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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

+ + +

October 9, 2013
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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SHARON TIMBERLAKE, M.S.H.S., RAC, CCRA	Industry Representative
KRISTINE R. MATTIVI, M.S., PT	Consumer Representative
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M E E T I N G

(8:00 a.m.)

DR. PAGE: Good morning. I'd like to call this meeting of the Circulatory System Devices Panel to order. It's now 8 a.m.

I'm Richard Page. I'm Chair of the Department of Medicine at the University of Wisconsin in Madison. I'm a cardiologist/electrophysiologist. And to start off, I'd like the Panel to introduce themselves. I'll start over here to my left with Dr. Zuckerman. Please state your area of expertise, position, and affiliation.

Dr. Zuckerman?

DR. ZUCKERMAN: Good morning. My name is Bram Zuckerman. I'm Director, FDA Division of Cardiovascular Devices.

MS. CURRIER: Good morning. I'm Judy Currier. I'm the Patient Representative. My background is math and systems analysis, and I'm a patient too. Thank you.

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

DR. BORER: I'm Jeff Borer. I'm a professor and Chief of the Division of Cardiovascular Medicine at State University of New York, Downstate Medical Center.

DR. BLUMENSTEIN: I'm Brent Blumenstein, a biostatistician. I work as a consultant here in Washington, D.C.

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DR. PATTON: I'm Kris Patton. I'm a cardiac electrophysiologist at University of Washington.

DR. LANGE: I'm Rick Lange. My background is in interventional cardiology, and I am Vice Chairman of Medicine at the University of Texas in San Antonio.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. WEISFELDT: Myron Weisfeldt. I'm Chair of the Department of Medicine at Johns Hopkins, and I've had a long interest in cardiovascular devices.

DR. YUH: Good morning. I'm David Yuh, Chief of Cardiac Surgery at Yale University.

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

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa. I'm Clinical Professor of Medicine at OHSU. I'm an interventional cardiologist, and I'm the Clinical Chief of the Knight Cardiovascular Institute.

DR. JEEVANANDAM: I'm Val Jeevanandam. I'm Chief of Cardiac Surgery at University of Chicago.

DR. OHMAN: I'm Dr. Magnus Ohman. I'm a cardiologist, interventional cardiologist, Professor of Medicine at Duke, interest in clinical trials.

MS. MATTIVI: Kris Mattivi. I'm the Consumer Representative, Manager of Analytic Services at CFMC and 20 years experiences as a clinical physical therapist.

MS. TIMBERLAKE: Good morning. My name is Sharon Timberlake. I'm the Industry Representative. I'm employed by OmniGuide Surgical. I specialize in medical devices and clinical regulatory and quality affairs.

DR. PAGE: Thank you. I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in today's meeting 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 premarket approval application for the CardioMEMS, Incorporated CHAMPION HF Monitoring System.

If you've not already done so, please sign the attendance sheets that are on the front tables by the door. Jamie Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

Ms. Waterhouse?

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member

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Statements.

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

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have 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.

Related to the discussions of today's meeting, members and consultants of this Panel have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of

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their spouses or minor children and, for purposes 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 information related to the premarket approval application for the CardioMEMS HF Pressure Measurement System, sponsored by CardioMEMS. The CardioMEMS HF System is a permanently implantable 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. The company has proposed the following expanded indications for use. "The CardioMEMS HF Pressure Measurement System is indicated for measuring pulmonary artery pressures in patients with New York Heart Association Class III heart failure."

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

Sharon Timberlake is serving as the Industry Representative, acting on behalf of all related industry, and is employed by OmniGuide Surgical.

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We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an 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.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting on October 9th, 2013: Dr. Jeevanandam, Dr. Borer, Dr. Cigarroa, Dr. Weisfeldt, Dr. Milan, Dr. Patton, and Dr. Blumenstein.

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. Richard Page to act as temporary chairperson for the duration of this meeting.

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This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on September 27th, 2013.

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

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is 410-974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

I would like to remind everyone that members of the public and the 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 AnnMarie Williams at the registration desk.

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

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

DR. PAGE: Thank you very much.

Before we get started, I'd just like to remind the Panel that the

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microphones need to be turned off if you're not speaking. That actually really improves the acoustics here in the room. In addition, for the duration of this Panel meeting, all of our conversations are part of the minutes, so I just ask that there not be any side conversations. This is a very distinguished Panel. We want to hear everything you have to say, but we need to have it entered into the Panel deliberations and the transcript.

We will now proceed with the Sponsor's presentation from CardioMEMS for both the Sponsor and the FDA. We've got a timer for 90 minutes. We'll ask you to keep to that. There is going to be a warning light at two minutes. And now we welcome the Sponsor's presentation.

DR. YADAV: Good morning. I'm Jay Yadav, cardiologist at Piedmont Hospital in Atlanta and founder and CEO of CardioMEMS. Thank you, Dr. Page, Dr. Zuckerman, Panel members.

On behalf of everyone at CardioMEMS, I wanted to share with you today our work over more than the past decade. We do appreciate the Agency holding this advisory panel meeting despite the partial government shutdown.

As Ms. Waterhouse stated, the CHAMPION system is indicated for the measurement and monitoring of pulmonary artery pressures in patients with New York Heart Association Class III heart failure who have been hospitalized in the previous year. Physicians can use this information to manage and prevent heart failure hospitalizations.

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Now, let me review some of the events leading up to this Panel meeting today. We started the CHAMPION clinical program in 2006 and completed it actually last year, in 2012. We started with a 50-patient feasibility study in U.S. and Europe and South America. On the basis of the results of this, we were able to start the CHAMPION randomized trial. We started in 2007 and finished with its primary endpoint and secondary endpoints met in mid-2010.

After the randomized access portion was finished, and Dr. Adamson will describe this in more detail, we began the open access portion in which all patients' pressures were accessible to their physicians. On the basis of the randomized access data, we submitted the PMA in late 2010. The FDA held an advisory panel meeting in late 2011. At the panel meeting, there was concern raised about certain nurse communications from CardioMEMS to the investigative sites, and there was concern about both the number of communications -- there was uncertainty about the number of communications as well as the possible confounding effect of these communications on the assessment of device efficacy. The Panel found that the device was safe, but felt that they could not distinguish the effect of the nurse communications from that of the device and thus did not vote for approval.

The FDA sent us a not approval letter in early 2012. We met with the FDA after the receipt of that letter and had multiple meetings and

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discussions with the FDA and developed a plan to address these concerns. And I'll review some of that with you. And we'll obviously go through that in great detail today.

One of the key elements, one of the key issues at the last panel meeting was what is the exact number of these communications and phone calls. We developed a third-party audit plan at the request of the FDA and approved by the FDA, which was conducted by Becker Consulting, led by Ron Johnson, who was former head of compliance of the FDA and who's present here today.

Becker audited CardioMEMS as well as all 64 sites in person. They reviewed all communications. And they determined the number that fit the definition of nurse communications. And of interest, the number that they determined matched the number that we had provided to the FDA.

In parallel, we had the opportunity to have the CHAMPION Clinical Events Committee, headed by Dr. Alan Miller, adjudicate all of the events in open access, all hospitalizations and deaths. And please note that in open access, there were no nurse communications, so as you can see, this provides an excellent opportunity to assess the device efficacy in the absence of nurse communications.

Further, in collaboration and consultation with the FDA, we developed a statistical analysis plan to analyze all of this additional data.

We also, working with the FDA, developed a clinical analysis

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plan, which was conducted by Dr. JoAnn Lindenfeld and Dr. Milton Packer, who read all of the communications provided by Becker Consulting and made a clinical determination as to their influence and impact.

All of this information was then presented in the PMA amendment to the FDA earlier this year, and this is the information we'll share with you today at this Advisory Meeting.

Let me note that, and many of you were present at the last panel meeting, that today we're able to present to you a far greater amount of data. The focus of the last panel meeting really was the primary endpoint, which was the first six months of randomized access and represents about 270 patient-years. And although we touched upon the randomized access, we were not able to present it in full detail. So today we'll share with you an additional 12 months of randomized access data or about 500 patient-years, and 13 months of the open access experience, or another 400 patient-years. So you're going to see a significantly greater dataset today than last time.

Joining me will be Dr. Phillip Adamson and Dr. William Abraham, co-principal investigators of the CHAMPION Trial, and they'll present the design and the primary results of the CHAMPION Trial. Dr. Packer will present these new analyses that I've just mentioned to you that have been gathered over the last two years in support of device efficacy, and Dr. Lynne Warner-Stevenson will present the clinical need and

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clinical significance of the CHAMPION Trial results.

Also joining us today are the chairpersons for clinical trial oversight committees. Dr. Lindenfeld was chairperson of the DSMB, and Dr. Miller was chairperson of the Clinical Events Committee. The statistical advisors present are Dr. D'Agostino, who designed and supervised the propensity analysis that Dr. Packer will be presenting to you, and Dr. Ogenstad and Dr. Holcomb.

Let me review with you briefly the design of the device. It has three components, the wireless implantable sensor, which goes into a branch in the pulmonary artery, and the home electronics unit, which the patient uses to take readings. And these are transmitted automatically to a secure website database, where the patient's physician and nurses can review the information in real time.

The device is somewhat different than other devices you may have seen. It is a truly wireless device, has no batteries, no leads. It is also the first medical device which is completely waveform fabricated like the chip in your cell phone or laptop. It has no moving parts. It is hermetically sealed, i.e., there's no gas exchange, leading to excellent performance. The nitinol loops that you see are 10 mm in diameter, the same size as a Swan balloon, and they're much bigger than the sensor, ensuring the sensor resides in a branch which is much larger than the sensor body, allowing excellent blood flow and prevention of thrombosis.

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The concept behind the sensor is relatively straightforward. The key is a capacitor, which is two conducting plates separated by a gap. It is coupled to an inductor coil. As the pressure changes, the gap between the two capacitor plates changes. And this is, as the name suggests, this is a microelectromechanical system device, thus the name CardioMEMS. And we're measuring single nanometer deflections of these plates.

As the capacities change, the frequency of the device shifts. We can measure this with great precision, and we can take 2,000 readings per second, creating a very high fidelity waveform for you to review.

It is truly wireless in the sense that both the transmission as well as the energy are provided wirelessly. The design of the sensor originated at Georgia Tech University, the wireless energy and transmission capabilities at MIT, and this leads to a very reliable device.

The sensor is tethered to a over-the-wire delivery system, fairly straightforward and traditional. The blue cap that you see is the retention device, and releasing that releases the sensor from the distal end.

I'll show you a brief video reviewing the implantation. It starts out with the right heart catheterization. A transfemoral approach is typically used once the Swan is in place. We recommend a hand injection to see the distal pulmonary bed. Then the balloon is deflated. A wire is passed through the Swan lumen, and the Swan is removed. And the over-the-wire delivery system is then advanced over the wire. The blue cap that you saw

earlier is released. The sensor deploys. And so the implant only adds about seven minutes to a right heart catheterization. It is radiopaque because it has a little bit of gold inside it. The patient then takes readings at home. The readings are 18-second readings which are transmitted to the website and accessible to the physician or nurse taking care of the patient.

The data is presented in a very intuitive, graphical fashion. The red line is the PA systolic pressure. The blue is the mean and the green is the diastolic. And individual readings are easy to access, and Dr. Adamson will show this to you in more detail.

And now I will turn it over to Dr. Adamson to review the study design with you. Thank you.

DR. ADAMSON: Thank you, Dr. Yadav.

