch couldn't prevent decompensation leading to hospitalization.

Something's missing.

From a cardiovascular physiology perspective, we hypothesized that cardiac filling pressures was the missing piece of information. For many years, several of us in this room have studied hemodynamics from implanted sensors. The sensors measured pressures accurately and provided very good information, but remember, no one had seen continuous filling pressure measurements in ambulatory heart failure patients before.

As Dr. Stevenson mentioned, we discovered that pressures peaked prior to hospitalization, and we designed trials that predominantly responded to changes from the patient's baseline. These trials, COMPASS-HF and REDUCE-HF, were both underpowered and neither had a uniform approach to treating the pressures. A 21% trend for hospitalization in

COMPASS-HF was not significant statistically but did provide encouraging support of the hypothesis. REDUCE-HF had no trend for effect but was terminated early and could not assess the trial's hypothesis.

From these trials, however, we learned many previously unknown aspects of heart failure pathophysiology. First, patients with high filling pressures were at the highest risk for hospitalization even when traditional clinical assessments were stable. We discovered that lowering those pressures in patients with high filling pressures lowered their event rates, and third, the protocols assumed that providers knew how to treat pressures, but we found that education and guidance was required for physicians to adequately respond.

We called upon these lessons to formulate a trial that appropriately test the hemodynamic management hypothesis. This is the CHAMPION Trial design. A better way to test this hypothesis was to provide actionable pressure information supported by treatment guidelines and ongoing education. We felt this approach was the best way to improve clinical outcomes.

As mentioned, over the 15 years, we've learned a great deal about the relationship between pulmonary artery pressures and heart failure, and these key elements obtained after significant effort and study were implemented in the CHAMPION Trial design.

As you can imagine, the CHAMPION Trial was designed to be

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different from previous hemodynamic studies.

Let's now review the details outlined in the FDA approved study design.

The trial was a prospective, multicenter, randomized controlled, single-blinded clinical trial that enrolled subjects with persistent New York Heart Association Class III heart failure symptoms regardless of ejection fraction. The enrollment sites included a mixture of academic and community-based facilities. After successful implantation of the CardioMEMS sensor, the protocol was designed to enroll 550 patients who were randomized to a 1:1, to a treatment group or to a control group. Patients in both groups were implanted, and both groups daily uploaded pressure information from home.

An important design feature of this trial was that all patients remained in their original randomized group until the last patient finished six months of follow-up. This allowed a preplanned, supplementary analysis of efficacy endpoints after an average of 15 months of experience.

Standard heart failure management was provided to both groups. The intervention tested in this trial was that the treatment group had active medical management of their pulmonary pressures added to their standard of care. To accomplish this, investigators did not have access to pressures from the control group.

To further support patient blinding, scripted calls were made

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when pressure-based medication changes were required in the treatment group. The frequency of calls was carefully matched to the control group, again using protocol-defined scripts without medication changes.

Now, let me illustrate the information flow in this trial.

Patients uploaded pressures daily, which were automatically displayed on a secured website. The investigator team reviewed the pressure information at least weekly. The website had an automatic e-mail notification system that contacted investigators if an individual subject's daily pressures were outside a user-defined threshold. Physician investigators then made treatment decisions and discussed those with the patient if necessary.

The website also automatically notified the investigator if pressures had not been reviewed in the prior week.

The Sponsor reviewed automatic alerts and monitored compliance with the protocol providing nursing follow-up as needed.

Inclusion and exclusion criteria are listed here and are in your Panel packet. In brief, New York Heart Association Class III heart failure patients with a previous hospitalization were enrolled. Patients had to be stable, maximally tolerated medical management as recommended by the AHA/ACC guidelines. Specific pulmonary artery anatomic criteria were determined at the time of implantation procedure.

As one would expect, patients with a history of recurrent pulmonary embolism or deep vein thrombosis were excluded from the trial.

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The CHAMPION Trial had two primary safety endpoints. In the first, we evaluated whether or not the freedom from device- or system-related complications at six months exceeded a pre-specified OPC of 80%. In the second analysis, we evaluated whether or not freedom from pressure sensor failures at six months exceeded 90%.

Our tests of hypotheses were based on exact binomial test methods.

The CHAMPION Trial had one primary efficacy endpoint. In the associated hypothesis, the study evaluated whether or not the rate of heart failure hospitalizations was lower than the rate observed in patients receiving standard care. The statistical method used to estimate hospitalization rates and to test for significant group difference was based on a pre-specified negative binomial regression approach.

Now, these statistical methods were agreed upon with the FDA prior to beginning the trial.

The CHAMPION Trial had four secondary efficacy endpoints. To address our goal of lowering the plateau as mentioned by Dr. Stevenson, we evaluated the change in pulmonary artery pressure over time, additionally, the proportion of subjects hospitalized for heart failure, days alive out of the hospital for heart failure, and quality of life as measured by the Minnesota Living with Heart Failure Questionnaire.

The CHAMPION Trial Steering Committee and national principal

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investigators developed a pressure management strategy that was implemented in the protocol, and this strategy was used to guide investigators' treatment of pressure. The trial's investigators and the Agency were notified in the protocol that pressures were to be treated specifically according to the guidelines outlined in Appendix E. Additionally, Appendix E states that specific recommendations would be made based on these guidelines.

I'd like to provide you with the specific instructions outlined in Appendix E since this is a part of the protocol that had such an important part of appropriately testing the trial's hypothesis.

Again, we intended for this part of the protocol to provide a specific treatment strategy to respond medically to elevated pressures in the treatment group. This was the intervention tested in the trial. An elevation of pressure, either from baseline or chronic, was first assumed to be from excess intravascular volume and was treated with an increase or change in diuretic management. If pulmonary pressures remained elevated, the mechanism of the pressure increase was assumed to be related to vascular resistance. This led to a recommendation of vasodilator therapy.

Subsequent increases in pressures above the patient's stable baseline were considered to arise from acute volume accumulation, and this led to changes in diuretic therapy until the baseline pressures were reestablished.

If pulmonary pressures remained high despite all medical management, investigators were encouraged to evaluate other potential etiologies such as dietary indiscretions or medication non-adherence, and investigators also were encouraged to look for additional comorbidity such as sleep apnea.

Finally, hospitalization was encouraged in the treatment group if patients remained clinically unresponsive to outpatient medical therapy.

It's important to remember the ultimate treatment decisions for individual patients were always made by the local site investigators who were in direct contact and control of the patient's care.

In addition to specific guidelines provided to treat pressures in the treatment arm, an extensive general education and training program was provided to the sites. This impacted both arms of the trial. These efforts included multiple investigator meetings, conference calls between local investigators and the national principal investigators, and multiple newsletters. These efforts started at the site initiation and continued throughout the trial and included efforts aimed at investigators and coordinators. All of the educational efforts were made to encourage standard of heart failure care.

Now, let's review the study conduct. The CHAMPION Trial represents the largest and longest duration of hemodynamic monitoring trial performed to date. The trial design was the result of significant collaboration

between the national principal investigators, the steering committee, and the Sponsor, and was agreed upon and approved by the Food and Drug Administration.

After extensive feasibility studies demonstrated that the sensor was accurate and the patient home electronics as well as the information website were user friendly, the CHAMPION Trial began.

The first patient entered the trial in August of 2007. Safety was closely monitored and reviewed before subsequent increments of patients and study sites were allowed. Ultimately, 550 patients were enrolled at 64 U.S. sites with the last patient enrolled in mid-2009 and the last patient reached 6-month follow-up in early 2010.

The PMA submission we are reviewing today was submitted in December of 2010.

The CHAMPION Trial was executed with close oversight of several important and independent committees. The Clinical Events Committee was staffed by six experienced heart failure trialists and led by Dr. Alan Miller. It was blinded to the patients' randomized status and determined the relationship of all adverse events. This group adjudicated all clinical endpoints, including whether hospitalization for heart failure.

The Data Safety and Monitoring committee, led by Dr. Joanne Lindenfeld, interacted with the Sponsor and the FDA to monitor safety as the trial progressed. Data was stored and analyzed by an independent center

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with an independent statistician liaison.

Now, I'd like to point out how the trial's protocol identified the responsibilities of the national PIs and the Sponsor. Monitoring by the national PIs in this trial provided assurance of protocol compliance, which encouraged uniformity of pressure-based treatment strategies. The FDA-approved protocol used in this trial stated, "Consultation with the national PIs is encouraged to optimize the success of medical management of pulmonary artery pressures." National PIs were available for teleconferences with investigators and hemodynamic rounds formats along with other educational activities such as investigator meetings.

The standard operating procedure which was included in the IDE dated June of 2007 directly called for the Sponsor also to monitor adherence to the protocol. Furthermore, the Sponsor was expected to make specific recommendations to investigators about Appendix E guided medical changes. Manual e-mail alerts and inquiries were expected of the Sponsor according to this SOP and were to be based solely on pressure information. The Sponsor did not control patient care and did not implement treatment in patients. If recommendations were made, the investigator was ultimately responsible for deciding to change patient's medical management in the context of the investigator's relationship with the patient.

I'd like to go over the e-mail alert system that was in place for the CHAMPION Trial. First, automated e-mail alerts were generated by the

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website if pressures exceeded a preset alert threshold, and these were sent directly to the design study personnel as you can see in this one sent to me. These e-mails provided detailed information about systolic, diastolic, and mean pressures for that day's transmission and included weight forms for review. The e-mail provided a link that directly allowed the user to go to the CHAMPION URL website to allow easy login and review of trends to help with decision making.

These e-mails were sent directly to the investigators and simultaneously to a CardioMEMS automated review process. The investigators caring for the patient was then expected to make medication changes according to the protocol. Worsening pressures or unusual readings were flagged and directed to study Sponsor personnel consisting of expertly trained clinical nurses. A small number of e-mails were then generated by the Sponsor's nurses and sent directly to the investigators and forwarded to the study's national principal investigators.

The content of those e-mails included one of two specific themes. First, the Sponsor's clinical nurse could inquire about how the investigator team planned to implement the protocol-mandated medical responses for pressures in question. Secondly, the e-mails could contain a review of how the protocol guidelines would apply to that specific patient's treatment. Again, the steering committee designed this part of the protocol and expected the Sponsor and national principal investigators to provide this

level of supervision to ensure that the trial's hypothesis was adequately tested.

The two types of manually generated e-mails to investigators are illustrated here using actual e-mails sent during the course of the trial. These e-mails are provided in larger format in your Panel packet.

An inquiry e-mail is shown on the left side of the slide, an inquiry e-mail displaying pressures and illustrating that they were persistently above recommended levels.

A recommendation e-mail is illustrated on the right side of this slide. The content of these e-mails illustrated the worrisome pressure trends and provided information about how the protocol treatment guidelines may apply. Occasionally local site investigators and coordinators would discuss treatment guidelines with one of the two national principal investigators. Again, ultimate decisions to apply protocol therapy guidelines were made by individual local site investigators responsible for the patient's care.

To put these communications into perspective --

DR. ZUCKERMAN: Excuse me, Dr. Adamson. Per FDA's conversation with Dr. Yadav and Mr. Cowart this morning, we agreed that data that has not previously been reviewed by FDA would be noted in your presentations. So I would like for the transcriptionist to indicate that that prior slide has not been reviewed in detail by FDA, number one, and if you can clearly indicate in your presentation, and other speakers for the

company, which data have not been reviewed in detail by FDA. Thank you, sir.

MR. ADAMSON: You're welcome.

This slide and data has not been reviewed by the FDA, and what this slide does is puts the communications into perspective. There were 44,000 PA pressure readings from treatment patients that were uploaded to the website. The investigators logged in 12,750 times according to the protocol and executed the treatment strategies after review of the pressures at the local sites.

During this time, 193 recommendation e-mails were sent, and those are shown in red.

Now, let me show you how this was done by giving you a couple of patient examples. Let me first orient you to the graph shown on the upper right-hand side of the slide. You've actually seen this before in Dr. Yadav's presentation. The Y axis is pressure in millimeters of mercury, and the X axis is time over six months. The red line represents the daily pulmonary artery systolic pressures, the green line diastolic, and the blue line the mean PA pressures.

This patient had unexpectedly high pulmonary pressures at implant that were not apparent from physical examination or other clinical assessments. The initial intervention was to increase diuretic therapy, which had some effect, but pressures remained elevated. A long-acting nitrate was

added next, and over the next few weeks you can see that the pressures responded nicely and remained stable during the follow-up period.

In the second patient example, shown in the lower right-hand side, it's clear that the patient's pressures are increasing. This suggested a change in volume, but the addition of hydrochlorothiazide to the loop diuretic therapy did not adequately control pressures. This time the hydralazine dose was increased as was the loop diuretic dose, and the pressures responded nicely. Later, another increase in pressures was detected, and this second event was control by an increase in the patient's loop diuretic therapy, again successfully restoring pressures to baseline.

Now, we all know how complex heart failure polypharmacy can be, and these examples illustrate the profound window in the heart failure pathophysiology that implantable hemodynamic monitoring can provide. This data enabled the physician to identify high pressures that many times can't be detected using traditional methods, and our failure management system provided a means to monitor the effect of medication changes with the goal of maintaining the health of the patient: the right medication at the right time with the ability to monitor effect and tailor intervention.

So, in summary, it's clear that heart failure hospitalizations remain a serious problem. We tried several ways to reduce this burden, and they simply aren't adequate to meet the clinical need.

The CHAMPION Trial design is based on a robust database

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developed over several years of experience with implantable hemodynamic monitoring, and this database strongly supports the hypothesis that pulmonary artery pressures are the key lesion that leads to heart failure symptoms. The CHAMPION Trial was built on this experience, and it adequately is designed and empowered to assess whether monitoring pulmonary pressures can improve our ability to manage heart failure.

It's a real world trial and included academic and community-based practitioners. Investigators included heart failure specialists, interventional cardiologists, and electrophysiologists supporting the generalizability of the results.

Finally, rigorous design features provided in the protocol allowed excellent execution of this trial, and a uniform approach to pressure-based heart failure care. The methods used in the execution of this trial now constitute a rich database to generalize educational and training efforts to maximize the potential for widespread application of the methods.

I certainly appreciate your attention, and now I'd like to introduce my co-principal investigator, Dr. William Abraham, who will discuss with you the results of the CHAMPION Trial.

DR. ABRAHAM: Good morning, and thank you to the FDA and to the Panel for the opportunity to be here.

As mentioned, my name is William Abraham. I'm a Professor of Internal Medicine and Director of the Division of Cardiovascular Medicine at

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the Ohio State University. In my capacity as co-principal investigator for the CHAMPION Trial, I'm a paid consultant to CardioMEMS. However, I hold no equity in the company.

My role here is to provide you with the results of the CHAMPION Trial. I am supportive of this PMA submission because it represents a substantial step forward in our treatment of heart failure patients.

The CHAMPION Trial was performed across 64 participating U.S. sites, including both academic and community hospitals with a broad geographic distribution as shown on this slide. The majority of sites were non-academic. Site principal investigators and managing and implanting physicians included heart failure specialists, interventional cardiologists, and electrophysiologists.

These sites performed medical chart screening on 723 potential CHAMPION Trial subjects, of which 98 were chart screened failures and 625 went onto a screening visit. Fifty subjects in the latter group were screened failures, and 575 subjects went on to attempted right-heart catheterization. Twenty-five of these subjects were not implanted with the CHAMPION sensor for the reasons shown on the slide. While these 25 patients were not randomized and thus were excluded from the efficacy analysis, they were included in the safety analysis.

Thus, 550 patients were implanted and randomized 1:1 either

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to the treatment arm or to the control arm. Specifically, 270 patients were randomized to the treatment arm, and 280 patients were randomized to the control group.

There were 26 study exits in each group that occurred prior to the 6-month follow-up visit. Most study exits were due to death, 15 in the treatment group and 20 in the control group. Other causes detailed on this slide accounted for relatively few study exits, while 244 patients completed 6-months follow-up in the treatment group and 254 patients completed 6-months follow-up in the control group. All 550 randomized patients were included in the primary safety and primary and ancillary efficacy analyses according to the intent-to-treat principle as outlined in the statistical analysis plan.

At baseline, the study groups were well matched. There were no statistically significant or clinically meaningful differences between the treatment and control groups. The average age was about 62 years, similar to other randomized controlled trials in heart failure. Minority populations, particularly African-Americans, who comprised 23% of the study participants, were generally well represented. More than 20% of patients had a preserved left ventricular ejection fraction and the prevalence of comorbidities was as expected for a heart failure population.

The utilization of device therapies was also high with about two-thirds of patients having either a CRT, CRT-D, or ICD device.

The baseline use of evidence-based guideline recommended heart failure medications was high, well balanced between the two groups, and consistent with other recent trials in heart failure. All but three patients who were not treated with an ACE inhibitor, ARB, or beta blocker had source documentation of intolerance. The use of neurohormonal inhibitors and antagonists and loop diuretics was high particularly when one considers that 21% of CHAMPION patients had an ejection fraction above 40%, a group in which the mandate for such therapies is unproven and unsupported by evidence-based guideline recommendations.

A concern may be raised about the doses of neurohormonal antagonists used in this trial as not being maximal. Maximal means the largest dose that can be utilized in treating patients. Optimal describes the highest tolerated dose for a given patient.

In heart failure clinical trials, including those with forced titration protocols, the actual dose achieved for most drugs is about 50% of maximal. CHAMPION achieved or exceeded these levels.

Now, let's turn our attention to the primary results of the CHAMPION Trial.

As shown on this slide, both primary safety endpoints were met with very high degrees of statistical confidence underscoring the remarkable safety of the device. As noted previously, there were two primary safety endpoints in the CHAMPION Trial, freedom from device- or system-related

complications and freedom from pressure sensor failures assessed at six months. Analyses of these endpoints included all 575 enrolled patients.

Since all enrolled patients underwent an implantation procedure, and all randomized patients were implanted with a pressure sensor, comparison of safety endpoints to pre-specified objective performance criteria was performed. These criteria were based upon complication and failure rates for other heart failure monitoring devices and similar to objective performance criteria accepted by the FDA.

As shown, freedom from device- or system-related complications at 6 months was 98.6% with a lower confidence limit of 97.3%, and freedom from pressure sensor failures at 6 months was 100%. This means that there were very few device- or system-related complications and no pressure sensor failures during the 6-month period of primary follow-up.

In addition, no device- or system-related complications or pressure sensor failures occurred after six months, supporting the long-term safety and durability of the device and system.

Let me turn your attention to the primary efficacy endpoint. The primary efficacy endpoint of the CHAMPION Trial, the rate of heart failure hospitalizations at six months, was met with a very high degree of statistical confidence and clinical significance. At 6 months, there were 84 heart failure hospitalizations in the 270 treatment patients yielding a hospitalization rate of 0.32 compared to 120 heart failure hospitalizations in

the 280 control subjects for a hospitalization rate of 0.44 yielding a significant relative risk reduction of 28% associated with a p-value of 0.0002.

To place this result into further perspective, the number needed to treat to prevent one hospitalization over just six months is eight. This NNT compares very favorably to other standard approaches used in cardiovascular disease and heart failure management.

Another way of looking at this primary outcome at six months and its durability over the full duration of study follow-up is through this graphical representation of cumulative heart failure hospitalizations. The significant 6-month reduction in heart failure hospitalizations seen in the treatment group depicted in red is durable over an average follow-up of 15 months with a relative risk reduction of 37% over this full duration of follow-up. Rather than any indication of loss of treatment effect, there is an apparent improvement in efficacy over prolonged follow-up with a relative risk reduction in heart failure hospitalizations of 45% from 6 months to the end of study.

As noted by Dr. Adamson, there were four pre-specified secondary efficacy endpoints in the CHAMPION Trial. All four were met.

Hierarchical testing was pre-specified in the CHAMPION statistical analysis plan for the assessment of these secondary endpoints. The first of these was the change in mean pulmonary artery pressure over six months measured as an integral of the pressure curve. This cumulative

measure of a change in pressure over time includes pressure changes throughout the entire period of follow-up rather than simply at the beginning and end of the study. The use of the CHAMPION sensor resulted in a significant reduction in mean pulmonary artery pressure while mean PA pressure increased slightly in the control group.

The second of the four pre-specified secondary efficacy endpoints was the proportion of patients hospitalized for heart failure over six months. This endpoint was also met. Significantly fewer treatment patients were hospitalized for heart failure compared to controls. Fifty-five of the 270 treatment patients, or 20%, were hospitalized compared to 80 of the 280 control patients, or 29%.

The third of the four pre-specified secondary efficacy endpoints was the number of days alive and out of the hospital for heart failure over six months. This endpoint was also met. This endpoint has been difficult to meet in prior heart failure clinical trials, and the magnitude of difference between treatment and control is often difficult to interpret even when positive since most patients are alive without hospitalization over the duration of the study particularly when the study duration is six months or less. Thus, it is informative to review this endpoint over the full study duration where the difference between treatment and control increases to more than 12 days.

The fourth or last of the four pre-specified secondary efficacy

endpoints was quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire at six months. This endpoint was also met. Recall that a lower score is a better score, indicating better quality of life, according to the quality of life instrument used. At six months quality of life was significantly better in the treatment group compared to the control group. The magnitude of difference of 5.4 points compares favorably to other proven successful approaches in the treatment of heart failure. For example, the average effect on this quality of life score seen with an ACE inhibitor or a beta blocker is about three to five points.

In sum, all four of the four pre-specified secondary efficacy endpoints were met in the CHAMPION Trial.

The only pre-specified subgroup analysis of the CHAMPION Trial was by left ventricular ejection fraction, comparing those with a reduced versus a preserved ejection fraction using an ejection fraction cutoff of 40%. In regard to the primary efficacy endpoint of heart failure hospitalizations, this analysis demonstrates the clinical benefit of therapy guided by the pulmonary artery pressure monitor in both groups of patients.

The finding of reduced hospitalizations in the preserved ejection fraction group is particularly important as no previous trial of drug or device therapies has proven effective in this group of patients.

At the FDA's request, a post hoc subgroup analysis of the heart failure hospitalization rate according to gender was performed which

demonstrated a significant difference. You may be asked to comment on this. Compared to the treatment group, more than twice as many women in the control group, seven versus three, died within six months. This raises the possibility of mortality as a competing risk contributing to the reported difference in outcomes with respect to gender. This possibility is supported by the Kaplan-Meier curve shown on this slide depicting freedom from heart failure hospitalization or death in women. The trend for worse outcome in women seen for heart failure hospitalization alone is completely reversed when mortality is also considered.

Now, let me take you through the adverse events summary. There were 81 anticipated adverse events occurring in 69 patients within 30 days of the implant procedure. In interpreting these results, it is important to note that adverse events were reported regardless of causality to the implant or implant procedure and using the broadest of definitions, including events such as upper respiratory infections, urinary tract infections, bronchitis, and atrial and ventricular arrhythmias occurring remote from the implant procedure. As will be shown, the majority of these events were not device or procedure related. They were mostly attributable to infections and arrhythmias and were of little clinical consequence.

Here are the 81 investigator-reported anticipated adverse events reported on the prior slide and all other investigator-reported adverse events. Three of the latter were adjudicated as procedure-related events.

The FDA took the total number of anticipated adverse events, regardless of device or procedure-relatedness, and added the three procedure-related adverse events to derive a total of 84 events in 72 patients and a 30-day procedure and anticipated adverse event rate of 13.1%.

This table shows all device and procedure-related adverse events, including the 8 device- or system-related complications reported for the primary safety endpoint, 9 procedure-related adverse events, and 17 device-related adverse events. We took a conservative approach by including 16 device-related events reported by the investigator but not adjudicated as such by the Clinical Events Committee. These 34 events result in a device or procedure-related adverse event rate of 5.9%.

Let's take a closer look at the nature of the device- or system-related complications. A device- or system-related complication was defined as any adverse event that was or was possibly related to the system and at least one of the following: was treated with invasive means, resulted in death, or resulted in the explant of the device. As noted previously, at six months, there were eight device- or system-related complications. The details of these eight events are presented on this slide and in the clinical study report. Of the eight DSRC, two events, the sensor did not release and in situ thrombosis associated with the Swan-Ganz balloon, were adjudicated by the CEC as definitely related to the device or system. The six other events were adjudicated as possibly related.

This abbreviated SAE table lists serious adverse events by major category and by treatment group. Using standardized categories, the majority of SAEs were attributable to cardiac disorders; respiratory, thoracic and mediastinal disorders; and infections and infestations. As noted, the vast majority were not device or procedure related.

The lower SAE rate observed in the treatment group was primarily due to the reduction in heart failure hospitalizations. This figure shows Kaplan-Meier curves for all-cause mortality over six months' follow-up. The event rates are low and the confidence intervals are broad, so that there is no statistically significant difference between treatment and control groups.

Remember that the CHAMPION Trial was not designed nor adequately powered as a mortality study.

However, using a conventional time to first event analysis, combining mortality from any cause or heart failure hospitalization, a common primary endpoint in heart failure clinical trials, there is a statistically significant 31% relative risk reduction in the treatment group compared to control subjects. This observation also supports the efficacy of a CardioMEMS pulmonary artery pressure monitoring system.

Let's take a look at how these improvements in the treatment group were achieved. The premise behind the CHAMPION Trial was that ongoing knowledge of pulmonary artery pressures would drive medication

changes that would lower pulmonary artery pressures and improve outcome assessed as a reduction in heart failure hospitalizations. This proved to be the case.

On average, there was nearly one incremental medication change per patient per month in the treatment arm versus the control group. This difference was driven entirely by knowledge of pressure, and the number of non-pressure-based medication changes was the same in the two groups.

This latter observation is shown on this slide in data not yet reviewed by the FDA. There were about 1,060 non-pressure-based standard of care medication changes made in each group over the first 6 months of follow-up.

In addition, this slide demonstrates that other standard of care heart failure interventions, such as treatment of sleep apnea, were well balanced between the groups during follow-up.

Thus, the only difference in patient care between the treatment and control groups was the 1404 pressure-based medication changes shown on this table. This amounts to 0.88 pressure-based medication changes per patient per month.

The most common medication changes were up or down titration of loop and thiazide diuretics. Guiding diuretic changes by pressure resulted in no significant change in the net average diuretic dose from baseline to six months as will be shown on the next slide.

This slide depicts the change from baseline in total daily doses of major heart failure medications. Loop diuretics are normalized to furosemide-equivalent doses. ACE and ARBs are normalized to enalapril-equivalent doses. Beta blockers are normalized to carvedilol-equivalent doses.

In the CHAMPION Trial, there were relatively minor but significant increases in ACE and ARB and beta blocker dosing in the treatment group compared to the control patients. As noted, the most common medication changes were up or down titration of diuretics such that the average change in loop diuretic dose between the two groups was not statistically different at six months. Significant up-titration of long acting nitrates also occurred in the treatment group as driven by protocol recommendations for pressure management.

This slide presents an example of a protocol specified e-mail communication intended to support pressure-based medication change. Please notice that the recommendation made regarding an extra dose of diuretic is consistent with the guidelines presented in Appendix E of the study protocol. You may see other examples of e-mail communications in the FDA presentation. These are consistent with the guidelines outlined in Appendix E and the ACC/AHA heart failure guidelines, and we are prepared to speak to these individual communications in more detail during the question period later today if desired.

For now, let's take a look at the frequency and type of these e-mail communications and their impact on pressure-based medication changes in data not yet reviewed by the FDA. The frequency of these e-mail communications was low and became lower over time. During the first six months, about half of these were inquiry e-mails and half were recommendation e-mails as described earlier by Dr. Adamson.

As the rate of such e-mails fell, the distribution of e-mails shifted to inquiry e-mails, and no e-mails were sent after patient unblinding. Fewer than 10% of pressure-based medication changes were made on the basis of these e-mails, and only about 5% during the first 6 months were made in response to a recommendation e-mail. Thus, 90% of the pressure-based medication changes were made independently by the investigator. The percentage of pressure-based medication changes made independently by the investigator increased to 93.4% after 6 months and to 100% after unblinding.

To put this into perspective, of the 1404 pressure-based medication changes, only 61 were made within 72 hours of a recommendation e-mail.

The principal findings of the CHAMPION Trial confirming the underlying premise of the study are summarized on this slide. As confirmed by the results of this prospective, randomized, single-blind parallel control trial, monitoring of pulmonary artery pressure resulted in a significant

number of medication changes that significantly lowered pulmonary artery pressure. This pressure reduction was associated with a highly significant and clinically meaningful reduction in the risk of heart failure-related hospitalization as well as a better quality of life at six months.

As noted earlier, patients remained in their single-blind state until the 550th patient reached 6-months' follow-up to allow for a prolonged follow-up evaluating the durability of treatment effects over a longer period of time. The average follow-up in the CHAMPION Trial was 15 months with the longest patient follow-up being 30 months.

Safety and efficacy, secondary and supplementary analyses were performed over this full study duration. Some of these analyses were presented earlier, and selected analyses will be presented in greater detail now.

This full study duration analysis further supports the safety and reliability of the CHAMPION pulmonary artery pressure measurement system as no device- or system-related complications or pressure sensor failures occurred after six months. Such a safety record for an implantable device used in cardiovascular medicine is remarkable.

Over the entire duration of follow-up, there were 158 heart failure hospitalizations in the 270 treatment patients resulting in a hospitalization rate of 0.46, compared to 254 heart failure hospitalizations in the 280 control subjects for a hospitalization rate of 0.73, a significant

relative risk reduction of 37% and a number needed to treat to prevent 1 hospitalization over 15 months of just 4. This result was shown graphically earlier in the presentation.

The reduction seen in heart failure hospitalizations occurred with no increase in non-heart failure hospitalizations at six months and over the full duration of study follow-up. Thus, there was no tradeoff in heart failure hospitalizations for non-heart failure hospitalizations.

Kaplan-Meier curves for mortality over the full duration of follow-up until patient unblinding also supports the long-term safety of the pressure monitoring system. The analysis demonstrates no difference between groups with a hazard ratio of 0.81 favoring the treatment group.

Time to first event analysis, combining death from any cause and heart failure hospitalization over the full duration of study, also strongly and significantly favors the treatment group with a 27% relative risk reduction in this combined endpoint.

Further support for the efficacy of the CardioMEMS Pulmonary Artery Pressure Monitoring System may be seen following unblinding of the trial in data not yet reviewed by the FDA. The lowered rate of heart failure hospitalization in the treatment arm was maintained, and the higher rate of heart failure hospitalization in the control group during blinded follow-up was lowered to a comparable level.

Parenthetically, no inquiry or recommendation e-mail

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communications were sent following unblinding.

Finally, let me address some specific FDA trial concerns. The FDA is concerned that we made specific treatment recommendations for the treatment group only. A uniform, high-level standard of care was provided for both groups, as is evident in the low rate of heart failure hospitalizations seen in the control arm and the balanced standard of care interventions shown to you earlier.

Pressure management for the treatment group was an essential part of implementing this new treatment paradigm. We designed Appendix E to be different from previous studies in making specific recommendations, and consultation with the PIs was recommended.

The FDA is concerned that the level of interaction between the Sponsor and clinical investigators was inconsistent with FDA expectations. I want to remind you that Appendix E of the protocol was designed and revised with FDA oversight.

The FDA is concerned that these actions may bias the results. The measures put into place to assure a high level of investigator compliance with PA pressure goals was an integral part of the protocol and testing of the hypothesis.

Finally, concern is raised that these measures would not be duplicated in the postmarket setting. While Dr. Yadav can speak to this issue in a more authoritative way than I can, the company has made a commitment

to education and support designed for the postmarketing setting. In this regard, many approved devices require higher levels of postmarketing support.

In summary, the CHAMPION Trial met all pre-specified primary and secondary safety and efficacy endpoints. I will say that again because it's so important. The CHAMPION Trial met all primary and secondary safety and efficacy endpoints.

Heart failure management using the CardioMEMS Pulmonary Artery Pressure Monitoring System resulted in a significant reduction in heart failure hospitalizations, specifically a 28% reduction in heart failure hospitalizations at 6 months. Based only on the 6-month result, this result is clinically meaningful. For every 1,000 heart failure hospitalizations occurring today, in the intended patient population, use of the CardioMEMS Pulmonary Artery Pressure Monitoring System would result in avoidance of 280 of these heart failure hospitalizations, and again, that's over just 6 months.

Device and procedure safety and device reliability were excellent and unprecedented for a heart failure device trial. In addition, the safety and effectiveness of the device was maintained during longer-term follow-up. Significant improvements in pulmonary artery pressures, the proportion of patients hospitalized, the number of days alive out of the hospital, and quality of life were also seen in the treatment group.

A 37% reduction in hospitalization rate was seen over the full

duration of study, and no additional device- or system-related complications or sensor failures were seen.

The safety of the CardioMEMS Pulmonary Artery Pressure Monitoring System is truly remarkable when taken on its own and particularly when viewed in the context of other implantable devices used in the management of heart failure.

In conclusion, the risks of this system are low, the benefits are high, and thus the CHAMPION Trial demonstrates a highly favorable risk/benefit profile for the CardioMEMS Pulmonary Artery Pressure Monitoring System in the intended patient population. The CardioMEMS CHAMPION Heart Failure Monitoring System represents a significant improvement in heart failure management for patients with New York Heart Association Class III heart failure and a heart failure hospitalization in the last 12 months leading to fewer heart failure hospitalizations and better patient quality of life.

I would now like to invite Dr. Holcomb to the podium.

DR. HOLCOMB: Good morning. Thank you, Dr. Abraham.

My name is Richard Holcomb. I'm a statistical consultant to CardioMEMS. I have received consulting fees from the company, but have no other financial disclosures to make.

My comments to you this morning will be brief.

You have heard a presentation on the results from the

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CHAMPION study from the Sponsor. You will also be hearing shortly the results of an independent assessment presented by the Food and Drug Administration. We believe that those results will reconfirm that the primary and secondary endpoints were met when analyzed using the pre-specified statistical methods contained in the original approved protocol and statistical analysis plan.

Two other observations will possibly be made. Other analyses approaches to event count and model such as that used in the study will be used to explore the clinical study results. Most other realistic candidates for these modeling efforts will lead also to significant findings. Not surprisingly, there are some models or approaches that can result in non-significant borderline results.

The results from a tipping point analysis may also be shared with you to address the issue robustness. The observed differences in hospitalizations, the primary endpoint for the study, 84 versus 120 or a difference of 36 events, would have to be reduced by 13 events or equivalently a reduction in the relative risk of 28% to 16%, not a trivial number to lose statistical significance.

We believe that it should also be kept in mind that the results for the primary endpoint have a p-value of .0002, not a borderline value. There was also consistency in the significance of the findings across all primary and secondary analyses in both the original follow-up period and the

extended follow-up period. These are all measures of robustness.

We believe that you will also be presented with examples of the principles of appropriate study design and the importance of avoiding bias in clinical studies. For the record, we entirely support these principles of good study design that you will hear.

However, the proper application of good study design principles must be informed by the study protocol involved. You will hear that the two study arms are treated differently as a potential criticism. This is not an example of bias in our view. The treatment interventions in the two study arms differed by design. In the treatment group, there was standard of care plus a protocol-driven attempt to effectively manage PA pressures; in the control group, only standard of care.

The CHAMPION study took extraordinary lengths to otherwise achieve comparability between the two study groups, including implanting of the device in control subjects, collection of data on PA pressures without use of them in the control group, and additionally matching every telephone call that was made in the treatment group to a random telephone call in the control group.

You will hear that subjects were blinded only in the study treatment group. Yes, this was a single-blind study. Investigators, of course, could not be blinded. By protocol, they had to consider the PA pressures under the management of the treatment of subjects.

Most importantly, the final evaluators of the primary study endpoint, members of the CEC, were blinded to the study group.

In summary, we believe that treatment interventions differ by design. We do not view this as an indication of study bias. Yes, treatment interventions to directly mediate PA pressures were intended to indirectly reduce the risk of HF hospitalizations as an overall goal. There was, however, no attempt by any communication by the Sponsor to influence whether or not any given patient got hospitalized, the primary endpoint. No one familiar with HF management believes such a hospitalization is an elective event.

Thank you for your attention, and let me introduce Ty Cowart from CardioMEMS.

MR. COWART: Good morning. I'd like to thank the Panel and the FDA for the opportunity to provide a few brief comments.

I'm Ty Cowart. I'm the Vice President of Regulatory Affairs for CardioMEMS. I am an employee of the company. My comments this morning pertain to the investigational device exemption for the study.

To date, there have been over 65 supplements to the IDE that were submitted to and approved by FDA between October 2006 and November 2011. We've closely worked with the FDA during the IDE study period, and we've been very fortunate to have their involvement over the course of the IDE study, and to provide a reference indicator to you within the IDE study itself, there are over 17,000 pages of information that have

been submitted to FDA as part of the IDE. There have also been three different lead reviewers for the IDE during the clinical trial.

When we were reviewing the IDE history, it came to our attention that as it pertains to Appendix E, there were a series of clinical policies that were submitted to FDA as part of the IDE supplement within the June 2007 time period. The policies within this particular supplement contained several home monitoring policies, and I wanted to point out a few of those policies or a few of those points within the policies themselves.¹

Although this information was part of the IDE supplement, I think in this particular case, some further discussion and confirmation with our FDA colleagues is needed as well, but the policy detailed the procedure that the nurse would use for ensuring protocol adherence, and that allowed the nurse to basically review the pressure data, and it also allowed the nurse to contact the site investigators fully complying, making sure that Appendix E was complied with, within the protocol and making treatment recommendations. Also within the policy was an example of an e-mail that would be able to sort of be used as guidance as well for the nurses to use, and you will see this is very similar to some of the other e-mails that you will hear about today.

I think it's important to note a couple of things here, and that is

¹ Correction: The policy mentioned, SOP000105, was not submitted to FDA for review under the IDE or PMA

that the policy isn't new. It's been around and been implemented. It was used to provide details to the nurses during the clinical trial.