Dr. Page and Panel members, FDA, my name's Phil Adamson. I'm a heart failure cardiologist from Oklahoma City, and I serve as a co-principal investigator of the CHAMPION Trial. And in this capacity, I have received consultation fees and speaker honoraria from the Sponsor. I do not have an equity interest in the company.

I sincerely thank the FDA for organizing this Panel, especially given the governmental situation at this time.

Over the last 30 years, I think we've been very pleased to see significant reductions in coronary deaths. But at the same time, we've seen increases in heart failure hospitalizations of epidemic proportions. The

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impact of hospitalizing a patient with heart failure is certainly not trivial, and the very process of developing congestion that causes myocardial stress, resulting in troponin leak, systemic activation of adverse neural and hormonal control and contributes to overall worsening of the disease syndrome.

It's become clear that crisis management of heart failure is not a successful strategy. Instead the heart failure community agrees that prevention of heart failure hospitalizations is an important strategy to meet the goal of preventing disease progression.

In fact, heart failure hospitalization represents the best metric of non-fatal disease progression for heart failure. And the CHAMPION Trial was designed to address this very critical problem facing those who regularly care for heart failure patients.

Our most recent understanding of the events leading to decompensation illustrates why current tools to manage these patients are limited. It's now clear that exogenous volume retention, originally thought to be the prime driver for congestion, may play a smaller role compared to endogenous fluid redistribution. This volume shift changes the primary lesion leading to heart failure symptoms, which is increased pulmonary artery pressure.

With regard to pulmonary artery pressures, data from previous hemodynamic monitoring trials demonstrate two general points

that are important to consider. First, patients who live at high filling pressures are at high-risk for hospitalizations. Lowering those pressures is associated with a lower risk for hospitalization. And, secondly, increases in pressures that precede symptoms and hospitalizations can be detected two to three weeks in advance of events.

Therefore, it was reasonable to develop the hypothesis tested by the CHAMPION Trial that management of heart failure patients would be better in reducing hospitalizations if medications were adjusted based on direct measurements of pulmonary artery pressures unless there was a clear indication from real-time clinical assessment of the patient.

The steering committee and principal investigators designed this trial to include broadly applicable inclusion and exclusion criteria. The trial enrolled subjects with New York Heart Association Class III heart failure symptoms who were hospitalized in the previous 12 months without regard to ejection fraction. There were 64 investigator sites, which included both academic and community disease management settings. And importantly, investigators included all cardiology subspecialties. All investigators then, by nature of their fellowship training, were well versed in understanding cardiovascular hemodynamic pathophysiology.

So the CHAMPION Trial was a prospective, randomized, single blind controlled study that enrolled 550 patients. Importantly, I bring your attention to the fact that all patients underwent hemodynamic evaluation by

right-heart catheterization during the procedure in which the pulmonary artery sensor was implanted.

After successful sensor implantation, patients were randomly assigned to a control or treatment group, and all patients daily uploaded pressures from home. Signs and symptoms of heart failure were actively monitored and used to make treatment decisions in both groups, but the control group was actively treated only using standard clinical parameters coupled with a baseline hemodynamic evaluation. In fact, face-to-face assessment of control group patients averaged about 6.4 times in the six months spent evaluating the primary endpoint, which matched the face-to-face encounters in the treatment group. The difference between the subjects was that daily pressure information was made available to investigators in the treatment group patients.

Now, the primary endpoint, which I'll talk about in just a minute, was evaluated after six months of these strategies, but all patients remained in their original randomized group assignment until the last patient finished the six-month follow-up. This design allowed an evaluation of the endpoints after longer-term follow-up.

And please let me orient you to the design of this slide, as it will be similar to subsequent slides throughout this presentation. The dashed red line represents time in which pressures were uploaded but not made available to the investigators. The solid green line represents time

when pressures were made available and acted upon by the investigators. To summarize, then, hemodynamic information was made available for all patients at the time of sensor implantation, but ongoing pressures from the sensor were only available in the treatment group until the last patient finished six months of follow-up.

The trial's safety endpoints measured device- or system-related complications and pressure sensor failures. Safety was assessed in all patients since they all received the sensor and was compared to an objective performance criteria that was set prior to the trial onset. It was set at 80%, which was commonly used in device trials.

The primary efficacy endpoint was very simple. We compared the rate of adjudicated heart failure hospitalizations between the treatment and control groups. In addition, the trial evaluated four secondary efficacy endpoints in a hierarchical manner, including the change in mean pulmonary arterial pressure, proportion of patients hospitalized for heart failure, days alive outside of hospital, and quality of life, as measured by the Minnesota Living with Heart Failure Questionnaire.

The steering committee seriously considered the fact that current heart failure disease management relies heavily on maintaining volume stability using diuretics based on a variety of strategies combining signs and symptoms. And since there's no evidence base to guide dosing of diuretics and vasodilator therapy, the protocol makes general suggestions

for hemodynamic management in the trial. As such, the protocol included recommended goals for pulmonary artery pressures and encouraged investigators to modify medications to achieve those goals. For example, the general treatment suggested for elevated PA pressures are shown in this slide. This strategy first assumed that pressure elevations were the result of excess volume, triggering a need for diuretic therapy intensification. Then, addition or increase in vasodilator therapy was encouraged by the protocol to further reduce pressures to goal.

The specific trial conduct is shown in this schematic. Let's start over here with the patient who uploaded pressures, and that information on a daily basis was transmitted to a secured website. In the treatment group, pressures were displayed on our user-friendly web-based interface that investigator teams could review. And I'll show you that in just a second. The protocol required investigators to review pressures at least weekly, and the website automatically reminded investigators about login compliance and provided alerts to the site personnel in the event that pressures were outside of goal ranges.

Then pressure-based medication changes were made by the physician investigators, and the sites communicated those decisions directly with the patients. All pressure-based medication changes were then recorded using a case report form.

An example of an automatically generated alert is illustrated in

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this slide. Designated local site investigators were notified when any pressure value from the daily upload was outside the alert thresholds. The content included the average pressures from the uploaded measurement and the pressure waveform for review.

Additionally, the notification directed the investigator to the full website for further analysis. So when directed to the website, investigators securely logged in and chose a patient of interest. They were able to view uploaded pressures and trends, and hovering the cursor is shown here over an area on the graph, identified the specific values for that day's upload and displayed the recorded waveforms. By the way, the patient names in this example are fictional and don't violate privacy laws.

Typical independent committees provided oversight of the study conduct. Protocol implementation by local sites was monitored by the Sponsor to ensure good clinical practice. As I mentioned earlier, PA pressures were communicated to principal investigators by logins to the website and by automated alerts. Case report forms documenting medication changes in response to pressure changes were very important pieces of information regarding the conduct of this trial.

Now, I know you've heard and read a lot -- a variety of descriptions about nursing communications to the sites in the CHAMPION Trial, but the reality is that at any given time during the five years of this trial, the Sponsor had two or three full-time nurses who were charged with

multiple tasks, including general monitoring of good clinical practice, regulatory compliance of the 64 sites. These responsibilities included assisting site initiation, capture of serious adverse events, medication changes, and review of inclusion and exclusion criteria during screening.

As you can imagine from your clinical trial experience, sometimes case report forms documenting medication changes were submitted in a very timely manner, and sometimes they were delayed. Intermittently, if nurses noted that pressures were persistently elevated and no information about medication changes were reported on a case report form, the nurses could initiate a communication to the local site coordinator intended to be a reminder of the Appendix E guidelines as how the protocol was expected to be followed. Physicians who had complete and real-time knowledge of clinical status were the sole decision makers regarding the management of the patients. The nature and potential impact of nurse communications will be discussed in great detail by Dr. Packer later in this presentation.

So let's put all these communications in perspective. In the first six months of the trial, there were about 44,000 home readings, five uploads per patient per week, approximately 32,000 automatic alerts. Site investigators logged into the website about three times per patient per week for 27,000 communications. And then, likely, because physicians routinely treated elevated pressures, according to the protocol, the 511 nurse

communications were obviously infrequent.

So, finally, the unique design of the CHAMPION Trial allowed potential for several supplemental analyses. Patients were followed in their original randomized assignment until the last patient finished six-month follow-up, and that allowed for a total of 17.6 months of randomized, single-blinded analysis of the treatment strategy. This time period is designed at random access for further presentation in this time.

Also note that nursing communications only occurred in the randomized access phase of the trial, shown here as a blue dashed line. After the last patient finished six months follow-up, pressure information was made available in the former control group, and this time period is called open access, or Part 2.

Open access follow-up averaged about 13 months, and no protocol compliance monitoring was performed, but all events were captured and adjudicated by the Critical Events Committee. The open access period now allows for a variety of comparisons, including event rates between former control group and the control group and provided a period of time without nursing communications. These important time periods of the trial will be closely examined in the next presentations.

I certainly thank you for your attention, and it's now my pleasure to introduce my co-principal investigator, Dr. William Abraham, who will present the primary results of the CHAMPION Trial.

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DR. ABRAHAM: Thank you very much.

My name is William Abraham from the Ohio State University, and as mentioned earlier, I was a co-principal investigator of the CHAMPION Trial. As such, I received consulting fees from CardioMEMS. I have also received speaker honoraria. However, I hold no equity in the company.

It is now my pleasure to present the results of the CHAMPION Trial, beginning with patient disposition. This figure illustrates patient disposition over the entire randomized and open access periods of the trial. Of the 550 implanted patients, 270 were randomized to the treatment group and 280 were randomized to the control group. The primary reason for study exit was death. At the end of the randomized access period, 177 treatment and 170 control patients were available and entered the open access period.

The baseline characteristics of the CHAMPION patients were well balanced across groups. Twenty-one percent of the CHAMPION population had an ejection fraction of greater than or equal to 40%. The utilization of other device therapies, such as implantable cardioverter defibrillators, was high. At baseline, patients were well treated with guideline-recommended heart failure medications. Treatment was well balanced between the two groups.

Although the baseline medications were similar in the two patient groups, once pulmonary artery pressure information became

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available, the number of medication changes was much greater in the treatment group than in the control group. This difference was driven entirely by the use of pressure-based medication changes in the treatment group.

Medication changes based on signs and symptoms were common and similar in both groups. This represents ongoing background standard of care management of heart failure patients in both groups. In addition, there were 1404 medication changes made on the basis of pressure in the treatment group. This equates to just less than one pulmonary artery pressure-based medication change per patient per month. The majority of these pressure-based medication changes were increases or decreases in the doses of diuretics and nitrates, as intended by the treatment algorithm in the protocol and presented earlier by Dr. Adamson.

Use of the device was highly effective in reducing heart failure hospitalizations, which was the primary efficacy endpoint of the study. At six months, the hazard ratio for treatment versus control was 0.72, yielding a highly significant 28% relative risk reduction for heart failure hospitalization. At six months, the device also demonstrated an exceptional safety profile, with very few device- or system-related complications and no pressure sensor failures, so that both primary safety endpoints were met. Over the entire duration of study follow-up, including Part 1 and Part 2, there were no additional device- or system-related complications, yielding the safety

profile demonstrated on this slide.

Over the longer duration of the entire randomized access period, averaging 17.6 months, the treatment effect was sustained. Ninety-seven heart failure hospitalizations were prevented, representing a relative risk reduction of 33%, and the number needed to treat to prevent one heart failure hospitalization was only four.

The CHAMPION Trial also met all of its prespecified secondary endpoints with significant reductions in pulmonary artery pressure, few patients hospitalized for heart failure, more days alive and out of the hospital for heart failure, and improved quality of life.

You will note that in FDA's Executive Summary, FDA has a concern regarding the durability of the quality-of-life improvement since the 12-month findings were not statistically significant when compared to the significant improvement observed at six months. Please note that only 60% of patients were available for this particular analysis since some patients exited randomized access prior to 12 months, and some patients, during the randomized access period, had less than 12 months of follow-up. Remember, randomized access ended when the last patient enrolled completed six months of follow-up.

To explore the impact of these missing data, a last observation carried forward method was used to impute these missing values in accordance with an intent to treat analysis. As you can see, this quality of

life endpoint met the prespecified criteria based on the LOCF imputation approach, with a p-value of .0054 at six months and a p-value of .0267 at 12 months.

While not designed or adequately powered for mortality, CHAMPION demonstrated trends favoring the treatment group at six months and over randomized access, with hazard ratios of 0.77 and 0.80, respectively. Moreover, the commonly used heart failure trial endpoint of freedom from death or heart failure hospitalization demonstrated a significant reduction in risk in the treatment over six months and also over the entire randomized access period.

Finally, over the entire randomized access follow-up, significant reductions were not only seen in heart failure hospitalizations and the combined endpoint of heart failure hospitalizations and death, but also in all-cause hospitalizations and the combined endpoint of all-cause hospitalizations and death.

This latter finding is particularly remarkable when viewed in the context of other successful drug and device trials in heart failure. Many of these trials demonstrated reductions in heart failure events but failed to show reductions in all-cause events.

I would now like to introduce two issues raised during the first FDA review. The FDA raised concerns that CardioMEMS nurse communications made it difficult to interpret the results of the trial.

Milton Packer will present the data and analyses to address this concern in the next presentation.

The FDA was also concerned about a treatment by gender interaction, which I will now address. In a post hoc analysis for the six-month primary endpoint period, the interaction p-value for the treatment by gender interaction was 0.01. This was very puzzling since there seemed to be no plausible biological explanation for such a finding.

Since the first panel meeting, we have explored the possibility of a treatment by gender interaction in great detail. After extensive analysis in control women during the first six months, a low rate of heart failure hospitalization due in part to the competing risk of death appeared to be the most plausible explanation. This small number of events in control group women make analyses based on this group very imprecise and potentially very unreliable. So we agreed with the FDA on an analysis of treatment by gender, taking into account the full randomized access period and the competing risk of death.

Regarding death, women in the control group had a high early mortality when compared with the treatment group. During the first six months of randomized access, there were seven deaths in the control group, but only three deaths in the treatment group. And, importantly, the difference between the two groups occurred very early during follow-up, thus preventing the subsequent occurrence of hospitalization and

rehospitalization more often in women in the control group. To put it simply, fewer control women were alive and at risk for hospitalization compared to women in the treatment group.

So to account for the competing risk of death, we analyze the effect of the device on the combined risk of death or hospitalization for heart failure during the entire period of randomized access. In agreement with the FDA, this was our primary analysis to test for the presence of a treatment by gender interaction. As you can see, the effect size in women was not meaningfully different than in men, and the interaction p-value was highly insignificant at 0.69.

In the briefing documents that the committee has received, the section on treatment by gender interaction includes tables such as this one, which lists the results of numerous different statistical models that have been used to look at the presence of a treatment by gender interaction in different ways. It's important to emphasize that the first of these depicted by the Kaplan-Meier curves on the prior slide represents the model and significance level prespecified in the statistical analysis plan, and it demonstrates no treatment by gender interaction.

Having shown that there is little reliable evidence to support the presence of a treatment by gender interaction, I would like to directly address the efficacy of the device in women. In its review, the FDA has estimated the effect size of the device by examining the change in the rate

of heart failure hospitalization when patients in the control group move from randomized access to open access. In the transition from randomized to open access, physicians caring for patients in the control group are provided with access to pulmonary artery pressures for the very first time. In the transition from randomized access to open access, there was a meaningful decrease in the rate of hospitalizations for heart failure. Importantly, a meaningful decrease was seen in men and in women, and the magnitude of the decrease was similar in men and in women.

In summary, during randomized access, there is no reliable evidence supporting the presence of a treatment by gender interaction. Furthermore, during open access, women and men in the control group have a similar decrease in the rate of heart failure hospitalization when their physicians are provided with access to pulmonary artery pressures for the first time, thus supporting the efficacy of the device in both sexes.

I would now like to introduce Milton Packer to present new analyses from the CHAMPION Trial to further support device efficacy.

DR. PACKER: Thank you very much, Bill.

Dr. Page, members of the Advisory Committee, members of FDA, ladies and gentlemen.

(Technical difficulty.)

DR. PAGE: Dr. Packer, I'm sorry. The protocol, generally, is that the Sponsor needs to stay at the lectern. And actually, in point of fact,

I'm finding it very distracting having my view here and the other members there. If there is a pointer available, we can have you use the pointer, but otherwise, we're missing your pointing on the board. So may I ask you to take a spot at the lectern?

DR. PACKER: I'd be happy to. I usually give most of my talks --

DR. PAGE: I'm sure that's the case, but we usually give talks this way, so we'll ask you to abide by our protocol.

DR. PACKER: In any case -- boy, it's so far away.

(Laughter.)

DR. PACKER: In any case, so the question that arose is to what degree did these nurse communications, did they have an influence on this process. So what I'd like to do is to show you analyses to provide further support for the efficacy of the device in reducing the rate of hospitalizations for heart failure, and specifically to distinguish the influence of nurse communications from knowledge of pulmonary artery pressures in reducing the rate of hospitalization for heart failure.

So I'm going to show you three distinct lines of evidence. First, I'm going to address the question: Is there a meaningful effect of nurse communications? I'm going to focus on the six-month primary endpoint period, and I'm going to focus on characterization of nurse communications and their influence on physician prescribing. Then I'm going to focus on the question: Is there a meaningful effect of the device without nurse

communication? So I'm going to do that in two ways. First, I'm going to focus on the six-month primary endpoint period, focusing on patients who are not the subject of a nurse communication, and secondly, looking at the entire duration of the trial, both randomized and open access, focusing on periods without a nurse communication.

So let us take a look at all three of these. And before I begin, I want to put all of these three lines of evidence into perspective. In its documents that it has sent to the committee, the FDA has said, in their view, it's hard to interpret the p-values that are going to be shown -- by the way, I'm going to show very few p-values -- because no study success criteria could be defined a priori and because this study was not originally designed with these analyses in mind. The study is not powered for these analyses. Multiple analyses were conducted on the same data. And preservation of Type I error was not attempted.

Let me try to put these into perspective. By definition, this study could not be developed a priori to address concerns that were raised following completion and analyses of the data. Second, the analyses you're going to see today were not carried out with the goal of making a negative study into a positive one. These analyses were carried out to evaluate the robustness, not the presence of the finding of a positive result. Third is a primary hypothesis and statistical methods to test those hypotheses, and specific predictions on those hypotheses were defined a priori for each

analysis and agreed upon with FDA.

And lastly and I think most importantly, for these analyses, statistical power and multiplicity of comparisons are not relevant concerns since the goal was to show that all of these analyses, not just one, not just two, all of the analyses produce results that were consistent with each other and with the original prespecified analysis of the primary endpoint.

So let me look at the first line of evidence. Again, this is a focus on the effect of nurse communications during the six-month primary endpoint period. Again, I just want to cover one point that the FDA said in its review. In the FDA Executive Summary, it says the protocol was not designed to monitor the capabilities of the Sponsor's nursing staff to monitor and correct physician-directed therapy.

Let me just clarify. The CardioMEMS nurse communications did not correct any physicians' therapy and did not represent an ongoing monitoring routine. Second is their concern was that these communications, regardless of whether they were consistent or inconsistent with the protocol, have the potential to introduce bias. Well, they had the potential, but the question is did they? Did they introduce bias?

So the important thing was to make sure that all nurse communications were identified. That was the first step in our methods. And, in fact, a third-party audit was done to identify these nurse communications. It was a plan developed in conjunction with the FDA.

Becker Consulting performed an onsite audit both at CardioMEMS and all the clinical sites, and all together, 511 nurse communications were identified by the audit during the six-month primary endpoint period, and no communications were identified during the open access period.

Now, the second step in this methodology was to identify the communications that mentioned the potential for a patient-level change in a specific medication and then to find, identify the communications that were followed with a concordant change in medications within seven days. Let me say that this represented the most important part of our work because it was based on minimal assumptions, and the goal was to determine if the nurse communications had an impact on physician prescribing.

Lastly, and really more as an afterthought, we tried to take the number of nurse communications followed by a concordant change in medication, and we tried to estimate the influence of these on the rate of hospitalization for heart failure. And this was based on assumptions based on the results of clinical trials in the literature. And let me just say that this represented a minor part of our work. The FDA has raised concerns about it. We agreed that these were based on certain specific assumptions.

And so what I would like to do is focus your attention on the major part of our work. And let me say that in order to do this, there were two cardiologists identified a priori in agreement with FDA and CardioMEMS, myself and Dr. JoAnn Lindenfeld from the University of Colorado, who is

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here, and we independently of each other reviewed each nurse communication identified through the audit. And we followed a conservative methodology to identify which communications, in fact, had any suggestion of a medication change or were followed by a concordant change in medication at the site.

So this is the methodology we used. We identified a nurse communication as mentioning the possibility of a medication change if it posed a question, if it suggested or recommended even the possibility of any medication or any change in a class of medications. The FDA asked us to do within a seven-day window. For reasons related to timing of the communications, we actually widened this to an eight-day window. Third, if a communication contained multiple mentions or recommendations but the management was altered to be concordant with only one recommendation, we considered it to be concordant. And, third, if a communication referred to a change in a member of a class of drugs at a specific dose or by a specific route and the change was made in any member of a drug class at any dose, any route regardless of clinical significance, we considered that to be a concordant change.

So I'll just give you two quick examples. If the communication said consider Lasix 40 mg IV and the site within eight days added Bumex 1 mg orally, we considered that to be concordant. If the communication said might the patient benefit from nitrates and the site prescribed nitroglycerin,

one tablet under the tongue once daily -- I know that seems unlikely; it happened -- we consider that to be a concordant change in medication.

So here's what we found. 511 nurse communications were identified by a third-party audit during the six-month primary endpoint period. 251 never mentioned a medication change. The FDA was very, very comfortable with these communications. 260 included mention of a drug change. And let's break these down a little bit more. Of the 260 that included the mention of a drug change, they had a total mention of 531 medications in these communications. But this is what's interesting. Only 85 of the 531 medication mentions were followed by a concordant change in medications within eight days. 84% of the mentions of medications were not followed by a concordant change within the eight-day period of time that we used.

Now, you might ask why were so many nurse communications not followed by a concordant medication change. Let me just emphasize, the fact that they were followed by a concordant change doesn't mean that the communication actually caused the medication change. But one can reasonably assume that if a communication wasn't followed by a concordant medication change, it didn't have an influence. So most of the nurse communications mention medications in a formulaic manner.

We reviewed every one of these nurse communications. And we analyzed not only their content but their structure, their tone, and their

intent. And these communications were sent without knowledge of symptoms or signs or laboratory values or recent changes in medications. Hence, they sort of served a function similar to automated alerts. But the nurses monitored the physician responses to pulmonary artery pressures only intermittently. And thus the nurse communications were not sent even in as timely a manner as the alerts. And the nurse communications only were sent if there was no medication response in the electronic case report form. But the entry of these medication changes often took days. Frequently, the communication mentioned a change that had already occurred, triggered by knowledge of pulmonary pressures at the site itself.