The final point I would like to make here is these policies were also made available during the bioresearch monitoring audit with CardioMEMS in March of 2011. I went through the policies with the investigator, making sure that there was a clear understanding, and there were no observations or issues noted.

I'd like to thank you for your time and attention. I'd like to turn the podium back over to Dr. Yadav.

DR. YADAV: Thank you, Ty.

As you've heard this morning from the speakers, particularly Dr. Abraham, the CHAMPION study clearly demonstrated an acceptable level of safety and effectiveness. We are committed to continue to gather additional information regarding CHAMPION in the commercial setting. Several tentative designs for this are under consideration. One of these has been supplied in your briefing book for your review.

Further, we've been approached by a number of professional societies regarding performing national registries in conjunction with them. We are looking at one of these options, perhaps a registry with a board, composed of members from different professional societies, and this may provide the bodies a most rigorous way to evaluate this data in a broad population, and we'll be working on this further.

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Education and training, as you've heard, were a critical part of CHAMPION, and many, many tools were used to accomplish this. It started with in person training in the cath lab for the physicians and nurses involved in the implant procedure and calibration. There was also training of the nurses regarding patient education and patient use of the device at home. Further training was provided in the heart failure clinic setting regarding use of the website, the interpretation of the data, as well as following of heart failure keeping guidelines in general and specifically for pressure-based management.

All of the current technologies that are available for education were utilized and will be utilized, animations, videos, PowerPoint presentations, multiple newsletters as you've seen. Examples of some of these are attached in the addendum including a typical PowerPoint presentation of the nurses, as well as a typical newsletter of the 47 that were issued during this study.

In the commercial setting on the website, we would be able to provide additional information regarding training for doctors and nurses as well as interactive materials such as guidelines, case studies, ranging from simple to complex, as well as interactive self-assessment tools.

The basics of the system are conceptually outlined here and have been discussed during the previous presentations. There would be an overview of the pathophysiology of heart failure, the particular role of filling

pressures outlined by Dr. Stevenson, further review of current guideline-based heart failure management, part of the ACC/AHA guidelines.

Building upon that, there would be education on specific management to pulmonary artery pressure since that is not a new concept in the acute setting, but a somewhat new concept in the chronic setting, and this would again completely replicate the excellent guidance that is detailed in Appendix E, building on the ACC/AHA guidelines.

Lastly, there would be a series of case studies. Dr. Adamson walked you through a couple of these quickly. We have many of these from the clinical trial that allow people to understand how their colleagues have managed patients, and I would emphasize in CHAMPION, this really was a two-way street. We learned a lot from the sites also and what different experience clinicians were using to manage their patients, these challenging patients.

Further, I would add that the electronic infrastructure and human infrastructure in CHAMPION that you have seen described in a fair amount of detail, be replicated exactly in the commercial setting. We have a lot of experience with this. It appears to work well. The nurses and doctors who have utilized it have been very positive about it. It's been built with their input, and we would absolutely continue it in the commercial setting. There's no incentive for us not to continue with the commercial setting. Any opportunity to interact with customers and nurses and doctors, we welcome,

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by companies, and this provides a very scientific patient-oriented mechanism for doing that, and this will be replicated precisely as in the CHAMPION Trial.

In conclusion, I would say that we have heard, and we all know this, that heart failure remains a significant problem for us clinically despite major advances over the last 20 years. As one thinks about developing technologies to improve the medical management of heart failure, one would think about a sensor that was small, easy to use, safe, easy to implant and easy to manage, and provided long-term accuracy and reliability in an ambulatory outpatient setting, and I think the CHAMPION device has met all of those designed requirements. We've also shown that the pressure-based management strategy is very safe, reduces heart failure hospitalizations, and improves quality of life. The CHAMPION Trial in NYHA Class III patients, the previous hospitalization met all of its pre-specified safety and efficacy endpoints.

Thank you, Mr. Chairman. We'll be happy to answer any questions.

DR. BORER: Thank you very much, Dr. Yadav and the rest of the team, for a very comprehensive presentation and for staying within your 90 minutes.

Before I move to the next question, I'd like to ask everyone in the room to please be certain to silence your cell phones, put them on vibrate or put them on silent. It becomes very intrusive if they make noise.

Okay. Now, does anyone on the Panel have a brief clarifying question for the Sponsor? Remember, we're going to have a lot of other opportunities today to ask questions. It's going to be a long day.

Let me define for you what I mean when I say clarifying question. That means that we should at this point ask the Sponsor if we're not clear on what was done, maybe why it was done, perhaps even what was found since we saw some results. What we don't want to take time to do now is to question the interpretations that we've heard. We're going to hear a FDA presentation. Then we're going to have plenty of time to ask interpretation questions.

So with that in mind, does anybody on the Panel have a brief clarifying question about what was done or perhaps why?

Yes, Dr. Lange.

DR. LANGE: Thank you. Obviously one of the endpoints was pressure sensor failure. Can you just tell me what the definition of that was?

DR. YADAV: Yes. Thank you, Dr. Lange. That was defined in the protocol as an inability to get readings after any troubleshooting on the external electronics was accomplished.

DR. LANGE: Thank you.

DR. BORER: Yes, David. And excuse me, let me just remind everybody, I should have done this, if I don't mention your name properly, please mention your name because the transcriptionist needs to be sure of

who's talking.

DR. SLOTWINER: Absolutely. David Slotwiner. Could you just clarify for me the contact that the investigators had with the patients who were randomized to the control group, what the structure of that interaction was?

DR. YADAV: Certainly I can define that, and if one of the clinicians would want to add to that, I would welcome that. They were asked to provide standard of care that they would normally do in their practice using whatever techniques they utilized, weight measurements, et cetera, depending on their standard of care. And then we wanted to make, the Agency wanted to make sure that the other contact was balanced. So if they made a phone call to change a medication, based on pressure in the treatment group, there was a randomly matched phone call to a control group patient, and these scripts were actually in the protocol. It was very tightly scripted. So additional accidental information was not imparted to the patients to maintain patient blinding.

DR. LANGE: Specifically to follow up -- this is Dr. Lange. Could you tell us what that scripting was? I mean when you picked up the phone or somebody picked up the phone and called, did they ask them what the weather was like, where they lived or, you know, what was going on?

DR. ADAMSON: This is Phil Adamson from Oklahoma City. I think it's important to realize that the randomization did occur to pick a

control subject if pressure-based interactions were made with the treatment subject group. Actually if I could see this slide, SS-16, I'll show you the script actually that occurred, if I could have that projected.

Essentially the treatment group -- well, the script was developed to try to minimize such interactions and simply get to the point. So you see here on this slide, the treatment group received a call that said, hello, and this is so and so. Thank you for taking your heart failure pressure measurements. At this time, we would like you to change your diuretic or whatever the recommendation was, and please continue to take your daily heart failure pressure measurements. Thank you.

The control group then would be called and a similar type of script, hello, thank you for taking your pressure measurements. At this time, we're not making any changes to your medications. Please continue to take your daily measurements.

Now, remember that when patients were instructed about the trial and when the process of informed consent was obtained, they were instructed also that they would randomly receive telephone calls, and we told them that it wasn't necessarily that if you received a phone call and we didn't make changes, that it implied which group they were in. So this was the script, actually a protocol-driven script for those contacts, and they were equally matched.

DR. BORER: Yes, Val.

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DR. JEEVANANDAM: Val Jeevanandam. I have a couple of questions that are outside of the scripting. One was, you know, all of this, the inclusion criteria was based on their Heart Association class and looked at hospitalizations. There's no difference in mortality in these two arms. Why wasn't or was exercise data included in this trial, like a six-minute walk would have been reasonably easy to include in these trials to see if there's actually a functional improvement with looking at hemodynamic monitoring?

The other question I had is if you look at the control arm, hemodynamic monitoring was recorded but it wasn't given to the investigators. Was there a correlation there between higher PA pressures and hospitalization in the control arm because you would have that data?

DR. YADAV: Thank you, Dr. Jeevanandam. I understand you've asked two questions. Why were other parameters perhaps not measured such as a six-minute walk? And then secondly, what is the impact of the PA baseline, PA pressures and outcomes? And I'll ask Dr. Abraham to address those.

DR. ABRAHAM: Well, certainly consideration of some exercise measurement would have been great, and I think as the steering committee thought about the design of the study, you know, there's only so much you think you can do with a particular study. It would be great to explore that in the future.

The one thing that I do want to highlight though, while it's not

a direct measure of exercise capacity like a six-minute hall walk, quality of life was improved, and while I didn't show you the data, we can try to find the slide and bring it up for you. Quality of life was improved in the treatment arm in those patients who were not hospitalized, suggesting that there's an independent effect on quality of life, that even if you're not hospitalized, your quality of life is still improved by lowering the pressure.

Now, your other question was in regard to pressure measurements and what happens to them, and we have two observations. One is -- let me go ahead and actually put this slide up now, QL-5, since I mentioned it. You ought to see the data. This is the quality of life data, stratified by treatment group and by those hospitalized and not hospitalized, and you can see on the right-hand pair of bars, those patients who were not hospitalized during the primary period of follow-up, and you can see the significant improvement in quality of life seen in the treatment group. So I think that tells us something about chronic lowering of ambulatory pressures in heart failure patients and the effect that it has on a meaningful endpoint. While not a six-minute hall walk, I think this is still clinically relevant as well.

Now, in regard to pressure, there are really two observations here. One is that baseline elevated pressures are associated with an increased risk of hospitalization, and the second is that pressures increase in the days to weeks preceding hospitalization.

Dr. Borer, I don't know how much of that data you want us to

show at this time, during clarifying questions or not, but I'm happy to share it with the group.

DR. BORER: Why don't we wait until later with that please, Bill.

DR. ABRAHAM: Okay.

DR. BORER: I'd like to go back to the scripting before we go off to something else because my questions were similar to those asked, but I'm going to go a little further because the answer confused me a little bit. Who made the telephone calls to the patients?

DR. YADAV: Sure.

DR. BORER: My understanding was the calls were being made to investigators --

DR. YADAV: Right.

DR. BORER: -- but now I understand that calls were being made to patients, and I would like to know who was making them, both to the control and to the treated patients.

DR. YADAV: Thank you, Dr. Borer. Sorry about the misunderstanding. If I could have this slide up again and then the number of phone calls, please. This script was for the investigators. Phone calls were made by the investigators and nurses who took care of the patients at the site, the site nurses and investigators, not the company. The concern was that the nurses at the sites, that Dr. Lange was suggesting, may impart other information accidentally. So we didn't want them to talk in a spontaneous,

ad hoc manner, and so this script was supplied. I think this was done in the COMPASS Trial, too. So this is a very tight script for the nurse coordinator at each site to utilize.

If I could have the next slide up. Go to the next slide up, please.

This just shows you the number of phone calls made by research nurses and doctors to their patients, and it's fairly well matched between the two groups. Thank you.

DR. BORER: Thank you. Okay. First, Dr. Ferguson and then Dr. Slotwiner.

DR. FERGUSON: Can you explain how medications were titrated in the control group? Was there a clinical assessment at the time of the telephone call? Was there any change in follow-up visits between the control group and the treatment group?

DR. YADAV: The control group, and I'll have Dr. Adamson perhaps talk more on this. The control group really managed a standard care per that doctor's habits and patterns. Now, the study did require study-mandated visits that are made in both groups with the same frequency, one month, three months, six months, et cetera, but the rest of the management was dictated by the standard of care by that physician and nurse.

DR. ADAMSON: So the study protocol required study visits at one, three, and six month intervals. Again, this is Phil Adamson. Excuse me.

And then six months after that until the end of the trial, and there was no prohibition for unscheduled or regularly scheduled clinic visits and assessments for either the control or the treatment group, but for study assessment, that was one, three, and six months and then six months after that.

If I can see SS-7, I can show you actually the number, the average number of unscheduled clinic visits that occurred during the conduct of the trial. In the bottom, you see the unscheduled clinic visits, and this is the average plus or minus the standard deviation of clinic visits in the 270 treatment group patients and 280 control group patients, and you can see they were equally matched throughout the six months of follow-up.

DR. BORER: Okay. Dr. Slotwiner and then Dr. Cigarroa.

DR. SLOTWINER: Thank you. So I'm still trying to understand the phone calls. The control group, were they ever scheduled to receive a phone call if it wasn't triggered by a call to one of the study patients?

DR. ADAMSON: This is Phil Adamson again. And the question was there ever scheduled phone calls to the control group without being triggered by the treatment group? No, the protocol was designed to allow the frequency of pressure-based medication changes that the local site would do with the treatment group and then to match that frequency which we couldn't predict, but match that frequency with a randomly assigned control call. So there was no study-related phone call that was scripted that went to

the control group in a scheduled manner. It was generated by the need for the site to act on pressures and change medications in a treatment group patient.

DR. BORER: Dr. Cigarroa.

DR. CIGARROA: Can you clarify, since one of the primary endpoints here was hospitalization, can you elaborate on the approach and who determined whether a patient was hospitalized on what objective criteria and whether there were any differences between the treatment and control groups?

DR. YADAV: Thank you, Dr. Cigarroa. I think Dr. Abraham.

DR. ABRAHAM: Dr. Abraham here again. Yeah, I've got a slide I can show you some data. We'll work to get that slide up for you in a moment.

Admission decisions were to be made based on clinical grounds. In fact, the definition for heart failure hospitalization in the protocol required that there be signs and symptoms of worsening heart failure and then patients be admitted to a hospital for at least an overnight stay and during that time be treated appropriately with heart failure medications. And so the decision to admit patients was to be made on the basis of clinical grounds, clinical worsening of heart failure, not based on pressure measurements per se, and the route of admission for the vast majority of patients was via the emergency department.

Let me have this slide up on the screen.

So you can see here that most patients were admitted through the emergency department by non-study physicians. The study sponsor reviewed these ER records for evidence of interaction between the emergency room staff and the principal investigator and found little evidence of such. If you look at the number of patients that were admitted from study visits, the numbers are low and virtually the same, and if you look at the number of patients who were electively admitted from an outpatient clinic, similarly the numbers are relatively low and about the same. And so the majority of admissions came via an emergency department with the decision to admit made by an emergency physician not involved with the study, and that really accounted for the small p-value seen in regard to the primary endpoint. Slide down. Thank you.

DR. BORER: Before we go to Dr. Ohman's question -- don't sit down yet. When these patients were admitted, were pressure measurements made in hospital, and if they were, were they made with the device, and if they were, were they made in both the control and the treatment group?

DR. ABRAHAM: Yeah. So for all intents and purposes, no pressure measurements were made in the hospital. The way the protocol was designed was to allow patients to bring in their home monitoring system when hospitalized and still transmit data from the hospital, but that rarely, if ever, occurred. There are a lot of difficulties with using a modem-based

system from inside, you know, a hospital's four walls. And so, you know, in fact, I think it's an interesting question because one might wonder whether or not the impact could have even been greater had we used pressures in hospitalized patients, but we didn't, is the bottom line.

DR. BORER: Dr. Ohman and then Dr. Lange.

DR. OHMAN: Yeah, Magnus Ohman. I have three clarifying questions regarding the robustness of the information particularly as it relates to the primary endpoint or efficacy endpoint.

So, first of all, I noted that you excluded some noncompliant patients, but it was an intent to treat study. So I presumed the noncompliant patients were actually included in the primary efficacy endpoint. I just wanted to be sure that that's the case. That's number one.

The second one is around atrial fibrillation. About half your patients, 45% or so, had atrial fibrillation where typically there's a fair bit of variation in the pulmonary pressures due to the atrial fibrillation as opposed to the heart failure per se. So it would be helpful to see the subgroup and if there is an interaction term with that, and I realize you can't give that off the bat.

And the third question is, what about the learning curve? I sort of got the sense here that as the trial went along, doctors got smarter at this, less e-mails, whatever we want to call about, talk about, but I think it would be very helpful to look at the first half of the study versus the second half of

the study, looking at the efficacy endpoint to understand that a little bit better, and I realize that we'll have to look only at the six month information for that.

DR. YADAV: Thank you, Dr. Ohman. I understand you've asked three questions. One is what happened to the patients who were withdrawn for noncompliance by the site? Second is A-fib patients. And lastly is there a learning curve, there appears to be a learning curve, and can we speculate more about that?

Maybe we'll start out with the statisticians, and then maybe Bill can comment on A-fib and the learning curve.

DR. HOLCOMB: My name is Richard Holcomb. Dr. Ohman, your first question had to do with robustness. Over the primary endpoint of this study, which was through six months, we had very few people that withdrew from the study, less than 10% and most of those were deaths. In the intent to treat, that was the population, there was no imputation, but all patients' time in study was incorporated as part of the analysis model.

DR. OHMAN: So that makes the noncompliant patient be in or out?

DR. HOLCOMB: The patient would be in as long as they resided in the study, up until the point that they were removed. Any events that they had or any time without events were included.

DR. BORER: Just to -- can I just ask you something about that

before we go onto the next question? You didn't impute anything, but did you carry forward any analyses to the end if people were withdrawn earlier?

DR. HOLCOMB: No, not in the primary analysis. There was no imputation -- last value carried forward is a common one, but we have a relatively short follow-up period through six months and very few who withdrew. So that was not necessary.

I will add that in the evaluation of longer-term results, there were sensitivity analyses that imputed data, including methods like last observation carried forward, and those presented the results that you were provided.

DR. BORER: Okay. Bill, were you going to add to that answer now?

DR. ABRAHAM: I was going to address the other two.

DR. BORER: Okay.

DR. ABRAHAM: So there were questions asked about atrial fibrillation. Now, remember that this will be a post hoc and unplanned analysis, but a stratified analysis was performed of the 255 patients who had atrial fibrillation at baseline, and the 295 patients who did not have atrial fibrillation, and there were some differences between the group as I recall in terms of distribution of age, gender, the presence of concomitant device therapy such as CRT and CRT-D devices, baseline serum creatinine, race, and other items. So we have to take all that into account, and let me see -- let's

go ahead -- which slide here. Stratified -- let's look at SA-89. Sorry for the brief delay in getting these slides up for you.

So here is the subgroup analysis, rate of hospitalizations, looking at patients with atrial fibrillation versus no atrial fibrillation. And this is an unadjusted analysis I believe, right, Rich?

DR. HOLCOMB: Unadjusted.

DR. ABRAHAM: Okay. Unadjusted. So let's have that slide down, and let's go back to slide CR-10, because I think this speaks to the question of learning curve, although, you know, this is complex because I think there are a lot of things going on here that account for these cumulative heart failure hospitalization curves.

As I mentioned during the primary presentation, if you look at the relative risk reduction from 0 to 6 months, it's 28%. If you look from 6 months through the end, to unblinding, it is actually 45%, and so, you know, Dr. Ohman, like you, I do take this to mean, at least in part, there may be some learning curve and physicians, clinicians are getting better at using this as time goes on, but remember that hospitalizations also increase risk for recurrent hospitalizations, and as you lower the hospitalization rate earlier, that may result in a ongoing effect to lower hospitalization over time, and there may be other factors as well. So I don't want to overstate that conclusion.

DR. OHMAN: Well, Dr. Abraham, I'm sorry. Just to follow up

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with that. This is a little bit different than that. I was looking at the first half of the patients overall versus the second half. This shows that -- it is not directed to what I was trying to get at. So you may have to look for that.

DR. ABRAHAM: Yeah, we'll look for that data.

DR. BORER: And if you'd like, if it's going to take a while to find it, we can see it after the break.

DR. ADAMSON: I would say, this is Phil Adamson again, to address your issues as well, I think one has to remember that at the implant procedure, right heart catheterization was performed in all patients. So the control group had the benefit of the right heart catheterization information at the time of implantation, and all the pressure information from that data was subsequently utilized, and that may account for some of the early lack of divergence of those treatment arms. Thank you.

DR. BORER: Dr. Lange and then Dr. Milan and then Dr. Jeevanandam and Dr. Brindis.

DR. LANGE: Again, just some clarifying questions. With regard to the ED or admissions from the emergency department, if you would clarify whether those were physician directed, whether the physician saw a pressure recording and told the person to go to the emergency department, which would be fairly typical, or whether the person just felt unwell, the first thing.

Second is in the scripting, was there admonition to the physician to discourage hospitalization? In other words, it's one thing to say

we want you to adhere to medications and follow this and nothing to say, please, we're trying to avoid hospitalizations.

And the last question directed to the statistician is, the number needed to treat, was that based upon the number of hospitalizations or the proportion of patients who were actually hospitalized. Thank you.

DR. YADAV: Great. Thank you, Dr. Lange. So the first question is regarding any directions or information from the physician regarding hospitalization based on pressure. And the second was, did the scripting go beyond what we just outlined? And the number needed to treat, is that based on the number of hospitalizations or number of patients?

DR. ADAMSON: This is Phil Adamson, and it's a very good question. I think there's several ways that we looked at this phenomenon of emergency department-driven hospitalizations. One would be to survey the actual medical records to see if some reference to the primary provider was made to say that, that the patient said that Dr. Jones sent them to the emergency room. And we found very little of that, if any. The emergency department physicians were not allowed, nor was anyone in the hospital allowed, to interrogate the device in order to protect the blinding of the trial.

Finally, if one looks at how pressures change before hospitalization, it turns out that they do change as we've shown over a long period of time. There's very seldom in which we see a pressure that changes abruptly that leads to a hospitalization. So we didn't expect really to see

providers see an acute change in pressures that startled them and said please go to the emergency department. That was the reason that we required weekly review of the pressures that were uploaded daily.

And if I could see PD-24. I want to show you a little bit to illustrate what I just described to you.

What you see here are the pressures on the Y axis and time on the X axis up to six weeks prior to a defined event. A defined event one day before was either a heart failure-related hospitalization or a non-heart failure-related hospitalization. You see the treatment in red and the control in blue, and several points I think that can be learned from this, and that is that the pressures do increase over a long period of time.

Now, we demonstrated that in other clinical trials, and the magnitude of change was similar, although patients in the treatment group started at a slightly lower pressure, very reassuring that we were doing what we were trying to do.

Now, the other question is if bias led patients to be held out of the hospital by the investigator until things were catastrophic and the patients had to be put in the hospital, one would have expected to see their pressures far higher than the control group patients, especially if the control group patients were preferentially hospitalized in order to change the outcome of the trial, but what we found was that the pressures were even lower in the treatment group patients compared to the control patients at

the time of heart failure admission.

And, finally, what I think is also very reassuring is that when the hospitalization was adjudicated as not related to heart failure, the pressures did not change either prior or before.

I'll let the statistician answer your question about number needed to treat.

DR. LANGE: Before the statistician, did you want to address the issue of prompting with regard to the script?

DR. ADAMSON: Sorry, yes. Again, Phil Adamson. This scripts were very clear, and the site personnel were instructed not to add to the script, and individuals in the trial who were consented as part of that consent process were told you will be given phone calls. They will be scripted. We're not trying to be rude, but we're going to be very clear and very concise, and so they didn't expect us to go on about their grandchildren and see how their weights were. So this is very scripted, and we purposely trained the site personnel not to embellish or to encourage, just simply to make the changes in the treatment group or make the calls in the control group.

DR. HOLCOMB: Richard Holcomb. Dr. Lange, your question was the estimate of NNT, was it based on hospitalizations or patients? Obviously multiple hospitalizations are important to this population, and the NNT reflected a reduction in the hospitalization rate. So it was based on hospitalizations.

DR. BORER: Okay. Dr. Milan and then Dr. Jeevanandam and Dr. Brindis, and then we're going to have to stop for a break.

DR. MILAN: Okay. My question is about the phone calls again and the matching in the control group. It sounds like it was a protocol driven call that was generated to a random control patient for every call that was made to a treatment patient. So I would have expected those calls to be perfectly equal. I was surprised to see that there were 3.0 calls per patient for the treatment patients and 2.5 calls per patient for the controls. So maybe you can tell us why that was.

And then I still am -- it was partially answered with the last question, but I'm still trying to decide, it's sort of an echo of Dr. Ferguson's question, what if during this scripted call the patient says, oh, I'm so glad you called. I'm so short of breath I can barely get up the stairs. I mean, you know, fundamentally your investigators are physicians or nurses or whoever; how was that dealt with?

DR. YADAV: Let me try to answer the first part, and then we can have Dr. Abraham or Dr. Adamson.

Some of the smaller sites may have only had one treatment, no control patients. So it's hard to get it perfectly balanced. That's why you see the 3 versus 2.5, and I think as we've shown in the previous slide, it's not statistically different.

Regarding if the patient said, you know, I'm not feeling well or

something, they were asked to call their doctor. They were asked to make a clinical phone call at that point and not a study phone call, and do you guys want to comment on that?

UNIDENTIFIED SPEAKER: You answered it.

DR. BORER: Okay.

DR. MILAN: In follow-up, it's a half call per patient. So it looks like it would be about 140 calls different between the control and the treatment patients. Is that right? Am I thinking about that right?

DR. YADAV: These are calls per patient per site. So at each site, on average there were -- if this is done per, because the matching was done per site, we wanted to make sure that within that physician's patient community and people enrolled, there was balance. So this is -- I can try to get you the other number, but this is done per site. At every site there were three treatment calls and three control calls.

DR. BORER: Okay. Would you like to see the more complete data, Dr. Milan? Okay. After the break --

DR. YADAV: Sure, we can look for that.

DR. BORER: Okay. Dr. Jeevanandam.

DR. JEEVANANDAM: Val Jeevanandam. I have a question about these admissions. When patients were admitted, do we have data on the duration of that admission and exactly what was done during that admission? Were these admissions that required heart failure therapy or

were these admissions that required, you know, just a shot of IV diuretic? And how many patients who were admitted ended up having a right heart cath to look at their PA pressures?

DR. YADAV: Thank you, Dr. Jeevanandam. This is regarding the nature of these hospitalizations. Dr. Abraham.

DR. ABRAHAM: Yeah. So, first of all, you know, to come back to the definition of the heart failure hospitalization, remember patients were hospitalized with worsening signs and symptoms of heart failure, and they had to be admitted for at least an overnight stay, and they had to receive some form of heart failure therapy like an intravenous diuretic or a vasoactive agent, and just to reassure you that these were real heart failure hospitalizations, the average length of stay in the treatment arm was 7.0 days. The average length of stay in the control arm was 8.8 days. So on average, these were not trivial heart failure hospitalizations, associated with a length of stay that would be expected or even slightly longer than expected.

DR. BORER: I'm sorry. I didn't hear. Did you answer the question about the pressure measurements that were made during the hospitalization? Were Swan-Ganz catheters put in?

DR. ABRAHAM: Do we have the data? We may see if we can find that. I'm not sure that we have it but --

DR. YADAV: They were allowed to do a right heart cath if it was clinically indicated.

DR. ABRAHAM: Right, right. If there was a clinical indication, if a clinician wanted to do a right heart catheterization, they could do them, you know, clinically. We'll have to take a look and see if we have the data.

DR. BORER: Okay. Last question before the break, Dr. Brindis.

DR. BRINDIS: Yes, in the protocol it talks about the encouragement of the use of intravenous diuretics to avoid admission, and I was wondering if you could talk a little bit about how often that was utilized, any difference between the two groups and, you know, maybe even comment on that strategy and how we're doing it in the rest of the world.

DR. YADAV: Intravenous diuretic used in outpatient settings. Maybe you can just comment on the practice of intravenous diuretics is what Dr. Brindis is asking.

DR. BRINDIS: And how it was utilized here, if it was encouraged to avoid admission.

DR. YADAV: Yeah.

DR. BRINDIS: The differences between the groups.

DR. ABRAHAM: Yeah, let me have this slide back up. This came from the main presentation, and again I need to note that this data, at least the data on the bottom part of the slide, has not been reviewed by the FDA. But here you can see the numbers for outpatient utilization of intravenous diuretics, 23 in the treatment arm, 26 in the control arm, 8.5% versus 9.3% respectively. You know, the utilization of IV diuretics is relatively small when

you compare it to the, you know, nearly 1,000 changes in oral diuretic doses. So, you know, this is probably consistent with clinical practice. Some clinics use it. We've got a large outpatient heart failure clinic at our university. We don't use outpatient IV diuretics. So there's some variability in practice, but I think this is probably fairly reflective of clinical practice, and importantly, it was the same in both arms.

DR. BRINDIS: Chairman, I need some direction from you because I know it was talked about gender issues, but I don't know if you would want more data related to that at this time.

DR. BORER: I think that will be a big topic for discussion. Let's hold it until after we hear the remainder of the presentations.

Okay. It is now by my watch 10:15. We're going to take a 15-minute break and begin again at 10:30.

(Off the record at 10:15 a.m.)

(On the record at 10:30 a.m.)

DR. BORER: I'd like to call this meeting back to order.

At this time, the FDA will give its presentation on this issue. Commander James Cheng will introduce the FDA presentation.

CDR CHENG: Good morning. I'm Commander James Cheng. I'm the team leader for the FDA review of the CardioMEMS submission under discussion today.

The FDA Review Team for this submission is composed of

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scientists, engineers, statisticians, and medical officers. Today's discussion will focus on the statistical and clinical data submitted by the Sponsor in support of this PMA.

Today's FDA presentation will discuss the FDA analysis of the Sponsor's study results as well as what FDA considers to be important aspects of the conduct of the study that may impact the interpretation of the study results.

It should be noted that the FDA analysis of the clinical trial data was performed without consideration of the trial conduct issues that will be presented at the end of the FDA's presentation. It should also be noted that the FDA does not take economic issues into consideration when determining whether to approve a device.

The FDA presenters are as follows. The statistical overview will be presented by Dr. Yonghong Gao. The clinical results and considerations will be presented by Dr. Randall Brockman. A discussion of the study medical treatment will be presented by Dr. Ileana Pina. A brief discussion of the proposed post-approval study will be presented by Dr. Shaokui Wei. Dr. Brockman will present a discussion of the study conduct issues, and then a presentation on study design issues and conclusions will be presented by Dr. Greg Campbell.

The Sponsor provided preclinical and clinical data in support of these proposed indications for use. The preclinical data was submitted to

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FDA as a series of modular submissions beginning in 2008. There are no outstanding preclinical issues regarding the data that was submitted by the Sponsor.

The next FDA presenter is Dr. Yonghong Gao.

DR. GAO: Good morning. I'm Yonghong Gao, FDA's statistical reviewer of this PMA submission.

Today I will present the statistical results of the CHAMPION study which was conducted to establish the safety and effectiveness of the CardioMEMS Heart Failure Monitoring System.

The first several slides will give a brief overview of the CHAMPION pivotal study. Since the Sponsor already gave detailed description of the study protocol, I will only highlight some important points here.

The CHAMPION study was a two-arm randomized trial. The objective of the study was to show that CardioMEMS is safe and superior to the standard of care in reducing the rate of heart failure-related hospitalizations.

The trial was single blinded. Only patients are blinded to the randomization assignment. The investigators knew which arm a patient was in. That knowledge could have some impact of the behaviors of treating patients which could introduce bias to the assessment of the device performance.

There are three primary endpoints, one for effectiveness and two for safety. All were assessed at six months' follow-up. This slide presents the hypothesis associated with the primary endpoints. Note that to assess primary effectiveness, a two-arm comparison was conducted. However, for the two primary safety endpoints, there was no control. Thus for safety, performance goal-based hypotheses were tested, and data from both arms were combined in the hypothesis testing. The overall study success criteria was that device would meet all three primary endpoints.

Here are some other important aspects of the CHAMPION study. The CHAMPION study had a planned interim analysis when half of subjects had six months' follow-up information. At that time, unblinded analysis of the primary safety and effectiveness endpoints were conducted. O'Brien-Fleming boundaries were utilized to account for the interim look, and therefore the p-values for the interim and final analysis were set at .005 and .048.

The study protocol pre-specified four secondary effectiveness endpoints which compare the two arms of the trial. Those secondary endpoints are listed on this slide. Only if all primary endpoints were met, a hierarchical testing procedure for secondary endpoints were planned and was to stop once a Type I error rate exceeding .05 was found.

It should be noted that the FDA analysis of the clinical trial data was performed without consideration for the trial conduct issues that will be

presented at the end of the FDA's presentation. Those conduct issues should also be taken into account in the interpretation of the statistical outcomes of this trial.

Now, I will present CHAMPION study results.

This slide shows the result of the analysis of primary safety endpoint 1. The objective was to show that the freedom from device- or system-related complication rate is more than 80%. Out of 575 subjects, 567 were free from this event resulting in a point estimate of 98.6%. The lower bound of the exact 95.2% confidence interval is 97.3%, which is larger than the performance goal of 80%. So this endpoint was met.

This slide shows the result of the analysis of primary safety endpoint 2. The objective was to show that the sensor failure-free rate is more than 90%. Out of 550 subjects with implanted sensors, all were operational with 0 sensor failures at 6 months. The exact 95.2% confidence interval was 99.3% to 100% with the lower bound of 99.3%. The lower bound is larger than the performance goal of 90%. So this endpoint was met.

Now, let's look at the primary effectiveness endpoint, the number of heart failure-related hospitalizations within six months. There were 84 heart failure-related hospitalization events for 273 treatment subjects and 120 events for 280 control subjects. The event rate for treatment arm was .32 events per patient per 6 months compared to a higher rate of .44 for the control arm.

The Sponsor's pre-specified analysis model was negative binomial regression with number of hospitalizations as dependent variable, treatment and six month follow-up time as predictors. The Sponsor's negative binomial regression indicated a p-value of .0002.

However, there are some detailed modeling options that were not pre-specified in the protocol. These options mainly concerned how to correct overdispersion.

The CHAMPION data indicated some level of overdispersion as the observed variance is larger than the observed mean. If overdispersion is not appropriately accounted for in the analysis, then the estimates of the standard of errors are too small which leads to a smaller p-value.

There are several different approaches to correct overdispersion when modeling count data. Since there is no consensus in the literature regarding the best approach to deal with overdispersion, FDA explored the following models in analyzing CHAMPION data, basic Poisson regression.

Poisson regression with variance-scaled to correct for overdispersion. Since CHAMPION data had large number of zeros with larger number of patients having zero hospitalizations, a zero inflated Poisson regression was used in data modeling. Negative binomial regression was specified in the protocol. So we also analyzed data with basic negative binominal regression, negative binominal regression with variance scaled to

correct overdispersion, and zero inflated negative binomial regression.

All of the above parametric models require one assumption, which is that occurrence of the incremental events is independent of the previous event. This assumption may not hold for CHAMPION data. So we also took a non-parametric bootstrap approach to analyze CHAMPION data.

This table presents the p-values for treatment effect under each of those different models. All the models give similar point estimates of the treatment effect. So differences in these p-values represented different ways to estimate standard error.

The Sponsor's model is shown on the first row with a very significant p-value. The non-parametric bootstrap method gave a non-significant p-value compared to critical value of .048. So from this table, we can see that the p-value is very sensitive to the model used. Some of them are statistically significant. Some of them are not.

FDA routinely assess statistical methods for robustness by trying various alternative approaches in analysis. The table in previous slide shows the Sponsor's analysis of the primary effectiveness endpoint is not robust with respect to the methods used for estimation of some parameters of the negative binomial model.

Another way to assess the robustness of the trial result is to conduct a tipping point analysis which is to see under what condition trial result could be changed. FDA's tipping point analysis indicated that under the

Sponsor's model, if 13 more heart failure-related hospitalizations are added at random to the patients in the treatment arm -- by the way there are errors in this slide. The second bullet there from 80 to 93 should be 84 to 97. So if 13 more heart failure-related hospitalizations are added at random to the treatment arm, the result is no longer statistically significant at .048.

Thirteen hospitalizations can be interpreted as one more heart failure-related hospitalization per 21 patients in the treatment arm.

And for the bootstrap model, if only two heart failure-related hospitalizations are added to the treatment arm, the p-value for treatment effect exceeds .1.

Since all primary endpoints were met, the four pre-specified secondary endpoints were tested at a significant level of .05 in a hierarchical testing procedure. All four endpoints were tested for superiority of the CardioMEMS device. The CHAMPION data indicated that the device met all those secondary endpoints.

FDA also assessed the robustness of one second endpoint, that is secondary endpoint number two, proportion of subjects hospitalized with heart failure. If the number of hospitalized patients in the treatment arm is increased only by 3, from the original 55 to 58 out of 270 treatment patients, the p-value is no longer significant at .05. The additional 3 patients can be translated to 1 more hospitalization per 90 patients.

Important supplementary analyses were conducted by the

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Sponsor to provide more insight on the performance of the device. Those were survival analysis, heart failure-related hospitalization-free survival analysis, sensor performance calibration, and gender analysis.

The following several slides present details of those analysis results.

This slide presents a Kaplan-Meier survival curve of the treatment arm and the control arm over the whole study duration. The two curves overlap with each other, and a non-significant p-value indicates no statistical significant differences between the two survival curves. So the device has failed to show a significant survival benefit over the control.

If heart failure-related hospitalizations is incorporated in the treatment benefit in addition to survival, then the two survival curves separate. This graph shows time to death or first heart failure-related hospitalizations for the two arms. From this plot, we can see that the device demonstrated significant benefit in reducing time to death or first heart failure-related hospitalization. The hazard ratio was estimated as .73. Since the estimated hazard ratio is less than 1, this analysis indicates a lower hazard for the treatment arm.

The sensor of CardioMEMS was calibrated using a Swan-Ganz catheter. This Bland-Altman plot provides information on the level of agreement between the sensor and the Swan-Ganz catheter. The plot is based on 43 patients who underwent 85 physician-initiated right heart

catheterizations using Swan-Ganz PA mean measurement. The Y axis shows the difference between PA measurement for a given patient. The X axis shows the average. The mean difference was 1.0 mmHg with limits of agreement of -8 and 10.

Females are historically underrepresented in clinical trials, and it is often observed that cardiovascular devices demonstrate different treatment effects in males and females. So FDA asked the Sponsor to analyze the data stratified by gender. Here is the result.