So here are our concordant medication changes, 85 of them. And you can see there are 75 changes in diuretics and nitrates that were concordant. Let me just please remind you that, all together, during the six-month primary endpoint period, there were 1,068 total changes in diuretics and nitrates that the investigator related directly to knowledge of pulmonary artery pressures. And, therefore, these 75 changes represented only 7% of the total number of changes in medications represented and triggered by knowledge of pulmonary pressures.

Similarly, there were 10 changes in neural hormonal antagonists and hydralazine. All together, triggered by knowledge of pulmonary pressures at the sites, there were 336 changes in medications other than diuretics and nitrates. So these 10 changes represented only 3%

of the total number of medication changes that were other than diuretics and nitrates.

Let me put this into a different perspective. Because of knowledge of pulmonary artery pressures, as an average, an investigator made a change per patient about six times during the six-month primary endpoint period just based on their knowledge of pulmonary pressures. The influence of nurse communications was such that a medication change was concordant only once in every three patients during the entire six-month period. So investigators made changes on their own based on knowledge of PA pressures 18 times more frequently than changes that were concordant with a nurse communication. And we still, by the way, can't conclude that simply because there was concordance within eight days that there was causality.

So having said this, we think that, gee, if the changes in medications that were concordant with a nurse communication represented such a small percentage of the medication changes related to knowledge of pulmonary pressures, it's really unlikely they represented a major influence on the difference in hospitalization rate. If it was 5% of the medication changes, could it have been more than that for all the hospitalizations that we're seeing?

Well, we tried to get an estimate of this, and this is where the FDA, I think, raised questions about the assumptions that we were making.

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And we tried the best we could. You can see in your briefing documents, we used a rather laborious methodology to calculate the number of hospitalizations prevented based on clinical trials. I will spare you all of that and simply say that we determine, based on the results of randomized trials, that potentially these changes would have been capable of preventing only one to three hospitalizations for heart failure. And, remember, at the end of the six-month primary endpoint period, the difference between the two groups was 36 hospitalizations for heart failure, and the end of full randomized access, the difference was 97 hospitalizations for heart failure.

So our conclusion just looking at the nurse communications and looking at the concordant medication changes was that nurse communications potentially influenced a very small fraction of the medication changes that were triggered by knowledge of pulmonary pressure and thus were unlikely to have meaningfully influenced the treatment effect seen in the CHAMPION Trial.

So that represents our first line of evidence. Now we want to go on to our second line of evidence. In this line of evidence, we asked whether there was a meaningful effect of the device without nurse communications, and we did that by focusing on patients who were not the subject of a nurse communication during the six-month primary endpoint period.

In order to do that, let me just take you quickly through the

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methodology that we followed. There were 270 patients in the treatment group, but 99 went through the entire primary endpoint, and their sites never received a nurse communication regarding their care. And what we wanted to do was find a part of this control group that would be similar in all of the baseline characteristics to the treatment group without a nurse communication.

The conventional statistical approach to doing that is a method called propensity score matching. The intent is to create a matching which is so close as it would yield two groups that were so similar as if they had been created by the process of randomization. And just to make sure that this wasn't a fluke, this was done 30 times, 30 iterations, and just to make sure that each of these was, in fact, representative of the data in the database.

After a propensity score matching, all of the balancing requirements were met for each variable. This propensity analysis was led by Dr. Ralph D'Agostino, Jr., who's here and I'm sure would be delighted to answer any questions that you might have about this.

Now, this is how different the groups were if you compared the treatment compared with no communications to the entire control group. But once propensity score matching was achieved, the variance between these two groups was really quite small, and that's the intent of propensity score matching.

So here is the rate of hospitalizations for heart failure in the treatment group without nurse communications. This is the rate in the propensity matched control group, .41 in the control group, .21 in the treatment group, neither group had nurse communications. You can see there's a 48% reduction in risk. The FDA has verified these analyses and has verified the magnitude and significance of this risk reduction.

But the FDA has raised a somewhat different question. They've asked, gee, are the patients who didn't get a nurse communication, are they representative of the whole population? Is it possible that these patients were healthier, that they didn't get a nurse communication because they were healthier? And yes, there was treatment effect in these patients, but were they representative of the whole population?

Well, it's a little bit hard to know that precisely, but let me share with you what we did to try to address this question. There is no doubt that the best way to establish risk in the population is to look at their event rates. And so what we did was we looked at the event rate in the propensity matched control group. Remember this is a control group which is considered to be virtually identical to the treatment group because of the process of propensity score matching. The rate of hospitalizations for heart failure in this group was .41, and this is the rate of hospitalizations for heart failure in the entire original randomized control group, which is .44.

So just based on the similarity of these two numbers, it would

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be fair to say that there's no evidence that the groups that were not the subject of a nurse communication were healthier or at lower risk than those who were the subject of the nurse communication, and therefore, we would conclude in a representative subgroup, knowledge of pulmonary pressures was accompanied by a reduced rate of heart failure or hospitalizations in the absence of nurse communications.

Sorry for the interruption. Much better. I'm now going to present the third line of evidence. Third line of evidence also addresses the question of is there a meaningful effect of the device without nurse communications. We're going to focus on the entire trial, and we're going to specifically focus on periods without a nurse communication. Now, you've already seen this schematic. I just want to remind you again of what it shows so that you can understand the analyses that I'm going to show you in the next few minutes.

In the change from randomized to open access, the treatment group, their physicians continued to have access to pulmonary pressures, but nurse communications stopped. The control group had no access to pulmonary pressures, but then their physicians were given access to pulmonary pressures for the first time. But this was done without nurse communications. And I'm going to show you four analyses that will enable you to separate the effects of knowledge of pulmonary pressures from the effects of nurse communications in looking at the transition from

randomized to open access.

Here's the first analysis. This is an analysis within the control group when it moves from randomized access to open access. Remember these patients, their physicians have new access to pulmonary pressures with no nurse communication. So the question addressed in this analysis is: What's the effect of new access to pulmonary pressures without nurse communications? And here are the rates: .68 in the control group, .36 when they move to open access and have knowledge of pulmonary pressures -- this is a 48% reduction in risk -- and association with the provision of knowledge of pulmonary pressures for the first time.

Now, when you look at these raw numbers, they don't tell the whole story because these are just average rates over a meaningful period of time. So what I want to do is actually show you in a far more granular manner what these rates represent.

So if you look at these curves, these curves represent instantaneous, unbiased rates and risks of hospitalization of heart failure at each point in time during the trial. And this is the rates and the randomized access period. This is the rates in the open access period. Now, I just want to point out that the X-axis here is not calendar time. The X-axis here is days from implantation. And that is the reason that these two curves overlap so that the patients, for example, here during the randomized access period or the patients who entered the trial early, earlier in the trial, and the patients

here in the open access period were patients who entered the trial at the very end of the trial.

Remember the patients began entering open access after the last patient had completed about six months of follow-up. And the first hospitalization for heart failure during this period of time occurred about here. You can see just by looking at the patients at risk how, in fact, they diminish over time in the randomized access period but increase over time as patients enter the open access period.

And so what you're seeing here is all the data. It's not commingled; it's not created with any assumptions. These are the actual instantaneous risks. And you can see that the rate of hospitalization as one moves from no knowledge of pulmonary pressure to knowledge, new knowledge of pulmonary pressure, the rate falls from .68 to .36.

Now, that was our first analysis. The second analysis was, well, if we just maintained access to pulmonary pressures but stopped communications from the nurses, would that change anything? And here are the hazard curves for the transition in the treatment group from randomized open access -- you can see they overlap on top of each other. It's .48 when they had knowledge of pulmonary pressures with communication; .45, knowledge of pulmonary artery pressures without nurse communications. The slopes of these lines are right on top of each other. And so the conclusion from this analysis is maintained access to

pulmonary artery pressures in the absence of nurse communications is accompanied by maintenance of a reduced rate of hospitalization for heart failure.

Third analysis. During open access, the two groups had -- their physicians had similar access to pulmonary artery pressures but no nurse communications. Essentially, during open access, these two groups were pretty similar in terms of what was going on with respect to knowledge of pulmonary artery pressures, and so you would expect that similar access to pulmonary pressures but no nurse communications would result in similar rates of hospitalization for heart failure, and that was what was found.

Here are the instantaneous hazard curves in the control group during -- the former control group during open access, the former treatment group during open access. And these are similar to each other.

So our conclusion was similar access to pulmonary artery pressures in the absence of nurse communications is associated with similar rates of hospitalization for heart failure.

Last analysis. When you look at the transition from randomized to open access in the control group, there is the possibility, and we worry about this possibility, that there may be longitudinal confounders. And so what is important is to compare the change here in this group with the change in this group because this will help us accommodate for the presence of longitudinal confounders that may have been secular to the

conduct of a trial as a whole.

So the analysis I'm going to show you is the delta in this group versus the delta in this group. And here it is. The delta in this group is .52 hazard ratio; the delta in this group, .93 hazard ratio. The ratio of the ratio, so to speak, or the difference of the deltas represents a 44% reduction in rate, with a p-value of .004. It's the only p-value I'm going to show you here because I think this represents the most persuasive of all of the analyses.

Now, the FDA reviewed these and agreed that these longitudinal analyses represented the strongest part of all three parts of our stool, so to speak. But they wondered, gee, you know, baseline covariates weren't assessed at the beginning of Part 2. They worried about differences in study compliance and mortality rates. They wondered if it was really possible to compare these because maybe the patients at the beginning of open access weren't really comparable; maybe the patients during randomized access died or exited differentially. And they wondered whether the groups remained balanced at the beginning of open access.

And they also specifically said, look, you know, there's seven patients with noncompliance here and 10 patients with noncompliance here in the treatment group during open access. This from a percentage point of view represents a doubling in noncompliance, and they worried about that. Let me just emphasize that all of these categories represent in some way under the rubric of noncompliance. These are just different terms to say

that patients didn't follow or complete the study procedures in the protocol. Withdrawn consent, investigator decision, lost to follow-up, these pretty much represent the same things.

So when you consider that as part of the way that studies are conducted, you realize very quickly that the reasons for noncompletion other than death were strikingly similar across groups and across time. About 16% of the patients during randomized access didn't complete for reasons other than death, similar across treatment in the control. About 13 to 15% didn't complete during open access, similar between treatment and control. And if you look at this as a function of time, this is the cumulative hazard curves. And you can see the reasons for noncompletion other than death are similar, overlapping during the entire duration of follow-up in the treatment and in the control groups.

Now, what about mortality? Here, the mortality rates --

DR. PAGE: I'm going to interrupt for just one minute to just make a time check. We have 18 minutes left, and I just want to remind the Sponsor that we have 90 minutes total, and your completion and Dr. Stevenson's and the wrap-up need to be completed at 90 minutes. I'm sure you've rehearsed this. Maybe my reminder is unnecessary, but I just want to remind you of that.

DR. PACKER: And you can see the difference in -- here are the death rates. And you can see -- you know, it's really interesting. When

physicians were given access to pulmonary artery pressures for the first time, the mortality rates were a little bit lower. Here, during open access when physicians were given access to pulmonary pressures for the first time, the rates were a little bit lower. Gee, one would love to say that this indicates there's a beneficial effect on mortality, but we can't say that. These number of events is really small. The differences are small.

And, in fact, if one looks at the characteristics of noncompletion in the control and treatment groups during the entire period of randomized access regardless of how we look at this, the exiting of patients during randomized access was similar in the two groups, and the type of patients who exited during randomized access, their actual rate of hospitalization for heart failure in noncompleters was similar in the two groups.

And that's why when, in fact, the Sponsor made an effort to actually look at the clinical characteristics of the patients at the start of open access, to the best of their ability, they were able to show that for all of these variables, 177 patients in the treatment group, 170 in the former control group, no difference in these covariates and no difference in these covariates. Let me just emphasize quickly that these covariates that have an asterisk were updated by the Sponsor after the PMA amendment was submitted, so they have not been formally submitted, have not been reviewed by FDA. But all the other data were in the FDA amendment.

So here is, I think, the fourth analysis, the summary of the fourth analysis, the one that accommodates for longitudinal confounders. And now you may ask just what would happen if we took this key analysis and adjusted for covariates, because that's what you would want to do to make sure that differences in covariates didn't affect the results. And this is what we found. Here is the original model. It has a frailty term to try to accommodate for unmeasured covariates. But here's the covariate adjusted model. You can see whether you adjust for covariates or not, the differences are not meaningfully different. It's pretty much the same.

So that's why these curves are so interesting. You'll notice that these curves actually show you the exiting of high-risk patients. Look at these curves. You can see that there is a slight, gradual, progressive decrease in the risk of hospitalization for heart failure, as patients with higher risk exit from the trial. It's a gradual slope both in the control group and a gradual slope in the treatment group. When the treatment group moves to open access, that slope is maintained. But look what happens in the control group. This sudden drop in the rate of hospitalization of heart failure is not related to an attrition of high-risk patients. This sudden drop is not the maintenance of the same slope. There is something else going on here. And the only reasonable explanation is that this represents the effect of new access to pulmonary artery pressures.

Let me just illustrate this in one additional schematic. Here's

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the attrition rates in the control group and the treatment group during randomized access. If one then superimposes the curves during open access and adjusts them for the rates of hospitalization seen at the end of randomized access at the time when the first patient in open access had a hospitalization for heart failure, you can see exactly what you might expect. The two groups divergent during randomized access converge during open access as knowledge of pulmonary artery pressures brings their rates of heart failure and hospitalization together again.

Let me just emphasize for the record, it doesn't matter where you would merge these curves. The finding of convergence would be the same.

So three distinct lines of evidence, you can see them here. Let me just conclude for you what we were able to find. Number one: Nurse communications infrequently coincided with a change in medication and thus could not have meaningfully contributed to the observed treatment effect. Two: Treatment group patients who were not the subject of a nurse communication had a significantly lower rate of hospitalization for heart failure than the propensity score matched control group. Three: New knowledge of pulmonary pressures without nurse communications was associated with a reduced rate of hospitalization for heart failure, which could not be readily explained by longitudinal confounders.

Three distinct lines of evidence -- by the way, each with their

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own limitations, each with their own caveats. But the limitations of each of these are different. The caveats are different. And yet all three, in fact, point to this same finding. And that finding is, in fact, very, very consistent with the primary prespecified endpoint. I have a fondness for primary prespecified endpoints. And this trial met its primary prespecified endpoint. And what we saw in the ancillary analyses is highly consistent with what we see here.

The FDA, in its briefing document to you, concluded it is important to consider the totality of effectiveness data presented although each analysis on its own has its flaws and limitations. The consistency of these results, with three distinct, non-overlapping lines of evidence are notable and should be considered when assessing whether the CardioMEMS device is effective. All of these, together with the primary endpoint, are highly consistent with device efficacy.

I'd like to turn the podium over to Dr. Lynne Stevenson who will present a clinical perspective of the data.

DR. STEVENSON: Thank you very much. I greatly appreciate the opportunity to present today the overall clinical relevance of this program. I have no financial relationships with any industry. I receive no compensation for my time or reimbursement for my travel.

As someone who takes care of heart failure patients every day, I'm here because I need help taking care of them. As we face the epidemic

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of heart failure in an aging population, we're ready for a new strategy to monitor and manage our patients as they go about their daily lives at home.

We've changed the landscape of heart failure as disease progression has been decreased with proven medical and rhythm device therapies. However, once a patient has been hospitalized for heart failure, most symptoms and rehospitalizations relate to congestion, which is elevated filling pressures. Our immediate inpatient goals during hospitalization include relief of congestion. After discharge, the first outpatient goal is to prevent rehospitalization and then, over the longer term, optimization of proven therapies to decrease disease progression. But in order to do this, we have to be able to maintain optimal filling pressures.

At initial heart failure diagnosis and during serial evaluation throughout the life of the patient, a Class I recommendation is that volume status should be assessed. Currently, when the patient is in front of us, we do this by looking at the venous pressure, peripheral edema, each of us has a couple other tricks, and we ask about orthopnea and symptoms. Then at each clinic encounter, we adjust our therapies to treat any evidence of rising filling pressures and to move towards target doses of the newer hormonal therapies. But rehospitalizations remain high, over 20% in the first month and up to 50% in the next six months.

With all the clinical assessment and biomarkers we have now, why can't we monitor patients well enough to intervene and prevent more

of these hospitalization? Well, maybe if we could examine our patients every day, we could prevent more of these rehospitalizations. However, on most days, we don't see the patients in heart failure clinics. We don't see them in device clinics. We don't see them anywhere because they're at home.

And when we can't see them in front of us, we need to find the right signal to follow them at home. This signal has to reflect the physiology that leads to hospitalization. And it's not just enough to get a signal that something bad is going to happen. What do we do with that? The signal has to guide us into action of how to prevent it, which is usually to reduce the filling pressures. But getting the signal still isn't enough. The signal has to respond fast enough so we can reevaluate them at home to see when we need to do further intervention to avert hospitalization.

What is the best signal from patients at home as congestion recurs? I used to be one of the most ardent advocates for the daily weight drill. Two pounds of increased weight in two days, you double the diuretics. 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 early after discharge.

We thought weights worked because we underestimated how often patients lose real body weight and gain fluid because the hepatosplanchnic congestion decreases their appetite and gives them poor

nutrition, but then the weight doesn't change. Now, it's certainly true that when we can't see our patients and they're at home, weight-guided management is much better than nothing, and that's why it's part of the control arm of all management strategies, as it was for this trial. But we have overestimated its reliability. And when the signal from the weight-guided management wasn't working, we blamed the patients or we gave them scales with bigger numbers or we gave them scales that talk.

Well, how about if we actually do the scales and symptoms more often and do it every day? This was tested very rigorously by the Yale research group in a large NIH Tele-HF trial. Although we've tested many patients in many similar trials of intensified contact, this is the largest example of the failure of more frequent contact to change the outcomes. 826 patients were randomly assigned to the telemonitoring arm with daily weights and symptom communication. There were nearly 30,000 direct calls, a median of 21 per patient in a six-month period. But even this intensive intervention did not change the combined endpoint of death and hospitalization or heart failure hospitalizations, equally high in both groups. So something is missing from this monitoring strategy, and perhaps it's the right signal.

The European trial, the TIM-HF, showed exactly the same negative result when managing patients by intensification of reporting of weights and symptoms, 50% rate of all-cause readmission and death.

We learned a great deal about these events from the COMPASS Trial of implantable hemodynamic monitoring. In this trial, the strategy for control patients did include careful weight management, and the overall weights did not increase consistently prior to events. On the other hand, as you can see in the graph of the right side, the right ventricular pressures rose consistently prior to heart failure events.

Many other studies in heart failure have been done since the CHAMPION Trial began. Several have been done by the national Heart Failure Network with the NHLBI. But these trials have not made any progress on how to take care of patients who are at home.

This is new data recently presented from a post hoc analysis of the DOSE and CARRESS Trials from the network of patients hospitalized with decompensated heart failure. Now, this care, it's as good as it gets. Eight academic centers with dedicated heart failure specialists, dedicated research nurses following patients closely with a specific focus on congestion.

This pie shows the outcome over the 60 days after discharge for patients who were free of clinical evidence of congestion at the time of discharge. So even during a short period of 60 days, only 35% of patients shown here in the blue part of the pie stayed free of clinical congestion. The remainder showed either moderate or severe relapse of congestion.

Even what should be the most experienced and dedicated care is not good enough. We don't have the tools in our hands now to maintain

freedom from congestion even early on when contact is intensive.

Now let's review the CHAMPION results in the context of the current evidence-based treatment strategies for heart failure, including drugs and devices. Remember that the CHAMPION Trial was tested in the background of all of these currently recommended therapies. It provides additional benefits on top of that. The relative risk reduction in CHAMPION is similar to that achieved with the primary therapies of beta blockers and ACE inhibitors.

In the current trial population of CHAMPION, Class III patients with recent hospitalization, it was four patients needed to treat to prevent one heart failure hospitalization.

The next slide depicts this impact in a bar graph, an impressive potential to decrease hospitalizations on top of all the other standard therapies we have.

Is this a benefit limited to academic centers? This shows that the 61% of centers that were in the community had just as much benefit as in the 39% of academic centers with very similar risk reduction.

We've become exquisitely sensitized to the national problem of heart failure readmissions at 30 days. As you know, this includes all-cause hospitalization, both heart failure with low ejection fraction and preserved ejection fraction. This readmission rate is in the range of 20 to 25% across the country. We have looked at the 30-day readmission rate for heart

failure hospitalizations during the randomized portion of the CHAMPION Trial. Although the CHAMPION population doesn't necessarily represent all the heart failure in the country, it studied both low EF and preserved EF, and it is notable that the all-cause rehospitalization rate in the control arm is 23%, comparable to the national average. The 30-day all-cause rehospitalization in the treatment arm was only 14%.

Looked at in totality, the potential impact of pulmonary artery pressure monitoring as performed in this trial is consistent and large. Regardless of whether we look at heart failure hospitalizations alone, all-cause hospitalizations or all-cause hospitalizations and death, reduction of 29 events for every 100 patients treated.

With the management program designed for CHAMPION, we improved outcomes because this signal-driven strategy hits right at the fundamental physiology of heart failure once it progresses despite neural hormonal antagonists. It's easy to deliver better care in the light when we have the tools to see what we're doing.

We will learn much more about how to do this better as we gain experience with this strategy, but this is not just another stack on therapy for heart failure. The reason I'm here today is that when I look ahead, I believe this strategy has the potential over time to change heart failure, not just to lighten the burdens every day or to decrease the number of hospitalizations, but to decrease the grim progression to right ventricular

failure, the grim progression to cardiorenal syndrome, which affect all low EF and heart failure with preserved EF.

I believe that we can work together to reshape the entire landscape of heart failure. We're not there yet, but we have the right signal to follow.

As we enter the era of pulmonary artery pressure monitoring to improve the life for our patients with heart failure, I believe that we've now come to the end of the beginning.

And now I'd like to reintroduce Dr. Yadav to summarize.

DR. PAGE: And, Dr. Yadav, you may have already been aware of the yellow light by our 90-minute timer. We only have a minute and a half. We can grant you a few extra minutes, but we do ask you to keep it within the predetermined period of time as best you can.

DR. YADAV: No problem, Dr. Page.

DR. PAGE: Thank you.

DR. YADAV: You heard from the important speakers. I will wrap up very quickly.

Thank you, Dr. Stevenson, for that clinical perspective. In summary, the CHAMPION Trial met its efficacy endpoints as well as safety endpoints and further demonstrated a meaningful reduction in all-cause hospitalizations and mortality.

The concerns raised by the FDA in its review have been

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addressed. When the competing risk of death is considered, there is no treatment by gender interaction, and during the totality of the trial, we can see a benefit in women comparable to men.