For the treatment arm shown in the first column, the event rates for males and females are about the same. For control arm, shown in the second column, the event rates were quite different for males and females. The female control patients had a much lower event rate than male control patients.

Looking at the first row, the male patients, the event rate for six months increased from .32 to .53 from the treatment arm to the control arm. But for the female patients, corresponding to the second row, the event rate decreased from .32 to .19 per 6 months from the treatment arm to the control arm. The reverse treatment effect in those two subgroups indicated a qualitative interaction between treatment and gender.

FDA conducted a treatment by gender interaction test. The test gave a p-value of .01. We concluded that the data indicated differential treatment effects for males and females on this endpoint, and thus the device

should be assessed separately for males and females.

FDA used variance-scaled Poisson regression to analyze data stratified by gender. For the males, the treatment effect is statistically significant indicated by a very small p-value. The point estimate of IRR, which means the incidence rate ratio, is larger than 1 indicating treatment benefit. An IRR of 1.668 means that the males' rate of heart failure-related hospitalizations increased about 67% from treatment arm to control arm.

For females, the treatment effect is not statistically significant, which could be caused by lower power due to the small sample size for females. More importantly, the point estimate of IRR is less than 1, indicating a reverse trend. Here IRR of .603 means that female patients' rate of heart failure-related hospitalizations decreased by 40% from treatment arm to control arm.

To have a better understanding why data indicated qualitative interaction between treatment and gender, we break down the data into four subgroups, female treatment, female control, male treatment, and male control. The distribution of the number of hospitalizations of those four subgroups are given in this table. To read the table, just look at the first row. The female treatment subgroup, 62 patients had 0 hospitalizations, 8 patients had 1 hospitalization, 4 patients had 2 hospitalizations, et cetera. The values in the parentheses are relative frequencies. The last row gave the aggregated distribution. Note that male controls had more repeated hospitalizations

than any other subgroups.

Here is a plot of cumulative hospitalizations over the study duration for females. There is no significant difference between the two arms in cumulative heart failure-related hospitalizations. The estimated hazard ratio is greater than 1, favoring the control arm.

However, for male patients, there was a significant difference between the two arms in cumulative heart failure-related hospitalizations. The estimated hazard ratio was .57 indicating that males in treatment arm had significantly lower cumulative hospitalization events than in control.

So we have the following conclusion on gender-related analysis. For the heart failure-related hospitalization rate at six months, the data demonstrated different treatment effects in males and females. The treatment arm had a statistically significant reduction in the rate of heart failure-related hospitalizations for males but not for females.

For the cumulative heart failure-related hospitalizations over the study duration, the data indicated a different treatment effect in males and females. The treatment arm showed a statistically significant reduction in the number of heart failure-related hospitalizations for males but not for females.

Here is the summary of FDA's statistical assessment of the CHAMPION pivotal trial. First, there are some general concerns with study conduct that will be addressed in the latter part of FDA's presentation. Those

conduct issues should be taken into account when interpreting the statistical outcomes of this trial.

General concerns aside, the trial appeared to meet its primary and secondary endpoints.

For effectiveness, there was a significant treatment by gender interaction in this trial, with the only benefit in males.

This concludes my presentation. Now, Dr. Randall Brockman will present the clinical considerations of this study.

DR. BROCKMAN: Well, good morning. I'm Randy Brockman. I'm a Medical Officer in the Division of Cardiovascular Devices at FDA. I was the primary clinical reviewer for this file.

My background is in cardiac electrophysiology. I'm not a heart failure specialist. Thankfully Dr. Ileana Pina, who is a heart failure specialist, also reviewed the file and will provide some comments as well.

Heart failure is clearly a major public health problem. In order to try to help clinicians manage their patients with advanced heart failure, CardioMEMS developed their heart failure monitoring system. On the screen, you'll see a picture of the sensor itself with the dimensions given. I won't go into detail since the Sponsor's already gone into or covered the device design.

Better information may allow clinicians and patients to improve heart failure management and may reduce the need for hospitalization for heart failure. In order to determine if frequent access to pulmonary artery

pressure readings could reduce the need for hospitalization for heart failure, the Sponsor studied their system in a clinical study called the CHAMPION Trial. You already heard the study design discussed.

My presentation will cover the clinical points of the trial as I list here. Because some of this has been presented already, I'm going to try to concentrate mainly on FDA's interpretation of the data. At the end, I'll come back and I'll also discuss FDA's findings based on inspections conducted by our Division of Bioresearch Monitoring and our concern for bias in trial outcomes.

The enrollment criteria were much more extensive than this list, but the major criteria included New York Heart Association Class III symptoms, at least one heart failure-related hospitalization within a year prior to enrollment, all patients were to be on appropriate background heart failure medical therapy. Exclusion criteria dealt with poor renal function as well as a history of recurrent pulmonary embolism or DVT.

As has been noted, I'll also add that enrollment was not contingent on left ventricular ejection fraction such that patients with heart failure and preserved ejection fraction were included.

Patient accountability has been covered already. So I'll go past it.

The Sponsor did cover demographics. I'll just point out that the study largely enrolled white males. The baseline ejection fraction was about

29%. Etiology of heart failure was about 60% ischemic, and the time from the qualifying heart failure hospitalization to baseline was about 120 days in both groups.

Dr. Pina will discuss the medical therapy, but overall, the subject demographics were pretty well matched between the two arms.

The Sponsors also covered the implantation. So I'll pass that.

So let's go onto the study results. As you've heard, there were two primary safety endpoints. I'll just make a couple of observations.

Primary safety endpoint number 1, freedom from device- or system-related complications, didn't capture procedure-related adverse events, and I will come back to that.

Primary safety endpoint number 2 assessed pressure sensor failures, but as was asked earlier, pressure sensor failure was defined pretty narrowly on the protocol. According to the protocol, a pressure sensor failure occurs when the sensor malfunctions to the point that no readings can be obtained from it after all attempts are exhausted, including troubleshooting the system to relate any problems with the electronics components. So when you interpret the results from primary safety endpoint number 2, just please keep this definition in mind.

So primary safety endpoint number 1 was freedom from a device- or system-related complication through six months. The analysis population included all patients that underwent a right heart cath, whether

or not the sensor was planted. The cohort was 575 patients.

The protocol included a performance goal of 80%, and the protocol included a definition for this endpoint. A device with system-related complication is an adverse event that is or is possibly related to the system and at least one of the following: is treated with invasive means, results in the death of the patient, or results in the explant of the sensor.

So eight patients experienced device- or system-related complication. That left 567 out of 575 patients or 98.6% who were free from a DSRC. The lower confidence bound was 97.3%, which exceeded the pre-specified performance goal of 80%. So primary safety endpoint number 1 was met.

These are the device- and system-related complications as reported by the sponsor. I think the sponsor did go through these. I'll just mention that they included things such as a sensor failing to deploy, a TIA, a chest pain syndrome, hemoptysis requiring bronchoscopy, sepsis with the patient subsequently dying after care was withdrawn, a wide complex tachycardia, an arterial embolism, and a thrombus which formed in the pulmonary vasculature.

Well, of course, any adverse event is unfortunate. The rate of DSRC events reported by the Sponsor did not raise concerns for FDA.

Primary safety endpoint number 2 was freedom from pressure sensor failures through six months. The analysis population included all

patients that had the sensor implanted. That was 550 patients. There was a performance goal of 90%, and I've already read the definition of pressure sensor failure. There were 0 pressure sensor failures as defined in the protocol. So the freedom was 100% with a lower 95.2% confidence bound of 99.3%. That exceeded the performance goal of 90%. So primary safety endpoint number 2 also was met.

If we look at survival through the first 6 months, there were 15 deaths among 270 treatment patients, 20 deaths among 280 control patients. The death rates were similar between the two arms. The overall proportions of deaths was 6.4% through 6 months. FDA believes the overall mortality rate in the current study compares reasonably well to published reports of similar patient populations with advanced heart failure, prior heart failure hospitalization, and severe LV systolic dysfunction.

I did a extensive review of the records for the patients that died during the trial, especially focusing on the patients that died in the first six months. I was particularly concerned about the potential for pulmonary occlusion due to the sensor. I didn't find conclusive evidence that the sensor played a major role in the deaths of any of these patients.

If we look at a plot of the survival curves over six months, you can see they're pretty similar.

This table summarizes the CEC adjudication of deaths at six months. The most common causes of death were heart failure and sudden

cardiac death. These two groups accounted for almost 70% of the deaths in the first 6 months. The cardiac procedure death followed a heart transplant. The cardiac other death was a ventricular dysrhythmia. Non-cardiac causes included things such as COPD, sepsis, and GI bleeding. There was no clear association between the investigational device and subject deaths.

This is a plot of survival over the study duration. Again, the curves are similar and even overlapping. There's no apparent survival difference between the groups. Based on this plot, if you look at the one-year mortality rate, it appears to be about 12% for both groups.

This table presents serious adverse events through the first six months. The total numbers are somewhat similar, about 45% of treatment subject and about 55% of control subjects experiencing a serious adverse event. All serious adverse events were adjudicated by the CEC.

This table presents the most common serious adverse events through six months. The most common events included heart failure. Well, the most common event was heart failure. Other common events included an ischemic syndrome, ventricular arrhythmias, infections, renal dysfunction, hypotension, and dehydration events.

The Sponsor also provided an analysis for procedure-related adverse events. I show this primarily because the primary safety endpoint number 1 didn't include procedure-related adverse events. There were seven procedure-related adverse events listed here, hemoptysis, atrial fibrillation,

cardiogenic shock, fever, two episodes of groin hematoma or groin pain, and then an episode of prolonged hospitalization to restart warfarin.

This table presents the renal function parameters at baseline, six months, and then the change from baseline to six months. Creatinine rose .1 mg/dL in the treatment arm and .07 mg/dL in the control arm. GFR decreased by 3.1 mL/min/1.73m² in the treatment arm and by 1 in the control arm. So the changes in renal function are relatively small.

FDA interpreted this to suggest that pressure guided treatment of heart failure does not have a substantial detrimental effect on renal function over six months. FDA finds this reassuring because changes in renal function have been correlated with outcomes in heart failure patients.

Early on in the trial, we were concerned about the potential for pulmonary embolism or occlusion. There was no clear evidence that any pulmonary embolism occurred as a result of the sensor during the trial based on both clinical events and based on limited autopsy data.

If we move onto effectiveness, the primary effective endpoint as you've heard was the rate of heart failure-related, or HFR, hospitalizations through six months. All hospitalization events were reviewed by the Clinical Events Committee and adjudicated in terms of being heart failure related or not related.

The CEC charter included a definition of hospitalization and heart failure-related hospitalization, which I'll be happy to read to you if

you'd like. I think it has been pretty well covered already.

In the treatment group, 55 subjects experienced a total of 84 HFR hospitalizations resulting in a HFR hospitalization rate of 0.32 events per patient per 6 months. In the control group, 80 subjects experienced a total of 120 heart failure-related hospitalizations, resulting in a HFR hospitalization rate of 0.44 events per patient per 6 months. The p-value reported by the Sponsor is 0.0002. The endpoint appears to have been met, but I'll remind you that this result does not take into account the potential impact of trial conduct issues that we'll discuss later.

For the six-month analysis, the Sponsor reported the number needed to treat to prevent one heart failure-related hospitalization was eight. FDA performed an extensive review of the clinical summaries of the hospitalization events. Overall, FDA generally agreed with the CEC adjudication.

So, the primary effectiveness endpoint appears to have been met. However, the clinical risk reduction is from 0.44 to 0.32 HFR hospitalization per patient per 6 months. Therefore, the absolute risk reduction is 0.12 heart failure-related hospitalization event per patient per 6 months. FDA will ask the Panelists to provide a discussion of the clinical significance of this finding.

There were four secondary endpoints for which hypothesis testing was pre-specified. I'm going to discuss the results of several of these,

the proportion of subjects hospitalized for heart failure, days alive outside of the hospital, and the quality of life data.

For the proportion of patients hospitalized for heart failure, the absolute difference was 8.2%. For days alive outside of the hospital, the absolute difference was 2.3 days. And the number of days hospitalized, the absolute difference was 1.6 days.

For the quality of life data, the absolute difference in the Minnesota Living with Heart Failure Questionnaire score at 6 months was 5.4 points favoring the treatment group, and I'll just mention that a 5-point change in the Minnesota Living with Heart Failure Questionnaire score is often thought to be clinically significant. The change from baseline to 6-month scores reflect a net change favoring the treatment group of 3.2 points.

The Panelists will be asked to discuss the clinical significance of these findings.

Now I'd like to turn the presentation over to Dr. Ileana Pina.

DR. PINA: Good morning. I'm Ileana Pina. I'm Associate Chief of Cardiology for Academic Affairs at Montefiore Einstein. I'm a heart failure transplant cardiologist and a consultant to the FDA in the Office of Device Evaluation for CDRH.

The inclusion criteria for medical therapy in this trial did not include therapy for heart failure with preserved ejection fractions since, as well said by the Sponsor, we really do not have the greatest of guidelines for

this. For low ejection fractions, the patient needed to be on stable, optimally up-titrated medical therapy, recommended according to the current guidelines and standard of care for heart failure therapy. And it included an ACE inhibitor, an atrial receptor blocker at stable doses when an ACE inhibitor was not tolerated, a beta blocker if tolerated with stable up-titrated doses, and if intolerant to ACE, ARB, or beta blockers, documented evidence must be available and, if intolerant to all of those, combination therapy with hydralazine and oral nitrates should be considered.

It is also important to review the intended process of care for the group that was randomized to treatment. The standard of care heart failure management was recommended plus heart failure management based on the hemodynamic information obtained from the measurement system.

The investigator or their designee would review the PA pressures from the home monitoring unit, and the investigator or designee of the investigator would be alerted by CardioMEMS if those parameters were exceeded. If the pulmonary pressures were elevated, the investigator or the designee should make medication changes according to Appendix E.

Shown here are the mean of the mean pulmonary pressures, and you can see that they were elevated at baseline, and the definition of optivolemic or optimal pressures was between 10 and 25. More changes were made to the treatment group as has already been presented by the Sponsor.

The treatment for optivolemic comes from Appendix E, which includes baseline chronic aggressive therapy for low ejection fraction, ACE or ARB or other vasodilator, if not tolerated, to target dose; digoxin, diuretic, electrolyte replacement; consideration of spironolactone, which is a drug that we're seeing more and more in trials; nitrates to appropriate doses as tolerated; and beta blocker, either administration and/or up-titration according to guidelines when the subject was not hypervolemic.

The treatment for the hypovolemic recommendation also comes from Appendix E, and it includes, among other things, to add or increase or change the diuretic, to add a thiazide diuretic or IV doses of loop diuretic; add or increase nitrates; start or re-educate in salt intake and fluid; and if poor perfusion was meant to be present, admission with IV agents, hemodynamics, or clinical evidence that suggested IV diuretics, telemetry monitoring, or the IV therapeutic agents. In addition, Appendix E included incorporating the recommendations set forth in the ACC/AHA 2005 Guideline Update for Heart Failure, which was at the time of the trial the most current one.

In this slide, and the Panel has this table because I know it's a little harder to see, the red circles show the maximal doses recommended as target, and these are appropriately taken from the clinical trials. Below them are the forced titration doses, which are the doses in clinical trials where doses are actually forced to be up-titrated. Usually these are double-blind,

placebo-controlled trials.

The baseline medical therapy is shown here. The ACE and ARB percentages appear to be low in current clinical trials. However, the Sponsor has submitted to the FDA that 21% of patients indeed were intolerant to ACE or ARB. The nitrate percentages were 23, and the hydralazine were 13 and 11 respectively. The beta blocker dose levels of percent were acceptable and high.

Looking at it in a different way, this is the fraction of the maximal dose for ACE inhibitor, fairly well balanced at baseline. You can see that the treatment group at six months had had some increase in the percentage toward maximal dose. No change at all in the control group. And for the beta blockers, similar at baseline and a small increase in the treatment group and really a very small increase in the control group.

The medical therapy at six months is also worth reviewing. You can see that the percentage of patients on ACE and ARB did not really change. The beta blocker percentage actually dropped a bit, and there was a difference in hydralazine and nitrates between the treatment and the control groups. Also notable is the loop diuretic doses did seem to come down.

So briefly, in summary, the percent of patients on ACE and ARB appear to be low. However, I have mentioned the Sponsor's assertion of intolerance, and the percent target doses appear to be low for both ACE, ARB, and beta blocker.

And now Dr. Wei will continue with the post-approval suggested study. Thank you.

DR. WEI: Good morning. I'm Shaokui Wei, an epidemiologist in Division of Epidemiology, Office of Surveillance and Biometrics.

Today I will talk about the post-approval study that have been proposed for the CHAMPION Heart Failure Monitor System submitted by CardioMEMS.

The presentation is based on latest post-approval study outline submitted to the FDA on August 11, 2011.

Before we talk about the post-approval study, we need to clarify a few things. The discussion of the post-approval study prior to the FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

The plan to conduct the post-approval study does not decrease the threshold of evidence required by FDA for device approval.

The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

The reasons for conducting post-approval study are to gather postmarket information including, first, the long-term performance of the device; second, data on how device performs in the real world in the broader patient population that are either treated by community-based physician and

specialist, opposed to the highly selected patients treated by investigator in clinical trials; third, evaluation of the effectiveness of the training programs for the use of device; fourth, evaluation of device performance in the subgroups of the patients since the clinical trial tended to have a limited number of patients or no patients at all in certain vulnerable subgroups of the general patient population; and finally, to monitor adverse event, especially where the adverse event that were not observed in clinical trials.

In addition, post-approval study can also address any other issues that may be identified by Panel member based on their expertise.

Now, I will present an overview of Sponsor's proposal followed by our assessment.

The Sponsor proposed to conduct a prospective, multicenter, open-label trial conducted in the U.S. to evaluate the long-term safety and effectiveness of the CHAMPION System in patients with heart failure.

The proposed post-approval study is powered to address the following hypotheses test.

For the safety, freedom from device/system-related complications at 6 months is less than 80%. Freedom from pressure sensor failure at 6 months is less than 90%.

For the effectiveness, the 12-month heart failure-related hospitalization rate is greater than or equal to 12-month rate in the year prior to enrollment in the post-approval study.

The study population will be all subjects who signed the informed consent form and satisfy the inclusion/exclusion criteria at the baseline visit with a maximum of 967 patients.

All patients will be scheduled for a follow-up visit every six months for a period of two years.

Now, I will move onto the assessment of the post-approval proposal. The Panel will be asked to discuss this issue in the afternoon session.

First, analysis plan tests the safety endpoint at 6 months and effectiveness at 12 months with descriptive analysis through 24 months, FDA believes that safety and effectiveness needed to be formally assessed via the hypothesis tests at 6 months.

Second, the effectiveness endpoint compares the 12-month heart failure-related hospitalization rate post-implant to the rate in the year prior to receiving of the device. FDA would like the Panel to discuss if this before and after comparison is appropriate for the post-approval study.

Third, FDA would like the Panel to discuss if any other effectiveness endpoints should be included as secondary endpoints.

And, finally, FDA would like the Panel to discuss whether the device effectiveness should be evaluated in the women with heart failure.

This concludes my presentation. Dr. Brockman will talk about study conduct.

DR. BROCKMAN: Randy Brockman, FDA.

Okay. So I'd like to shift now to discuss some issues FDA became aware of through our inspection process. This information was not provided in the PMA. I'll spend the next few minutes discussing the topics presented to you in FDA's addendum to our Executive Summary.

The Sponsor was aware of the pressure readings from the sensor, and the protocol allowed the Sponsor to contact sites regarding the sensor pressure readings. The protocol does not say anything about the Sponsor making treatment recommendations to clinical sites for individual patients. This is a quote from the approved protocol.

"The Investigator or designee will review the PA pressure measurements from the home monitoring unit. Alert limits are automatically set as described in Appendix E. The investigator or designee will be alerted by CardioMEMS, if those parameters are exceeded. If the PA pressures are elevated, the investigator or designee should make medication changes according to the recommendations in Appendix E."

Appendix E of the protocol contains recommendations for the management of hemodynamic parameters. It was included in your Panel pack as an appendix to FDA's initial Executive Summary and also as an appendix to the addendum to our Executive Summary.

The Sponsor was aware of the randomization assignment. The Sponsor contacted clinical sites on a somewhat regular basis. Based on an

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inspection of e-mail communications, those contacts, which were patient-specific, frequently contained recommendations for medical management that were at times rather specific and individualized to meet patients' needs, and also included recommendations for diagnostic testing. The e-mail recommendations from the Sponsor were limited to the treatment group subjects only.

This is an example of an e-mail communication from the Sponsor to an investigational site that does not concern FDA.

On 11-16-2009, a CardioMEMS nurse wrote, "Just wanted to make sure you are aware of upward trend of PA pressures for a specific subject. Do you know if site investigator plans on any changes to his medications?"

On this slide and on the following several slides, I'll reproduce excerpts from e-mails sent by the Sponsor to investigational sites. These are examples of some of the e-mail messages that concern FDA. I'll point out, again, that these types of communications were sent only for subjects in the treatment arm.

On 8-21-2009, a CardioMEMS nurse wrote, "I wanted to alert you to a specific subject's increase in pressures over the past week with a mean of 42 today. She responded nicely to extra Lasix back in May. Would you consider this again?"

On 12-29-2008, a CardioMEMS nurse wrote, "I wanted to alert

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you of an increasing trend in the mean of the subject. Although his mean pressure trend remains relatively flat, his pressures have an upward trend. We are seeing several patients in the trial experience post-holiday rise in pressures most likely due to dietary indiscretion and medication noncompliance. Do you think this patient would benefit from a few days of increased diuretic until his pressures return to baseline? I also noticed that this patient is on metformin in the face of renal insufficiency which may be contributing to difficulty in managing his volume status."

So the Sponsor has indicated that they were simply following the protocol and/or Appendix E. Appendix E does not mention metformin. Appendix E doesn't mention stopping or discontinuing medications other than diuretics.

On 2-4-2009, a CardioMEMS nurse wrote "1. PCWP 17 with PAM at 49 at implant -- consider increasing Lasix mg dose or frequency. If not responding well to Lasix, consider switching to Demadex and/or adding a PRN thiazide.

"2. Add hydralazine/nitrates to current regimen and up-titrate to optimal dose as tolerated. Once optimized on H/N and pressures still elevated -- consider pulmonary vasodilator, i. e., sildenafil."

Appendix E refers to diuretics in general as well as vasodilators but does not specifically refer to Lasix, Demadex, or in particular, sildenafil.

On 10-30-2008, a CardioMEMS nurse wrote recommendations

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that include "PCWP 14 suggests increased volume -- consider increasing Lasix to 40 mg BID or switching to Demadex if bioavailability a concern with Lasix. Consider using PRN thiazide to facilitate diuresis. Up-titrate Diovan to optimal dose as tolerated (160 mg BID). Add hydralazine and nitrates to current regimen up-titrating as tolerated. Evaluate patient's current compliance with treatment of his obstructive sleep apnea. Consider re-evaluation of patient's sleep breathing disorder diagnosis (OSA vs Central Sleep Apnea) and options for treatment."

This message includes pretty specific suggestions including reevaluating a treatment group subject's compliance with and diagnosis of sleep apnea. Appendix E does not mention sleep apnea or sleep disorders at all.

I'll let you read most of this message. I'll just skip to the bottom. "Would you consider challenging her with sildenafil in addition to adjusting her diuretic regimen by switching to Demadex or possibly using outpatient IV diuretics?"

I'll point out that the primary effectiveness endpoint captured in-patient hospitalization events such that this outpatient treatment would not be captured as a HFR hospitalization. I'll also point out that Appendix E does not use the word outpatient.

On 11-4-2009, a CardioMEMS nurse wrote, "I just wanted to make sure you and the site investigator are aware of the elevated PA

pressures for this subject. There may be some benefit from an increase in her hydralazine/nitrate or, as we have discussed before, an increase in diuretic. If the site investigator would like to bring the patient into the clinic for IV diuretics and transportation is an issue for her, please give me a call."

Again, Appendix E does not mention clinic or outpatient.

Appendix E also doesn't mention hydralazine.

On 7-29-2009, a CardioMEMS nurse wrote, "I appreciate the update. It sounds like he is getting more difficult to manage, especially with his hypotension. I also noticed that his heart rate, his HR has been up into the upper 80s where it has been running consistently in the 70s.... I know that in the past he received intermittent outpatient inotropes. Has there been any consideration in starting him back on this?"

Appendix E does not mention outpatient inotropic therapy.

Outpatient IV inotropes would not be captured as a HFR hospitalization and therefore would not contribute to the primary effectiveness endpoint.

This message reflects a physician's acceptance of the treatment recommendations made by CardioMEMS. This is just one example.

On 2-10-2009, a CardioMEMS nurse wrote, "1. PCWP 36 with PAM 42 at implant -- consider increasing Lasix mg dose or frequency."

Several other recommendations were also made. Later that day, the site investigator wrote, "Great. I would like to see these regularly. Go ahead and have patient take extra 40 mg of Lasix daily at 2 pm for 5 days."

On 5-9-2008, a CardioMEMS nurse wrote "Once I get a current update from you regarding these cases, I can make some recommendations regarding medical management. I look forward to hearing from you and working together to manage these patients. Feel free to call me anytime if you have questions."

On 5-7-2008, a CardioMEMS nurse wrote, "Feel free to call me anytime if you have questions regarding the medical management of your treatment arm patients. I look forward to working with you to optimize their medical therapy."

On 12-26-2008, a CardioMEMS nurse wrote, "I wanted to alert you that this subject's mean pressure went from 27 on 12/24 to 53 on 12/26. Do you think this warrants her to take an extra dose of diuretics today? It is the holidays, and we expect pressures to increase, but we still want to prevent her from going to the hospital."

I'd like to point out that I'm showing you only a sample of the relevant e-mail communications FDA identified. I apologize for the small text on the screen.

Medical therapy recommendations were also provided by the national principal investigators.

On 11-16-2007, one of the national PIs sent the following email to CardioMEMS after talking with the principal investigator at a specific site. "I spoke with the site principal investigator this morning. We had a very

collegial and productive discussion about hemodynamic monitoring in general, and his patients in particular. It sounds like patient #2 is very ill and will likely be made DNR. Patient #3 has had persistent elevation in her PA pressures, despite escalation of diuretic dose. Following a CardioMEMS employee's conversation with the site principal investigator yesterday, he increased the furosemide dose from 80 mg bid to 120 mg bid (the patient was previously to 10/25 on 40 mg BID). The patient does not have any clinical signs of extracellular fluid volume excess. The patient does, in fact, have substantial mitral regurgitation. I suggested that he consider starting a long acting nitrate and letting me know what happens; we may need to back off of the diuretic, if the nitrate works."

So based on other e-mails, the opportunity to confer with national PIs was offered to other site investigators as well. Now, to be fair, Appendix E of the approved protocol does address this. It states consultation with the national PIs is encouraged to optimize the success of medical management of PA pressures. However, the level and detail of involvement is greater than FDA expected.

So FDA is concerned that these actions may have biased the trial results. The Sponsor made treatment recommendations to investigational sites for subjects assigned only to the treatment group. The national principal investigators reviewed individual subjects with site investigators and made specific treatment recommendations. The Sponsor

told FDA that these interventions were intended to ensure compliance with the protocol, and clearly some of the interventions recommended by the Sponsor are consistent with Appendix E of the approved protocol.

While FDA acknowledges the Sponsor bears responsibility for ensuring compliance with the protocol, the level of interaction between the Sponsor and the clinical investigators regarding individual subjects' treatment plans was not consistent with FDA's expectations based on the protocol.

And I'd like to point out, that FDA is not specifically questioning the appropriateness of the treatment recommendations from a clinical or medical perspective. Our concern is the source of the treatment recommendations.

So FDA is concerned that the management recommendations by the Sponsor and the national PIs for individual study subjects in the treatment arm only may bias the results because these efforts may have minimized hospitalization for treatment group subjects without a comparable effort for control group subjects.

Additional, FDA believes that the measures taken by the Sponsor would not be duplicated in a postmarket setting.

This is an example e-mail alert provided to FDA by the Sponsor in the original PMA submission. The text of the alert is fairly straightforward, simply stating that a pressure threshold for a specific patient was exceeded. Please note that this sample e-mail does not contain any therapy

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recommendations. FDA believes this type of e-mail alert is practical and could be implemented in a postmarket phase. However, FDA feels that the content of this e-mail alert is quite different than the content of some of the e-mail messages the Sponsor sent to clinical sites during the trial, and that an e-mail alert such as this one would not replicate the level of involvement with patient treatment plans that the Sponsor had during the clinical trial.

So substantial therapy recommendations were made only for treatment group subjects. As a result, FDA is concerned that we can't conclude that the effectiveness result seen for the treatment group is due solely to the device.

Given the potential bias introduced by the study conduct, FDA is concerned that we cannot make an accurate risk/benefit determination for this device.

I would like to turn the presentation over to Dr. Greg Campbell.

DR. CAMPBELL: Good morning. I'm Greg Campbell. I'm the Director of the Division of Biostatistics in CDRH.

I'd like to offer some overarching clinical trial considerations from a statistical points of view.

First, concerning diagnostic devices in general, there are fundamentally two ways to evaluate diagnostic devices. The first is with a diagnostic performance study. This is usually a comparison to a gold standard. So there's a gold standard for truth, and then the performance of

the diagnostic device is compared to that gold standard.

The second type of study is a clinical outcome study, and the diagnostic device is studied according to whether it has an effect on the clinical outcomes. The advantage of this second clinical outcome study is that it can allow the direct causal inference that any clinical effect on patients is due to the diagnostic device.

So concerning these clinical outcome studies, they're difficult to do for diagnostic devices. They pose challenges to those of us who are only familiar with therapeutic clinical trials. It's the information that's provided by the diagnostic test that is under study. In particular, does that information make a clinical difference?

In most such studies, it is very helpful to see if the physicians who actually had that information used it or found it helpful. Namely, at the individual physician level, did that information make a difference or was it ignored?

So just making some general comments about randomized trials and bias reduction, the fundamental idea is to control for all possible variables, and then plan to treat both of the arms, the treatment and the control arm, exactly the same way and randomly assign subjects to one of the two arms. Then if there is a difference in clinical outcome, then it can be inferred that the cause of that difference is the diagnostic device. And so in this case, if the only difference between the two arms is the effect of the

device, then one can make that conclusion.

So in terms of bias reduction in randomized clinical trials, if the two arms are treated differently, this can introduce a potentially large and unknown bias. In CHAMPION, the two arms are treated very differently in terms of recommendations by entities outside the clinical site. In general, concerning masking, if you fail to mask either the subjects, the investigators, or the third-party evaluators, this can introduce a bias. In this study, only subjects were blinded in this study, but let me go on to say, that for these diagnostic outcome studies, it's impossible to mask the treating physicians from the output of the diagnostic device, and we're well aware of that.

However, patient-specific recommendations that the Sponsor provided to the clinical sites can be problematic. In general, the Sponsor has not remained masked or blinded and has made differential patient-specific recommendations in only one of the two arms.

Secondarily, it's desirable to have an endpoint that cannot be directly and easily influenced by knowledge of which group a subject is in. That unfortunately is not the case in this PMA, where the primary effectiveness endpoint is heart failure-related hospitalizations, but that's not why we're here today.

The planned objective then is to evaluate the effectiveness of the CardioMEMS diagnostic device in terms of heart failure-related hospitalizations in subjects. This is done then with a diagnostic clinical

outcome study. There's a potential bias if physician behavior is affected by things other than through diagnostic device information. There were protocol guidelines which are provided in Appendix E help to minimize this bias.

The concern, however, are these extra interventions that Dr. Brockman mentioned in his most recent presentation.

There were reminders to investigators in the one arm that could keep treatment patients out of the hospital. There was close monitoring of only patients in the treatment arm by CardioMEMS heart failure nurses, resulting in differential patient-specific recommendations. There were consultations between the clinical sites and the national principal investigators regarding treatment strategies for particular patients only in the treatment arm, and there were recommendations for treatment strategies that could keep only patients in the treatment arm from heart failure hospitalization.

So at issue then are what are the possible causal inferences that could explain any difference in the two arms? Could it be the incorporation of the hemodynamic information from the CardioMEMS diagnostic device into physician decisions that ended up reducing heart failure-related hospitalizations? Or, a second explanation is that the CardioMEMS nurses and national principal investigators made differential patient-specific recommendations initiated by them only in the treatment

arm to the clinical sites and that the result of that was the reduction in heart failure-related hospitalizations. And it could be that it's a combination of those two, and that's really at issue here.

The dilemma then is that, another way to say this, the effect of this study is confounded. It is confounded by the information from the diagnostic device and these “extra interventions.” So the possible bias from this confounding is of serious concern here and, given the sensitivity analyses presented earlier by Dr. Yonghong Gao, concerning the primary effectiveness endpoint in her robustness studies, this bias could have produced some or all of the significant effectiveness results seen in this trial.

So consider the following thought experiment. Suppose you did a randomized controlled clinical trial with two arms. The one arm had standard of care and the other had standard of care plus extra interventions, but there's no diagnostic device here. There's just extra care added to the one group in the form of the oversight by a clinical support team of nurses at a central location who provide advice upon request to prevent hospitalizations and who also make contact with the investigators at times to suggest changes in therapy. I submit it would not be surprising to see a difference in the two arms in the study.

So this brings us then to the intended use. How is the device intended to be used?

The proposed indications for use statement put forth by the

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Sponsor do not specify an automated or personalized effort by the Sponsor for the device. If the intention of the Sponsor was to use the device as a major part of a clinical decision support system, then that system would be what would be evaluated as part of the trial, along with the diagnostic device. The protocol then would include, for example, the algorithm that specified the automated e-mails to the physician, the content of those e-mails, and a more tailored approach by CardioMEMS nurses and others that would then make patient-specific recommendations. This study did not evaluate that system.

So, in conclusion, concerning these overarching considerations, confounding of planned intervention, namely the use of diagnostic CardioMEMS information by the treating physician, and the extra interventions which are the differential patient-specific treatment recommendations, renders interpretation of this trial problematic.

Which intervention caused the observed outcome?

The CHAMPION Trial does not provide an unbiased estimate of the effect of the device. It is not clear what, if any, effect of the study is due to the device itself. Further, the effect of the device in a real-world setting, if this device were to be approved, is unknown.

The FDA Review Team would like to thank particularly Dr. Felipe Aguel for his valuable input and guidance throughout the review.

We would also like to thank members of the Panel for their

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attention and consideration. This concludes the FDA presentation.

DR. BORER: I want to thank the FDA speakers very much for this lucid and comprehensive presentation.

We have time now for the Panel to ask brief clarifying questions, and again, I would like to urge all the Panel members to limit their questions to clarifications about what was said, what was done, not interpretative questions because there will be many of those, and really they should wait until we can speak with both the Sponsor and the FDA, which is after this session is done.

So let me ask the Panelists if there are any questions of interpretation? Burke.

MR. BARRETT: Burke Barrett. I have a brief clarifying question on the gender analysis, and I'm looking at the FDA's slide 27. And it appears that in the treatment arm, the effect rates are similar, in fact, the same between the males and the females. And that there's a difference in the control arm in the rates between the males and the females, and I'm wondering during your review of the PMA if you gained any insight as to why the rate in the female control arm is lower than the male?

DR. AGUEL: My name is Felipe Aguel. I'm going to be moderating the question and answer session, and I'll ask Dr. Gao or maybe Dr. Pina to come up to answer that question.

MR. BARRETT: Is the question clear? I'm looking at the

treatment arm, and I'm saying that seeing that the HFR hospitalization rate of males and females all being .32, and I'm looking at the analysis saying that there's not a difference between treatment and control females, when I look at the nominal rates within the females, I mean in the control arm, it's .53 for the males and .19 for females. So it looks to me nominally at least like the rate in the females is different, and I just wondered if you gleaned any insight into that.

DR. PINA: Ileana Pina again. Thank you for your question. We did look at that, and there were some differences between the male and female cohort, and for example, atrial fibrillation, which we now know is a bad marker, was 51% in the males and 33 in the women. The women were also more likely to be the group with the higher ejection fraction, so more of what we call HEF/PEF in the female group. Even though we know that even HEF/PEF has a lot of hospitalizations, so there were some differences that we examined, and maybe Yonghong can talk about if they were significant or not.

DR. GAO: This table, it gives some significant predictors for the outcome of number of hospitalizations, and when we look at the male and female, see how different they are in terms of these predictors. So the table shows that age is quite different, for male and the female, and AF is significantly different and baseline BMI and the cardiac output, but we didn't look at those specifically for control group.

MR. BARRETT: Thank you.

DR. BORER: Dr. Lange.

DR. LANGE: I have a couple of clarifying questions again. I want to ask about the gender, and then I want to move onto the e-mails for a second.

With respect to the gender, if females die, more females in the control group had died and being less available for hospitalization, whether that affected the results or not.

In regard to questions about the e-mails, did FDA have access to all the e-mail correspondence? And can they give us an idea of how often the e-mails deviated from the protocol? And is there a group of patients in the treatment group that did not have e-mails sent that are analyzable?

DR. AGUEL: So, the first question had to do with deaths among females, and I'll ask Dr. Gao to come up and answer that, and the second question regarding whether FDA had all e-mail correspondence related to the trial conduct and whether there's a cohort of patients that's still analyzable who didn't receive those e-mails, I'll ask Dr. Brockman to answer that question.

DR. GAO: Okay. About the death, I think within the first six months, the control females have had seven deaths and the treatment for the females have three deaths. That's what I remember.

DR. LANGE: And would that have affected the number of hospitalizations for the first six months?

DR. GAO: Well, I did not look at that part.

DR. BROCKMAN: Randy Brockman. So did we have all e-mails?