The different lines of evidence presented by Dr. Packer are concordant and demonstrate that we can distinguish the benefit of the device from nurse communications; that the nurse communications could not have had a meaningful impact on the primary endpoint; that in patients who were never the subject of nurse communication, there is a meaningful reduction in heart failure hospitalizations; and that in periods where there are no nurse communication, there is a meaningful benefit of the device.

We have shared with the FDA and with you a draft study outline. This is a draft. We are fully committed to a robust post-approval, with a large sample size of 1,200 patients, a long duration, and adequate power to address various subgroups of interest. We would also look at compliance as well as the training and education program.

In conclusion, the magnitude, consistency, and durability of the evidence provide reasonable assurance of device safety and effectiveness. Further, the favorable benefit-to-risk profile as well as the clinical utility and significance discussed by Dr. Stevenson are supportive of the approval of this PMA.

We thank you for your time, and we'll be happy to address any questions.

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DR. PAGE: Thank you very much. I appreciate the very clear presentation from the Sponsor. It's now time to ask the Panel whether you all have any brief clarifying questions for the Sponsor. Please remember that the Panel may ask questions during the Panel deliberations as well. So right now, it's just brief clarifying questions with regard to the presentation.

I see Dr. Cigarroa and Dr. Yuh and Dr. Borer and Dr. Blumenstein, in that order. Dr. Cigarroa?

DR. CIGARROA: So, again, for the Sponsor, this is a particular question on a point of clarification during the open access period. The issue or the potential for longitudinal confounders was raised. There is a lot of information during the randomized access period on the number of symptom-related changes in medications as opposed to pressure sensor-triggered changes in medications.

Can you comment during the open access period with regards to the control and treatment arms with regards to the number of pressure sensor-triggered changes, respectively, and symptom-related changes in medications?

DR. YADAV: Thank you, Dr. Cigarroa. The open access study was designed to mirror a real-world application, and data was gathered on all adverse events, but the sites were not required to fill out the same CRFs as in the randomized access regarding the details of their care.

DR. CIGARROA: Thank you.

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DR. PAGE: Dr. Yuh?

DR. YUH: Yes. Thank you very much for a very clear presentation. Dr. Packer, I wish I had you in my medical school, a very clear, clear presentation.

I didn't have the benefit of being around at the first meeting with this Panel, but do you have PA pressure data after any medication changes prompted by the CardioMEMS device was acted upon? In other words, I'm trying to see if there was actually an effect of knowing what the PA pressures were in guiding medical therapy. Do you have any data with respect to that?

DR. YADAV: Thank you, Dr. Yuh. And I think Dr. Adamson can help answer that question.

DR. ADAMSON: It's hard to answer that question from an individual perspective, but we did, as part of the steering committee, have a great interest in that concept. So one of the secondary endpoints of the trial was were pressures at the end of the trial, when we were guided by pressures, were those pressures lower, and they were significantly lower in the treatment group compared to the control group.

So, in individuals, pressures do track medication changes, but I don't have that quantified.

DR. YUH: Do you have any slide or do you think you could prepare a slide perhaps over lunch that might show that data? I mean, I'm

just interested if indeed the effect of this device is to guide medical therapy, that you should see a decline in PA pressures at the individual level after the device prompts a doctor to change the medications. Otherwise, if you don't see that, is there some other effect that the device exerts?

DR. ADAMSON: So we can provide you with information after lunch break. But again, in individual patients, we do see changes that respond to medical therapy, both diuretics as well as vasodilator therapies.

DR. ZUCKERMAN: Okay. To make the request more specific, Dr. Yuh, are you looking for a slide like 121, which instead of showing data from the COMPASS Trial just shows data possible from the CHAMPION Trial?

DR. YUH: Yeah, something along those lines would be helpful.

DR. YADAV: Yeah, well, certainly. We can certainly show you -- this was a secondary endpoint. We could put up Slide 381. And this is for the overall population. And certainly this would mirror what would happen in an individual patient. We can try to get you some patient examples, but this is for the overall population. One sees that the pressures are reduced over time in the treatment group versus the control group. Thank you.

DR. PAGE: Dr. Yuh, does that satisfy your question, or are you still looking for more details in terms of patient-related response?

DR. YUH: It really doesn't because it just shows an aggregate decline in PA pressures. It doesn't show individually -- I mean, it doesn't show -- it's not convincing to me enough.

DR. PAGE: So, ideally, what you'd be asking for is to know the pressure before and then after intervention based on the pressure to see whether there was evidence that the pressure actually dropped in response to the intervention?

DR. YUH: Exactly, exactly. And as a corollary, you know, you had access to PA pressures before the readmissions. Were they elevated? I'm just trying to establish a direct cause and effect with respect to the device.

DR. YADAV: Right. I think we can share with you -- I think what you're looking for really is case studies and examples, and we're happy to share them. We have lots of those.

DR. PAGE: Dr. Cigarroa, did you have another comment on this very issue?

DR. CIGARROA: I do. So to follow up on that, we certainly know that the correlation between PA diastolic pressures and pulmonary capillary wedge pressure and the absence of pulmonary hypertension correlates well, and they're typically within 5. As mean PA pressure rises, the correlation between the PA pressure and LV preload certainly begins to fall apart. So along those lines, it would be interesting if you separate it by degrees of pulmonary hypertension because I think that in individuals who have minimal elevation in PA pressures, there may be something observed that may be distinctly different than the presence of moderate or severe

pulmonary hypertension.

So if, in fact, it can be broken down accordingly, that would be extremely useful.

DR. YADAV: Thank you.

DR. PAGE: Thank you. Next is Dr. Borer.

DR. BORER: Thank you. I actually had two questions, but one of them has just been dealt with extensively. So here's a minor one. I'm not even remotely suggesting that this -- after all the data that were presented on the post hoc analyses would alter my conclusions about the nurse interventions, but just as a detail, since we're going to be asked to draw inferences based on basically incomplete data, good data but incomplete data, my recollection was that it wasn't a matter of nurse practitioner or study nurse suggestions alone, but the study nurses regularly went to a doctor before they gave their recommendation, particularly in complicated situations. And the doctor was the PI. So these patients had the benefit of advice from one of the finest heart failure doctors in the world. Now, the numbers seems so small that it probably doesn't make any difference anyway. But I just want to know for sure was it the nurses alone or was it -- is my memory correct that it was the nurses plus in some cases the doctor?

DR. YADAV: Thank you, Dr. Borer. Is the finest heart failure physician in the audience or -- just joking. Which one? Dr. Abraham?

DR. ABRAHAM: Yeah, I think the most direct answer to your

question is that it was the nurses acting alone. This was, you know, in fact, I think, some misunderstanding, although a flattering one, for Dr. Adamson and I in the initial panel, when we were given great credit with having been involved in many of these communications. But the reality is that we were not.

DR. PACKER: Jeff, can I just clarify since I'm the one that actually looked at nurse communications. I know you're suggesting that perhaps every one of these medication changes was discussed with Bill Abraham or Phil Adamson -- by the way, I wouldn't want that job if that were the case. One, that wasn't the case. Two, the nurses did not make prescribing decisions. The nurses at the sites received the nurse communications and discussed it with the local PI who made that decision based on all of the available data, clinical status, lab, physical findings, et cetera, without discussing it with anyone at CardioMEMS. So that is a very important point. This was a physician-driven decision at the local site without a communication back to CardioMEMS.

DR. PAGE: Thank you. Next I saw Dr. Blumenstein.

DR. BLUMENSTEIN: Yes. I'm going to ask for four clarification displays of data, some of which might be shown now, some of which you might work on later.

I would like to see the distribution of the length of hospitalizations for both arms and a comparison between the arms of those.

A subpart of that is how is it that you computed the rate when a hospitalization prevented a further hospitalization? In other words, were the rates computed taking into account the time the patient wasn't available to get a hospitalization because they were hospitalized?

The second question is how many events per patient? I would like to see the distribution of the number of patients that had only one event, the number of patients that had two events, and so forth.

I would like to see a Kaplan-Meier graph of heart failure free survival with tick marks instead of those confusing numbers down at the bottom that are hard to interpret; that is, tick marks for censoring.

And, finally, I would like to see Kaplan-Meier -- the same Kaplan-Meier for the propensity score matched subsamples with tick marks.

DR. YADAV: Okay.

DR. ZUCKERMAN: So, Dr. Blumenstein, for your requests one and two, do you want them separately demarcated for Parts 1 and 2 of this trial?

DR. BLUMENSTEIN: I'm really interested in Part 1.

DR. ZUCKERMAN: Just Part 1?

DR. BLUMENSTEIN: Yeah.

DR. YADAV: Thank you, Dr. Blumenstein. We'll work on that and get that to you after lunch.

DR. PAGE: Thank you. When we wrap things up, I may ask you

to summarize those specifics in case I didn't get them just right,
Dr. Blumenstein.

Ms. Currier had a comment or question?

MS. CURRIER: Yes. Thank you. I was interested when you insert the device, the CardioMEMS device, you do a right heart cath. Do you then check how the device works in relation to the CardioMEMS? In other words, do they get the same pulmonary pressures?

DR. YADAV: Yes, thank you, Ms. Currier. Yes, that's exactly what is done. The device is calibrated with respect to the right heart catheter at the time of implant.

MS. CURRIER: Okay. And do you check it every checkup later to see whether the pulmonary pressures it's sending are the same as what you would get with the right heart cath?

DR. YADAV: Yes. That was done in the feasibility study of 50 patients, and every patient had a mandatory right heart catheterization. And that provided the stability data which allowed us to do the CHAMPION randomized trial. So that data was shared with the FDA back in 2006 and was found to be satisfactory.

During CHAMPION, there were many examples, I think almost 100 of patients having repeat right heart catheterizations for clinical reasons, which gives an additional opportunity to look at sensor stability, and it was very stable.

MS. CURRIER: Thank you.

DR. PAGE: Thank you.

I've seen Dr. Lange, Dr. Weisfeldt, Dr. Blumenstein again, and Dr. Ohman. I'll remind the Panel -- and Dr. Jeevanandam. I'll remind the Panel that we will have time to ask questions after -- during our further discussion period. I might ask you to focus on if there are specific homework areas that we need to address now because those are -- that's an opportunity I don't want to miss out in this pre-lunch interval.

Dr. Lange?

DR. LANGE: Thanks for mentioning the 100 patients that had repeat cath. If you could show that data for stability in this patient population and the timing from when their implant was to when the cath was done, that would be terrific.

DR. YADAV: Sure. We can certainly do it, thank you.

DR. LANGE: I just have one clarifying question. Back on Slide 14, it looks like there were 32,000 automated alerts that would indicate that the pressures were elevated?

DR. YADAV: Um-hum.

DR. LANGE: And go to Slide 17 -- I just want to make sure I understand it. We can talk more about it later. I just want to make sure I understand --

DR. YADAV: You would like Slide 17 now?

DR. LANGE: Yes, sir.

DR. YADAV: We got 28 now.

DR. LANGE: I'm sorry. Slide 34. My apologies, my apologies.

DR. YADAV: Right, the medication changes?

DR. LANGE: Yeah. So those --

DR. YADAV: Thank you.

DR. LANGE: So 1,400 medication changes?

DR. YADAV: Yes.

DR. LANGE: And when those were made, by the way, the comment was made that they were made on the basis just of PA pressures. That is, nobody contacted the patient to find out if they had symptoms? In other words --

DR. YADAV: Correct.

DR. LANGE: In other words, somebody just made a medication change without finding out whether the patient had symptoms or not?

DR. YADAV: Well, remember, it's the patient's physician making these changes, so --

DR. LANGE: Right, but the comment was made is that these are based only on knowledge of the PA pressure, not symptoms --

DR. YADAV: Right.

DR. LANGE: So the physician got the PA pressure and did not contact the patient to find out whether they had symptoms or not?

DR. YADAV: Well, I'll let Dr. Abraham address it in more detail --

DR. LANGE: Okay.

DR. YADAV: -- but just in terms of methodology, there's a CRF that the sites filled out, and one of the boxes they had to fill out was the reason for the medication change, the primary reason, not the only reason, so you're right, this may be a little misleading. It's just the primary reason. So I'm sure they considered other information also, but Dr. Abraham can address that.

DR. PAGE: Dr. Weisfeldt?

DR. ABRAHAM: Yeah -- oh, would you like me --

DR. PAGE: Oh, I'm sorry. Please go ahead if you have --

DR. ABRAHAM: No, I just wanted to further address this question. So remember that the CHAMPION Trial was designed as a single blind study, so we made sure that the interactions between study personnel and the patient were scripted, and we also made sure that we equalize the number of interactions. So, you know, the script, if there was a prompt for a medication change, and we may be able to show you the exact language for that script -- I don't have it in front of me right now -- but when something like, you know, based on the available information that we have now, which could be symptomatic, could be clinical, could be knowledge of PA pressures, here is what we want you to do. And so we did, in fact, there was

an interaction with the patient. It may have included some discussion of symptoms that went on in the control arm as well as in the treatment arm.

DR. PAGE: Thank you.

Dr. Weisfeldt?

DR. WEISFELDT: I guess continuing that line of questioning, can you define how communication did occur between the nurse and the physician? Was this all electronic or was it recorded? How was this audited, and from my remembrance of the first panel, there was very considerable concern about advice in the treatment arm that didn't have to do with medication but had to do with other aspects of the proper management of patients with heart failure.

DR. YADAV: Thank you, Dr. Weisfeldt. I think perhaps Dr. Packer, since he reviewed all these communications, can address that.

DR. PACKER: JoAnn Lindenfeld and I looked at every one of these communications, and we reviewed them independently of each other. These communications -- and let me just make sure that this is clear -- that these communications were part of routine compliance measures. The communication went from a CardioMEMS nurse to a nurse coordinator at the site, not the physician, a nurse coordinator at the site, and the nurse coordinator then would, you know, sometimes respond, sometimes not. By the way, we were given the entire record of the communications. So we not only got the nurse communication going forward, we got the local nurse

communication coming back.

And so, one, no direct communication in 99% of cases with the PI. It was to the coordinator. The coordinator then had to either respond, make a judgment whether he or she was going to talk to the PI about it. As you can see, a lot of these were, like, you know, not responded to at all. The total "advice" regarding patient management only focused on medication. Nothing else. It wasn't focused on, gee, gee, it would be nice if this patient could exercise more or could -- it was not general advice about the treatment of heart failure.

The only thing that happened during the trial that was interesting was there was a belief on the part of the PIs that maybe if someone had sleep apnea, that it should be diagnosed and treated, but that advice was given to both treatment arms. And by the way, almost no one listened to it.

DR. PAGE: Thank you.

Dr. Blumenstein?

DR. BLUMENSTEIN: Yes. I'm wondering if you attempted to do a Cox proportional hazard model with time-dependent covariates when you combined the data from your randomized clinical trial and your descriptive convenience sample analyses from the open access period?

DR. YADAV: Dr. Holcomb, do you want to address that or do we need -- could you repeat the question? I want to make sure I understand

it.

DR. BLUMENSTEIN: Right. I'm wondering if you attempted to do a Cox proportional hazard regression modeling when you combined the data from your randomized plus the open access portion of the data.

DR. HOLCOMB: Yes. In fact, the Cox proportional hazard model was the model chosen with the Andersen-Gill modification. The primary model included covariates, and covariates were not included in the traditional time-dependent manner but were included by period. So, in effect, they were adjusted by changes in their value from the randomized period to the open access period.

DR. BLUMENSTEIN: Well, the reason I'm prompted to ask this was that I'm -- it wasn't clear whether it was the same patient who may or may not have had an event in the random access period who was then subsequently in the model or whether that patient was considered to be a different patient.

DR. HOLCOMB: No, the patient identity was preserved throughout the model. So the covariates were updated on a patient-specific basis. So events were tracked by model. The identity of the individual patients were associated with the covariate values.

DR. BLUMENSTEIN: So you were looking at the change in the hazard ratio as a result of, say, a change in treatment status; is that correct? Is that the way I'm understanding it?

DR. HOLCOMB: The actual specification of the model, I believe, is in the briefing book, and it includes variables that indicate the period, they indicate the treatment group, they indicate a frailty parameter, and then covariates as a matrix associated with each of the individual patients so --

DR. BLUMENSTEIN: But these are baseline covariates?

DR. HOLCOMB: These are baseline covariates for the randomized period updated for the open access period when that updated information was available. Otherwise, left value from baseline carried through. So there were a few covariates for which there were not updated values, but the original baseline values were used for those, and those covariates that could not be updated were relatively few in number.

DR. BLUMENSTEIN: Okay. Thank you.

DR. ZUCKERMAN: Okay. Dr. Holcomb, could you just stay there a moment just for -- to help us all out. Were you just discussing the Andersen-Gill models from Slide 105 in that discussion?

DR. HOLCOMB: The Andersen -- let me put up Slide 149 -- 105? Yeah, this is the results of the analysis. Slide 149 actually has the specification for the model that we used, and this, I believe, was in your briefing materials. Can we put up 149? This is the actual expression of the model that we used. So this is what I was trying to describe.

DR. ZUCKERMAN: Sure. So it used time-dependent covariates,

and you used Andersen-Gill to look at repeat hospitalizations for each patient to try to do your best here? Is that a summary?

DR. HOLCOMB: That's a very good summary, yes, thank you.

DR. PAGE: And I might ask Dr. Blumenstein to explain this slide to the rest of us a little bit later as we need to address it during our discussion.

DR. HOLCOMB: Um-hum.

(Laughter.)

DR. PAGE: We are past the time for our break, but I want to make sure that any further clarifying questions are addressed. And we have four people in line, and we have Dr. Zuckerman who wants to make a comment.

DR. ZUCKERMAN: Okay. Question for Dr. Stevenson later. On Slide 125, you showed us some preliminary evidence that academic center versus community center was not an important covariate for getting a good result with this pressure monitoring system. Have you specifically looked at what are the predictors of good results, which sites did well and not and what are key variables? And even with respect to this slide, there's no estimate of variability so that even though the means look similar, how much variability is there, and so forth?

DR. PAGE: So, Dr. Zuckerman, are you asking for that to be addressed after the break during discussion period, or do you want --

DR. ZUCKERMAN: After the break, just to better understand how these results could potentially be generalizable in a real clinical context.

DR. YADAV: Thank you, Dr. Zuckerman.

DR. PAGE: Thank you. The questions I have, people on deck, are Dr. Ohman, Dr. Jeevanandam, Dr. Patton, and Dr. Cigarroa.

Dr. Ohman?

DR. OHMAN: Yeah. I want to follow up on Dr. Blumenstein's comments. It's very important for us to see the covariates that you used in the analysis.

DR. YADAV: Sure.

DR. OHMAN: So like, I like the statistical modeling, but I need to see what variable went into it to sort of clarify this piece about the covariate analysis during Part 1 and Part 2 of the study. So that was the first thing.

The second thing is it's traditional when you do Andersen-Gill modeling or Andersen-Gill analysis that you actually present the raw data first so you can understand the frequency distribution of repeated hospitalization so you can better understand those. And you can do that later, in the importance of time.

DR. YADAV: Okay.

DR. OHMAN: But it's important for us to understand.

DR. YADAV: Sure.

DR. OHMAN: Is it one versus two or is it -- you know, what is the frequency?

DR. PAGE: Dr. Jeevanandam?

DR. JEEVANANDAM: So having been part of the first panel, I will say that this is -- was a very nice presentation. You guys did a great job of auditing back into those communications, because the first time around, those communications were a little nebulous, right? We felt we had cheerleaders that were leading the patient towards not being admitted as opposed to just medical therapy.

Having said that, a couple of questions. In terms of these communications, I don't think his question was actually answered in terms of what actual communications occurred. Were they e-mail, were they text, were they voicemail, were they telephone conversations? And were each one of these actually documented?

I think I would want to have that --

DR. YADAV: I can answer that now if you'd like.

DR. JEEVANANDAM: Okay.

DR. YADAV: Thank you, Dr. Jeevanandam. Yeah, so there were -- the vast majority were e-mails, and there were some telephone calls, but most of the telephone calls were documented in an e-mail. There were logs of the telephone calls, both CardioMEMS as well as the sites, which were audited by Becker.

DR. JEEVANANDAM: Okay. So in other words, all communication whether they were in any form were documented and audited?

DR. YUH: Yes. And indeed Becker audited all communications, so there were thousands of communications. Literally, every communication whether written or verbal was audited by Becker. So it was a far larger set than the nurse communication set actually.

DR. JEEVANANDAM: So my other question is when you -- if you look at page 28 -- I guess it's Slide 56 -- you know, it says that there's only 500 PA pressure nurse communications. Yeah, it's a small number, but that's a very important number because those are the numbers where you had abnormalities that weren't being acted upon, right, so that's a select number.

And it's later said that there was a concordance of 10%, so that is that there were high PA pressures where the nurse actually talked to the physician and there was a change in management? I think that's what you're saying of about 10%. So what would happen to the analysis if those 10% -- we just assume those 10% would lead to an admission. Was there still difference in that control arm versus the treatment arm if you assume that those 10% were things that we would miss going forward, because there wasn't a nurse?

And my last comment is if that was going to occur, why can't

the patient be alerted to an abnormal PA pressure and they could contact their physician because, you know, if those 500 events -- those were physicians who knew the result or they didn't go into check the result, but theoretically, they were alerted to it, and they were not acting on it. If you tell a patient, hey, your PA pressures are elevated and you need to be acted upon, I suspect that they will force their physician to at least address it.

DR. PACKER: I certainly hope not.

DR. JEEVANANDAM: It happened 500 times.

DR. PACKER: Not -- I'm all in favor of patient empowerment, but can you imagine a patient having a device that reminds them every time their PA pressure is elevated and they --

DR. PAGE: Dr. Packer, I'm sorry. Right now this is question and answer --

DR. PACKER: Okay.

DR. PAGE: And unless there's a specific answer to a specific question he had, we'll save this for the discussion --

DR. PACKER: I want to answer your question.

DR. PAGE: -- as we ask further -- for further comments. Is there a specific question, Dr. Jeevanandam, that you asked --

DR. PACKER: You did ask a specific question, so let me give a specific answer --

DR. PAGE: I'm asking Dr. Jeevanandam did he have a question

that is as yet unanswered.

DR. JEEVANANDAM: Yes.

DR. PAGE: Please state that for us and then Dr. Packer can address it.

DR. JEEVANANDAM: It stated here that there was a 10% concordance of where the nurse recommended an action and the action was taken. And let's say at a worst-case scenario, those things prevented readmissions. What would happen to the analysis if we assume those things would cause readmissions and we took those out?