I guess it depends on how you define all. I was given copies of e-mails the Sponsor said included some version of a treatment suggestion. So do I have all communication between the Sponsor and the sites? No. You know, I don't have e-mail communications about adverse events. So assuming that those didn't have anything else relevant in them, I do have copies of all the e-mails that contained treatment recommendations.

Your question about how often were those e-mails -- did they contain things that deviated from the protocol the way we view it? My assessment is more qualitative than quantitative. The number of e-mails is fairly extensive. So I can't answer that at the moment, and I really don't think I could answer it after the break either.

And then you asked, the fourth question, I think part of my response to it may also answer the third one as well. E-mail communication was only one way there was communication between the Sponsor and the sites. There were also phone calls. I'm not saying what was in those phone calls, but I do know that there were phone calls. We have no way to know how often they occurred or the content of those calls. So I think a quantitative analysis would have some limitations.

DR. LANGE: Thank you.

DR. BORER: Val.

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DR. JEEVANANDAM: So this study design was obviously a collaboration between the FDA and the Sponsor. Why was this type of communication allowed? I mean it would seem that a much clearer trial would have been something where there was an e-mail alert that went out if the PA pressures went up, and let's see how the trial site deals with the elevation in PA pressures. This seems to be, you know, you're right, something that when you presented it, it's a management system. It's not just a PA pressure and a number. So why did the FDA allow it, or I mean you may not be able to answer to that question.

DR. BROCKMAN: The content of the communications is different than we expected. So my reading of the protocol and Appendix E said the Sponsor would contact the sites regarding the pressure readings and, if the pressure readings were elevated, would alert the sites to that effect. That's what we thought would happen in the trial.

DR. ZUCKERMAN: Dr. Jeevanandam and Dr. Brockman, perhaps you can bring up FDA's slide 83 again to again just underline what FDA's expectations where.

DR. BROCKMAN: So this is an example of an e-mail message that was sent from the Sponsor to a site that doesn't concern us. This e-mail basically alerted the site, the pressure reading's up and it was an inquiry, you know, if there's any planned changes, but didn't make recommendations.

DR. JEEVANANDAM: So the Sponsor went beyond what the

FDA had thought that they were going to do. So this was a little bit beyond just an analysis of the data. This was an interpretation and recommendation based on the data.

DR. BROCKMAN: The level and detail of the recommendations in the e-mails is beyond what FDA expected based on the study protocol, based on our understanding of the protocol.

DR. BORER: Before we go on to Dr. Cigarroa, can I just ask you to add onto that? Communications were encouraged with the national PIs. Was it expected that those interactions would be only for the treated patients, or would it have been acceptable to call to ask for advice on how to treat patients who were in the control group?

DR. BROCKMAN: So I think anything that's matched between the groups probably would not have raised a big problem for us. I think some of the communications dealt specifically with the PA pressure readings, which, of course, you couldn't discuss for the control patients.

DR. BORER: Well, weren't there any communications between investigators and the national PIs about control patients? Do we know?

DR. BROCKMAN: I don't have the answer to that.

DR. BORER: Okay. Dr. Cigarroa?

DR. CIGARROA: Returning to the gender analysis and comparing the control and treatment death rates for women, was there a differential percentage of patients experiencing events with heart failure in

setting to preserve ejection fraction versus depressed left ventricular systolic function?

DR. AGUEL: So I'll ask Dr. Pina to answer that question.

DR. PINA: I'm Ileana Pina. I don't think we have the specifics of whether those hospitalizations were more HEF/PEF or HEF/REF. Maybe Yonghong has some information.

DR. GAO: Okay. I did some data analysis using the model, I think it's the variance-scaled Poisson model, and I adjust for a lot of covariates in my regression model. First, I tried all the important covariates that should be included in the model, and the gender by treatment interaction, effect is very significant, and then I deleted some of the non-significant covariates from that regression model only with the significant covariates in my regression, and the interaction between gender and treatment is still very significant after adjusting all the important covariates.

DR. ZUCKERMAN: So, Dr. Cigarroa, I don't think we've addressed your question specifically. It's a question though that's important, and perhaps we can ask the Sponsor to do some homework during the lunch period to give you the table I think you're looking for.

DR. CIGARROA: Thank you.

DR. BORER: I have a fundamental question that I thought we would have dealt with a little earlier. Maybe we can do it now, and then we can go on to everybody else's questions, clarification questions. That is why

does the indication for the device, the FDA presented it, and it is in the Panel pack from both sources, the Sponsor and the FDA, but I don't quite understand the way that it's worded. Is the indication for approval to provide a device that will allow pressures to be measured, or is the indication to provide a device that will specifically be used to guide the management of patients with heart failure? Both are mentioned, but they're not mentioned as if they were together, and I'd like a little clarification here.

DR. AGUEL: So the proposed indications for use is up on the screen, and the intended use of the device is both. It's not just to measure a pressure but also for that pressure to be used in managing patients.

DR. BORER: Okay. I would just suggest that perhaps someone might want to think about the wording a little bit to make the linkage more clear, and I say that just on the basis of historical precedent for other approvals that have been made.

Okay. Other issues, clarifying questions. Dr. Slotwiner and Dr. Ohman.

DR. SLOTWINER: I have a question about the study design and why the FDA found it acceptable. Looking back at the other heart failure studies in this area, and there are three that -- I'm not a heart failure specialist, but there's Tele-HF, TIM-HF, and TEN-HMS which all looked at managing heart failure without invasive monitoring, which were negative studies, and then there were COMPASS-HF and REDUCE-HF, which were both

studies looking at managing heart failure with invasive monitoring where both the control group and treatment group were treated equally. It seems like in this study design, it was stacked against the control arm because they just weren't contacted in a regular fashion, and I'm just wondering if that was acceptable to the FDA and if -- it seems like a problem with the contact is not unexpected or unsurprising from the way it was designed.

DR. AGUEL: I'll ask Dr. Brockman to answer that question.

DR. BROCKMAN: So I want to make sure that -- maybe I wasn't clear. The e-mails that I just showed went from Sponsor to clinical sites, not to patients. So none of the e-mails I showed were contacts between the Sponsor and the patients in the trial. The contact between the investigators and the patients, we attempted to match. That was the matching phone call. So there were protocolized visits at one, three, and six months, and then every six months thereafter. Of course, nothing prevented non-scheduled visits in either arm, you know. The physicians were allowed to take care of their patients as they saw fit.

If a pressure-guided medication change occurred resulting in a phone call to a treatment arm subject, of course, that couldn't occur in the control group because they didn't have access to the pressures. So contact was supposed to be matched with just a random call to a control group subject.

Our goal was that contact between the clinical sites and the

patients in the two arms would be as matched as we could make it according to the protocol.

DR. SLOTWINER: I guess the phone calls are pretty closely matched, but it doesn't seem like what triggered the phone call is evenly matched. The control group received a random phone call whereas the subject, the treatment subjects received a phone call for a specific reason. In these other studies, the phone calls were evenly distributed, and so it's regular contact with both groups. So I think it's sort of, as Dr. Campbell mentioned, this study was really a treatment strategy test versus the device, and the other studies were really, the strategy was taken out of it, and it was just the device and didn't come out significantly. So --

DR. BORER: Dr. Ohman.

DR. OHMAN: Yeah, this is sort of interesting because it's hard to denude providers the ability to educate. So one of the features here, I think, is interesting to see is, for example, I noticed most of these e-mails were in the beginning of 2009. I don't have the study date to do a line, but how much of this is really about bringing the investigative sites to an educational level of heart failure management that's quite high, that is to say more than you would expect from a general cardiology practice?

I have to say the e-mails, the recommendations are excellent. I mean if you manage heart failure, they're really good.

But I think what you need to think about and maybe you've

done this, have you looked at a sensitivity analysis that remove all the patients with e-mail? They were identified, right. So it's almost like intention to treat versus treatment received, in this case reversed (i.e., no e-mail). That's one question.

And the second thing is, was there any level to which the frequency of at least e-mail that you can measure, were they more concentrated in the beginning of the trial or in the beginning of the site experience in this trial, which come to mind?

DR. AGUEL: So Dr. Brockman will answer both of those questions.

DR. BROCKMAN: So I'll just point out that the study started 2006-2007. So the e-mails 2008-2009, I mean those were dispersed. I can't tell you that they were evenly dispersed over the entire course. Again, I mean there was a lot of correspondence, and while I did a reasonably good sample, it was still a sample of the correspondence.

We did talk about trying to do some quantitative assessment of this, but in part because we got this information late and because it was a sample, and also because what we have are the e-mail communications, not the phone conversations, I think we would be making a tremendous number of assumptions to do those analyses. They're not impossible to do, but it would include a lot of assumptions.

DR. OHMAN: And I just want to add that the glass is also half

empty or half full. So it may be that in the -- the patients in the control arm actually received the benefit of this education because there must have been patients with similar characteristics but without the PA value known to them. So it can go either way.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: I just have a question about contacts again. So as for the scripting, the people who had the PA monitors were called when their PA values were elevated, and then there was a matched call to a control patient that said that there was no difference in recommendation of their therapy.

So does that mean that the people who were actually being followed with their PA monitors, the unblinded group or the ones that were being managed because of their PA numbers, they'd never get any kind of a negative calls, or were all the negative calls only going to the group that was blinded?

According to the script, it says that there's a call that says your PA numbers are elevated and we want you to increase the diuretic. And then a corresponding call was then made to a control arm patient saying, you know, as per your PA numbers, we're not going to change your therapy. So were calls that said we're not going to change your therapy ever done to the treatment arm?

DR. AGUEL: My understanding is that those calls were not

made to the treatment arm, but if I am mistaken, maybe the Sponsor can clarify.

DR. JEEVANANDAM: It just creates a big bias because then it's not really blinded because the second you get a call saying we're not going to do anything to your therapy, then you know you're not being followed.

DR. ADAMSON: This is Bill Adamson, and I appreciate the clarification question. At the time of informed consent, the patient was instructed that they would receive telephone calls and the recommendations thereof would not necessarily connote what group they were in.

The pressure-related treatment changes that required a telephone call from the investigator to the patient were scripted. None of the scripts suggested that the pressure treatment or the pressures were used in evaluation of the patient. It simply encouraged them to upload the data, and we'd recommend that you change medications.

The scripts also that were then generated to the control group patients simply encouraged them to continue uploading information from home, and there was no recommendations.

So, in essence, what you're saying is, yes, the treatment group patients had changes and the control group patients had no changes, and that was consistent through out the trial and matched between the two groups.

The obvious problem here as you alluded to is blinding, and in

an unplanned evaluation of a survey of patients after the unblinding period occurred, we found no signal that they were unblinded by that process. The pressure calls were low as we mentioned earlier and equally matched between the two groups.

DR. JEEVANANDAM: Thank you. I have just one more question about the male-female because I think that's a big point. You know, basically there's two problems, right. Either the females that were in this trial were a different population than the males because they were younger, they had less atrial fibrillation, et cetera, and perhaps that's why there was no treatment difference in that patient population. And if that's true, then I'm wondering if you can separate out the females who are at high risk or at low risk and compare them to the males in a similar population to see if there was a difference in hospitalization or if it be that females are much more attuned than males to their bodies. So the second they feel that there's something wrong, maybe they're getting therapy earlier. So I'm just trying to figure out the male-female because right now it looks like the females really don't benefit from this device.

DR. AGUEL: So I'll ask Dr. Gao to answer that question. I think she did some analysis of the covariates between males and females.

DR. GAO: Yeah, I did a lot, looked at the data in many different ways trying to explain why male and females, you know, different in this trial, and my conclusion is after adjusting all the covariates should be adjusted in

the model, you know, the interaction between the treatment and gender still there. So I cannot explain it away. Just say male and female are just different.

DR. BORER: Dr. Brindis.

DR. BRINDIS: So I share the FDA's concern about the potential confounders related to what we are actually measuring. Are we measuring the system? Are we measuring the high quality of input that we're having from a national level. I would love to have Lynne Warner Stevenson or Bill Abraham to be at my beck and call for the management of my patients, but I would be interested in the FDA's feeling about the results after the unblinded period, when it became unblinded, and was there a difference at that point where the controls and the treatment arm had pretty much equal benefit? Are we still measuring the device or are we measuring national input or is there -- how was interactions going on from a national level to the sites after they became unblinded? Do you understand my question?

DR. AGUEL: Yes. So I think the Sponsor had a slide earlier today about that, but right now I'd like to ask Dr. Brockman to see if he has any insight here.

DR. BROCKMAN: It is interesting, but I believe that's data that we had not received before. So I'd rather not comment on it.

DR. BORER: Can I ask, Dr. Evans, do we have -- are you fully clear with and satisfied with the way the robustness analyses were

performed?

DR. EVANS: Yeah, I don't have any issues with the analysis, and I don't have any clarifying questions. I've got plenty of comments to be discussed later.

DR. BORER: Dr. Ferguson?

DR. FERGUSON: I hate to keep harping on the female question, but I do think there is a question that we haven't answered yet which is if the females were treated differently, especially the females in the control group who seemed to do much better than everybody else, were there any differences in medication therapy between the male and female controls, between the female controls and the female treatment group? Was there more contact? More follow-up visits in the female controls? Do we have any idea about that information?

DR. AGUEL: So I don't think we have that information available. Perhaps the Sponsor can clarify after the break.

DR. ZUCKERMAN: Okay. So that's a key point and, Dr. Borer, if you could direct the Sponsor to do that. In the Sponsor's presentation, the whole male-female issue seemed to be dismissed by just showing the Panel one slide that indicated at 15 months perhaps there wasn't a significant effect, but as the FDA has pointed out, there's a very significant treatment interaction, a p-value at the 6 month time point. So perhaps if you could ask Panel members to clarify their questions for the Sponsor and the Sponsor

after lunch could present more data on the gender issue.

DR. BORER: Okay. I will do that. In addition, one of the issues that's just been raised is treatment and use of drugs. I'll presage that question that I'll ask later, but it's not for now about the differential use of drugs. So some homework on this might be useful for the Sponsor.

Anyway, Dr. Ferguson, do you want to restate what exactly you want so that the Sponsor can come back with the right information after lunch?

DR. FERGUSON: Sure. I'd like to see differences in medical therapy between male and female control patients and between female control and treatment patients in terms of dosages, medical therapy, if that's available, and I'd also like to know if there's a difference in number of contacts in those groups.

DR. BORER: Yes.

MR. BARRETT: I'd like to just follow up on the question that Dr. Brindis was asking. It got me thinking. The e-mails that seem to be the most concerning to the Agency are e-mails directly from the Sponsor to the sites that mentions these treatments, and I'm curious in your review if you noted the time point in the study the patient was in. In other words, were females limited to the time period from implant to the six-month follow-up or did that kind of interaction continue after the six-month period because we do have e-mails --

DR. AGUEL: So I don't think FDA has that information. The Sponsor seems to have that. Maybe they can clarify after the break. Do you have anything to add to that, Dr. Brockman?

DR. BROCKMAN: No.

DR. BORER: Okay. Perhaps we can hear more about that after lunch also, the distribution of e-mails. Dr. Jeevanandam?

DR. JEEVANANDAM: I mean if we're going to ask for more data, is there any way to let's say just compare patients with atrial fibrillation and no atrial fibrillation, male-female, and see if there was, you know, just a simple comparison to see if that made a difference. It seemed like there were, when the FDA presented it, there were like three or four big variables that seemed to be different in the -- in the population of e-mails. So if you can pull the most important variables and just compare male-female and see if there's a difference in hospitalizations.

DR. PINA: Ileana Pina. In the slide that we showed with the differences, there was a difference in atrial fibrillation burden between men and women.

DR. JEEVANANDAM: Right, so I wanted to see if you think the patients who had no atrial fibrillation, females and males, and see if you could see the difference in hospitalizations or not.

DR. PINA: I don't think we have that, but that would be good if we could get it.

DR. BORER: Dr. Brindis?

DR. BRINDIS: Since we are just on information finding, I don't think I saw a breakdown or a slide of the actual EFs for women. You mentioned that there were more women -- there were 100 percentage of women who had preserved EFs, but we didn't get a number. So that would be great if we had the breakdown particularly with the understanding by the Sponsor that the benefit of the treatment seemed to be higher in preserved EF versus not, yet we've heard a suggestion from the FDA that there were a higher percentage of women with preserved EF.

DR. PINA: We do have that. So for the women, this is Ileana Pina again. For the women, 31.8, in other words 32% of the women have ejection fractions greater than or equal to 40 compared to 17.8% for men. So nearly double.

DR. BORER: Okay. Yes, Myron Weisfeldt.

DR. WEISFELDT: The major drug treatment difference between the two arms was the use of nitrates, and because of previous studies, I think most people are familiar with, it raises a question of race and -- analyses and whether, in fact, if you will, the females were all Caucasian and the males were African-American.

DR. PINA: So that's actually an excellent question. Overall, the trial had a very good percentage of African-Americans. 31.8% of the women were African-American compared to 19.5% of the men.

DR. BORER: Now, are there any other clarifying questions?

Yes, Dr. Ferguson.

DR. FERGUSON: I have a question about the accuracy of the device. You mentioned that a treatment or a sensor failure was defined as inability to obtain any reading. Do we have any idea about the accuracy of the readings? Does this drift over time, or is there any variance in the readings that might suggest that over time the accuracy isn't apparent?

DR. BROCKMAN: Randy Brockman. Yes, we do. While we're pulling that up, I was just asked to remind the Panel, I appreciate all the questions about the e-mails. We are concerned, and just to remind you that the e-mails were not something that we had knowledge of in the PMA. We found it only based on our inspections. That was relatively recent. So we did think it was important information to bring to your attention, but it is something that we've just recently become aware of. So when you think about some of our answers, please keep that in mind.

Okay. So the question that was about sensor accuracy. Everyone got an assessment at implant. So at the initial implant, there was a right heart cath, correlated to sensor performance at that time. There was not a protocol requirement for a subsequent right heart catheterization. So patients didn't have to come back in for right heart cath, but there were a number during the trial. As you can see, 43 patients underwent 85 physician-initiated right heart catheterization procedures. So we do have some

information.

If you can go to the next slide. Oh, this got small. Pardon me.

Okay. So this slide shows the Bland-Altman analyses of the simultaneous PA mean pressure obtained at implant on the left and then during follow-up on the right, and obviously there are a whole lot more data points in the analysis on the left.

I will just point out that you make sure that you see that the scale over here is very different than the scale over here, so a larger scale. Just so you're aware of that.

At implant, the 95% limits of agreement were between -2 and 2.2 mmHg. During follow-up, the limits of agreement were 10.4 mmHg to -8.43 mmHg, and just so you know, the comparative right heart cath procedures performed over here occurred on an average 265 days after implant. So this is the mean.

You can go to the next -- or I can do that.

Then this is for the systolic, again at implant and at follow-up. I can read you all the numbers if you'd like, but you can see the limits of agreement presented on this analysis. So this is systolic, and here is diastolic. I'll just point out over here, during follow-up, the average difference for the diastolic, the average difference was -4.4 mmHg with limits of agreement from 16.3 mmHg to -7.4.

DR. BORER: And before we go onto Ms. Currier and

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Dr. Cigarroa, Dr. Lange had a question specifically about this slide.

DR. LANGE: Specifically about this slide. Since the Swan-Ganz catheter is the gold standard, maybe you can show us the data, not with an average of the two, but just versus the Swan-Ganz catheter for those three pressures.

DR. BROCKMAN: So I don't have plots for that.

DR. LANGE: Would it be possible over lunch to do that? If not, I understand. But is it possible?

DR. BROCKMAN: Yeah. I'd have to look and see if I actually have these individual data points from which to generate a plot or not. I'm not sure I have that.

DR. BORER: Okay. Ms. Currier?

MS. CURRIER: I keep getting sort of baffled by the FDA's concern that these e-mails weren't sent to the control group. Now, you've had an example of an e-mail that you thought was appropriate from the nurse. It couldn't have been sent to a control group, would it, because it would have broke the blind nature of the study.

DR. AGUEL: That's --

MS. CURRIER: Am I incorrect there?

DR. AGUEL: That's a great point. Those e-mails could not have been sent to the control patients because the control patients didn't have a PA pressure measurement to trigger the sending of that e-mail. I think FDA's

concern isn't that they weren't sent to the control patients. The concern is that they were sent to the treatment patients.

MS. CURRIER: Yeah, I get that. Okay. I just wanted to make sure I was correct there. I would love to have one of those --

DR. BORER: Dr. Cigarroa?

DR. CIGARROA: Just a couple of points of clarification as it relates to baseline demographics. Do you know what the percentage of patients in the control versus treatment group had either a dyssynchronous present at baseline, (2) functional mitral regurgitation, or (3) from the time of implantation of a CRT device, given that all three of those are well ascribed in impacting subsequent hospitalization rates?

DR. PINA: We do have that. The ICD yes group in the control arm was 40%, 36.8 in the treatment arm. So just slightly different, and for CRT, it was pretty balanced between the two groups, roughly 15%.

DR. CIGARROA: But as a follow-up to that, do you know the duration of implant, given that CRT impacts remodeling and that can occur beyond three months or nine months?

DR. PINA: No, we do not have that information. Maybe the Sponsor does.

DR. CIGARROA: Anything about the functional MR or the presence of dyssynchronous?

DR. PINA: Not in this table over here, no.

DR. BORER: We were presented data on MR baseline by the Sponsor I believe, were we not?

DR. CIGARROA: If we did --

DR. BORER: Let's see if we can get the data from another source after the lunch break.

Okay. Seeing no more questions -- I'm sorry.

DR. WEISFELDT: This is sort of a complicated question which I'm I guess -- is this the time when we talk about additional data that the Sponsor might bring to us?

DR. BORER: If you want to. We have a chance to hear it, so this would be the time.

DR. WEISFELDT: So there was a slide presented to us that showed the correlation between the rise in both control and intervention patients of pulmonary pressure predicting, if you will, hospitalization, and I wonder whether the Sponsor has any data in the treatment arm that might examine whether such a rise in pulmonary artery pressure in the treatment arm was intervened with and there was a drop in pressure that would temporally, regardless of the e-mails and the way it was done, evidence that the treatment arm, the actual intervention for elevated pulmonary pressure resulted in avoiding hospitalization.

DR. BORER: I'm not sure exactly what you mean. Does the Sponsor understand?

DR. BOURGE: Bob Bourge from UAB. Not specially it hasn't been analyzed because that wasn't the goal of this study, but from COMPASS, yes, where we were trying to stop those peaks from occurring, and we showed that and it's been published.

DR. BORER: Dr. Milan.

DR. MILAN: I have another question about sensor reliability, and that is on page 106 of the Sponsor's packet. They described 19 sensors that needed recalibration, and I just -- they don't really appear anywhere else. All we hear is that there were zero failure rates in these devices, and we saw these plots that showed that there's, you know -- correlation between implant and follow-up. Were these 19 sensors part of those 43 patients who had 85 right heart caths performed at the physicians' discretion or were these separate? I'd just like to hear a little bit more about those.

DR. AGUEL: I don't think FDA has that information. Again, it's something that the Sponsor will need to answer after the break.

DR. MILAN: Great.

DR. BORER: Mr. Barrett.

MR. BARRETT: Yeah, Burke Barrett. I just wanted to make sure, Dr. Borer, before we break, there's a chance to review the questions in particular for the Sponsor so that they're clear on what they're being asked to go back and look for over lunch.

DR. BORER: Okay. We can do that. I have a list in front of me

that I've been trying to keep up. I may not have been comprehensive. So we should do that. We wanted to know about the responses of the doctors to the pressure in the first half of patients versus the second half of patients, to see if there was some evidence of a learning curve.

We wanted to know -- well, we have several questions about the pressure. There was a table that Dr. Cigarroa wanted, and unfortunately I don't have the details, but maybe you can repeat it.

DR. CIGARROA: Sure. It relates to women and whether or not those individuals who experienced hospitalization control versus treatment, whether there were any differential rates in the presence of heart failure in setting a preserved systolic function versus depressed.

DR. BORER: Okay. These are questions that the Sponsor will have to provide for us I believe, not the FDA. That's the last chance we'll have to ask them before the break.

In addition, there was a question for the Sponsor and for the FDA about the distribution of e-mails, that is what was the timing of the e-mails that were sent in relation to the intervals of the study.

Finally, we wanted some atrial fibrillation comparisons, some of which we've heard about, and there were some additional atrial fibrillation incidences or occurrences among the controls and the treatment group, male and female, and I guess that was pretty much it.

Were there others? Yes, Dr. Cigarroa.

DR. CIGARROA: I also wanted to know whether the baseline demographics, we had any information relative to control versus treatment with regards to prevalence of the synchronizing functional MR and time of implantation of CRT to randomization.

DR. BORER: And Dr. Milan.

DR. MILAN: So this is for the FDA. We've been told there's a significant interaction between treatment and females, and I just want to be clear, I think that was for heart failure-related hospitalizations. If we had that same analysis for heart failure-related hospitalizations and death, that might be useful because I think the Sponsor's claim is that there's a competing risk of death that makes the hospitalization look significant.

DR. BORER: Okay.

DR. FERGUSON: I asked for differences in medical therapy and follow-up visits between --

DR. BORER: Yeah, I will have a question about that, too, but I think you have those stated. Okay. Yes, Dr. Brindis.

DR. BRINDIS: I was interested in the national PI behavior after the unblinding.

DR. BORER: I'm a little diffident about saying we're done with the questions but -- okay. It's almost 12:30. We're going to break here for lunch. We have to be here at 1:15 because that's when the Open Public Hearing is scheduled.

(Whereupon, at 12:30 p.m., a luncheon recess was taken.)

AFTERNOON SESSION

(1:15 p.m.)

DR. BORER: Okay. It is now time, it's now 1:15, and I'd like to resume the Panel meeting.

We'll proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Lieutenant Russell will now read the Open Public Hearing disclosure process statement.

LT RUSSELL: Good afternoon. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group'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. Thank you.

DR. BORER: Thank you. We have only one pre-registered speaker, Dr. Michael A. Carome, who will have 10 minutes to present. Please keep an eye on the lights there, and then we have four others who have come forward today, each of whom will be given three minutes, and you'll have to keep your eye on the signals there, too.

So I will begin the public portion of the meeting by asking Dr. Carome to make his statement.

DR. CAROME: Good afternoon. My name is Dr. Michael Carome, Deputy Director of the Health Research Group of Public Citizen. I'm testifying on behalf of myself and Dr. Sidney Wolfe, the Director of our group. We have no conflicts of interest.

We oppose FDA approval of the CardioMEMS system PMA because, one, the design and conduct of the single pivotal clinical trial evaluating this device have multiple features that all created readily apparent bias with respect to the effectiveness endpoints in favor of the experimental group. Two, the device has known short-term risks of serious harm related to implantation of the procedures, as well as likely unforeseen long-term risks.

And, as a result of one and two, there's insufficient data to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweigh its risks.

In terms of effectiveness, CardioMEMS conducted a single pivotal trial to evaluate its device that was prospective, multicentered, randomized controlled, and single-blinded to subjects only. The design has been covered in detail already, and I won't go into that further.

While statistically significant differences were seen in each of the pre-specified primary and secondary effectiveness endpoints, as well as many other supplementary endpoints, see the table here, the absolute difference shown in the column marked red, between the treatment and control groups, for the most endpoints was relatively small. Assuming these endpoints were due to actual benefits of the device, the benefits of widespread clinical use from this device in a real-world setting would certainly be less than was seen in the clinical study.

Also, there was no difference in mortality outcomes between the two groups shown here, and there was no statistically significant difference in all-cause hospitalization rates at six months.

Several features of the design and conduct of the study created a readily apparent bias in favor of the treatment group. Thus, it is highly conceivable that the differences seen in the effectiveness endpoints were due in large part or entirely to bias. These features included the following: a

single-blinded study design. This is one feature of the study that could not be avoided. Nevertheless, the clinical investigator awareness of each subject's study group assignment may have influenced decisions regarding both medical therapy and whether to hospitalize a patient, both of which could directly affect the primary and secondary effective endpoints. For example, investigators hoping to show that the CardioMEMS System was beneficial may have been more likely to admit a control group subject than a treatment subject.

There was a committee blinded to the study assignments that evaluated the effectiveness endpoints regarding hospitalization. However, this blinded review did not mitigate the apparent bias that resulted from clinical decisions being made by the unblinded clinical investigator managing the subject.

Number two, there were consultations with the national principal investigators regarding medical management of treatment group subjects only. The protocol, approved by the FDA, included a provision in which the clinical investigators at each of the sites were encouraged to consult with the national PIs who were presumably experts in the field of congestive heart failure to optimize the success of medical management of PA pressures. Apparently no such encourage for consultation was provided with respect to the medical management control group subjects whose care might have been enhanced had the site clinical investigators consulted with

the national PIs with the same frequency as the treatment group subject. Such unbalanced consultation with the national PIs introduced a bias into the study design that favored the treatment group.

Thirdly, there was unbalanced content and frequency of telephone contacts between the investigators and the treatment group subjects versus control subjects. The protocol, approved by the FDA, included scripts for telephone contact with both subjects that were generic in nature. Whenever a subject was contacted in the experimental group, a randomly selected subject in the control group was then contacted. These were not comparable study interventions. Treatment subjects received telephone contacts that were based on contemporaneous, subject-specific clinical information, i.e. the PA pressures and included medication changes. Control subjects, on the other hand, received random generically scripted calls unrelated to any pertinent contemporaneous contextual clinical information that may have warranted medication changes.

Furthermore, the mean number of telephone contacts per treatment group subjects was slightly higher than the mean number for control subjects. Such imbalances in the content and frequency of the telephone contacts between the study groups introduced bias that again favored the treatment group.

And, finally, as has been discussed in detail, there were subject-specific treatment recommendations provided to individual site investigators

by nurses employed by the Sponsor. This is the most egregious source of bias that was introduced and identified by the BIMO inspection. The inspection revealed that nurses working for the Sponsor made medical recommendations for heart failure management for specific subjects during the course of the trial, limited to treatment group subjects only. The sponsor contacted investigational sites during the trial regarding recommendations for treatment group subjects with respect to starting, stopping, or titrating medications for heart failure, including doses, intervals, and duration. Such communications between the site investigators and the Sponsor-employed nurses who were highly motivated to show a difference that favored the device occurred via a known number of e-mail contacts of 1.5 contacts, e-mail alerts per patient for the first 6 months, and there were an unknown number of telephone contacts.

Such contacts between Sponsor employees, who were highly motivated to affect the outcome of the study in the direction to favor the CardioMEMS device, and individual site investigators regarding management of treatment subjects is not only highly unusual but, in combination with the lack of investigative blinding, created a high degree of bias in favor of the treatment group.

Similar contacts and treatment recommendations by independent study nurses for control subjects based on monitoring of clinical parameters almost certainly would have improved the effectiveness

endpoints in such subjects.

In responding to the BIMO inspection findings, the Sponsor argued that the contacts fell within the scope of the protocol as submitted to the FDA under the IDE. This argument is irrelevant. Such procedures create a bias regardless of whether they were pre-specified in the protocol or not.

In responding to FDA's concern about study bias, the Sponsor stated the following: However, the FDA has not provided to date any evidence from the study to support a finding that these contacts resulted in bias being introduced into the study results obtained.

The Sponsor fails to recognize the insidious nature of bias which can influence investigator actions and judgments in subtle and not so subtle ways, and the paramount importance of ensuring before a study begins that the study is designed and conducted in a way that eliminates or minimizes bias to the greatest extent possible.

Once a study is completed, it is impossible to prove how much of a difference between the study group outcomes resulted from the bias and how much was from actual differences between the interventions being tested.

In this case, most epidemiologists would conclude that the multiple features of the study design and conduct described above created readily apparent bias and prevent any valid conclusions from being drawn about the effectiveness of this device.

Finally, consultations with national PIs and treatment guidance from nurses that was patient specific, nurses employed by the manufacturer, are all artificial, non-real work interventions that would not carry over to routine clinical practice if this device were approved for marketing.

In terms of risk assessment, the procedure for implanting the CardioMEMS sensor is an invasive procedure that has many known risks of harm, including the following listed here.

Furthermore, given the limited testing of this device in animals and human subjects, there is insufficient data regarding the long-term risk associated with this permanently implanted device.

In concluding, in summary, our recommendations are as follows: We strongly recommend that the FDA, in order to protect public health, not approve the PMA application for the CardioMEMS system because, one, the design and conduct of the single pivotal clinical trial evaluating this device have multiple features that all created readily apparent bias with respect to the effectiveness endpoints in favor of the experimental group, thus preventing any valid conclusions from being drawn regarding the device's effectiveness.

Two, the device has known short-term risks of serious harm related to the implantation procedure as well as likely unforeseen long-term risks.

And, finally, as a result of one and two, there's insufficient data

to provide a reasonable assurance that the device is effective for the proposed indication or that the benefits of using the device outweighs risk.

Thank you for your attention.

DR. BORER: Thank you very much, Dr. Carome.

We have four additional people who have presented themselves today. They have an order, but I only have their first names. Here we go. It's Thomas Murray, Mary Lou Osevala, Walter Pieschel, and Dr. Warren Strickland in that order. Each of them has three minutes to present. We'll start with Mr. Murray.

MR. MURRAY: You introduced me. I guess you can hear me. I'm from Omaha, Nebraska. I don't have any interest in any groups here or any investments.

About nine years ago I had a heart attack. I had triple bypass surgery. About two years later, my heart stopped completely. I was LifeFlighted in a helicopter to Bryan Heart Hospital in Lincoln, Nebraska. I was out of it, and my wife and children allowed or talked to the specialist, to implant a defibrillator and a pacemaker in my chest. Awhile after that, after they had implanted the defibrillator, my heart stopped beating entirely, and I was LifeFlighted in a helicopter from Omaha to Lincoln, Nebraska, and they -- that's when they put the pacemaker and defibrillator in.

I was walking about two miles every day before that, and I had to quit walking after they implanted the defibrillator and the pacemaker.

Not too long after that, I started having problems breathing. About midnight or 2:30 in the morning, I'd wake up and I'd feel like I was drowning. I couldn't get any air in my lungs whatsoever. I think I know what a drowning person would feel like. My wife would drive me to the hospital, fortunately about three blocks from our home, and they would give me some shots, put me on oxygen, give me some medicines to make me be able to breathe again normally. I might stay in the hospital three or four hours or one, two, or three days.

While this was going on, Dr. Kruger who implanted the pacemaker and defibrillator was seeing me about every 90 days as a follow-up to the implants. He asked me if I'd like to take part in this CHAMPION study, and I said okay.

The procedure to implant this device was like a lot of other procedures I had already had. I had had heart surgery three times before that. This machine sends my pressure readings every morning to the heart hospital doctor and then by satellite. I just lay on the machine and turn it on. It only takes a couple of minutes to do it and it transmits the data. The doctor can evaluate the information, and he'll have his nurse call me and say, if necessary, take some more diuretic or glipizide pills, two more for three days in a row, and if nothing changes, the nurse will call back and say go back and take what was your normal medication assignment.

After I get it booted up, it just takes 19 seconds to send this by

satellite to the doctor's office. I think if I was impaired more, it would be possible for my wife to just go through this procedure for me if I couldn't do it myself. If the pressure's off, the nurse in the doctor's office will call and say take some more so many days and then stop.

DR. BORER: I have to ask you to sum up, please, if you would.

MR. MURRAY: Sure.

DR. BORER: You're a little over time.

MR. MURRAY: Okay. If the nurse called me to take the Lasix, I do what she says, and after I started taking these instructions from the nurse, I joined a health spa. I walk a half an hour in the morning and the afternoon on the bicycle or treadmill, and I can go down and have coffee, and I don't have to worry about three blocks from the house being transported to the hospital because I can't breathe. So I'm pretty well sold on this CardioMEMS machine myself. It's done a lot of good for me, and I'm sure it could for a lot of other people. My life is a lot better than it was three years ago by far. Thank you for listening to me and for your time.

DR. BORER: Thank you very much, Mr. Murray.

The next speaker is Mary Lou Osevala.

MS. OSEVALA: Good afternoon. My name is Mary Lou Osevala, and I have no financial disclosures other than CardioMEMS reimbursing for transportation and lodging.

I am a heart failure nurse practitioner practicing at Penn State

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Hershey Medical Center, which is located in Central Pennsylvania. It is an academic medical center that serves a quaternary territory. Our heart failure programs provides comprehensive care, including heart transplants and mechanical support.

My experiences as a nurse run the gambit from rural home healthcare to cardiac intensive bed care nursing. With that being said, I have witnessed absolutely heroic care by families and caregivers in assisting their loved ones with heart failure to remain in their home. The opportunity to participate in the CHAMPION study for me was a demonstration of meaningful use of technology bridging the gap of the ICU hemodynamic monitoring to where the patient prefers to be, at home.

In heart failure disease management, I rely on open communication with patients, several who live over 100 miles away. Most of this is through telemonitoring. A phone call is made to the patient, and a series of questions assessing symptoms of heart failure and self-reported weight changes are discussed. Medications are adjusted based often on subjective data, which sometimes will warrant a clinic visit, lab work, or an emergency department visit.

Using pulmonary artery pressure readings provides the objective data that is often missing in our current labor-intensive attempts of prospective early intervention in predicting heart failure decompensation. Taking the guesswork out of outpatient medication titration has been

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tremendously satisfying to me. It has provided me the additional information to individualize maximization of medication based on the patient's baseline pulmonary pressures, not necessary the idea textbook one, but where the patient is not symptomatic with hypervolemia, hypovolemia, or profound fatigue. Even more important, all this can be done without the patient being admitted to the hospital, without a clinic visit, allowing the patient who lives 100 miles away to receive quality treatment, thereby reallocating scarce resources like hospital beds and emergency department staff to attend to the patients who need them.

As I mention limited resources, we all have been affected by past and current economic constrictions. There is not enough clinic time, healthcare providers, and resources to provide face-to-face care for the millions of Americans living with heart failure, nor is it practical.

In order for heart failure disease management programs to intervene in this complex vulnerable population, we need safe, reliable, efficient tools as seen with the CardioMEMS Pulmonary Artery Pressure System, to partner with patients and families in providing consistent quality care.

Though there are a plethora of studies involving the theme of close follow-up and other mechanisms of remote monitoring using technology, the addition of the objective data provided by the pulmonary artery pressure sensor helps guide treatment, including heart failure

treatment or palliative care before the moment of crisis.

Thank you.

DR. BORER: Thank you very much, Ms. Osevala.

The next speaker is Walter Pieschel.

MR. PIESCHEL: Good afternoon. I'm Walter Pieschel, and I am a patient under the care of Ohio State. I'm from Richwood, Kentucky. I thank the Panel and the FDA for the opportunity to present my experiences to you.

A brief medical history, I started in '96 with a heart attack. I went about 11 years with medication that kept me going pretty well. I had a pacemaker and defibrillator installed while I was in that period of time. In 2007, however, I, in March, had a sudden cardiac death attack for which the defibrillator did its job. A week later, I had three more incidents where the sudden cardiac death came on, and once again, the defibrillator did its job. For four months, I did pretty good, and then I went into flash pulmonary edema. When I got everything evaluated, I also had pneumonia, kidney issues, blood clots, and dehydration to go along with the flash pulmonary edema.

So I had the whole package, and I came through that. Two months later, I went again and had flash pulmonary edema, and it was at that time that a nurse practitioner who was in the hospital kept coming to me and telling me that our local hospital had put in a heart failure clinic and strongly recommended that I was a good candidate to visit them.

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So I did do this, and at the time, I found out that Dr. Abraham from Ohio State had apparently set up the health clinic for the hospital there in Northern Kentucky, and that if I wanted to get involved in a program, he would interview me. So on my next appointment, Dr. Abraham did come and interviewed me, and on the next two visits that I came, he was also there, and I had three opportunities to talk to him. He then offered to have me come up to Ohio State where he said they had a program that he thought could help me because at that point everything was pretty grim with what everybody had told me my condition was. And he said I believe we can get you back to some state of normal life.

So this was pretty interesting to me. I liked the idea, and I did go up and start to go over all the paperwork and all the forms. I did get hung up for a couple of days when I saw the line, if it doesn't work. I wasn't quite sure if I was going to go with this, but I did overcome that. I did sign all the paperwork and agreed to go ahead and go through the program.

I then was taken by Dr. Hassan who did the surgery. I found it to be a very simple, easy surgery that took just about an hour. They did keep me then overnight for observation, took the time to show me all the equipment that I would be using and how to use it. Again, it was very simple equipment. There was no problem to it. A little bit large in size, but still very transportable.

At that point, I came back home with all the equipment.

DR. BORER: Excuse me, Mr. Pieschel. We're going to have to ask you to sum up. We're running a little over time.

MR. PIESCHEL: Okay. Basically what I did then real quick, I used the equipment, I found it, generally speaking, it took less than five minutes. It gave me a very big boost in confidence. I did not have the worries that I had from all of the other things. I personally credit this particular device with me being alive and talking to you today. I honestly believe that with all my heart, and the thing I look forward to the most, is the day that this device, this CHAMPION, can be used by thousands of other people who have heart failure because I feel that heart failure is life and this gives us a second change of life. Thank you for the opportunity to talk to you all.

DR. BORER: Thank you very much. We have one more speaker, and then we'll see if the Panel has any questions for any of the speakers.

The final speaker is Dr. Warren Strickland.

DR. STRICKLAND: Thank you, and good evening. I'm Warren Strickland, an interventional cardiologist from Huntsville Hospital in Huntsville, Alabama, and I have to say, Whoa, Tide.

I served as the PI for the CHAMPION study at our hospital. I'm not a paid consultant, nor do I have any other financial involvements or arrangements with CardioMEMS. I personally provided my own transportation in order to stand before this Panel today.

As such, we have a large, single specialty group that consists of 30 cardiologists, and we serve a large community there in Northern Alabama. We have predominantly a rural population with a high prevalence of heart disease and a high concentration of congestive heart failure.

As with most of you all who are involved in clinical care, heart failure touches our clinical practice and has a huge impact on our community in terms of a significant and challenging problem with management, particularly with decompensation and readmissions.

We do, however, have a success heart failure program that has been instrumental in managing our patients.

I stand before you today to share with you some of my experiences and observations as a result of the CHAMPION Trial. Given the high prevalence of congestive heart failure in our community, we were, in fact, the high enroller in the CHAMPION Clinical Trial. We, in fact, enrolled 45 patients.

As a result, I did about 90% of the implants and 90% of the follow-up and really developed a real feel for the device and its utilization in managing patients remotely with hemodynamic monitoring.

Again, this study provided a tremendous amount of clinical insight in managing these patients with New York Heart Classification III heart failure.

You know, it became very obvious early on in this clinical study

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that each patient was unique, that they had their own hemodynamic footprint and a pharmaco-hemodynamic fingerprint. For instance, you could take a patient who had a mean PA pressure of 45 mmHg, and he may become quite symptomatic and require an intervention. Then the same patient with the same ejection fraction would have a mean PA pressure of 45 mmHg would be totally asymptomatic. As such, each patient responded differently to different therapeutic interventions such as ACE inhibitor titrations -- titrations.

Therefore, templating management was difficult and almost impossible and really required tailored individual management, and that's what really this study demonstrated very clearly: that each patient was a little bit different. They had a specific therapeutic window that really only the PI who knew that patient could really make the appropriate interventions.

Now, the web interface was very intuitive, efficient, and I was able to review the pressure trends quickly with my nurse and made the appropriate medication changes. In fact, my nurse and I would sit down about once a week, look at the trend data sets, and make the appropriate adjustments to the medication. Again, it took about 30 minutes per week.

The alert system provided a good backup and reinforcement, and these would actually come directly to my BlackBerry. Patients who had pressure alerts, we would respond to those immediately, give those patients

a call, and some would require intervention and some would not.

In conclusion --

DR. BORER: Excuse me. Okay. Go ahead.

DR. STRICKLAND: -- having the pulmonary artery hemodynamics made our clinic more efficient by giving us physiological, actionable information versus the guesswork on the basis of clinical science and symptoms that we have historically employed.

Thank you very much. Are there any questions from the Panel?

DR. BORER: Thank you very much, Dr. Strickland.

Is there anyone else who wishes to address the Panel from the public?

If not, are there any questions from the Panel for any of the five people that we've heard?

Okay. Seeing none, I will thank all the speakers for their important comments, and we'll continue with the remainder of the agenda. The Open Public Hearing is now officially closed.

We'll now begin the Panel deliberations. This portion is open to public observers, but public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers. During this portion of the agenda, we will open up the floor to both the Sponsor and the FDA.

The Sponsor, more than the FDA, were asked some specific questions this morning, and we'll begin with the Sponsor perhaps if you want to respond to the specific questions that we asked. Dr. Yadav, if you're going to assign roles, that will be fine or anyone else.

You did ask first about the issue of the learning curve, and you're going to tell us about that, the first half of the patients versus the second half in terms of interventions.

DR. YADAV: I think we're still working on that slide for that. I think we should hopefully have that. Dr. Abraham is ready to address the e-mail question --

DR. BORER: Okay.

DR. YADAV: -- if that's okay with you, sir.

DR. BORER: Sure.

DR. ABRAHAM: Well, thank you very much. Bill Abraham again, and I think we need to go very carefully through this whole issue of e-mail communications. This has come up multiple times. A specific question was asked of the Sponsor before the break about the frequency of these e-mails, and what happened to the frequency of these e-mails over time. So I want to take you through some data and then address some other issues around this particular concern regarding the e-mails.

I think it's important to preface the discussion, and I think part of this was implicit, if not outright stated in Dr. Ohman's comments that, you

know, this is a different sort of management system. This is not a therapeutic device. So if we put it in and leave it alone, it's not going to result in any patient benefit. And it's probably more than a simple diagnostic. This is a monitoring and management system, and as we discussed the trial, I think it needs to be thought of in that way.

So let's take a look at some of the frequency data that we've been able to compile for you during the break. If I can have the first slide up.

Just to put these recommendation e-mails, the number of them, into context, during the 6-month period of primary follow-up in the CHAMPION Trial, patients in the treatment arm made 44,000 pressure measurements. Investigators who were required to log on at least weekly reviewed pressure data on these patients 12,750 times, and there were 193 recommendation e-mails. Now, I've not included the inquiry e-mails because I think the FDA went on the record as saying that they were not concerned about the inquiry e-mails. It was the recommendation e-mails that caused them a bit of concern. So 44,000 pressure measurements.

DR. ZUCKERMAN: Dr. Abraham?

DR. ABRAHAM: Yes.

DR. ZUCKERMAN: Could I just remind you, I believe this slide is the same as CH-29 that you showed this morning? It looks the same. It's very important for the record to indicate when the FDA has not reviewed these data. Also it's very important to include an asterisk --

DR. ABRAHAM: Yes.

DR. ZUCKERMAN: -- when it also --

DR. ABRAHAM: Correct. And so, in fact, the reason I missed it as well is because it is on the bottom of this slide, but I think it's obscured by the black curtain at the bottom, the asterisk that says data not yet reviewed by the FDA.

Okay. So let's go on to the next slide, CR-3, which answers this question of what happened to the frequency of these recommendation e-mails over time. As you saw during the first 6 months of study, 193 recommendation e-mails. This results in a rate of 0.12 recommendation e-mails per patient per month. This decreased to 131 recommendation e-mails over the subsequent 9 months, after 6 months to unblinding for a rate of 0.05 recommendation e-mails per patient per month, and then after unblinding, there were no recommendation e-mails made and, in fact, there were no e-mails of any sort.

Now, I do want to contrast that because I think this needs to be put into perspective, and again I should mention data not yet reviewed by the FDA here as well, but if you look at the PA pressure medication changes per patient month made independently by the investigator, the numbers are 0.81 in the first 6 months, 0.25 from 6 months to unblinding, and 0.23 after unblinding. That helps put the numbers of 0.12 and 0.05 into some context.

Now, what was the impact of these recommendation e-mails

on outcomes? So let's go to the next slide.

So we're looking at the treatment patients up to six months, and again the data here have not been reviewed by the FDA. You can see treatment patients whose investigators received an e-mail, those who didn't receive an e-mail, and then the control group of patients who didn't receive an e-mail. The 6-month heart failure hospitalization rate in those receiving e-mails was 0.36. Those not receiving e-mails was 0.26, and those in the control arm was 0.44. So while I don't believe there's a difference --

DR. YADAV: Can I just interrupt?

DR. ABRAHAM: Sure. This slide was made during lunch. That last column is post-unblinding. So it is all patients, former treatment, former control. So that should be post-unblinding. Sorry for the confusion.

DR. ABRAHAM: Yeah. So let's just focus on the two center columns, which are e-mails or no e-mails up to six months in the treatment arm, and I apologize for the error on the slide. You know, it would be hard to argue that there was a difference in outcome between those receiving e-mails and those not receiving e-mails. If anything numerically, the rate is a bit higher in those receiving e-mails. So perhaps Dr. Adamson and I versus the Sponsor's nurses gave some bad advice to these patients.

Let's go to the next slide.

DR. YADAV: Actually, I misspoke. That slide is labeled correctly. That is a control rate up to six months just for comparison sake.

DR. BORER: Can you speak into the microphone?

DR. YADAV: I'm sorry. I misspoke. That is the control rate up to six months. The after unblinding slide is coming up. So that's in the first six months of the study. The treatment rate, 270 patients divided by e-mail traffic, no e-mail traffic, just a control patient rate for reference.

DR. ABRAHAM: Right. You'll remember the primary endpoint of the study, the rate was 0.44 in control and 0.32 in treated patients. So this is essentially the same data, but the treated patients are now stratified based on e-mails and no e-mails.

Okay. The next slide you have seen before, and I prefaced it at the time, and I will again, that this data was not yet reviewed, has not yet been reviewed by the FDA. Remember, and perhaps this wasn't stressed enough in the primary presentation of this data, that following unblinding, no e-mails were sent.

So we now see the outcome over the study duration during which e-mails were sent at the low frequency that you saw just reported on prior slides. The annualized rate of heart failure hospitalization in the control patients was 0.73 compared to 0.46 in the treatment patients. Following unblinding, the treatment rate remains at 0.46, again speaking to the long-term durability of the treatment effect, and now the heart failure hospitalization rate in the control subjects falls from 0.73 to .049, which is similar to that seen in the treatment arm. And again that occurred after

cessation of this e-mail support, and I think this speaks in part to again the comment that Dr. Ohman brought up earlier about a learning effect here and the fact that perhaps investigators get better and perhaps a little bit less reliant on support over time.

DR. BORER: Okay. Thank you. Dr. Lange.

DR. LANGE: I just have a couple of questions.

DR. ABRAHAM: Yeah, please, and then I've still got a little bit more for you, but go ahead.

DR. LANGE: The previous slide and this slide both, I just want to make sure I understand. Let's go back to the previous one.

DR. ABRAHAM: Okay. If we can go back to --

DR. LANGE: And so the no e-mail group would really represent those that didn't have a rise in their pressure, right?

DR. ABRAHAM: No, not necessarily. So, again, you know, what triggered the e-mails was really, you know, a persistent rise in a pressure or a pressure that didn't seem to be being addressed by an investigator or where an investigator might be struggling to bring the pressure down. So on the background of these e-mails, you know, there's ongoing management based on pressure. Remember I showed you earlier today that there were 1404 pressure-based medication changes and that compared to about 61 pressure-based medication changes that were made in relationship to an e-mail.

So there's ongoing pressure-based medication changes being

done independently by the investigator throughout.

DR. BORER: Can I just ask for a clarification here?

DR. ABRAHAM: Yeah.

DR. BORER: My understanding was that the e-mail was automatically -- was supposed to be automatically sent if a pressure threshold was passed, either high or low. So no e-mails would mean that that didn't happen. Is that right?

DR. ABRAHAM: So I'm specifically referring here to the e-mails that were of concern to the FDA, not the automatic alert e-mails that went out. So, remember, there are really three different types of e-mails here. Dr. Adamson took you through that earlier, but there is a simple computer-based automated alert if your patient's pressure falls above or below a level.

DR. BORER: Can I just ask --

DR. ABRAHAM: Yeah.

DR. BORER: -- for clarification from the FDA? Again, my understanding is that the FDA sampled e-mails once they learned about them being sent out, not that they looked at all the e-mails. They sampled them. And no e-mails here would presumably be in patients who didn't pass thresholds. E-mails would be in patients who did pass thresholds and either did or didn't get advice. We saw examples of both. We saw examples of e-mails that were sent as alerts and e-mails that had alerts plus advice.

So what you're saying now, Bill, doesn't sound totally

consistent with what we heard from the FDA. Can we have the FDA just make a quick comment, and then Bill can come back with the remainder of his response.

DR. BROCKMAN: Randy Brockman, FDA. So the e-mails I was provided were copies of e-mails sent by the nurses working for the company. I was not provided copies of the automated alerts. Does that answer your question?

DR. BORER: That's very helpful. Go ahead.

DR. ABRAHAM: Okay.

DR. LANGE: Then, Bill, on the next slide, in the unblinded part, there are about 90 patients missing in each group, in the unblinded. We're looking at 186 and 197 for the treatment and control?

DR. ABRAHAM: Right. The majority of that -- the majority of those were study exits due to death.

DR. LANGE: So did 90 people in each group die? Was mortality 25%?

DR. ABRAHAM: Well, you know, these were -- so the numbers on the left are inclusive of all patients randomized, the 270 and the 280, and then over this prolonged period of follow-up, remember by the time that last patient reached 6 months of follow-up, the first patient was at 30 months' follow-up. You had mortality and other causes of study exit along the way. I can take you back through that, but we looked at that early on in the

distribution of patients and disposition of patients and study exits. So these were the patients that were remaining at the time of unblinding.

DR. LANGE: Okay. Thank you.

DR. ABRAHAM: Okay. So -- and, Dr. Borer, you're good with the types of e-mails and where the focus of concern is?

DR. BORER: I am. I need to make sure that Mr. Barrett is because he asked the question.

MR. BARRETT: To me, this e-mail is complicated. It's clear, and I think that the Sponsor has gone and looked at a level of detail within the -- it's almost as if we need a event diagram folder for the different kinds of communications, but the particular kind of communication that I understood was a concern to the Agency was a subset of the direct communications that went from Sponsor personnel to the sites. You started with that subset, and then you provided some additional information about that level of communication with a tie-in. So I'm satisfied.

DR. BORER: Okay. There is one point that I would like to make before Dr. Abraham makes his comment, and you stay there because you have more to tell us. It is true that there were only 193 out of 14,000 possible interactions that resulted in e-mails, but I would put this in another context, and it doesn't require a response because there is no right answer. It's just something we have to be aware of.

We heard that a change in the prevalence events of 16 going

the other way would cause the loss of statistical significance of the outcome. So 193 is a small percentage of the total interactions, but if they impacted on patients who would not have done well had they not have had the interaction, that could have had an important impact on the interpretation of the outcomes. Whether it did or not, I have no idea, but I think we have to keep that number 16 in mind.

I understand how very difficult it is to do device studies, and this one clearly was the result of an intensive effort to do a good job, and a good job was done. But as we often do with device studies, at the end of the day, we're looking at a relatively small number of events, and even though there was great consistency here, the number of events was small, a relatively small change in that number, could change our interpretation. So I just put that out there for people to keep in mind.

DR. ABRAHAM: So, again, if I can be responsive to your comment, let's just go back a slide because again I think we just have to come back to the primary endpoint, the primary period of follow-up and what the outcomes were in patients who received e-mails and those who didn't, and I think it's also worth noting, if I haven't already, that there was no mandate for investigators to follow the recommendations of the e-mail and, in fact, in many instances they didn't. The ultimate treatment decision was always in the hands of the investigator when considering the totality of the data in front of them, which included pressure data and in a small number of

instances recommendation e-mails in treatment patients, but the investigator ultimately made the treatment decision. They sometimes ignored the recommendations. They sometimes implemented them. They sometimes implemented them in ways that were different from what was recommended, but I think the proof is in the outcome, and I think from the data shown on this slide, it would be difficult to make an argument that the e-mails account for that number of events that would shift us from a positive to a negative study.

DR. BORER: Well, I'm not sure we can actually draw any conclusions without it but, Dr. Brockman, why don't you make a clarification here.

DR. BROCKMAN: I'll try this microphone. That's Randy Brockman.

I just wanted to respond to your comment about the 193. I just would like to remind the Panel that that's not a number that FDA has confirmed. I just make that observation, and that's with respect only to the e-mail communication. I'd also like to remind the Panel that there were telephone communications that we have no way to quantify.

DR. ABRAHAM: So please allow me to respond to that. In fact, the protocol required that all of these interactions be documented in e-mails and inserted into the case report form. So all of these are documented, documented in the case report form and available for inspection by the

Agency.

DR. BORER: Okay. Did you want to continue responding to the points, or can we stop for Dr. Cigarroa? Dr. Cigarroa, do you want to --

DR. CIGARROA: This is continuing along the e-mail thing. I just want to make sure that I'm clear about the number, 193. Does the number of 193 come from a percentage of audits performed by the FDA on the overall e-mail chain? Or does it represent all e-mails having been reviewed that exceeded the threshold of what the FDA expected in the content of e-mails?

DR. ABRAHAM: Yeah, this represents all of the e-mails. Does anyone want to respond? I think it's --

DR. YADAV: So there are basically -- if we can maybe show slide CH-12 and then we can come back to Dr. Abraham's slides. So there's essentially three types of possible interactions from the CardioMEMS website or CardioMEMS nurses. One is this baseline automated reading system, which sends an alert automatically if a reading exceeds thresholds, and there's thousands. You saw 44,000 readings, many of them generated at large, okay, and the investigators logged on 14,000 times.

Then at the same time, that these pressure alerts are sent to the doctor, they're coming to CardioMEMS also, and they're flagged if they're persistent elevation, unusual elevation. The nurses look at those. There are about 380 or 90 of those. About half are inquiry e-mails. About half are recommendation e-mails.

The focus of Dr. Abraham's discussion is those half that are recommendations that the FDA's concerned about. So that's about 193. So that's what he's talking about now. Hopefully that clarifies it.

Maybe we can go back to NN-6 please.

DR. ABRAHAM: Okay. So I want to go back over what was designed in the protocol, what we intended. There are other folks here including Phil Adamson, Bob Bourge, Lynne Stevenson, and some folks in the audience who have participated for nearly two decades in heart failure disease management trials and in trials of implantable hemodynamic monitoring, and we applied all the lessons learned over that period of time in the design of this study, again realizing that if you implant a device and you don't use it, you're not going to have any impact on patient outcome.

So we really viewed all of what is contained in the protocol, particularly in Appendix E, as supporting the scientific soundness of the study in order to adequately test the hypothesis. The hypothesis was that making medication changes to lower the pressure would have a positive impact on patient outcomes as measured by heart failure hospitalizations and some secondary measures as well that you saw.

So I want to come back to Appendix E, and I want to clear up what I think are some misconceptions. One, Dr. Brockman reviewed with us a relatively large number of these e-mails communications and at times suggested that the guidelines that were recommended weren't included in

Appendix E, and I'm going to come back to that in a moment, but I want to point out that in addition to the specific guidelines outlined in Appendix E, the protocol also outlines that the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the diagnosis and management of chronic heart failure in the adult.

And again if we need to, if you desire, we can go through each of these cases, and we can talk about the guideline recommendation that supports each of the recommendation e-mails that was made. So I don't want you left with the impression that there were recommendations made, non-guideline recommended therapy. I think it's important for you to know that all of this was set up in advance.

In addition, if we can go to NN-77, and Ty Cowart took you through, I'm sorry, 7, and then 7, Ty Cowart took you through some of this but, you know, there was also a suggestion that the expectations between the study investigators or steering committee, the co-PIs and the study Sponsor and the FDA, were somehow not well matched, and again I want to make it clear that this standard operating procedure for medical management was part of the IDE submission². You can see the dates shown on the slide.

If we go to the next slide, NN-8, it outlines in very great detail, what was expected in terms of the procedure for ensuring protocol

² Correction: The policy mentioned, SOP000105, was not submitted to FDA for review under the IDE or PMA

adherence. Once a subject is enrolled in the study and randomized to the treatment group, the heart failure RN or the heart failure clinical nurse specialist will review the PA pressures on the CHAMPION database. Those nurses may contact the site to discuss a patient treatment initiated by the site PI or sub-investigator and advise them of the treatment guidelines and so on and so forth.

All communication with study coordinator, PI, or sub-investigator regarding patient management will be documented via e-mail and maintained in the clinical research chart and in the internal database. So none of this should be surprising.

We'll go to the next slide, please, NN-9, and you can also see here the detailed accounting of PI investigator involvement in the review of patients with similar, and this is an e-mail example, which was included in Appendix E, in a review with similar challenges, the following therapeutic strategies were recommended by the CHAMPION trial national principal investigators, Dr. William Abraham and Dr. Philip Adamson, and you can see that there could be treatments listed and why they were recommended.

So this is a monitoring and management system. Inherent to that management system is this level of support particularly with new users early on to help them understand ambulatory pressures and to be able to manage through that learning curve that Dr. Ohman noted earlier.

I think we showed this one, but we'll show it again just for

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some reassurance. NN-5 can go back up. This is the one that looks at the outcomes following unblinding when no e-mails were sent.

And then I'd like to follow that with the slide that's on my right-hand monitor that addresses the learning curve question. And you can see that the relative risk reduction is a bit greater in the second half of the primary 6-month period of follow-up compared to the first half, relative risk reduction of 22% in the first half or 3 months compared to 33% in the second 3 months or second half of the primary follow-up, and these data have not been reviewed by the FDA. Thank you.

DR. BORER: Thank you very much. For those clarifications.

Can we go onto the next -- yes. Yes.

DR. AGUEL: Felipe Aguel, FDA. I'd just like to point out that the SOP that was just presented and the attachment to that SOP was not part of the protocol. It was not in the protocol in the IDE. It was not in the protocol at the time of the PMA, and that the e-mails that you've seen today were not disclosed in the PMA. They were found during the inspections of the clinical sites by our Division of Bioresearch Monitoring, which are conducted to ascertain the study conduct, that the study conduct was appropriate. So I just wanted to point out that that is not something that was in the protocol.

DR. ZUCKERMAN: Okay. Just for the record, Dr. Aguel, you're referring to Sponsor slide CT-4?

DR. AGUEL: Yes. Yes, I believe that the slides that were just

presented were CT-4 of the main presentation.

DR. BORER: Okay. Thank you very much, Dr. Aguel. That's a helpful clarification. Can we go onto --

DR. YADAV: Well, I would just, Dr. Borer, if I could respectfully make one comment. I think the issue here, the confusion potentially is arising from (a) the understanding of the trial design, that this -- I think this has been emphasized that if you drop a sensor in and the doctors don't know what to do with it, nothing's going to happen.

Second, Appendix E in the protocol defines the parameters of the guidance. The SOP proceduralizes what we actually do, and it is a part of all internal company procedures, and that shows you the chain of logic in how this was implemented. And Mr. Cowart from the regulatory department has a comment.

MR. COWART: Yes, as I pointed out this morning, that policy was within an IDE. We have the documents. I think we have to have some additional discussions perhaps, but they were submitted as part of the IDE³.

DR. BORER: We have another -- before you go ahead, Val, unless it's on this particular issue, we have another question that has to be resolved.

MR. BARRETT: If I could just say in a general say, from an IDE

³ Correction: The policy mentioned, SOP000105, was not submitted to FDA for review under the IDE or PMA

point of view, that it's quite possible that both the FDA and the Sponsor are right. They've submitted a large number of IDEs over here. It's quite possible that this SOP wasn't in the protocol, either as to the IDE or as we produced it in the PMA, and a section of the IDE included, I don't know the specifics of the IDE, but it seems completely reasonable that they could both be correct.

DR. BORER: Val, is it on this point or can we --

DR. JEEVANANDAM: I do have it on this point. After the trial, I see there was no more e-mails. Does that mean that the company stopped? Did they not have to initiate an e-mail or was it because the -- everybody at that time was so good with looking at pressures that everybody was being properly monitored. I don't understand why there was no e-mails sent --

DR. YADAV: Sure.

DR. JEEVANANDAM: -- after it became unblinded, number one, and number two is, you know, we're talking about a system versus a monitoring number. Is the company thinking about maintaining the system, or are we just going to have this device put out there and have just raw e-mails as an alert because somebody has a higher or lower number without any of the support that we have here in this study?

DR. YADAV: Sure. Dr. Jeevanandam, those are excellent points. I think that really gets to some of the heart of the matter here. Could I have CH-27 up, please?

So, you know, these automated e-mails are generated all the

time automatically by the software, and so those are ongoing. They're ongoing now. They're ongoing right now. Okay. And they went on after unblinding. The way the study was designed is that after unblinding we follow patients for safety, for adverse events, hospitalizations, death, right. So that's after unblinding.

So this bottom part that you see, where the automated system flags, trends unusual e-mails for the nurse to review them, that stopped happening after unblinding, but the top part, the automated part continues. So the investigators can review all the readings and they get pressure alerts for every patient now, the former control included, and our expectation is, you know, I'm a scientist. You have to reproduce what you did in the experiment again. You have to do the entire experiment, right. So it means that whatever you did in the clinical trial is what you have to do in the commercial setting because you don't know. It's going to be a black box in the way. You have to do what you did, and so what we did was automated alerts.

Let me just point out that, you know, it's being made to seem like some enormous disease management effort. It's not. These are only responsive to elevated pressure. We had two nurses, two nurses, not even full-time, that performed this duty over the almost five years of this study. So this is actually pretty efficient. The e-mails tend to be very redundant. They're very protocolized. It's sort of -- I think Dr. Abraham pointed out, you

know, of those was 61 recommendation e-mail driven changes, 80% are diuretics. Of the 1400 other pressure-based changes, 80% are diuretics. So it's really not that complicated. It's a procedure. You get used to it, and we would have absolute intention of continuing. I think it's very important -- I mean I'm old enough that I don't want to trust automated things completely. I think that it's important that human beings be in that chain. So you want to have nurses review unusual readings and trends.

So we would absolutely continue doing that, and there's no reason why we wouldn't.

DR. STEVENSON: If we can have MD-13 up, I think we can actually get to your question, Dr. Jeevanandam, and also a question asked this morning about the learning curve. This looks at the medication changes over six months, and you can see in the treatment group, there's a huge number of interventions at the beginning. This is when we're trying to lower this plateau of pressures, and after that, it levels off considerably because, you know, in general as you suggest, they're getting onto it by that time.

If I could have NN-26, and this feeds into the question that you asked this morning about demonstrating to you that the changes that are made are the ones that are based on pressures, and that we are doing what we think we're doing. This looks at the average medication changes per patient per month. You see the large difference. More medication changes in the group in which we're monitoring them, the treatment group, and that

these are all pressure-based. The number of interventions that are made non-pressure-based are actually exactly the same in both groups.

If you want to give me the next slide.

And if we look at the impact of those changes, across the X axis here is the baseline PA pressure, and as we have proven in previous monitoring studies, if you start out with a high PA pressure, you have a higher risk of events as shown here. You can see that even those patients who started out with high pressures in the treatment arm, they had more events, but they had many fewer events than those patients who weren't monitored because what we were able to do was to effectively decrease their risk by treating these pressures, next slide, and you can see this well here with the area -- no, the previous slide. Not that one. The previous slide. The slide before that one with the bar graphs, please.

What this slide shows is what we did in terms of reducing the area under the curve for PA pressures. Those people who started out with relatively low PA pressures did not have a reduction in the area under the curve as you can see on the left side of this bar, but those patients who started out with high PA mean pressures shown on the right side, the treatment arm, that's where we had our big impact to lower those PA pressures in people who started out with high PA pressures, and that's how we were able to decrease their event rate over time. So this really closes the loop. We saw the signal. We responded to the signal. We were able to

decrease the pressures, and that's how we decreased events.

DR. BORER: Yes. Dr. Lange.

DR. LANGE: Lynne, two of the slides, this is the first time we're seeing them. So they fly by pretty fast. The first one --

DR. STEVENSON: The previous one. You want this one, the medication changes.

DR. LANGE: Two slides, just so you can clarify them for me.

DR. STEVENSON: Okay.

DR. LANGE: The first one looked at medication changes. It looked like -- you mentioned the medication changes took place in the 30 days. The curves for hospitalization don't divert for 90 days. So I surmise that. Then go to the next one. Go back to the first slide, I'm sorry, because it looks like again -- one more.

DR. STEVENSON: I'm sorry. This one or --

DR. LANGE: It's the graph, the very first graph that showed the treatment change of medication changes if you can.

DR. STEVENSON: I'm sorry. They're not together anymore. Are you talking about the one where it went up like this and went down, this one.

DR. LANGE: Yeah, that one. It looks like the medication changes take place in the first 30 days for treatment and control, as a matter of fact they're stable, but actually the curves don't diverge until after 90 days for hospitalizations. To me it just doesn't make --

DR. STEVENSON: Well, actually one of things that became very clear from previous hemodynamic studies is that those patients who sit a high pressure remain at risk for events. The events don't necessarily happen right away, but they're setting themselves up for events later on. So reducing the pressures now of the plateau will actually mean that you have a lower risk for quite a while.

DR. LANGE: Okay. So let's go to the first, the slide, the first slide after that because the way it looks like, just as it flew by, one more, here's the interesting slide. It looks like for the same PA pressure, the control group got admitted about two times as often as the treatment group.

DR. STEVENSON: No. What I want to emphasize, this is the baseline PA pressure, that curve that you're seeing. We tried very hard to lower those pressures after baseline. That was how we -- that's what drove the increased intervention early on in the monitored group because we saw they were too high.

DR. LANGE: Correct. That makes sense. I couldn't see it. It went by so fast, I didn't see the baseline. Thanks.

DR. STEVENSON: I'm sorry.

DR. LANGE: No problem.

DR. BORER: Okay. Yes, Dr. Ohman, on this point, because we do have some other questions.

DR. OHMAN: Yeah, I tried to get in on the other. I'm confused

a little bit, and maybe this is my ignorance, between what's in the protocol, what's in the Appendix, what's part of the IDE, and this is pure ignorance, but the protocol specifies the Appendix includes more information, and I guess this is a question both for the FDA and the Sponsor, and the SOPs operationalize those changes. So I'm wondering how -- we're all talking the same thing, right. So how could this break down, and I don't want to make it e-mail-gate, but it's bizarre that it is in or it is not in. Help me understand this because I'm ignorant to those details. Maybe this is the wrong question. I see Dr. --

DR. YADAV: Yeah, just speaking as a Sponsor, I'm not sure. The Appendix E was literally part of the protocol. It went to every investigational site along with obviously having been approved by the FDA. So it really is part of it. It really is the guts of how these patients were managed both by the investigators and also supervised by the Sponsor, and I think one thing to keep in mind is that, you know, we've all been in clinical trials over the years where sometimes studies don't go well because the Sponsor doesn't provide enough oversight, where the complication rate is too high because perhaps the doctors weren't trained adequately enough on say a new A-fibrillation system, the stroke rate is too high. So, you know, there are issues both ways, you know, that we try to be very specific in making sure that people actually complied with this protocol, and this is really very strong guidance from the steering committee and PIs, and you've got here the principal investigators of

the last two hemodynamic trials, Dr. Bourge from COMPASS and Dr. Adamson from REDUCE-HF. So this is really based upon their learnings from those studies.

DR. BORER: Okay. Yes, Dr. Zuckerman.

DR. ZUCKERMAN: Yes, Dr. Borer, for the record, Dr. Brockman has another comment that he wants to provide to the Panel.

DR. BROCKMAN: I'm sorry. I wanted to go back to a comment I made a few minutes ago. If we're thinking about the ability to replicate the trial conduct in a postmarket environment, I just wanted to clarify one point.

I think Dr. Yadav mentioned that there were two CardioMEMS nurses looking at the treatment patients. There were 270 patients, so you think 2 nurses, that's a fair number of patients. The e-mails I looked at, there were more than two nurses names on those e-mails. There were at least four or five. So if we're thinking about how many nurses it might take to keep track of all of these patients, I think I wouldn't use two as the number that you're working with.

DR. BORER: Before we --

DR. YADAV: I would just like to have --

DR. BORER: I want to move on, on this drug issue because something else really needs to be clarified for us, but you go ahead, Dr. Yadav.

DR. YADAV: I just want to clarify that Dr. Brockman was given

e-mails spanning 2007 to 2010. During the time, there is turnover. So, yes, there are different names. There are two FTEs over that time effectively.

DR. BORER: Okay. Thank you. Okay. You've been giving us information about drug advice and drug changes and whatever, primarily related to diuretics and short acting vasodilators, and when you showed us the data about other drugs, you said they were pretty much the same both groups. As I looked at them, I need some help here because, in understanding this, because I don't think they were the same.

The protocol says that everybody's supposed to be treated according to guidelines before they become randomized and enter this study, and the guidelines involve the use of long-acting drugs, ACE inhibitors, ARBs, beta blockers, that are supposed to be present, and the word you use is optimized; you know, I don't care about the word. It means that they're following some rules that are written in a book, that that's supposed to be done at baseline. And yet there was a difference in the use of beta blockers, ACE inhibitors, and aldosterone blocking agents as the trial went on. In fact, the treated group got more.

Now, you may say the difference is small, but I did some calculations as I was sitting there, 270 patients in the treated arm. I'm going to make an assumption here and, of course, it may be totally wrong, but we're all making assumptions. The beta blockers, ARBs, and ACE inhibitors and aldosterone blockers are known to improve survival and reduce

hospitalizations. They are not known as a group, and beta blockers specifically are known not to beneficially alter quality of life, which was another point that came up, but we'll set that one aside, but they are known to improve survival and reduce hospitalizations.

If you look at the differences between treated and control, for beta blockers, it was three percent, with the treated getting three percent more. If you multiply that by 270 patients, that means 8 events maybe were prevented by beta blockers. ACE inhibitors, ARBs, 4.4%, that's 12 events possibly prevented. Aldosterone blockers, same kind of calculation, 3 events. That means in total maximally if not all the patients were getting all the drugs, 23 events, minimally 12 events potentially different. I don't know that they were different. I don't know that these drugs actually prevented anything at all, but I'll come back to the difference of 16 that was shown in one of the FDA calculations to be the difference between statistically significant and not, and in the final modeling determination, only one of them would have created a concern, and here I see a difference in the use of guideline determined drugs that were supposed to be optimized at baseline, and among the e-mails we saw, there was at least one that suggested a change in the dose of valsartan. Now, I don't know how many others there may have been that suggested changes in doses of ARBs, beta blockers, or whatever, but my reading of the protocol did not suggest that advice was supposed to be given about changing these guidelines mandated or

guidelines suggested, drugs for chronic heart failure.

So I need some help here understanding why there was a difference between the treated group and the control group. You can speculate on what it might mean or whatever but, you know, I'm kind of concerned that some of the telephone calls may have been about changing doses of drugs that already were supposed to have been optimized, and I just need a little help understanding that.

DR. ZUCKERMAN: Okay. And before the Sponsor gives the reply, I believe the FDA analysis suggested that it would take only a change in 13 events rather than 16 events, Dr. Borer.

DR. BORER: Sorry, misquoted.

DR. ABRAHAM: Okay. Bill Abraham to address your concerns.

First of all, I want to remind you that at baseline, heart failure drug therapy was well balanced between the two groups, and that's shown on slide CR-6 from the main presentation.

I now want to go to slide CR-28 which looks at the changes in medications because I think that's where your concern derives, and let's talk through these, Dr. Borer, because, you know, first of all, remember at baseline, you know, an attempt was made to make sure patients were on optimal, i.e., best-tolerated drug therapy. And how do you determine best-tolerated drug therapy? It's based on patient tolerability. The patient cries uncle when you increase the dose to a level that's not tolerable, and you back

off a bit on that, and as I mentioned earlier, and I can support with a lot of literature, you know, on average, patients achieve about 50% of what would be considered maximal doses, and I think you agree with that.

So here's what we saw over the study, and the average increase in total daily dose of beta blocker in the treatment group was 3.5 mg, and in ACE inhibitors or ARB was 4.4 mg. Now, if we think about what impact that might have, remember the best literature we have, for example, the ATLAS Trial of ACE inhibitors shows that going from 2.5 or 5 mg of lisinopril to 32.5 or 35 mg, big increase, results in an insignificant effect on mortality and a very small effect on hospitalization.

Here we're looking at a 4.4 mg increase. Similarly, as you know, there aren't great dose titration trials for or dose ranging trials for beta blockade. The only two that I know of are the MOCHA Trial and the bucindolol studies, and they suggested you need at least a doubling, at least a doubling of the beta blocker dose in order to have a significant effect on morbidity, mortality, or reverse remodeling. But remember the average dose of beta blocker in this trial and carvedilol equivalent doses was about 30 mg a day. So a 3.5 mg difference is about a 10% change in the dose.

You know, I don't think that we can attribute the magnitude of benefits seen in this trial to those changes in neurohormonal inhibitors antagonists, and if I may just complete a thought, even if that's part of the ancillary benefit of having pressures, knowledge of pressures allows you to

increase doses of neurohormonal antagonists in patients whom you previously thought intolerant; that's a benefit of PA pressure monitoring as well. Thank you.

DR. YADAV: And, you know --

DR. BORER: Okay. That's very helpful, and you're right. I missed the fact that this was dose, but it is average dose which means that some patients didn't change at all and some changed a lot.

DR. YADAV: That's right.

DR. BORER: Yes, Dr. Brockman.

DR. YADAV: Can I just finish this?

DR. BORER: Yes.

DR. YADAV: That's right, Dr. Borer? I think one additional point that we learned in the study is that many times you couldn't use a patient's neurohormonal therapy at baseline because their pressures were too high, and with diuretic changes getting the PA pressure down, if the PA pressure is very high, you don't want to increase their beta blocker. Once you get the PA pressure down a little bit, then you've got some room to increase beta blockers. So there's some benefit to getting people less congested. Then you can actually elevate their beta blocker treatment.

DR. BORER: Dr. Brockman.

DR. BROCKMAN: It's Randy Brockman. Thank you. So, you know, the discussion about specific medications certainly is important, but I

think the discussion we had a little earlier about what was appropriate under the protocol was also very important. I learn by repetition. So I'd just like to go over this again if you don't mind.

According to the protocol, this is what they were allowed to do. The investigator or designee will review the PA pressure measurements from the home monitoring unit. Alert limits are automatically set as described in Appendix E. The investigator or designee will be alerted by CardioMEMS if those parameters are exceeded.

And I just wanted to remind you that the e-mails that I showed you earlier, at least we believe were not consistent with the protocol, included recommendations for specific drugs by names, doses, frequencies, and durations. Thank you.

DR. BORER: Thank you. I'm sure we're going to come back to all of this, but let me go to Dr. Cigarroa because one of the questions that we haven't had answered yet was his about the characteristics of the female contingent of the group.

DR. CIGARROA: Before we move onto that, may I just ask one additional question about the medication changes at baseline relative to follow-up? Substantial changes were made in doses of nitrates and hydralazine. Was that across the entire population or was that primarily restricted to certain subgroups?

DR. YADAV: We can -- if you give us a few minutes, we can

probably pull out some sub-analyses by that, by a different medication class. I think the team could work on that. You're interested by ethnicity, gender, et cetera?

DR. CIGARROA: Correct.

DR. YADAV: I think we may have that. We can look for that.

Thank you.

DR. BORER: Dr. Pina, before we go on.

DR. PINA: Just to follow up on your question -- Ileana Pina.

Just to follow up on your question about the vasodilator combination, the way the guidelines state it, the ACC/AHA guidelines is that this is a recommendation, combination on top of an ACE or ARB in African-Americans. In non-African-Americans for patients who are intolerant to both, it could be considered.

It is very unusual for us today to see hydralazine and nitrates even at baseline in our studies. But it is very common for us to see 95% ACE inhibitor or ARBs, and I'll give us an example. The latest NIH trial which Dr. Abraham was part of, where we had -- it was Class II, III. We had 95%.

So it is unusual, and at six months, I show that there was a difference in the treatment arm versus the control arm for both hydralazine and nitrates, but not much change in ACE or ARB, and to me as a heart failure specialist, I find that I can always go up a little bit more, you know, even in the control group. There's always room, and we've learned this from some of

our biomarker trials, that there's always a little room for, you know, a little fixing here and there. So I hope that answers some of it.

DR. BORER: Okay. Now, maybe we can go onto the data about women.

DR. YADAV: Thank you, Dr. Borer. If Dr. Holcomb can approach the podium, and then I think Dr. Abraham will follow up.

DR. HOLCOMB: I'm Rich Holcomb. I believe this discussion ended on quite a universally agreed upon conclusion previously with regard to men and women. I'd like to add to that discussion with some additional data.

This table here displays the results broken out by gender and, for cross-reference purposes, is identical in content to slide number 27 that was shown previously by the FDA.

If we could look at a couple of items in this table, just to point it out because it is interesting and it helps understand a bit what's going on here with regard to stability of inferences with regard to women. You will see that although women contributed 27% of the population in the study, when you actually look at the number of events over a short period of time, like 6 months, you note that we had only 14 events in the control group, which is a relatively small number for females.

So we're talking about relatively small numbers, and when you talk about small numbers in almost any counting model, there is issues of

stability.

One additional comment that I want to make here with regard to, in particular the disparity between men and women, in the treatment and control group, one example, additional example if we needed it of sort of dangers of small numbers is the fact that our single greatest outlier in terms of number of hospitalizations was a woman that had five hospitalizations within six months, and that was a female in the treatment group.

So that gives you a flavor of sort of what we're working with when we try to take a small group of data and perhaps extrapolate the results too much.

If we could have the next slide please, looking at again a result that you had seen previously, because we were looking at hospitalization as our primary endpoint, we also recall from previous results that were presented that we had an excess of deaths in the female population, and in particular in the control group. So most of the excess deaths that were experienced in the study were actually in females in the control group, and when you look at that, as a competing risk, you have those women who are essentially at high risk for potentially having a hospitalization removed from the analysis.

So this was raised in another question as well this morning. What happens when you consider both mortality and hospitalization in the combined analysis? And so these results show that. This is the first building

slide for that. If we could go back to the previous one. Just looking at the mortality for female patients, you see again a documentation of the fact that in this population of women, we indeed did have an excess of mortality associated with the control group.

Next slide.

Combined hospitalization and mortality for female patients, you see here that when we do that, the apparent disparity in the results for women disappear, and using a conventional endpoint which accounts for mortality shows that in this analysis the treatment group actually did better than the control group. The small numbers actually prevented this from achieving any kind of significance.

It was mentioned earlier this morning that there was a significant difference between men and women. Actually the small numbers of women in the subgroup, relatively small number, prevents you from drawing statistical conclusions about that very point.

So moving on, a question was raised about, well, is part of the reason that the difference that exists between men and women due to other factors? For males here, just for comparison purposes, we have a comparable plot of first hospitalization or death as a composite endpoint. Again, if you think back to the graph we just looked at, this is very close in terms of parallel separation between treatment groups and a hazard ratio here of .73 compared to .84 for females. So reasonably comparable hazard

ratios for the two groups.

What do we explain the difference beyond just gender for the two groups? If we could move onto the next slide.

This duplicates the kind of work that Dr. Gao did in terms of multivariate analysis where you tried to do an adjusted evaluation to determine whether or not there was a robust effect of treatment in the presence of other baseline imbalances. This analysis took all 19 baseline variables that we collected in the study, did both a forward and a backward regression analysis using a Cox model, and we ended up actually with a consistent set of predictors, and as expected, age, heart rate, screening, GFR, beta blocker dose, peripheral vascular resistance, and gender all remained as significant predictors in the model. After adjustment, the important takeaway here is that treatment was also significant with a p-value of .013.

The next thing that's important in this graph is after adjustment for baseline factors, the p-value for the treatment gender interaction is no longer significant, and it drops to a p-value of .940. So to me that says that in large part, the apparent interaction between treatment and gender can be explained by other risk factors that were presented by sign.

I know a question had been raised earlier today, were women different in the presence of AF or did they have different preserved EF function? This says that this collection of variables is similar to those and goes a long way to explain why we saw the differences in gender that we did.

I should have one more slide here. No, this would be -- I want to -- do we have the slide that shows the total duration of hospitalization rates? We don't have it. I'll just summarize that. If we can find it, we'll present it later. We do have it somewhere.

It turns out that if you examine the difference between males and females, not over 6 months, but over the full duration of the study which had an average follow-up of 15 months, that that apparent low value for females in the control group came up. So that's again support for the fact that it was probably an artifact associated with small sample size, and the difference between men and women diminished as additional data was gathered. Thank you.

DR. BORER: Dr. Cigarroa, Dr. Ferguson, anyone else, does that resolve the issues that you had with regard to men and women for the apparent disparity here?

DR. CIGARROA: I think that it may. I would still like to know the absolute value of women hospitalized control/treatment, and who died control/treatment that had preserved heart failure and preserved left ventricular systolic function?

DR. HOLCOMB: Yes, we will locate that data for you.

DR. BORER: Yes.

DR. GAO: Okay. I'm going to talk about the interaction between treatment and gender. So pull up the backup slides.

The Sponsor, they present their modeling. They show the interaction -- is not significant. Here I did my modeling. I'd like to point out the difference. I think the Sponsor model, they used negative binomial regression, and they use the follow-up time as one of the predictor variables, and we, the FDA review team, think that we should use that as offset variable. So that's one difference. Another difference, we used the Poisson regression model with the variance scaled to correct the overdispersion. So my modeling is Y as the number of hospitalizations, and then I first include all the important covariates that the Sponsor indicated in their multivariate regression. And then my result shows the treatment is significant and there is significant interaction between treatment and gender. And then later on, based on this big model, I delete some of the non-significant covariates. Next slide.

So I have a smaller model there, still use variance-scaled Poisson regression with follow-up time as offset variable, and then the result shows the treatment is significant and we have significant interaction between treatment and gender.

DR. BORER: Okay. Yes.

DR. HOLCOMB: Maybe a just a short comment on the apparent difference. It will come as no surprise to anyone that models and model assumptions are often as important as the data, and in this particular case, the analysis that I showed you was for a standard Cox regression model which

did take survival into account and appropriately dealt with censored observations. It's completely expected that if you use a Poisson regression with other choices for variance estimates, you may come up with a different result especially in this arena with small numbers. So these are not in conflict necessarily. Thank you.

DR. BORER: Okay. At this point, the standard template for these meetings is to go onto what's called internal Panel Deliberation. I'd like to change that just a little bit, and ask if there are any other major issues that haven't been resolved. Any data, any information that we need before we can go onto a more structured discussion. Dr. Cigarroa.

DR. CIGARROA: I'm still wondering whether any of the data regarding baseline demographics as it relates to functional MR and dyssynchrony and time from CRT implantation to randomization.

DR. BORER: I'm sorry. You had asked that before. Yeah, do we have some information?

DR. YADAV: Thank you, Dr. Cigarroa. We didn't have any time to make a slide up, but I can tell you what the information is.

So the protocol inclusion criteria which we went through it a little fast this morning, the senior briefing document, specified exactly what you're concerned about, that the CRT device, if they had a CRT device, it had to be in place for at least three months to ensure that their NYHA Class didn't change due to CRT device implantation. That was the inclusion criteria, and

actually the level of CRT devices is more like 60-plus percent because all the ICDs are essentially CRT-Ds. So although we broke it up, CRT, ICD, those are really CRT-Ds. There's a lot of CRT used, and they can correct me if I'm wrong, and we did not measure mitral regurgitation. We don't have echo data specifically telling us on the CRFs the level of mitral regurgitation. Did that answer your questions?

DR. ABRAHAM: Yeah, and let me just add while you heard the protocol requirement, that CRT be in place for a minimum of three months before enrollment, we actually do have data on the actual duration. If you look at time of implant to baseline for the CHAMPION Trial, the number for all patients averages 855 days. The median is 687 days, and there are no differences between the treatment and control groups. So these patients by and large had CRT for a very long period of time.

DR. CIGARROA: Thank you.

DR. BORER: Did you still want to know about functional MR?

DR. CIGARROA: They mentioned they didn't measure it, and then the only other area that I was interested in was whether or not there was a subset of patients that might have been a candidate for CRT but had not received it, and whether there was any potential difference in control versus treatment at baseline?

DR. YADAV: So the protocol required that all ACC/AHA Guidelines be met for optimal therapy, which includes CRT as part of those

guidelines in patients with reduced EF and the other appropriate indication criteria. So that was part of that, and there would have been a protocol deviation issued if patients had not met that.

DR. CIGARROA: Thank you.

DR. BORER: Okay. Are there any other major -- any questions?

Yes, Val.

DR. JEEVANANDAM: Before we get to our internal deliberation, I just want to clarify. So when we vote for this system, we're voting for the system and the support of the nurses that these patients in this trial received, and if that's true, then how does the Sponsor -- how are they going to support that? I mean are they going to have nurses? How about liability issues and HIPAA issues and stuff like that?

DR. BORER: Excuse me, if I might, Val, and please correct me if I'm wrong, Dr. Zuckerman, that's what we have to decide as to whether we're voting on. We're going to be asked whether when we get to final decisions about our opinions about this device, whether we believe we're talking about the effective device or the effective device plus guidance. Is that correct, Dr. Zuckerman?

DR. ZUCKERMAN: I think that's one of the major issues here, what was actually tested in this trial. If Dr. Yadav wants to give a very brief comment followed by a FDA response, that's okay at this time, but please make it very brief.

DR. YADAV: Certainly. I think I just want to be very unambiguous, as we've stated previously, we would replicate the findings of the CHAMPION Trial and the CHAMPION system, which includes every component, automated, manual, everything.

DR. ZUCKERMAN: Okay.

DR. MILAN: So I had asked about these 19 sensors that required recalibration at some point during the trial, some more details about those?

DR. ZUCKERMAN: Please wait, Dr. Milan, until Dr. Aguel responds to Dr. Yadav's comments.

DR. AGUEL: So we're asking for your input with these indications in mind, which is using the device to measure pressures and have the treating physician use those pressures to manage the patients. Does that answer the question?

DR. BORER: Yes, I think it does. That's question number one in our discussions questions. But I think we should hear the response to Dr. Milan's question because it is important to know how persistent the accuracy of the device is.

DR. ADAMSON: Phil Adamson here, and I'd like to address this very significant question by illustrating with several data points. We performed a feasibility trial, as you know, which part of that feasibility trial was to identify the accuracy of the device over time, and those data were

submitted to the FDA prior to the institution of the prospective randomized trial.

Now, I think one has to step back, as we all are cath lab aficionados, and remember how variable the baseline as well as the transducer height and zeroing many Swan-Ganz catheter systems are. So there is a fair amount of variability which has been demonstrated over time in Swan measurements, which was the measurement to which we compared. So there is some intrinsic variability that we can't control in the Swan-Ganz measurements.

So if one steps back and says, okay, what's the best comparator, maybe a milar (ph.) or maybe bench testing to find what the drift rate may be over time. We used the Swan in the feasibility studies. What you see here is data from the literature suggesting the sources of mean pressure error that's occurring with a fluid-filled catheter inserted in a pulmonary artery measuring the mean pulmonary artery pressure and how that propagated error can lead to a variety of variabilities.

So we first looked at bench testing, SP-4 if I could, and bench testing actually is not in human beings but can replicate many cycles obviously. These are seven sensors immersed in body temperature water and sent through about 7 million representative cardiac pressure cycles over around 17 years. You can see that there's a tremendous stability without much drift. The mean drift rate from bench testing was 0.02 mmHg per year.

The next slide, SP-6, if I could see that, actually looks at the feasibility trial data, and I believe one question was a regression analysis between the fluid-filled catheter and the heart failure sensor, and one can see a remarkable regression analysis, and again this was published as a result of the feasibility studies with diagnostic accuracy. Bland-Altman again reflecting, if you look there at the mean PA pressure with the Bland-Altman variance, 1.9 mmHg standard deviation.

So, the accuracy over time both from bench testing as well as from the feasibility study was established, and FDA had no questions about that.

Now, let's go to, in the prospective clinical trial, and remember that right heart catheterizations in this group of patients was not prohibited and was certainly encouraged if the investigator required the information from a right heart catheterization.

So, if I could see SP-8. There were actually 85 right heart catheterizations that occurred over time in the prospective trial, and we were able to, through CardioMEMS personnel in the cath lab, able to take simultaneous measurements during those procedures. We found that there were 19 patients in which recalibrations were necessary, and again, the definition of a sensor failure was if you couldn't communicate with the device. If the device could be recalibrated when identified as not calibrated properly, then that was not considered a failure.

So of those 19 patients, 9 had implant or right heart catheterization technique that did not meet protocol specified requirements. Again, that was resolved as a root cause by further education and emphasizing to the implanters the size of the vessel as well as angulation of the implant vessel, and during the right heart cath, we encouraged to try to minimize interference from ambient electrical signals that are in the cath lab, and we found that we fixed that root cause.

Eight sensors early in the trial had what we've, well, one batch of the sensors had a minor manufacturing flaw that was corrected, and again, we saw no sensor abnormalities after that, and again all of these sensors were recalibrated and worked functionally appropriately in the rest of the trial.

Two sensors had an incorrect sensor implantation at the implant, and that was again corrected through training.

So in this trial, we saw 19 patients that had a sensor that needed recalibration, and interestingly now, and throughout this trial as well, there's an automatic scanning mechanism in the website that doesn't require human interaction that identifies a difference between the mean PA pressure and the pulse pressure, and when we found that the implants needed recalibration, that relationship which is very predictable is lost, and so that scanning process is ongoing throughout all implants, and if sensors become in need of recalibration, they can be identified in the future. And when we

looked at those, 14 of the 15 recalibrations were identified by that scanning process, a very robust process that is in place and was in place in this trial that looks for abnormalities that may develop over time in calibration.

DR. BORER: Dr. Milan, are you satisfied?

DR. MILAN: Well, I just am curious about there were 85 regular caths in 43 patients, and of those, 19 sounds like needed recalibration. Do you think -- I mean that seems like a high percentage. Do you think that there was -- the fact that they needed recalibrating was what brought the patients to the cath lab for their right heart caths, or do you think it was just picked up at the time and that maybe there's some high percentage out there that need recalibration that we don't know about?

DR. LANGE: First of all, I'm not sure that 19 was a part of that 43. You have to tell us that.

DR. ABRAMSON: That's correct. So, remember, there were 85 right heart catheterizations in the 43 patients that were followed in the 6 months. The 19 did not necessarily come from that group, okay. I may have misspoke or not made myself clear. I apologize if that's true. There were 19 patients in whom the calibration scanning system identified errors, and 1 of those was not identified, which was found during a right heart catheterization. Jay will clarify that I think a little.

DR. YADAV: Let me clarify that. So this one patient that you see, this 14 versus 15, that is the 1 patient out of 83 that the algorithm did

not pick up and was picked up on the right heart catheterizations. These other 14 were recalibrated previous to their right heart catheterization. It was picked up very fast, and it could be calibrated actually through the implant. It was within days. So that was the mechanism. So there was 1 out of 83 that was a surprise.

DR. ADAMSON: And I apologize if I misspoke on that or didn't make it clear, but there were no obvious treatment algorithm abnormalities or clinical events that occurred in those patients as a result of this calibration problem.

DR. BORER: Val.

DR. JEEVANANDAM: I have question about this sensor, the sensor in the blood screen. Is there any evidence for protein buildup or any type of tissue buildup on the sensor, and is that going to affect the long-term durability of the sensor? Do you have any autopsy data or explant data?

DR. ADAMSON: We do have -- Phil Adamson again. We do have autopsy data as well as animal data, and the sensor, given its design, is neoendothelialized into the wall of the pulmonary artery. The endothelialization process does not change the signals being transmitted by the device. If the device is implanted, we found in an angulated artery, there is a potential for differential growth, and that led to two recalibrations of the sensor, but the sensor itself is covered completely by endothelium within 30 days of implantation, at least from animal studies, and when we looked at the

autopsy studies as well, it's a complete endothelium process, no nidus for thrombus or infection or other types of issues.

The cross-sectional area, remember, this small device affects maybe less than 10% of the cross-sectional area of the target vessel, and so it really is next to the wall and it's endothelialized.

DR. JEEVANANDAM: Right. If it's endothelialized over a period of time, the endothelium grows -- I mean it's not going to be a stable depth. So as it increases in depth, does it affect the sensor?

DR. YADAV: Right. That's a very good question. That's something we were concerned about from a design future perspective from the very beginning. That's one reason we chose the MEMS technology. The sensor is actually extremely rigid, and the gap is very small. So think of it as two manhole covers separated by a very small gap. So if you look at the compliance, I think you're getting into an interesting question, which would be compliance of the overall system, which is sensor plus tissue. The sensor is far more rigid than the tissue. So the soft tissue term contributes negligibly to the overall compliance.

Remember the first application we had is with an aortic aneurysm, where you've got a lot of thrombus, which is a much more challenging environment than the pulmonary artery application. So unless you've got bone growing on top of the sensor, the overall compliance does not change over time.

To address your question directly, Dr. Jeevanandam, this slide shows the sensor-Swan calibration over time. So you can see on the X axis, this is over time, and there's no apparent change in the relationship to a Swan over time. It remains pretty constant.

DR. BORER: Okay. We're going to have to move ahead here. The next section of our meeting is entitled Panel Deliberation, but we're going to try to stretch this a little bit so it doesn't become too freewheeling and we do get to a vote by the end of the day.

We have questions to the Panel that are in everyone's package in front of you, and we'll conduct our deliberations with respect to those questions. We'll take a break in about 25 minutes and shorten it a bit, and then we'll come back and we'll finish up with our deliberations and we'll go onto the voting.

The purpose of these questions is for the FDA to hear our responses. They don't have to be the same from everyone on the Panel. There may be some variation. We'll try to reach a consensus if we have one. If we don't, then that will be part of the record. The FDA needs this kind of guidance so it can make its best decision.

So I'm going to be asking a lot of people to respond to these questions, and eventually we'll come to a general opinion with some voting.

Okay. Question Number 1, is the one that took up most of the time in our discussions. That was trial conduct. The questions are in front of

everyone. If we can have them up on screen, that's fine. If we can't, we don't have to. Question Number 1 is Trial Conduct.

DR. ZUCKERMAN: The questions will be up shortly, but I would continue to just read it into the record.

DR. BORER: Yeah. Question Number 1. FDA is concerned that the conduct of the clinical trial may have biased the study results. Inspections coordinated by FDA's Division of Bioresearch Monitoring (BIMO) identified evidence that the Sponsor, which had knowledge of the randomization assignment, or the principal investigators routinely contacted investigational sites and made specific therapeutic recommendations for some treatment group study subjects, including titration of medication doses, addition or discontinuation of medications, recommendations for outpatient intravenous medication administration, the addition of medications that were not included in the protocol, and sleep study evaluation not included in the protocol.

FDA is concerned that the study results may be biased by these recommendations because investigators didn't receive similar treatment recommendations from the Sponsor for control group study subjects. FDA's interpretation of the protocol is that therapeutic changes were to be made by the study site investigators.

The information obtained through inspections coordinated by FDA's Division of Bioresearch Monitoring raises concerns for FDA that specific

therapeutic recommendations may have minimized heart failure hospitalizations for treatment group study subjects without an equivalent impact for control group study subject. FDA is concerned that the study results may be biased and that the ability to interpret study results may be compromised by the trial conduct.

And we've heard the detailed discussion about the basis of these concerns.

a. FDA is concerned that the specific treatment recommendations made by the Sponsor may have introduced bias into the study results. Please discuss whether or not you agree with this concern.

So why don't we start with that. We can start anywhere. Why don't we start with you, Val.

DR. JEEVANANDAM: I think, you know, we've had this discussion of whether this was part of the trial or not part of the trial, and I think Mr. Barrett just actually brought up a point that -- investigated further, but despite that, I think clearly the recommendations from the CardioMEMS site to the investigator site helped manage these patients perhaps when they came out of the hospital, and that's why I kept harping on it. If they're going to continue that after this is approved, then what they've shown is that the system works, which is their recommendation plus the device, and so then it becomes a little bit -- and not an issue for me. If they're only going to go with the monitoring, then it becomes a bigger issue.

DR. BORER: Dr. Brindis.

DR. BRINDIS: I actually think that this really does introduce a substantial confounder in the interpretation of the study, and I say that with all due respect to the investigators, and who I know were doing the best they can with a single-arm, a single-blinded trial, but there is no doubt in my mind that the expertise that they offer could clearly influence the number of hospitalizations in the treatment arm.

DR. BORER: Dr. Milan.

DR. MILAN: I agree with Dr. Brindis.

DR. BORER: And Dr. Cigarroa.

DR. CIGARROA: So I think that there is open to interpretation whether or not a threshold was crossed regarding what the initial design and belief that the FDA had relative to the investigators, number one. Two, clearly the expertise available from a central organization that is rich in heart failure experience is part of what impacted direct care for certain patients, and as a consequence, one can say either the system worked or it's a confounding variable.

DR. BORER: Okay. Dr. Lange, and in answering this question, I'd like to add a sub-question. If you agree with what the consensus seems to be thus far, do you think you can separate out what was due to device and what was due to the expertise of the advisors?

DR. LANGE: I agree with the three previous Panelists, and the

answer to your question, the short answer is no.

DR. BORER: I'm sorry. The short answer is no. Which?

DR. LANGE: Or nyet. The longer answer would be nyet. Can you separate out the difference between the two?

DR. BORER: Thank you. Okay. Dr. Evans.

DR. EVANS: So let me first thank the Sponsor and the FDA for their presentations. I realize there's a lot of complexities in these evaluations, and I appreciate all of the efforts to try to understand the data.

I do have significant concerns, not about the analysis of the study, but the design and conduct of this study.

The first lecture in my clinical trials course is called what's the question? What are you estimating? And in this trial, you can either estimate the effect of the device or you can estimate the effect of the device when used in combination with auxiliary management activities which might include Sponsor investigator interactions and site interactions with patients resulting in sort of personal attention to patients.

This study estimated the latter, which brings up the question which one do you want to estimate? Which one's important? Well, both of them are important. Unfortunately you can't estimate the first one. You can't estimate the effect of the intervention. Your answer, no, I completely agree with. It's perfectly confounded in such a way you can't estimate it. If you wanted to estimate the effect of the device only, you have to make sure

that your control group matches with respect to all the auxiliary management aspects of the trial. That didn't happen here.

So then the question becomes what do you get out of estimating the effect of the device when used in combination with these auxiliary management aspects? Well, I think that's an important question and, in fact, I think it's a very relevant question because any device, any intervention that is going to be used should be evaluated in the context in how it's used, how it's implemented. That's important to know. So I think as an aspect of it, that that should be evaluated.

Now, the issue is whether the medical management activities, the auxiliary management activities that are included here, whether patients who are not a part of this trial but who were to get this in practice, would they be receiving the same recommendations? In other words, are the recommendations that we were seeing in this trial a function or were they triggered by interactions from the Sponsor? If that's the case, well, in practice, people aren't going to get those sort of interactions. And so I think that's an important thing to think about is whether these auxiliary management activities are really the manner in which the device is going to be utilized in practice.

Which also brings up, we're doing randomized trials. Randomized trials are comparative in nature. You want to compare, these are essentially strategies, treatment strategies that have been outlined.

Now, the question is the device is going to be used as part of a strategy. The intent of the device, does that actually have the opportunity to create interventions, the opportunity for interventions, if so indicated?

That's a good thing. That's what the whole point is. But those have to be generated in the way in which the device is going to be used, and so the key question is whether many of these interventions that may have occurred are triggered from the Sponsor or whether they would be triggered in a clinical practice with similar use.

And it also brings up the aspect of what are you comparing to, the control group. I'm a little confused by this matching aspect. The strategy of the control group was essentially, well, the control group might get a phone call if something happens to another patient in the treatment group. I don't understand that strategy. And this sort of matching strategy is not going to retain the integrity of randomization. So I don't understand that matching aspect of it.

But, in general, I agree with what's been said.

DR. BORER: Thank you very much, Dr. Evans.

DR. ZUCKERMAN: Dr. Evans, could I just ask you to clarify one thing? Your comments were extremely helpful, the latter comments regarding generalizability of this trial. Could you also look at FDA slide 108? Would you agree with Dr. Campbell's comments that try in a nutshell I believe to summarize what you just stated? Or if you have a difference of opinion,

please discuss it.

DR. EVANS: Is this the dilemma slide? I notice it's one slide off.

DR. ZUCKERMAN: Yes, it's begins, the effect of this study is confounded. In the third bullet, he mentions the sensitivity analyses and what he makes out of that.

DR. EVANS: Yeah. So I think here a key is when you say the effect of the study -- we should say the effect of the device. Let's clarify. The effect of the device is confounded. If indeed by what you're terming the effect, you mean the effect of the device, yes, it is confounded. It's confounded with sort of the auxiliary management activities, and you can't tease it out because it's confounded in such a way that even complicated modeling isn't going to be able to be used to separate that. And I was using the term auxiliary activities. He's using extra interventions.

The possible bias from this confounding is of serious concern here, and given the sensitivity analyses presented earlier, bias could have produced some or all of the effectiveness of the results seen.

I think that it's difficult to quantify, if indeed what you're interested in is the effect of the device and not the device when used in combination with all the auxiliary things. It's very difficult to quantify what the effect of that would be. As I said, it's perfectly confounded in some ways.

I wasn't particularly concerned about the sensitivity analyses per se. I actually thought that there was one or two sensitivity analyses that

didn't hold up, but most of the sensitivity analyses held up, and actually I was comforted in some way with the consistency of the effects across different endpoints and things such as that.

What did concern me though is that the clinical relevance of the effects that were noted on almost all of the endpoints, even though consistency of positive effects were very marked and they were modest, and thus any effect of all the auxiliary stuff doesn't have to be much in order to wash it away.

So I would be concerned with the same sort of thing in that many of these, you know, the auxiliary activity could indeed account for these effects being seen.

DR. BORER: Dr. Ferguson.

DR. FERGUSON: Well, I think we're debating the word system. I mean the Sponsor seems to have one interpretation of the system, and the FDA seems to have a different interpretation of the system. By system, do we mean device or do we mean everything that comes with the device? And I think we need to clarify that.

DR. BORER: Well, what do you think was studied here?

DR. FERGUSON: Well, I think according to the Sponsor, it was the entire --

DR. BORER: What do you think? You've seen the data.

DR. FERGUSON: Well, I think the study was the entire system,

not just the device.

DR. BORER: Dr. Weisfeldt.

DR. WEISFELDT: I have the same series of conclusions but with a somewhat different intensity. As Dr. Stevenson said during her introduction, the problem being addressed here is a problem that has defied treatment and management repeatedly, that as the patient with Class III heart failure is hospitalized and the repeat hospitalization of those patients is an enormous public health problem, and there are failure after failure in the literature to show in any randomized fashion that we can improve that outcome.

To the credit of the investigators, they did this study in terms of the stated arms, and the analysis was done and showed that the primary endpoint was significantly different as well as all the secondary endpoints for the statistical analysis that they had pre-described.

So we're left with a study that shows that outpatient classification of medical treatment of this kind of heart failure patient, particularly with nitrates and hydralazine, reduces readmissions for heart failure, and we're left with a problem that we don't know whether this device was required for that benefit to be seen, and that's where I'm left.

If the same advice had been given to intensify medical management in both the control and experimental arms of the study, would we still have seen the same difference, or did the presence of this device

create a safety that we wouldn't have seen without it, or did it, in fact, provide reassurance to the physicians that they could intensify medical management and see a benefit of it? And we're left with that question unanswered.

DR. BORER: Thank you. Dr. Ohman.

DR. OHMAN: I want to congratulate both the FDA and the Sponsor for reviewing one of most challenging fields of medicine, namely randomized trial of diagnostic tests. It is very hard because it is usually mostly in the gray zone. Very few times do we have a diagnostic test that's black and white, and we move onto decision making.

Particularly when it comes to heart failure, which is probably one of the more multifactorial disease entities that we deal with, I would find it almost impossible to believe that you can have a diagnostic test and separate it from what I would like to say is the practice of medicine. It would be awfully hard.

Dr. Stevenson spent considerable time and effort to do the ESCAPE Trial randomizing patients to Swan-Ganz, and at the end of the day, we said, what did we learn from this? Well, we learned that this field is a lot more complicated than it really is with just one number, one decision.

So do I believe that the system, which I take to believe is the whole package, introduces confounding to the effect that you will find it very hard to figure out the device versus the rest of the system? Absolutely I

agree with everybody else.

But I will point you to another area which I was trying to get to in my question, and that is did the science really learn something for this? And while this trial was probably not large enough to detect this, you can see that patients enrolled in the second half actually had a proportional -- no interaction p-value but had a proportionally greater treatment effect which means something happened in the brains of the investigators, no offense to Dr. Abraham and others, but I think this is a learning iterative process, and what I've sort of taken away from this is that you can't really separate it.

Now, the e-mail issue and so on, we dissected that, and I think that's very hard, but in the pharma world, you sometimes had to do what I called -- analysis to try to understand that is, of course, highly advised because only the patients who can take whatever they take can actually take it, and therefore it's a bias, but in aggregate, when you look at pharma treatment or, in this case, helped decision making in the setting of PA pressure measurements, you get another flavor.

And then the final piece that sort of makes me believe that there's something here, is the fact when we disconnected this sort of e-mail traffic, beyond the six months, the patients who were in the control group who were then switched onto active management, the hospitalization rate fell.

So to me there is something here, but I'm not entirely sure how

you would do a different trial and dissect these issues out. So I believe it's confounding. I believe that I have been given assurance that the system offers something to the patient, and Dr. Stevenson and Dr. Abraham could be on the phone for me day and night, it would be terrific, among other people, because it actually -- there's something here that is offered that's beyond the device, but will that really affect how I see this overall device? Probably not.

DR. BORER: Dr. Slotwiner.

DR. SLOTWINER: Well, I agree with all that's been said already, and I don't want to belabor those points, but I think the device and the concept are beautiful, and I think that there was a flaw in the study design that really lent to the situation where those e-mails were possible. I think the treatment arm was a combination of medical management and advice along with the hard data that we got, and the other group couldn't get anything, and so it was a natural response by an enthusiastic, you know, investigator to try to do everything they could.

So, yes, if it's confounded, I think there really is something here. I'm not sure how to prove that, but I think if we look at the system as a whole, the device and the interpretation and management, I think there is something here.

DR. BORER: Mr. Barrett.

MR. BARRETT: Yeah. So specifically a comment on FDA's question 1a, I don't think that the subset of e-mails that the FDA was

concerned about introduced a bias to the study, but only, only because of the following context. While there were a number of important issues about the design and operationalization of this study, that perhaps weren't as well fleshed out as they should have been upfront, the study design was designed to treat the two arms differently, and from my point of view, once you agree that the additional information is only introduced, in this case, the pulmonary artery measurements, only introduced in the treatment arm, and once you agree that experts in the field, the national principal investigators can become involved in that kind of communication, to me it becomes less important who else is involved in that kind of information. It could have been nurses hired by the PIs. It could have been a core lab of nurses, nurses at the Sponsor.

So from my point of view, fundamentally in the design, it was acknowledged that the management of the two arms would be different, and only because of that do I answer the way I answer.

DR. BORER: Thank you. Mr. Dubbs.

MR. DUBBS: Well, I think that there are some issues related to the design and this confusion, and there's some questions, but to me, the overall monitoring, management, and early intervention is a great advancement, and I'm encouraged by it.

DR. BORER: Ms. Currier.

MS. CURRIER: Yes, I think this system is basically a data

collection system, and as such, the value depends on the clinician that's using it. If advice hadn't been given by CardioMEMS and was totally independent by the various doctors around, that would have introduced another whole variable to the whole thing. So you're always going to have this confounding that you're worrying about. It's just, you know, if they can get that evened out, that would be great.

It seems effective, and the patients and doctors who have used it seem to like it, who have come here.

I also thought it was really an important point that the nurse made about being able to treat people who are in the rural areas and can't make it to a hospital. You know, that kind of struck me when I was looking at this system, and I think that's a wonderful thing.

DR. BORER: Okay. Thank you. Thank you very much.

Dr. Zuckerman, I think that the consensus of the group is that it seems that something good happened here to the people who were in the treatment group, and that's true despite the fact they're small numbers, and Dr. Evans pointed out the potential for washing away the benefit with just a few small changes.

But the problem seems to be, although there are some dissenters, most people around the table cannot tell you that the device was critically important to this benefit. It seems like it probably was, but it's not clear the extent to which the device added to the great advice that the

treatment got.

So it does appear that there was confounding. It does appear that there was bias. It does appear nonetheless that something good happened, but we can't tell you exactly why.

Is that a sufficient answer for 1a?

DR. ZUCKERMAN: Yes, thank you.

DR. BORER: Okay. Then I will tell you that 1b has also been answered, and we don't have to go through that. We may have a little bit more of this during the day.

But right now we've reached a point for a break, and we're going to cut it to a 10-minute break.

Okay. We're going to have a 20-minute break because we have to set up the machinery for voting, and I can tell you from a prior experience here that the machines don't always work. So having the extra 10 minutes is probably a good thing.

Anyway, we'll take a 20-minute break, and we'll come back, and we'll have briefer comments on the remaining discussion questions, and then we'll go to voting.

(Off the record.)

(On the record at 3:55 p.m.)

DR. BORER: Okay. Let's get started again. I will avoid the impulse to ask the statisticians to give an estimate of the likelihood that the

machinery will work in the voting.

And we'll go on. Again b has been answered in the answers to a. In fact, we've heard opinions that will be relevant to many of the subsequent questions, and so we won't need extensive responses from everybody to all these questions. We'll hear some, and then determine if anybody disagrees.

Part c of Question 1, however, has a central core that requires some response.

FDA is concerned that the measures taken by the Sponsor would not be duplicated in a postmarket setting if the device were to be approved. Please discuss how the difference between how the study was conducted and how the device would likely be used in a postmarket setting should be taken into account when interpreting the study results.

We've heard some comments about that from Dr. Jeevanandam and from some others. Perhaps we can hear one or two statements and then see if anybody would disagree with what's said.

Why don't we start with Dr. Slotwiner.

DR. SLOTWINER: You caught me a little bit off guard. Well, I think, you know, as we've mentioned, the study really was that of a system, and to look at it as just a device that reads out numbers is not accurate, and so any postmarketing setting I think would have to reflect the setting in which it demonstrated a benefit. So I think clinicians who are busy often don't have

time to check all their e-mails or maybe register them. So that support that they got from, you know, from clinical nurse experts in the field is important, and I think that would have to be replicated in some way.

DR. BORER: Okay. Well, the FDA wants an opinion about whether it's likely that the system as we heard about it would be duplicated in the postmarketing setting if the device were to be approved.

Now, the Sponsor has said that it would, of course, reproduce everything that was done in the CHAMPION study.

Do you think that it's likely that everything could be reproduced for a market that might be the size of the market that this might be meant for?

DR. SLOTWINER: Well, it would be I think a first of its kind. We, certainly, in the electrophysiology world are familiar with remote monitoring systems that are overseen by the vendor, and alerts go through the vendor and if we don't respond, or indicated we responded, they will follow up. So while this would be a first, we have similar setups, and it's not inconceivable by any means that it could be reproduced.

DR. BORER: Okay. Dr. Ferguson, do you think that -- how would you respond to this question?

DR. FERGUSON: I completely agree with Dr. Slotwiner.

DR. BORER: Okay. Is there -- yes, Dr. Brindis.

DR. BRINDIS: Well, I think one of the comments is it's hard for

almost any randomized clinical trial and all the work that's done within it to be absolutely duplicated in a real world community experience. So you have to put that background in trying to answer this particular question. So I would use that caveat. But to me, I feel comfortable that the device does have a significant added value, that it would change practice, practice patterns. Whether we could actually fully reproduce what was done in the study would be unlikely, but I would say that for almost any randomized clinical trial.

DR. BORER: Okay. Does anybody have any opinion to add to what we've heard? Dr. Milan.

DR. MILAN: I think it would be difficult to replicate. You know, here we don't know how much of the benefit was the advice and how much was the device, and I think automated e-mails are likely to be, as David said, by busy clinicians, may be overlooked or may not be registered or may not be responded to quickly, and having someone nudge you and say, hey, that this alert came across your desk three days ago, what are you doing about it or even making suggestions, last time you did this, do you want to do that again, is very helpful.

I also think that the motivations are a little different in a study environment than they are in the real world. Do, for instance, when the Sponsor gives you the gentle nudge and says why don't you bump up the Lasix dose, you're less likely to fire back, mind your own business, it's my

patient, because you're the investigator. You're working with them to get the study done, and it's a collaborative effort. So I just think that -- I mean I just foresee some difficulties in reducing this to the real world.

And finally the part that maybe has not been addressed by the comments so far is the access to the experts, which if this is expanded greatly, I don't know that the experts will have the time to individually address patients.

DR. ZUCKERMAN: Dr. Milan, those comments are extremely helpful. Could I ask you to look at FDA slide 110 because it seems like the Panel is considering this treatment system as a clinical decision support system, and do we have a protocol that first of all evaluated such a system, and how do we generalize it in a post-approval setting? This is really what the question is getting at.

DR. MILAN: Well, we didn't hear about algorithms that were used, and I don't even know if there were standardized algorithms that were used in the trial. So I don't know how we could evaluate them. I think that would add to the difficulty of implementing this on a larger scale.

DR. BORER: Dr. Cigarroa.

DR. CIGARROA: A couple of comments. One, Appendix E was an algorithm that was utilized to guide therapy. As it relates to point c here, about if a device were approved, how might it be duplicated, I think the challenge really is in duplicating this in a scenario in which the data which is

being acquired is acted on in a timely fashion by a group of context experts in heart failure as opposed to the way many general cardiology practices occur, and that is how to go about managing a group of patients in which a primary benefit was demonstrated for those individuals who had a mean PA pressure of greater than 32, if I recall the slide. And so the average general cardiologist or the person spending time doing other aspects of non-heart failure therapy might be more challenged in that area, and so having the support structure I think to me is critical especially in that group of patients that demonstrated the benefit.

DR. BORER: Just one point. You know, if this system or device, whichever, were approved, the FDA could put in labeling instructions that limits its use to people in certain situations and not in others, just to keep that in mind.

DR. CIGARROA: People and a clear structure because it's not only the individuals. It's how the flow of information enters and then exits back to the patient.

DR. BORER: I think though that you've heard the range of opinions here, Dr. Zuckerman, that it is possible were this to be an approvable device/system, you know, were there sufficient information to allow that, it is possible that the system that was set up by the Sponsor could be reproduced as David Slotwiner said. There is some concern from several of the members of the Panel, however about whether it actually would be or

the practicality of doing this in this particular setting. Is that sufficient?

DR. ZUCKERMAN: Yes, thank you.

DR. BORER: Okay. Question d. The information identified in the BIMO inspection was not submitted by the Sponsor as part of the PMA. Please discuss whether this information is relevant to an evaluation of the safety and effectiveness of the device.

I think we've answered that one. I think we've sort of said that it is.

So let's go onto Question Number 2, Safety. The primary safety endpoint number 1 captured the proportion of subjects that were free from a device or system related complication through six months. There were 567 subjects out of 575 subjects who were free from DSRC. The DSRC events are provided in a table that we all have.

Freedom from DSRC was 98.6% with a 95.2% LCB of 97.3%. The pre-specified performance goal was 80% so that the endpoint was met. Please discuss whether the DSRC analysis results are accepted for the intended patient population.

How about Dr. Lange, what do you think about that?

DR. LANGE: Long and short answer, yes.

DR. BORER: Dr. Milan, you asked some questions about the safety issues. What do you think?

DR. MILAN: Well, I personally think that the procedural

complications should be included when you're evaluating the safety of this device because you can't place the device without the procedure. But from what I saw of those as well, I still think it has an adequate safety profile.

DR. BORER: Is there anybody who disagrees with that, those two opinions?

No. Okay. So the Committee believes that safety endpoint number 1 is adequately addressed.

Number 3, Serious adverse events were captured through six months in a pre-specified ancillary analysis. For the purpose of the trial, an SAE was defined as any untoward medical occurrence that:

- resulted in death
- was immediately life-threatening
- required hospitalization more than 24 hours or prolonged an existing hospitalization
- resulted in disability/incapacity
- resulted in a congenital anomaly/birth defect
- required intervention to prevent one of the above.

All serious adverse events were adjudicated by the Cardiac Event Committee.

Seven hundred twenty-four serious adverse events were reported in 276 subjects, with 50.2% of subjects implanted with the investigational sensor experiencing an SAE.

We have a table showing us the distribution of SAEs.

The most common SAEs prior to six months are presented in another table, and we've seen that in our Panel pack as well.

Please discuss whether the rates and types of SAEs reported for the first six months are acceptable for the indicated patient population.

Dr. Weisfeldt, what do you think?

DR. WEISFELDT: I thought they were what would be expected for the population as sick and complicated as these patients.

DR. BORER: Dr. Ohman, do you agree with that?

DR. OHMAN: I concur.

DR. BORER: Okay. Dr. Jeevanandam.

DR. JEEVANANDAM: The only thing that I noticed, if you start treating pulmonary artery pressures and the pulmonary artery pressures are elevated, then, you know, you're going to give the diuretics. And then you start seeing a slightly higher incidence of dehydration and renal dysfunction in the treatment group arm. So, you know, most of the therapies for heart failure, if you start drying them out, you're going to start paying the price with renal dysfunction. I think we're seeing that. I know there was another analysis in the FDA packet that I received that did a subgroup analysis and didn't look at -- they looked at the dialysis requirements and GFR, and they were not statistically different, but I do think that treating pulmonary artery pressures alone without treating cardiac output and other things is probably

going to cause more dehydration which mis-demonstrates.

DR. BORER: Let me push you a little bit further though. I mean certainly what you say is right, but look at the numbers here. There is 6 in the treatment group and 1 in the control group for dehydration out of arms of approximately 270 each. It doesn't sound like it's a real big problem, a problem for sure, and you have to watch it, but do you think it's a showstopper?

DR. JEEVANANDAM: No, it's not a showstopper. It's just something that needs to be looked at, and people need to understand that this type of therapy may lead to this dehydration phenomenon.

DR. BORER: Dr. Cigarroa.

DR. CIGARROA: And also notice as it relates to this issue that during the baseline right heart cath, the cardiac index was 2, 3. So we're not in a low output state at the time of randomization. So the issue of utilizing the device and system and mean PA pressures, I believe, is primarily restricted to the warm, not the cold patient population.

DR. BORER: Okay. Is there anybody who disagrees with the opinions that we've heard?

No. Okay. Dr. Zuckerman, I think the consensus of the Committee is that while there are certainly caveats that must be considered in using a therapy like this because problems could develop, that with this particular system or device, those problems are resolvable and they don't

represent a major safety hazard.

DR. ZUCKERMAN: Thank you.

DR. BORER: Now, we're going to move onto effectiveness. The primary effectiveness endpoint compared the rate of heart failure-related hospitalization at six months between the treatment group and the control group. There were 84 heart failure-related hospitalizations in the 270 treatment subjects compared to 120 in the 280 control subjects. The 6 month HFR hospitalization rate is then 0.32 events per subject per 6 months in the treatment arm, and .44 events per subject per 6 months in the control arm, with a p-value of 0.0002. The absolute risk reduction, comparing the treatment group to the control group, is 0.12 events per subject per 6 month. Heart failure-related hospitalization events would be reduced 12.5 heart failure-related hospitalization events per 100 patients per 6 months. The number needed to treat to prevent one HFR hospitalization is eight. Please discuss the clinical, it says here significance, the clinical importance of the observed primary effectiveness of the endpoint result.

Let me ask Mr. Barrett if you have a thought about that.

MR. BARRETT: No, thank you.

DR. BORER: You don't have a thought about it, okay. Very good.

MR. BARRETT: You were ready for one, I know.

DR. BORER: I was. Okay. Dr. Lange.

DR. LANGE: As Dr. Evans stated, the clinical significance ends up being a little bit somewhat marginalized by the fact that the total hospitalizations really wasn't down significantly even though the heart failure hospitalizations seemed to be.

One of the things we didn't consider is that if you compare this to people that don't have, you have to remember that everybody who gets the device ends up in the hospital. So that wasn't a part of this, and so you have to add in the time that they would do that, and then for the device-related complications as well wasn't a part of this as well. So that needs to at least be, at least be considered in this as well.

DR. BORER: May I just ask for a clarification? I heard one of the patients say that the insertion of the device took about an hour, which means that really it might not involve a hospitalization. It might involve merely an outpatient visit.

DR. LANGE: Well, it may possibly in the future, but in this particular trial, everybody was hospitalized overnight.

DR. BORER: Yes, that's right. You're quite right. Okay. So you think that the clinical importance of the observed primary effectiveness endpoint was modest?

DR. LANGE: Statistically significant, but again the clinical significance is not large.

DR. BORER: Okay.

DR. LANGE: Especially for a sick population.

DR. BORER: Dr. Ferguson, what do you think?

DR. FERGUSON: I agree. I really don't think I have anything to add to that.

DR. BORER: Dr. Weisfeldt.

DR. WEISFELDT: I would to some degree disagree in that heart failure readmissions are a big human health problem and treating eight patients to get one reduced hospitalization in only six months with a prospect of going forward from there seems to me to be a pretty major positive outcome of the study.

DR. BORER: Particularly since hospitalizations beget hospitalizations. Dr. Ohman.

DR. OHMAN: It's very hard when you have absolute, relative, and number needed to treat to get a handle on this, but I think one of the things to remember, many of the therapies that we apply every day, in and out, has a number needed to treat in the 35 to 60 range. So number needed to treat of eight is actually pretty powerful. Now, the delta, because the time period is short, is somewhat smaller. So I think it may fool you, but if you look at the whole overall picture, I think it has value.

DR. BORER: Dr. Brindis and then Dr. Jeevanandam.

DR. BRINDIS: Yeah, one, I think the study showed significance. It is effective. If you look at it on the yearly basis, number needed to treat is

even lower. It's one in four. I am impressed, if you look at subgroups, particularly the effectiveness in patients with preserved left ventricular function, it seemed even more impressive, and then we even get into the unblinded period.

So I think that it's a little more than modest, and particularly from a hospital perspective, although we're not going to talk about money, if they're not going to be reimbursed for a 30-day readmission that would be --

DR. BORER: You're right though. We're not going to talk about money. Dr. Jeevanandam.

DR. JEEVANANDAM: I agree. I mean I think decreasing hospitalization is important. You know, obviously it would have been great to look at functional result or to look at mortality. It wasn't powered for mortality. So we don't know and, you know, if you look at all admissions, not just heart failure admissions, that the statistical significant decreases doesn't even exist.

So I think it's a point of decreased hospitalizations, but again in the face of a management system that is designed to keep people out of hospitalization, I mean some of those e-mails, you almost have like a cheerleader saying, okay, come into a clinic and get dobutamine so you don't have to be admitted. So it's a huge bias there, and you almost have like a whole support mechanism that's cheerleading you on not to get admitted. So with that caveat, you can decrease admissions.

DR. BORER: Okay. Dr. Evans.

DR. EVANS: I just want to make a comment about interpretation particularly with number needed to treat. First of all, the quoted numbers are point estimates. In other words, they're measured with uncertainty. The upper bound for the number needed to treat could be much higher and perfectly consistent with results found in the trial.

I think you need also to interpret -- number needed to treat as a relative measure, and I think that both relative risk and absolute risk need to be interpreted in the context of each other. If you increase my risk of 1 in 10 to 2 in 10, that's a relative risk of 2, and very important. If you increase my risk of 1 in a 1,000,000 to 2 in a 1,000,000, it's also a relative risk of 2 and nobody cares. So it's all in context to where it stands in an absolute risk standpoint as well, and so I would just urge that in interpretation.

DR. BORER: Dr. Slotwiner.

DR. SLOTWINER: I just wanted to register my opinion. I think it is a significant number, and I think one thing we also heard from the patients is that it provides them a sense of something they can look at and control, and it is the whole team as Dr. Jeevanandam pointed out which makes this work. So I think it's significant.

DR. BORER: Dr. Cigarroa.

DR. CIGARROA: So the number is stated based on the trial design. It's statistically significant. The question is clinically what does that

mean, and relative to other studies, is it similar in magnitude or less? If one looks at the CRT dataset out of Care HF, this is substantially less significant in terms of both relative risk reduction and absolute benefit. So it's significant, but I would put it in the smaller range rather than moderate as it relates to heart failure readmission, not all cause.

DR. BORER: Ms. Currier, what do you think?

MS. CURRIER: Well, I thought it was significant. I'm not too sure about clinical significance because that's more for the medical types to say.

One of the things that I had thought and would answer to some point, a couple of points made, one by Dr. Milan, is that perhaps one of the problems in the ongoing thing is to have someone making sure it doesn't fall through the cracks, and I think one of the things that I saw when I read the design of the study was they took such care to keep the patient out of the loop. I mean the patient, you know, a liaison transmits the information, but they never get to look at it. Only the clinician looks at it, and I don't see from looking at the charts that it's that much beyond what a patient could understand, and if you allow the patient to look at this, then the patient would go, hey, doc, what's going on here, you know, if it starts going up. So I think that would be an interesting thing to add into it. Thank you.

DR. BORER: Okay, thank you.

Okay. It seems that we have a range of responses here. The

general opinion seems to be that, yes, something that's of some clinical importance has happened here, but it's difficult to know exactly how much. It's more than trivial, but it's not clear that it's more than moderate. And it is something that was produced by the entire system that was used in this trial. We can't tease out what caused what. Is that sufficient for your purpose, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, but I would like a little bit more clarification from Dr. Jeevanandam. I think what I heard you say, Dr. Jeevanandam, was that certainly this observed effectiveness result may be important, but you are not sure that it's reproducible in the real world?

DR. JEEVANANDAM: I mean I think there's going to be a lot of logistic concerns in the real world, right. You're going to have liability concerns. You're going to have HIPAA concerns, and outside the basis of a clinical trial, how is that cheerleader to keep them out of the hospital going to work?

DR. ZUCKERMAN: Thank you.

DR. BORER: Okay. Number 5, secondary/ancillary effective endpoints are summarized in the following table. We have the table.

Please discuss the clinical significance of the absolute difference in outcomes with respect to the proportion of subjects hospitalized for heart failure. Okay. Let's take that one first. Dr. Ferguson, do you want to take a crack at it?

DR. FERGUSON: I mean certainly it's more impressive looked at as a relative rather than an absolute difference in outcome, but I think you have to look at the aggregate of the primary and secondary endpoints, and I do think that the number needed to treat, you know, was impressive.

Two days outside of a hospital in a six-month period, I think, you know, I think that is significant for someone who suffers from heart failure. Are we going to comment on all the secondary endpoints or --

DR. BORER: Well, only the four that are highlighted here.

DR. FERGUSON: Sure. So I do also think that change in five points in the Minnesota Living with Heart Failure Questionnaire is a significant difference in the individual's quality of life. And in terms of the absolute heart failure hospitalization rate at 12 months, again I think that makes the number needed to treat even more impressive. I think it brings it down to around four. So I do think these support the primary endpoint.

DR. BORER: Can I just ask you before we go to other people about the Minnesota Living with Heart Failure score? A five-unit change is generally considered something that is clinically meaningful, but this is in a study that is single blinded. Now, the patients are the blinded people so that should work, but what do you think about that? Do you think there could be some exhortation that might be involved here in affecting the Minnesota Living with Heart Failure score?

DR. FERGUSON: I think that we still have the underlying

problem with bias, and I think it's going to affect every endpoint, but again I think given the parameters of the system, I'm not sure how else you would assess that.

DR. BORER: So you think that there is a meaningful change in the secondary endpoints. Dr. Lange and then Dr. Jeevanandam.

DR. LANGE: One of the things -- I don't know how -- the five-point change is kind of on the border of clinical significance. The one that's a little bit bothersome is that there were some people that were touched regularly, and that there were some people that got follow-ups at one month, three months, and six months. They're called the control arm. And there's some that were treatment and they got phone calls and e-mails and stuff like that, and so it's hard to tease that out because obviously the people that get touched more often by the system usually feel better about it. So it just makes it a little more difficult. I mean I'm glad they did it, and I'm glad it -- all their endpoints were positive, that is, they were statistically significant, but it just complicates it just a little bit.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: I think the proportion hospitalized for heart failure is significant, an eight percent difference. So that means eight percent less people were hospitalized. I think that's significant.

The days outside the hospital, you know, obviously that's confounded by people who came in and died or they might have had short

lengths of stays in the hospital. There may have been people who lingered in the hospital.

But I want to come back to this Minnesota Living. There was a slide that was shown that if you look at the Minnesota Living, the most statistically significant component were the people who were hospitalized. So that's just a surrogate market for some who is hospitalized. So if somebody's hospitalized, probably sicker, or just being hospitalized is giving them a worse quality of life. And the other thing is that if you look at the control group, I mean they came down by 7.4 numbers. So their life actually got better on this trial by, you know, it's the placebo effect of just getting a device in the pulmonary artery.

DR. BORER: Yeah, but my recollection is that if you look just at the people who were not hospitalized, I think we heard from the Sponsor that their Minnesota Living with Heart Failure score improved as well. So it wasn't just the hospital effect, but it is true that the change, the difference between the placebo group and the treatment group was very modest.

DR. ZUCKERMAN: Excuse me, Dr. Borer. I think we just want to correct one statement made by Dr. Lange, if the Sponsor wants to correct that because this is a very important discussion, and we just want to get the facts on the table. Dr. Yadav, did you want to make a comment?

DR. YADAV: Thank you, Dr. Zuckerman. I think, Dr. Lange, that you stated that the patients were touched by e-mails. The patients didn't get

any e-mails. They're all to the investigator, and the phone calls from the investigator/nurses are matched between the treatment and control.

DR. LANGE: Thank you. I stand or sit corrected. Thank you, Dr. Yadav.

DR. BORER: Yes, Dr. Evans.

DR. EVANS: I'd just again like to make a clarification about interpretation of this table. For all of these endpoints, you get significant p-values which essentially means that you can rule out there's a zero difference in favor of the device arm, but that doesn't mean necessarily that you see this estimate of 8.2% difference, that you've shown as an 8.2% difference. That's a point estimate, and it's measured with uncertainty. There's a confidence interval around it.

The appropriate way to interpret this is that you can rule out differences outside of that confidence interval with reasonable confidence. So if you're trying to determine whether you've shown that differences that have shown up are clinically relevant, you need to look at whether what you define to be clinically irrelevant is excluded by the interval.

And so I guess what I'm cautioning against is be careful about how to interpret this point estimate. It doesn't necessarily mean that these are what the differences are.

DR. BORER: Dr. Jeevanandam, did you have another point you wanted to make?

DR. JEEVANANDAM: No, sir.

DR. BORER: Okay. Dr. Brindis.

DR. BRINDIS: Well, I think we have some nice secondary endpoints that are significant with the usual problem with the confounders that we've talked about all along. I do want to acknowledge that some of these endpoints, particularly the Minnesota Quality of Life test, is patient-centered, and it would be nice if we had additional data related to walk tests or whatever, but I'm sure that our patient advocate appreciated the patient-centeredness of this second endpoint.

DR. BORER: Okay. So I think in summary, Dr. Zuckerman, the consensus seems to be that the secondary endpoints generally favor the scheme here and that they do have clinical relevance.

DR. ZUCKERMAN: Thank you.

DR. BORER: Number 6, when outcomes are analyzed according to gender, differences are apparent. The 6 month HFR hospitalization rate decreased for treatment group males, .32 events per subject for 6 months, compared to control group males, .52 events per subject per 6 months. However, the 6 month HFR hospitalization rate increased for treatment group females, .32, compared to control group females, .19 events per subject per 6 months. The interaction test between gender and treatment resulted in a significant p-value for the interaction term indicating that the device had a different effect on male and female. The difference appears to be the result

of better outcomes in the control group females compared to the control group males. The full study duration HFR hospitalization rate decreased for the treatment group males, .45 events over 12 months, compared to control group males, .83 events, while the full study duration HFR hospitalization rate for treatment group females, .47 events per subject per year, was similar to the control group females, .43 events per subject per year. All of these were post hoc subgroup analyses.

Please discuss the clinical significance of the six month and full study duration HFR hospitalization rate results when stratified by gender.

Wow. Okay. Let's see. Dr. Brindis.

DR. BRINDIS: So I really think this is a huge lesson for trialists, and we see this lesson periodically, but this is a real challenge for this trial. It's underpowered obviously for assessing gender. This is a post hoc analysis, but we're now left in this conundrum in how you would deal with this device in women based on this inadequately powered post hoc analysis. And when you think about what we have in the United States, where an increasingly aging population and particularly with more women at the elderly end and particularly with the issue of heart failure with preserved systolic function in women, I'm sure the Sponsor and the investigators wish they may have had a higher percentage of women in this study so they could better answer this particular question because I feel this is a huge conundrum here despite all the explanations that we were given by both the Sponsor and the FDA.

DR. BORER: Dr. Weisfeldt, what do you think?

DR. WEISFELDT: I agree with the point just made. It's a lesson, and I was reasonably satisfied by the Sponsor's presentation that this is a small subgroup and that this is not representative of the results of the whole study.

DR. BORER: Dr. Ferguson?

DR. FERGUSON: Well, I think we saw conflicting data from the FDA and the Sponsor depending upon the multivariate analysis that was performed, and maybe our statistician could weigh in on the relative merits of those two multivariate analyses because I am still concerned that there may be a detrimental effect in women.

DR. BORER: Dr. Evans, do you have any thoughts about this?

DR. EVANS: Yeah. Well, different models answer different questions, and they provide different estimates. So they're estimating slightly different things.

I think you're right that there's generally -- there's low power for two things. There's low power to actually assess the interaction itself, and there's low power to look at within subgroup types of issues.

In my opinion, I think there is evidence of some sort of gender device interaction or at least a very strong suggestion of that. What that means is that the effect of the device varies by gender, which also means that when we're evaluating what the effect of the device is, it's not one question.

It's two questions, one for each gender. And I think that's worth considering.

I think that I am concerned about the effects in women in particular. Because there are low numbers, confidence intervals are wide, and that sort of thing, and thus you have very little or not very much precision with which to base estimates on, and so I am concerned about that.

DR. BORER: Dr. Cigarroa, you raised some issues about women before. How would you respond to this question?

DR. CIGARROA: Conundrum. I believe that small numbers, potentially different outcomes if we were powered differently, but it may be that there is a real difference and the fact that we have conflicting results based on the corrective statistical measures used to assess it means that we can't answer the question, and we should know more about how the device and management strategy of women with heart failure based on mean PA pressures impacts outcome.

DR. BORER: Okay. Dr. Zuckerman, I think you just heard the best summary I can think of, of what everybody said, which is that we really don't know. The data are not sufficient for us to come to a conclusion about the impact of this system on women. The data as they're presented appear to be negative, but there are issues that make it very difficult to draw firm conclusions from those data because of the small numbers, wide confidence intervals, et cetera, et cetera, and we cannot tell you whether this is likely to be effective or not in women.

DR. ZUCKERMAN: Thank you. We heard some very good comments I believe, though, that Mr. Barrett wanted to be recognized --

DR. BORER: Yes.

DR. ZUCKERMAN: -- and then I'd like to say something if necessary in response to Mr. Barrett.

DR. BORER: Okay. Mr. Barrett, I'm sorry.

MR. BARRETT: That's kind of routine. No, it's always hard to talk to a statistical slide especially with Dr. Evans here, and with all the caveats that everybody's mentioned as far as this being a post hoc analysis and the ends being small, and I know the statistically correct term is that there's a treatment effect, but when I just look at the FDA slide 27, I see the rates in the treatment are between the men and the women, the males and the females are exactly the same. What I see are differences in the rates between the males and the females in the control group. So that's what I wanted to say.

DR. BORER: Did you want to respond to that, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. I'd like the Panelists to think very carefully about this question and Dr. Borer's summary comments because when we do get to the effectiveness voting question, Lieutenant Russell will remind us that effectiveness needs to be assessed in the intended patient population, and as Dr. Brindis indicated, the intended patient population includes a large number of women. Thank you.

DR. BORER: Okay. Thank you.

Let's move onto Question Number 7. Based on the safety and effectiveness endpoint data at six months, the available long-term follow-up data, and the secondary safety and effective analysis, please discuss whether you believe the overall data demonstrated a reasonable assurance of safety and effectiveness for the CardioMEMS CHAMPION HF Monitoring System in the intended patient population. Please provide a discussion on all of the key factors that influence your assessment.

I think we've done a good deal of that. Do you want formal comments about this at this point again, or do you want to wait for the voting?

DR. ZUCKERMAN: No, I would like to see if you can help the Panelists with this question, please.

DR. BORER: Okay. Okay. Well, let's discuss what is, of course, the key question, which is the relation of effectiveness and safety for the intended patient population. Do we think there's reasonable assurance of effectiveness and acceptable safety for the intended use for this system, and we need to discuss the whys and the wherefores, and we've just heard some concerns. Why don't we start with Mr. Barrett.

MR. BARRETT: You know, obviously this has been a difficult and challenging review today for the Agency, for the Sponsor, and I thought in particular Dr. Campbell's presentation this morning for me was very helpful

in sort of framing some of the challenges in designing studies for a device like this, an implantable diagnostic device where we can't simply look at the output of the device.

From a purely regulatory point of view, I see a Sponsor who embarked on a very long program, over multiple years, with a protocol that I think they probably and we would all agree in hindsight could have been better fleshed out, and certainly I think for the industry there's some important lessons learned, not just on gender but in the design of these studies for future sponsors and certainly some of the information could have been more highlighted.

But having said all that, with those caveats, the study was designed. It was agreed to. It was executed. It seems to me like it was well run, and it met all of the pre-specified endpoints. It doesn't take away from the important issues that the Panel has to deliberate on that the Agency's raised, but from a purely regulatory point of view, this is the kind of study that I hope, you know, when I'm at a company, that I can design and some day present to the Panel.

DR. BORER: Okay. So would you say that based on the information that we have available, you believe the overall data demonstrated a reasonable assurance of safety and effectiveness of the system in the intended patient population?

DR. BARRETT: I agree with that, and you used the word system,

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and that's been discussed a lot, and I'm sure that it will be discussed more, but I do think that, again what I thought I heard from the Sponsor this morning, and reiterated in the afternoon is that that was the intent, that is the intent going forward, and that's an important element of the design of the study and of the product as it's going to be used out in the future.

DR. BORER: Mr. Dubbs, what do you think?

MR. DUBBS: I think that notwithstanding the surrounding issues in terms of the communications, I think it's been shown to be effective, and I have no question that it's been shown to be safe.

DR. BORER: Ms. Currier.

MS. CURRIER: I agree that I think it's safe and effective.

DR. BORER: Dr. Slotwiner.

DR. SLOTWINER: Well, I feel very comfortable with the safety, and I think it comes down to the wording. The heart failure monitor system doesn't fully describe what was studied. I have a feeling or it's my suspicion that had there not been the e-mails back and forth, that it really wouldn't have changed dramatically, but I think the contact with the patients who are in the treatment arm was different, and so I think what was really studied, as has been said over and over again, was a heart failure management system, and I think that this could be a very effective tool for a heart failure team that may involve a group of nurses and leadership from one or several physicians along with patients. I think that heart failure really responds well to that sort

of team approach, and it doesn't need to fit into the model of one doctor, one patient that we traditionally think of.

So there are confounding factors that I think make it impossible to know if the device alone can explain the benefit, but the overall system, I think, did make a difference.

DR. BORER: Okay.

DR. ZUCKERMAN: Okay. I'd like to make one clarification before we continue. Commander Cheng, can you put up the actual indications that the Panel will be eventually voting on? The word system has been utilized loosely, and the system that you'll be voting on really only comprises the electronics, Dr. Slotwiner. It doesn't include all the important information supplied by highly trained nurses and other people.

DR. SLOTWINER: Thank you for that clarification. That's key.

DR. BORER: Can I ask you also, David, the question says for the intended patient population, and we've just highlighted that. Do you think that that's been demonstrated, that the effectiveness and acceptable safety for the intended patient population has been demonstrated if that population includes men and women?

DR. SLOTWINER: Yeah, I think the gender issue which was discussed just a few moments ago is obviously critically important. That hasn't been answered, and that would need to be further studied.

DR. BORER: Dr. Ohman.

DR. OHMAN: So with the idea that we are underpowered altogether if I come from population science, I would say that I look at the sort of totality of evidence, the primary endpoint, the secondary endpoints, and I get the sort of same message, namely that this has value. It does do important things as Dr. Weisfeldt pointed out, in a patient population that is awfully hard to manage, and it adds value.

So I believe that it's safe for sure, and the effectiveness is provided in a multitude of different ways that you can analyze effectiveness for heart failure management primary and secondary endpoints.

As to the issue with women, it is almost impossible when your control group performs much better than any other group in the study, and you're left with an unknown, and do I see anything here that would say women do significantly worse than men? That has never occurred because as we heard earlier, the men and women in the treatment group actually come out about the same. So I have to assume, but with a fair bit of latitude, that it is an aberration and it is slightly supported by the fact that when you look further out in the trial beyond the primary endpoint measure, that the curve stabilizes a little bit. So I believe that it is safe and effective.

DR. BORER: Okay. Let me ask a little further. Remember the points that Dr. Evans has made about point estimates in small groups and confidence intervals, you know, how certain are you from the data that we have that you can say that men and women actually respond similarly?

And the second point, you said that this treatment or this approach has value, and we just heard that when it comes to voting, we're going to be talking about a device as opposed to a device plus a group of doctors, nurses, et cetera. So what is it that has value and what about the issue of drawing inferences from these point estimates?

DR. OHMAN: So let me then take on the issue of the device versus the system sort of discussion. When I read the reports and some of the discussion, I recognized that what many of the heart failure doctors that I work with, I'm not a heart failure expert, isn't the sort of things they tell me. So if you ask me, in my environment, and I recognize that that is not the environment of the entire country, but at least in my environment, I believe that I see how this could work and how it could be used to effectively keep patients out of hospital. That's how I see it.

Now, projecting out to the entire practice of United States in heart failure, that's much harder, but I believe at least within the core of the country, there are situations in hospital setting or whatever, I can say, where I can see that this would have value. Does that answer your question as far as what --

DR. BORER: Yes.

DR. OHMAN: Now, as far as the uncertainty about women, I do believe again that in small trials, you will find aberrations, and how you deal with them is very, very hard. So I would almost point to Dr. Evans to sort of

guide us in this, but do I see that women did particularly worse than men, the answer is no.

DR. BORER: Dr. Weisfeldt.

DR. ZUCKERMAN: Okay. Before Dr. Weisfeldt speaks, because this is such an important point, and we still are having a little bit of difficulty understanding what the system is that was supposedly studied in this trial, I would urge you to look at the voting question sheet because it lays out in appropriate detail that the system includes the implantable sensor, delivery system, and the electronics unit and database. This is the sum total of the device under consideration today.

Dr. Aguel, did you want to add anything more?

DR. AGUEL: Felipe Aguel. What Dr. Zuckerman just mentioned and clarified is what is in the PMA and what is being considered today. The system includes those components and only those components as far as what was submitted in the PMA.

We've talked about a different system that includes nurses and clinical supports. That is not what we're considering today and not what was included in the PMA. Thanks.

DR. OHMAN: If I can clarify my point. I didn't need the CardioMEMS nurses in my situation is what I was getting at. I would be happy with the system if it came to me with the e-mail alerts, if I have to clarify that particular point.

DR. BORER: Okay. Dr. Weisfeldt.

DR. WEISFELDT: I can only repeat what I've said before, which is that the outpatient intensification of medical management of heart failure appears to be effective in reducing readmission rate, and I have no idea whether the device is helpful in that or not.

DR. BORER: Dr. Ferguson.

DR. FERGUSON: I think regarding safety, I share other Panel members' concerns about women. I think in men, it's been established to be safe. I do think the concerns in females are mitigated by differences in baseline characteristics which at least in some proportional hazard model was shown to mitigate the differences in effect, and I also think the analysis looking at both death and hospitalization was reassuring as well as the 12-month data.

But again, I think if the only components of the system are the sensor, the electronics, and the database without the clinical decision support system, I don't think effectiveness has been established, although drawing on Dr. Slotwiner's analogy earlier, if we could develop a system, a support system similar to remote rhythm management, it would certainly be a beneficial clinical tool for management of heart failure.

DR. BORER: Dr. Evans.

DR. EVANS: To me, the key phrase in this question is reasonable assurance, and as I had mentioned, I think the effect that's

estimated in this trial is the effect of the device with all of the additional interventions, and what we're being asked about is the device itself, and I don't think we can isolate the effect of the device itself in this trial. I don't know a way to isolate that, to have reasonable assurance to claim that the device is effective.

Now, I think that my clinical colleagues have about convinced me that it's safe, although one could argue that without these extra interventions, the safety profile might change as well, and I think that's worth considering as well.

I do think that in terms of the gender issue, depending on what model you believe there is, there could be evidence that there are differences between men and women, which when we start talking about effectiveness, again whether we're talking about efficacy, whether we're talking about safety, that that means that we have to be talking about it in two different pockets rather than lumping them altogether.

But I think the key point is that you can take two perspectives at this. You can take a perspective to say, well, if you believe the one model, that you can say, well, we don't have evidence to suggest that there's necessarily big differences between men and women, some models would disagree with that.

But to me, the burden of proof is in the other direction. We're being asked whether there's reasonable assurance of effectiveness and

safety, which means the burden of proof is proof to me there isn't rather than failure to prove that there is. And so I think that's what perhaps is where I come down is I'm not able with reasonable assurance to say that it's safe and effective in that sense.

DR. BORER: Dr. Lange.

DR. LANGE: I feel comfortable with its safety. I'm uncomfortable with a reasonable effectiveness for the caveats we've discussed, specifically about the auxiliary management issues, and the issue of gender just remains undefined because of the small patient population.

DR. BORER: Dr. Cigarroa.

DR. CIGARROA: I'm comfortable with the safety of the implant of the device. As it relates to a reasonable assurance of safety of the device, safety of the device and system in generalizability to the intended population, and that because I believe the outcome is heavily influenced by the system of CardioMEMS in addition to the device, I cannot with a reasonable assurance believe that it is safe and effective.

In addition to that, I would echo Dr. Evans' concerns about gender and as it relates to conflicting outcomes depending on how you correct for these variables.

And I would say that if one assumes that all of that was not a valid concern, I would say that efficacy is on the marginal, but in my eyes, the former comments I made remain a substantial concern to me.

DR. BORER: Dr. Milan.

DR. MILAN: Being unable to separate the benefit that is due to the extra interventions from the benefit of the device itself, I have a hard time saying that I've been reasonably assured of the effectiveness of this device in the proposed population of the device itself. I have remaining doubts or uncertainties about its benefit in women for the reasons that everybody has mentioned.

For the safety, I have to say that in the face of the benefits demonstrated by the device plus extra interventions, I have no concerns, but there are obviously some risks to putting the device in. We saw those today, and if those aren't balanced by effectiveness, then why would we accept those risks. So I think you can't just evaluate those in isolation.

DR. BORER: Dr. Brindis.

DR. BRINDIS: You know, this device actually is incredibly innovative and almost on the border of disruptive technology in the management of heart failure. When you think that we know that elevated pulmonary artery pressures lead to bad outcomes, when we have the idea and understanding that lowering pulmonary artery pressure improves outcomes, it's kind of an exciting concept that this device could have in the treatment of a terrible disease, Class III heart failure.

But as everyone said, we have all these issues related to the confounders of how the study was designed in terms of the expertise and

brilliance of the investigators. We have the conundrum of the gender issue.

Although on the other hand, when we see when it's unblinded, we see that in an integrated healthcare heart failure team, this added information has benefit, and so I can understand how it could possibly have a valued place.

I also as a personal physician will take home to San Francisco the understanding that I need to use more nitrates in my patients with heart failure. This was a clear-cut message for me, but based on what I've seen, I feel very comfortable the device is safe, but I don't think we've proved totally its effectiveness out in the context that we've been asked to today.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: So I agree with other people's comments. I think this is incredibly great technology. I think, you know, putting in something wirelessly that doesn't require power and you can get a continuous pulmonary artery pressure, it's almost like a dream come true in terms of managing these heart failure patients.

However, in the context of the indications for use, just the device itself has not been demonstrated in this trial without the support system to be effective. I think it's very safe, amazingly safe actually considering the fact that it's an implant, but I don't think that without the system it will be effective, and in terms of females, I don't think it's deleterious to females but clearly did not show effectiveness in terms of

decreasing hospitalizations in females. So in terms of the intended patient population, at least what they've demonstrated is that it's great in males but not necessarily in females.

So if questions are going to be as narrow in terms of what we're going to vote for, then I would have to say the system itself without the support mechanism has not been demonstrated to be effective, although I would love it to be effective, but I would like to use it.

DR. BORER: Okay. I'll summarize all that, but before I do, I'm going to do something I haven't done here, which is to give a little opinion of my own, if I may.

Intuitively I believe the device adds importantly to the medical advice; intuitively I believe that, but can I say that with reasonable assurance based on the data? No, unfortunately I can't.

Can I say that it is applicable to the entire patient population for whom it's intended? Well, again intuitively I think it is, but I can't say it with assurance because of the data that we have.

In addition, I have a problem in that I really don't understand the magnitude of the effect of this system, whatever it is, as it's applied because of all the issues involved in trial design here. I'm concerned that the trial was designed in a manner that really doesn't allow us to answer the key questions that need to be answered, and I am persuaded by Dr. Evans' arguments about the analysis of these data, that I really can't say from the

available data what the magnitude of the effect about applying the system, the device with the advice or the device without the advice certainly. So I have a problem. My intuition is lying on one side and my reason, with reasonable assurance, is not on that same side.

And I think that that probably summarizes what you've heard here, that everybody believes that something good happened here. We're not sure why totally. We're not sure what effect the device has had and what effect the advice has had. We're not sure what the effect is for the entire population for whom it's intended. And I would add that we're not sure of the effect size of applying it, but I have to add that that is a general I would say majority opinion. There were several opinions on the Panel that were just the opposite, that it is good, that it is effective.

Is that a sufficient summary?

DR. ZUCKERMAN: Yes, thank you.

DR. BORER: Okay. Let's go onto the next question then before we get to the voting, and that is the proposed post-approval study.

I won't read the preamble, except to summarize, and you must remember that a therapy has to be considered for approval based on the data that were performed for approvability. It cannot be approved based on data that one hopes to achieve after approval, but a post-approval study can be mandated and a post-approval study has been proposed, and we have to give some opinion as to whether it would be adequate were this device

approvable based on what we have.

The Sponsor proposed to conduct a prospective, multicenter, open label clinical trial to evaluate the long-term safety and effectiveness of the CHAMPION HF Monitoring System in subjects with heart failure. The safety hypotheses are to assess the freedom of device/system related adverse events at six months and the freedom of pressure sensor failure at six months. The effectiveness hypothesis is to assess 12-month HFR hospitalization rate compared to historical control HFR hospitalization rate in the year prior to enrollment in CHAMPION. The length of follow-up of this PAS is two years.

Should the device be approved, please provide a discussion on the appropriateness of the proposed post-approval study, the PAS, in the following areas:

- a. Whether 6 months and 12 months are appropriate lengths of follow-up over which the safety and effectiveness of the hypothesis should be tested;
- b. Whether the historical control HFR hospitalization rate in the year prior to CHAMPION is the appropriate comparator for effectiveness evaluation and whether a rate difference between the first and second year (improvement) of .09 in HFR hospitalization is clinically meaningful;
- c. Whether there are other effectiveness endpoints that should

be included as secondary endpoints; and

- d. Whether a specific effort should be made to study device effectiveness in women.

So we're being asked to give a general opinion about the post-approval study focusing on these four points. Why don't we try and do that. Let's start with Dr. Brindis.

DR. BRINDIS: Well, let's see. I like the concept of post-approval studies in general. You expected me to say that because there's always added information that we would get in a large population that would be germane for subgroups of patients that we don't normally have a chance to study adequately within a randomized clinical trial. We would learn more, for example, related to subgroups, related to diastolic dysfunction and dilated myopathies and understand more about that. Obviously the issue of women would be answered.

So I would encourage the Sponsor and the FDA, if they found themselves in this environment, to do a post-approval study.

The length of the study, I think that we might learn added value related to issues of benefit of not just readmissions, but even mortality if we had greater length of the study. So I would encourage a longer duration rather than a shorter duration.

In terms of the controls, we don't have a perfect environment here. If you use historical controls, you have the advantage hopefully of the

person being in their own system so that we've talked about the interplay of that and its importance. So that would be an advantage. If you tried to use a comparator of patients who, for example, were in an outpatient heart failure patient registry with Class III, that would be another way of doing it. In fact, you could actually have two comparators. You could have the patient as their own historical comparator and also a population comparator that do not have the device as an interesting way of doing such.

We talked about patient-centeredness related to endpoints. So I would encourage a utilization of quality of life metrics, at least in a subgroup and possibly even something related to a walk test or something of that sort. Maybe I'll stop there.

DR. BORER: You were on a roll. That's pretty good. Okay.

Dr. Milan, why don't you have at it.

DR. MILAN: Well, I'll say that coming from the electrophysiology world where, you know, every once in a while, not even that rarely anymore, we have to take devices out, and that was one of the things I wondered about. Would we ever encounter a clinical situation where this device would need to be removed? You know, it sort of comes down, is this more like a coronary stent where infections are almost unheard of, or is this going to be more like a heart valve or a pacemaker or defibrillator where infections do occur? And if it is like that, or even if they're rare, what are we going to do then?

So I think there's value in studying these for maybe even longer for the safety endpoints. You know, it all depends on what questions you're trying to answer in terms of how you design the post-approval study but I, for one, would be interested in seeing safety for a longer duration. These things are implanted for the lifetime of the patient, and right now we have mean follow-up of 15 months.

So that's probably my only comment, although I do agree with Dr. Brindis about the utility of gaining some information about the functional status of the patients, the six-minute walk. I think that's a great idea.

DR. BORER: Dr. Jeevanandam.

DR. JEEVANANDAM: I agree that the follow-up perhaps needs to be longer to look at whether these things cause other problems to the lung, but my question is the control arm. Looking at the year prior to enrollment in CHAMPION, which patient population exactly are they looking at? Because sometimes I mean these admissions or there is an evolution of heart failure. So if you look at a year before, they actually may be less sick than the year afterwards and the year following, right, so maybe actually looking at quick a less sick patient population. So I'm trying to figure out exactly what this control group is. I'm confused.

DR. BORER: Yes, Dr. Lange.

DR. LANGE: Just a couple of things. One is we've got this device implanted in 450 people that are still alive. So the long-term safety

could be just evaluated by following these patients and seeing whether the sensor still works and how they do. So I don't think redoing that part in another 500 people or 900 people is going to be helpful. It looks really safe initially. I think following the current population out longer will give us some information, tell us about it.

If it is approved, the question we're still going to ask is, is it the device, is it the system, and if you put the device in and don't use it for six months, and the other people use it without all the added auxiliary management, in other words, if you just send e-mails, will answer the question, and if the NNT is really eight, one in eight patients, within six months, you'll have that answer. So everybody will have gotten the device. You just don't use it again for six months like the control group, and the treatment group, you do use it but you don't use it with Dr. Adamson and Dr. Abraham on call. Use it in the real world setting.

DR. BORER: Okay. That presupposes, of course, that we define the system as the device, which we're going to be asked to do, and that that device without all the other stuff is approvable. If it's not, then what you're defining is not a Phase 4 study, but a Phase 3 study.

DR. LANGE: You're right.

DR. BORER: But, okay. But I think the point is well made. Does anybody else have any thoughts about this post-approval issue?

Yes, Dr. Evans.

DR. EVANS: Well, if I was thinking about post-approval studies, I guess the first, one of the things I would do is to try to enroll a study that's going to enroll more women. I think this seems to be a common issue that we're often unable to be able to with a great deal of confidence, estimate what sort of effects are happening in women, and I think maybe some concentration on that would be helpful.

I agree, at least to me, the data that would be helpful would be to make sure that the intervention is used as it's going to be used in practice rather than with the sort of special recommendations that are perhaps triggered by the Sponsor. So I think figuring out how to deal with that sort of auxiliary activity is important.

And I do think the longer-term outcomes would be important to follow as well, and if we were doing this in the NIH world and we really had interest in isolating these effects, I would not necessarily be using historical controls. I think I would still want to be seeing concurrent control groups, and even if you wanted to get really creative, you can have multiple control groups where you actually isolate what the effect of the device is, what the effect of the recommendations being made are, and you could have two or three control groups where you can isolate all of those effects.

DR. ZUCKERMAN: Okay. Those are very helpful comments by Dr. Evans and other people. The point that we haven't gone to though is that the Sponsor has suggested that they'd like to show in the post-approval study

a treatment effect of .09, which is a little bit lower or less impressive than the point estimate shown in this trial. Do people agree with that and are there any other comments regarding what would be an appropriate control group given that Dr. Jeevanandam has pointed to some of the complexities with choosing a non-randomized control?

DR. BORER: Does anybody want to talk about the margin of effectiveness here?

Okay. If not, I'll give you an opinion.

Particularly in the context of the design as it's proposed, I don't think it's adequate. I think it would be very difficult to interpret the meaning of an effect size of this magnitude compared to a historical control.

I think what you've heard though, if I may, to summarize what you've heard is that a post-approval study needs to be longer than what's being proposed here, that we care about additional safety endpoints not because one couldn't get them by following up these 400-odd people or 540 people, you could, but that's still a very small population. There are a lot of people with Class III heart failure.

So one would like to see more information about safety. Certainly one would like to be able to, as you've heard here, tease out what is device and what is advice. How to do that perhaps is beyond our capacity to define here today, but it will require some concurrent control groups because historical controls probably aren't going to be adequate, and that will take a

little bit of creativeness; that we certainly need more data about women, and there are several issues that have to be resolved there that would need to be resolved in a post-approval study.

And are there other effectiveness endpoints? You've heard a few, but the one that's been highlighted is QOL and other patient function assessments. Remember that in this study, the QOL assessment looked reasonable, sort of, but it's a single-blinded study, and not all patients provided QOL information. There was information missing. We didn't even talk about that.

So I think that you've heard there should be some other effectiveness endpoints. There should be a study of women. There should be concurrent control groups. There should be some effort to tease out better what's due to device and what's due to advice. And that the study has to be longer.

Yes, Dr. Milan.

DR. MILAN: I just have one other thing to add, which is maybe a better definition or a longer term follow-up of sensor performance. It looks like at implant, the sensors were very faithfully tracking with the PA catheters but that, during the follow-up, there was a greater amount of disparity between the sensor and the right heart catheter data, and so I just wonder if that continues to worsen over time or does it not? So that might be added.

DR. BORER: Okay. Is that adequate for your purpose,

Dr. Zuckerman?

DR. ZUCKERMAN: Yes. Just for the record, I'm reminded by the Sponsor that they did propose a 24-month follow-up rather than 12-month.

However, I think the particular details that you, Dr. Borer, and other people have focused on are really quite helpful for the Agency and Sponsor, and that's where we need to go. So thank you.

DR. BORER: Okay. Now, at this time, the Panel will hear, if there are any, summations, comments, or clarifications, first from the FDA and then from the Sponsor. Each will have 10 minutes to do this, and we do not expect to hear new data. We expect to hear a summary.

DR. AGUEL: Felipe Aguel. I will be presenting FDA's summation this afternoon.

You've heard today that the CHAMPION Trial met both primary safety endpoints. It also appears that the effectiveness endpoint was met using a pre-specified analysis.

However, FDA is concerned that the study conduct may have biased the study's effectiveness results. Can I have slide 81 please?

So I'll point out what was included in the protocol as it was FDA's expectation that the e-mail inquiries sent by the Sponsor to the study investigators would be limited to a notification that pressures are high, and that Appendix E of the protocol would then be followed by the investigator, and from the protocol it says, the investigator or designee will review the PA

pressure measurements from the home monitoring unit. Alert limits are automatically set as described in Appendix E of the protocol. The investigator or designee will be alerted by CardioMEMS if those parameters are exceeded. If the PA pressures are elevated, the investigator or designee should make the medication changes according to the recommendations in Appendix E.

There is no reference to specific treatment recommendations being made by CardioMEMS personnel.

The level of detail in the e-mails that were sent by CardioMEMS nurses was not in the protocol. The existence of those e-mails was not disclosed in the PMA, and the analyses presented today regarding the frequency of these e-mails and the effect of these e-mails was also not included in the PMA. The e-mails were only discovered during inspections conducted by FDA to audit the integrity of the study.

So you saw in FDA's presentation earlier today a handful of examples of patient-specific treatment recommendations made only for treatment arm subjects. FDA is concerned that it is not possible to ascertain whether the treatment effect demonstrated in the CHAMPION trial was due entirely to the device, entirely to the additional attention given to treatment arm subjects, or a combination of the two.

The Sponsor stated that this exact level of care could be replicated in a postmarket setting. However, FDA is concerned that a dedicated staff of nurses with patient histories and pressures as well as

access to the principal investigators for consultations as was done in the study would not be duplicated in a postmarket setting.

Can I have slide 177 please?

So this slide was presented by Dr. Brockman earlier today where the automated e-mail message taken from the Sponsor's training materials that was included in the PMA states, "A reading for the patient has exceeded the following threshold: PA diagnostic pressure should be above 2 mmHg exceeded by 1 mmHg. Please visit the CHAMPION HF system for further information. Please note that you can unsubscribe from this e-mail," et cetera, et cetera.

The point is that this e-mail message, which is what we understood was going to be done by the Sponsor, does not contain specific treatment recommendations.

In the analysis you saw earlier today, regarding the treatment e-mails, FDA cannot verify the number of e-mails that were sent, and it should be noted that the number presented, 193 e-mails, does not include any phone calls that may have been made which are referenced in some of the e-mails that FDA has found.

Can I have the IFU slide please, slide 6?

So FDA is concerned that the effectiveness results presented today do not quantify the effect of the device but the effect of the device plus additional attention from the Sponsor's nurses.

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I'll remind the Panel that you'll be voting on the indications for use which are projected on the screen, which were included in the presentations today and in the PMA. You'll also be voting on the device as it was described in the PMA, which is the implantable pressure sensor, the electronics units, and the database, and not on a clinical decision support system that would include a clinical management team.

Thanks.

DR. BORER: Thank you very much. Does the Sponsor wish to make some summary comments? Dr. Stevenson.

DR. STEVENSON: So we're losing the battle of hospital admissions, and it's a big battle. It's over a million each year, and most of those are readmissions.

So we need a new strategy. This strategy can't just be throwing more people and more phone calls at it. We've already done that. Over 3,000 patients, TENS-HF, TIM-HF, Tele-HF, called patients, told them more, asked them. It made zero difference. So there's nothing more to do in that range.

The problem is we don't have the right signal to make anything better. The physiologic signal that leads to readmissions is elevated filling pressures. Until we know about that, it doesn't make any difference to call patients more because we don't know what to tell them. I can't tell them to increase or decrease their diuretics if we don't know what we're treating. I

don't want to be adding nitrates if I don't know that their filling pressures are high to begin with.

So this artificial distinction between the signal and the system here, it's totally artificial because we need a new signal and we have to have the system to respond to it. So from the standpoint of the clinical team, we're having trouble dealing with this distinction because it clearly all comes together.

When we look at what we've seen in terms of the efficacy, we know that we do need a system. We tried to do it with just the pressure monitors and no education, nothing. That was in COMPASS-HF, REDUCE-HF. It didn't work. So we need both, and we're very sure of that now.

We didn't make that mistake when we did this trial like we did last time. So we had a system in place.

We've seen that this strategy improves outcomes in a meaningful way, depending on whether you look at the six months or the whole study, decreases hospitalizations by 25 to 39%. That's a huge impact. That's basically in the order of what happens with beta blockers, what happens with spironolactone-approved therapies, and it's more than what we see with ACE inhibitor therapy.

In terms of the benefit in women, if you add in the death and the hospitalization, there's no difference between what we see in the men and women. However, I would actually be interested as a spectator sport to

see what happens if we end up approving something just for women.

In terms of sustained, one of the most powerful things that we've seen is the fact that after it became unblinded, we saw the benefit sustained in the patients who had already been unblinded and the patients who hadn't. We saw them have the same benefit as the study group, and yet during that time, the only e-mails were the automated e-mails. There were no extra e-mails. There were no PI phone calls, nothing after unblinding, and yet you saw their hospitalization rate reduced just like the study arm. So there's something in this signal, and we think that's really the key, but it needs to be ruled out in the setting of the whole system.

I was only a site investigator. I was not a PI in this trial. I didn't talk to anybody. I just used the device to take care of patients, and I can tell you that we can make decisions we've never before been able to make. We finally have truly patient-centered care. I know how to take care of each patient now, and I have to tell you, I'm not going to learn how to take care of the next one from the last one because each one is truly individual. This is patient-centered care, and this is how we're going to improve the outcomes.

I believe this system should be evaluated in terms of the signal and the system that responds to it. I think it's very artificial to distract, to try to separate these, and I think the Sponsor is clearly committed to carrying this on.

And in my experience, with this system, we can improve the

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care of heart failure in a way that we can't with anything else that we can do now. We can keep patients out of the hospital, and we can improve their quality of life.

I'll turn it over to Dr. Yadav to discuss the integrated approach.

DR. YADAV: Thank you, Dr. Stevenson. Thank you, Dr. Borer.

You know, I just want to come back to the public health problem that we have. As Dr. Weisfeldt and others have indicated, this is a huge problem. We don't have great solutions. We have made progress with CRT devices in a subset of patients, but this is a medical management disease, and we have not provided tools to clinicians for better medical management. That's the whole issue that Dr. Stevenson summarized.

This has been a 10-year program. This study is a four-year study. These are very rigorous experiments. We can discuss a trial design. It was carefully thought out by very experienced clinical investigators who had done the previous studies in this field and realized that hemodynamics without education, because it's a new concept, would not work. So we provided education and support.

I think the benefit is very robust. Annualized reduction of 37%. That's very substantive.

Gender, it's an interesting discussion. It's not pre-specified. I can point to many examples in cardiovascular disease. You look at cardiac endarterectomy, bypass surgery. We can go on and on where we have

differences when we look at the rates in women versus men. We all understand that we still offer these treatments to women with taking the totality of information, and certainly in the post-approval setting, we'll have a lot more women to look at and explore this idea.

You know, I want to talk about -- if I could have the slides that I requested up please. CH-19, please.

I think we have demonstrated to you clearly that specific recommendations were in the protocol. It says you'll see even different than what's been done previously. There's no doubt about this.

Further, CH-26 please, there have been questions about the ability of the Sponsor to operationalize this in the commercial setting. Typically, when we look at these things, we'll have a positive trial, and then the company doesn't have a clear mechanism for how they're going to implement it in the commercial setting. Well, here we do. This operationalizes within the clinical trial, and it specified this. It was done well in advance. It specifies the type of nurses, RNs, CNSs that would be involved in this. I'm not sure why this is a surprise, whether it couldn't be done going forward.

Regarding IFU, I think we're getting into technicalities and semantics. The protocol actually says management system, IFU -- monitoring system. I think the full intention is to commercialize what's in the study. Why would you do something different? I mean I've seen a lot of IFUs. The

IFUs for whether it's stents, CRTs, LVADs do not say and the support staff of the sponsor, of the organization, but it's understood there's a support staff.

Would you do a CRT implant without support staff? You wouldn't. You probably couldn't. You surely couldn't manage them afterward. This is understood. If it needs to be explicit, it can be put explicitly in the IFU. The rest of the PMA does go on and describes the extensive training and support.

I think if that's the issue, I don't know how much further I can reassure you that the full intention with the design of the study has always been to have the entire system in practice. I think the way it was conducted in the study should give you reassurance that it has been operationalized and can be done going forward.

Further, I would add that this really was a real-world study. We had interventionalists, electrophysiologists. The leading role was an interventionalist. The second leading role was an electrophysiologist, and it was not a bunch of heart failure experts.

We have shown you information that the level of the manual e-mails is actually very small compared to the totality of communication. A lot is being made about Dr. Abraham and Dr. Adamson's involvement. They had I think 12 phone calls in the 6 months. The number of nursing e-mails is less than one e-mail regarding a patient in six months. Do we really think that's going to change outcomes, when only monitoring studies with

thousands of phone calls didn't change outcomes?

We also saw that over time, the e-mails were dramatically less and then disappeared completely, and the doctor did a really good job of taking care of the patients and achieved comparable rates to the earlier phase of the study, indicating that with education and training, they can do a very good job by themselves, and there's no reason why this couldn't happen in the real world.

I think ultimately it's up to you to decide if patients and clinicians will have a new tool, a new system to help them in managing this very challenging public health problem.

I'd like you to look at the risk/benefit equation here. The risk is exceedingly small for a permanent implant. I think Dr. Milan asked about removal. There were no removals in the clinical experience. We did remove one in the animal experience. We tested the hypothesis that it could be removed using an end-snare device. It is easily removable at six months in a pig model. So eventually it can certainly be removed easily. So I think the risk is very low.

The benefit is compelling, particularly the fact that there are increases over time, not diminishes.

Thank you for your consideration.

DR. BORER: Thank you very much, Dr. Jadav. Thank you to the Sponsor, the group as a whole, for a very comprehensive and enlightening

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presentation and likewise to the FDA for a comprehensive and very useful presentation.

Before we go onto the voting, we've heard some comments from our Consumer Representative, Mr. Dubbs; from our Industry Representative, Mr. Barrett; and from our Patient Representative, Judith Currier, but I'm going to ask them now singly or together if they have any final comments they'd like to make.

MS. CURRIER: Yes, I would. I would hate to see this very effective arrow in one's quiver to fight heart failure to be discarded at the moment. I mean I just think that, you know, even if you think that it's just reasonable assurance, I mean that's kind of a high standard, but for people not to be able to use this system that exists really I think, would be a shame, and I still encourage CardioMEMS to let the patient look at the information on the website.

DR. BORER: Thank you. Mr. Dubbs, do you have any final comment you'd like to make?

MR. DUBBS: Yes, thank you. I think we heard a lot today about personalized medicine, and it's used in a lot of different concepts, but to apply it here, where we have patient-centered information continuously available which allows modifications in medical management, in both a close and a geographically dispersed area, I think it's a wonderful invention. I think it will improve quality of life, and I think it should be approved.

DR. BORER: Thank you, Mr. Dubbs. Mr. Barrett, do you have a final comment?

MR. BARRETT: Yeah, I do. I'd like to thank the Panel for a really thorough review of an incredibly important pivotal study in a large patient population with a significant unmet need.

This program as we heard of clinical research has been ongoing for a decade. I believe that the study design for this study was solidified about five years ago, and it took four years to conduct this study and was conducted at, if I recall right, 60 or so sites with over 500 patients. It was a randomized, well-controlled study. All of the pre-specified endpoints in the protocol were met.

Outside of the six-month pivotal data collection point, the Sponsor presented a significant amount of additional supportive chronic data.

I am still struggling in my mind to understand how you study in a randomized controlled study a diagnostic device that provides a piece of physiological information without trying to do something positive with it from a patient management point of view, and I think that all of the dilemmas and conundrums that have been carefully discussed and dissected and debated by the Panel are real and appropriate, but when I step up above that and I look at the totality of the study and the design, the protocol and the endpoints, I find this is a positive study. Thank you.

DR. BORER: Thank you very much, Mr. Barrett.

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We're ready now to vote on the Panel's recommendation to FDA for this PMA. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit.

Jamie Waterhouse, the Designated Federal Official for this project will now read three definitions to assist in the premarket approval application voting process. Whoops, sorry. That's going to be read by Lieutenant Russell, and then Ms. Waterhouse will read the questions.

LT RUSSELL: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

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

Safety - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - There is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate direction for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

DR. BORER: Thank you very much, Lieutenant Russell.

The proposed indications for use statement for this product is as follows:

The CHAMPION HF Monitoring System is indicated for wirelessly measuring and monitoring PA pressure and heart rate in New York Heart Association Class III heart failure patients who have been hospitalized

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for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and to reduce heart failure hospitalizations.

The CHAMPION HF Monitoring System is used by the physician in the hospital or office setting to obtain and review PA pressure measurements. The CHAMPION HF Monitoring System is used by the patient in the home or other remote location to wirelessly obtain and send hemodynamic and PA pressure measurements to a secure database for review and evaluation by the patient's physician.

We will now proceed to the vote. Jamie Waterhouse, who I indicated earlier is our Designated Federal Official for the project, will go through the voting procedure. Ms. Waterhouse.

MS. WATERHOUSE: Please locate your handheld remote. For the next questions, press 1 to vote yes, 2 to vote no, and 3 to abstain. Please be certain of your response before you select your answer. Once a selection is made, there will be no opportunity to change your vote.

Before we begin, we will take a test vote to verify the voting devices are working properly. So for this, press 1 for yes, 2 for no, 3 to abstain. As you vote, your name will disappear.

DR. BORER: This is the very exciting part, and I want you all to know that I'm not allowed to vote unless there's a tie.

MS. WATERHOUSE: The poll is now closed. All devices appear

to be working properly. We'll proceed to the voting questions.

Question 1 reads as follows: Is there reasonable assurance that the CHAMPION HF Monitoring System is safe for use in patients who meet the criteria specified in the proposed indication?

Press 1 for yes, 2 for no, and 3 to abstain.

The poll is now closed. We'll proceed to Question 2.

Question 2 reads as follows: Is there reasonable assurance that the CHAMPION HF Monitoring System is effective for use in patients who meet the criteria specified in the proposed indication?

Please lock in your votes.

The poll is now closed.

The third and final question is as follows: Do the benefits of the CHAMPION HF Monitoring System for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please lock in your votes.

The poll is now closed. All votes have been captured.

I will now read each Panelist's vote into the record.

For Question 1, Dr. Lange voted 1 for yes. Dr. Cigarroa voted 2 for no. Dr. Slotwiner voted 1 for yes. Dr. Milan voted 1 for yes. Dr. Brindis voted 1 for yes. Dr. Weisfeldt voted 1 for yes. Dr. Evans voted 1 for yes. Dr. Jeevanandam voted 1 for yes. Dr. Ohman voted 1 for yes. Dr. Ferguson

also voted 1 for yes.

For Question 2, Dr. Lange voted 2 for no. Dr. Cigarroa voted 2 for no. Dr. Slotwiner voted 1 for yes. Dr. Milan voted 2 for no. Dr. Brindis voted 2 for no. Dr. Weisfeldt voted 2 for no. Dr. Evans voted 2 for no. Dr. Jeevanandam voted 2 for no. Dr. Ohman voted 1 for yes. Dr. Ferguson voted 1 for yes.

For Question 3, Dr. Lange voted 2 for no. Dr. Cigarroa voted 2 for no. Dr. Slotwiner voted 1 for yes. Dr. Milan voted 2 for no. Dr. Brindis voted 2 for no. Dr. Weisfeldt voted 2 for no. Dr. Evans voted 2 for no. Dr. Jeevanandam voted 1 for yes. Dr. Ohman voted 1 for yes. Dr. Ferguson voted 1 for yes.

Please give us a moment as we verify and tally the official votes.

On Question 1, the Panel voted 9 to 1 that the data shows that the CHAMPION HF Monitoring System is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 3 to 7 that there is not reasonable assurance that the CHAMPION HF Monitoring System is effective for use in patients who meet the criteria specified in the proposed indication.

Question 3, the Panel voted 4 yes and 6 no that the benefits of the CHAMPION HF Monitoring System outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Please pass the voting devices to the ends of the table for collection.

DR. BORER: I'm now going to ask the Panel members to discuss their votes. Correct me if I'm wrong, Dr. Zuckerman, but it's not necessary for people who voted yes to explain a yes vote. We're asking for an explanation of the no vote specifically as to whether a change in labeling or restrictions on use or other controls would have made a difference in your answer. Is that correct?

DR. ZUCKERMAN: Yes.

DR. BORER: Okay. I don't remember who voted for what, but on Question Number 1, there was one no vote. Dr. Cigarroa, would you like to explain the no there, particularly with regard to whether these issues that I stated would have changed your vote?

DR. CIGARROA: Certainly. As I stated during some of the discussions, I believe implantation of the device is safe.

I believe that again as it relates to the intended population, including female and gender, remains unanswered and that was part of the intended population, and since there are two analyses that conflict in results, I could not be reasonably assured of that statement.

Then third is applicability in terms of the potential of harm in the introduction of the device and making decisions on PA pressures without the entire support group that could potentially cause harm in that scenario.

DR. BORER: Thank you. Okay. On Question 2, we have seven no votes. Again, I don't remember exactly who was which. I tried catching them, but let's start at the end of the table. If you voted no, that is that there's not a reasonable assurance that the monitoring system was effective for use in patients who meet the criteria specified in the proposed indication, can you give us a sentence or two about why and tell us whether changes in labeling, restrictions on use, or other controls would make a difference in your vote. Dr. Jeevanandam.

DR. JEEVANANDAM: Sure. This was extremely painful because as a heart failure physician, I would love to have this entity to be able to use to monitor PA pressures. However, I think they demonstrated that it was a combination of the device plus a support mechanism, and that's exactly what Dr. Stevenson said. They've done the support mechanism without the device, and it doesn't work. They've done PA pressures without the support mechanism, and it doesn't work. And that's why they designed this trial with the support mechanism and the device. So I think with the support mechanism, this concept works.

I think in most institutions they don't need the support system, and maybe very advanced heart failure centers can just use the numbers and manage the patients, but I think if you're going to have this as a general applicability to the entire population, then the support mechanism does help. So, you know, if you look at what is defined as a monitoring system, you have

the implantable sensor, delivery system, the electronics.

If you added another component to it which was, as demonstrated up there, the support mechanism, then my vote would have been yes.

DR. BORER: Thank you. Dr. Brindis.

DR. BRINDIS: Well, I guess to repeat my comment earlier, I actually think this technology is innovative and borderline disruptive, and I clearly can appreciate its added value in terms of the potential management of heart failure and certainly listened to a mentor of mine, Lynne Warner Stevenson, with her passionate plea, also with my heart, want to see the Sponsor readdress issues so that hopefully we can approve beyond reasonableness related to effectiveness so that we can have this available to our patients.

The challenge here which was issues of the confounders, some of the zeal that was pointed out related to the FDA's discovery and the conundrum over women, which led to my no vote, and I would encourage the Sponsor to try to address these issues and bring forth this device at a future time to the FDA.

DR. BORER: Thank you. Dr. Milan.

DR. MILAN: So I share the enthusiasm of my two colleagues who just spoke about this technology and its potential for use in a high-risk population. At the end of the day, it was an inability to separate out the

device as defined in the voting sheet from the rest of the support system that was incorporated. I also feel that if that support system was incorporated, I would take another look. I think there were elements of that support system that will be difficult to implement on a large scale in the real world, and I'm thinking of specific things like one of the e-mails mentioned, let me know if there's a problem if the patient has difficulty getting transportation to the clinic. I mean those are things that are not going to be implementable in the real world, but I do think that if that were included, it would merit a second look.

DR. BORER: Thank you. Dr. Cigarroa.

DR. CIGARROA: So I, too, share the frustration of the challenge of managing patients with Class III heart failure, and the desire to be able to improve on how we make our decision making and so the concept of being able to monitor at least one facet of hemodynamics, say a PA pressure, is appealing to me.

But for all the reasons that I think the two of you mentioned, found it difficult to, with a reasonable assurance, obtain the primary efficacy, I voted no.

DR. BORER: Thank you. Dr. Lange.

DR. LANGE: My compliments to the Sponsor. I think the device is the cat's meow. It was fantastic. I think if this trial had been negative, we wouldn't be sitting here because we all want it to work, and I think in

Dr. Stevenson's hands and Dr. Abraham's hands and Dr. Adamson's hands, there's no question that it's beneficial. At least I don't have any question about it.

You've talked about the fact that when there's no protocol, if you monitor -- there's no protocol, that doesn't help. We know that from COMPASS-HF, and we know that from REDUCE-HF as well.

The question is if you have this in the protocol about somebody picking up the phone and calling you, does it make a difference? And there was sufficient concern on the Sponsor's part because on at least 150 patients, somebody picked up the phone and said, listen, we want to make specific recommendations. I mean making a protocol available to you isn't enough. We want to pick up the phone and make sure they're absolutely doing it. And so, again, that's the issue of trying to tease that out.

Again, what I wanted to tell the Sponsor is that the way the study as it was done was a positive study, and you're being commended. It was done very well. It was presented very well. We have no concerns about how it was done. The question is, is it applicable if I can't get Dr. Abraham or Dr. Adamson or Dr. Stevenson on the phone to help me answer the patients?

DR. BORER: Thank you. Dr. Evans.

DR. EVANS: These are such important data and such a novel and excellent idea, I hope that it's pursued.

But we were asked to evaluate whether there's reasonable

assurance of the effectiveness of the device, and for all the reasons we've discussed, I don't think we can isolate those effects in this study. So that's why I voted the way I did.

DR. BORER: Thank you. Dr. Ferguson, and remember, we did have three yes votes, and you don't have to explain the yes vote.

DR. FERGUSON: Mine was a yes vote, but I want to explain my yes vote. I voted yes just based on faith. I have faith that the Sponsor will follow through with a clinical support system that they promised and also faith that the FDA would hold them do it.

DR. BORER: Dr. Weisfeldt.

DR. WEISFELDT: As somebody very interested in hemodynamics and believing in hemodynamics, it's very personally disappointing to see the failure which is really based on the investigators themselves misperforming this study that is flawed. It is flawed because of the extra information and the fact that there was no linkage between the pressure changes directly and in the short term to the changes in treatment, and then all the other things that went on in the intervention arm versus the control arm that has been put forth by the FDA in looking at this study carefully just eliminated my ability to be able to support the device.

DR. BORER: Thank you. Dr. Ohman.

DR. OHMAN: Yeah, the reflection of this vote can go down as e-mailgate. I do believe if you look at my review of the information, that the

majority of patients did not have the undue influence, how it was recognized in a post hoc fashion is questionable for sure, and I think the totality of evidence suggested to me that there was actually efficacy here. There was efficacy when e-mails were not sent out other than the programmatic ones. There was the impact of the other e-mails in the broader magnitude, and the treatment effects as were described was not evident to me.

What I did notice though was there's a learning curve here, and that to me is maybe the most important take-home message, that actually even among diagnostics in a complicated field has a learning curve and actually you can learn a lot from this.

I sincerely hope that the Sponsor will carry on and make this even better in the future.

DR. BORER: Dr. Slotwiner.

DR. SLOTWINER: I voted yes, and I know I don't have to explain it, but I'd like to. I wasn't really planning to, but in the end, I think the device is just incredibly compelling as was the presentation by the Sponsor.

I recognize that there are limitations to the data, but I think it's very safe, and I think that being too semantic about the wording sometimes can be easy to say no, and I think people would use it reasonably and enthusiastically. I hope, I hope it gets out there.

DR. BORER: Thank you. Now, we have the third vote, the key vote which was the relationship of efficacy and safety, and perhaps we can

comment about that as well. The vote there was four to six, favoring nos.

We'll start with Dr. Slotwiner. You may want to briefly summarize anything else you want to state about this.

DR. SLOTWINER: I think looking at the risk and benefits here, the risk is really low, and I believe there's a benefit, and I believe it should be available.

DR. BORER: Okay. Dr. Ohman.

DR. OHMAN: Nothing further than what I previously said.

DR. BORER: Dr. Weisfeldt. Dr. Ferguson. Dr. Evans. Dr. Milan. Dr. Cigarroa. No.

Okay. I'd like to thank the Panel, the FDA, and the Sponsor for their extraordinary contributions to today's meeting.

Dr. Zuckerman, do you have any final remarks?

DR. ZUCKERMAN: No. I would just like to thank Dr. Borer for an extremely well run and handled session and all the Panel members here for taking time out to discuss a very important application. Thank you.

DR. BORER: Thank you. Before we adjourn, let me point out to everyone that we need to vacate the room as soon as possible. It's being used for an event tonight, and please be careful as the hotel has set up for a cocktail reception outside this ballroom. Having told you that --

UNIDENTIFIED SPEAKER: Can we stay?

DR. BORER: -- I will tell you that the December 8, 2011 meeting

of the Circulatory System Devices Panel is now concluded.

(Whereupon, at 6:02 p.m., the meeting was adjourned.)

C E R T I F I C A T E

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

CIRCULATORY SYSTEM DEVICES PANEL

December 8, 2011

Gaithersburg, Maryland

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