DR. PACKER: Let me just say one thing. You did ask one other question, which is an extremely important premise, which is that there was something special about the PA pressures with these nurse communications. The answer is no. For all of the PA pressures that got nurse communication, there was also a PA alert, and there were logins. These PA pressures were not higher. They weren't more special. They didn't precede a hospitalization. These were PA pressures that had only one characteristic, and that is that the site had not filled in the medication part of the case report form. So if a site did fill in the medication part in a rapid manner, no communication. If the site didn't, sometimes there was a communication, sometimes there wasn't. But the level of PA pressure in the -- for the nurse communications wasn't anything different than the other PA pressures. So that something very, very important clarification.

Second is these -- and that's why these nurse communications didn't trigger -- even if you say that every single one of the concordant changes were triggered by a nurse communication -- and by the way, we -- as you could see in the document, that seems very unlikely. Just the background changes in diuretics and nitrates would make concordance within eight days likely by chance alone. So the concept that each of these nurse communications actually triggered a medication and that each of these medications was somehow special from all the others and each of these would prevent a hospitalization is just not an accurate description of what happened in this trial.

DR. PAGE: Thank you.

DR. YADAV: Could I just add one comment, Dr. Page, to that last -- it'll be very brief.

DR. PAGE: Again, we're going to have --

DR. YADAV: Okay.

DR. PAGE: -- plenty of time for back and forth. Right now they're brief clarifying questions.

DR. YADAV: Thank you.

DR. PAGE: If I may, I promise we'll have an opportunity to discuss this, I'm sure.

DR. YADAV: Thank you.

DR. PAGE: Dr. Patton?

DR. PATTON: These are questions for after lunch. One of them is that I'm struck by, like Dr. Lange, the differences between Slide 28 information and the information on Slide 34, and I'm curious how four alerts per week translate into an average of one medication change a week. And I'm wondering if you have any data on what the PIs found to be actionable and non-actionable levels of alert, like, why did they change when they did, and why did they not change when they got these alerts?

And the second question I have is in our packet, you had information on medication doses, and whether you have information on medication dosages over time for the two groups. And I think that was it for my quick things.

DR. YADAV: Okay. Thank you.

DR. PATTON: Oh, and more information on your device-related complications. You mentioned that you had eight, but not what they were and how you followed those over time, too.

DR. YADAV: Sure. Thank you.

DR. PAGE: Just so that I'm clear, Dr. Patton, did you have specific further analysis that you're hoping for them to bring or just to have them discuss these issues?

DR. PATTON: I think the first one would be specific analysis if they have it.

DR. PAGE: And can you restate that for us, please, because

I'm -- we've got a list, and I hope someone else is keeping track of all of these bits of further information that we're requesting.

DR. PATTON: The first is whether you have information on what levels of PA pressure changes resulted in an action with respect to the PI's decision making or not action.

DR. PAGE: Is that question clear, Dr. Yadav?

DR. YADAV: Well, maybe -- can I try to address it a little bit here?

DR. PAGE: Sure.

DR. YADAV: You know, please keep in mind that the physicians -- the hypothesis was PA pressure plus signs and symptoms. So the physicians always had more information besides -- so as we all know in our clinical practice, there are patients whose PA pressure, you really -- you've got low blood pressure, you've got decreased renal function, et cetera. So I don't think one should assume that for every high PA pressure, the physician will do something because they may well not think it's appropriate to do anything. And I think that's the key concept here, perhaps, that we didn't communicate adequately.

So the physician always has more knowledge, and the goal is to reduce PA pressures, if possible, and if clinically not harmful. But we'll try to get you some more detail, but I think that's the overlying theme.

DR. PAGE: Dr. Lange, Dr. Cigarroa had his hand up unless this

is specifically following up on the point we were just discussing.

DR. LANGE: Okay.

DR. PAGE: Okay. Dr. Cigarroa?

DR. CIGARROA: So this is following up on a point. I'd actually like to be more specific. I'd like to know, given that there were over 32,000 PA pressure automated alerts, I'd actually like to know predictors that resulted in actionable items. So, you know, I think this goes to the issue of concerns about safety and efficacy, which if, in fact, is it the number of times that the PA pressure is elevated, what are the safety margins built in regarding systemic blood pressure, renal function, et cetera, because I think that we have to interpret it in that context because there were many that were not acted upon.

DR. YADAV: Right.

DR. CIGARROA: And I think that data is equally important as to the number of actionable items. So I'd actually like it as predictors of actionable items based on the number of PA alerts.

DR. YADAV: Yeah, and we'll try to see if we can address it. What I can tell you, and we can share this data in detail after lunch, is that renal function did not deteriorate over time, which is, I think, underlying your concern. And also please keep in mind that we looked at all-cause hospitalizations, and so we did not see an increased burden, as you're rightfully concerned, in hospitalization due to decreased renal function or

metabolic changes or something. So I think that should give you some reassurance that all-cause hospitalizations actually go down and are not either neutral or increased.

DR. PAGE: Okay. And Dr. Lange?

DR. LANGE: Just something to prepare over lunch. Go to Slide 70, please? And this goes to what Dr. Jeevanandam was asking for, which I think is a very reasonable thing to ask for. Let's go a sensitivity analysis, and we're going to include three groups. We're going to include all 260 patients in which a communication was mentioned. I know only 14% had an actionable thing, but we heard the reason that why they were contacted was because nobody filled out the CRF forms. So let's assume that all of those communications, all 531 communications mentioned were -- averted a hospitalization stay. That's a sensitivity analysis.

The other sensitivity analysis will include all 511 patients because one is said to be a recommendation. The other is an inquiry. But the inquiry actually involved reminding the sites of the responsibility to respond to an increased pulmonary artery pressure. That's not an inquiry. That's a recommendation. So let's do a sensitivity -- let's not do -- let's not talk about it now. We should do a sensitivity analysis of how that would affect things.

DR. PAGE: Let me just ask whether, Dr. Zuckerman, is that -- or for our statistical consultants, is that a reasonable expectation that they

could do a sensitivity analysis in the next two hours on this?

DR. PACKER: Can I just -- I'm sorry, Dr. Page --

DR. PAGE: I just asked a question of Dr. Blumenstein. Can you comment on that?

DR. BLUMENSTEIN: I don't know.

DR. PACKER: Dr. Page, if I --

DR. BLUMENSTEIN: I know it would be a challenge.

DR. PAGE: Yes, Dr. Packer?

DR. PACKER: Rick, let me assure you that if you said that every one of these 531 communications prevented a hospitalization -- and, remember, there were only 200 hospitalizations, you would have prevented more hospitalizations than occurred in the entire trial in both treatment groups. So that would be a rather draconian way of looking at it.

DR. LANGE: My point exactly.

DR. PAGE: So we don't have time for back and forth here, gentlemen.

So we are past the time for a break unless, Dr. Milan, do you have a specific issue that we need to --

DR. MILAN: Yeah.

DR. PAGE: -- address before?

DR. MILAN: Just specific follow-up to that slide, Number 70, I'm concerned, as I hear other people like Val and Rick, that the

communications were a tug on the sleeve of the physician to do something, not necessarily the physician was looking at the nurse to tell him exactly what to do, but just a reminder that, hey, this elevated PA pressure is out there, you haven't responded to it yet, do something. So it's this 84%, this n=446, where the recommendations of the nurse were not followed by a concordant change. Was there some other change made? So that's my question, some other medication change made whether it was concordant with the nurse's recommendation or not; was it a different change, was it a diuretic change instead of a nitrate? That's what I'd like to know.

DR. YADAV: Sure. We actually did look at that, and we can get you the details, but there was no -- which you're, I think, asking for, Dr. Milan, is there change in the frequency of treatment, of any treatment, pre- and post-nurse communication. We actually looked at that a long time ago, and we can dig it up again. And there actually isn't, but we can certainly address that for you.

DR. PAGE: Dr. Zuckerman, at this point I think we're ready for a break, but before we do, I want to try to summarize the outstanding issues. And I'm going to ask for those who raised the issues to help me in terms of making it clear to the Sponsor what we're asking for. And we'll look for what they can do and what they are unable to do over a short period of time. Does that sound reasonable to you, Dr. Zuckerman?

DR. ZUCKERMAN: Excellent, Dr. Page.

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DR. PAGE: So with that, I believe, Dr. Yuh, you had required more information in terms of individual response to pressure elevation. We saw the slide as a group, but was his question clear to the Sponsor in terms of what he was asking?

DR. YADAV: So I think, Dr. Yuh, you're looking for some examples in patients of what happened to their pressure before and after?

DR. YUH: If examples are the best you can provide on short notice, yes. But I guess the crux of the issue -- and I'm not a statistician, but some statistical evidence that you saw a measured response on your device to the therapies that that device prompted.

DR. YADAV: Isn't that what the treatment versus control is showing you for the pressures? I'm a little confused. I just want to make sure we address your concern.

DR. YUH: In a broad sense, it does. But I just want to -- I want to be confident in my mind that when a device signals an elevated PA pressure, that that prompts a medication change, that that same device recognized a response to that medication. I mean, your whole premise of all of this is that avoiding hospital readmissions is based on your PA pressure control. That's what your device is based on. That's what this trial is based on.

DR. YADAV: Well, I think I understand now.

DR. YUH: Yeah.

DR. YADAV: So you want to see that a change in medication, specifically a change in medication lowers PA pressure?

DR. YUH: No, the -- well --

DR. YADAV: Right --

DR. YUH: Yeah, that the action prompted by your device resulted in a measured response by that device --

DR. YADAV: I think we can try to put it together. I mean --

DR. YUH: Right.

DR. YADAV: -- I think we can try to put it together --

DR. PAGE: And, actually, Dr. Cigarroa made a very good point about whether you could get any more specific in terms of those with mild, moderate, and severe pressure elevations.

DR. YADAV: Sure.

DR. PAGE: Dr. Cigarroa, does that summarize what you had requested?

DR. CIGARROA: Yeah, stratified by degree of pulmonary hypertension in --

DR. PAGE: And we understand you'll do what you can do for us.

DR. YADAV: Yes, thank you.

DR. PAGE: But those are the outstanding questions up till the point of Dr. Blumenstein, who had four excellent issues that he wanted to

address and then one later. And, Dr. Blumenstein, I can't do justice to the quality and concise nature of your questions, so if you can just remind the Sponsor of the homework you were hoping they would be able to achieve before we return after lunch?

DR. BLUMENSTEIN: Yes. The distribution of the duration of hospitalizations by arm; the distribution of the number of patients with one hospitalization, two hospitalizations, and so forth; the Kaplan-Meier of hospitalization-free survival with tick marks showing censoring rather than the stuff at the bottom; and then the same thing, same Kaplan-Meier graph for the propensity score selected subsample comparing the arms.

DR. YADAV: Do we understand the last question? I understand the first ones. Is that doable? Okay. Yes, the experts understand, so that's good.

DR. PAGE: Thank you. We also had a request from Dr. Zuckerman, which I share, and that is for Dr. Stevenson to perhaps be able to comment on predictors of good results. We saw that academic and community look the same, but if you break that down, are there any data to suggest which centers would be -- have better results than others. Doctor --

DR. YADAV: I just --

DR. PAGE: Yeah?

DR. YADAV: Could I ask a clarifying question on that last question to Dr. Zuckerman?

DR. PAGE: You bet.

DR. YADAV: Dr. Zuckerman, are you referring to a poolability analysis? I just want to make sure we understand what you're referring to.

DR. ZUCKERMAN: You had 60 centers --

DR. YADAV: Right.

DR. ZUCKERMAN: -- and you broke them down academic versus clinical. You tried to suggest there's no difference, so if you look at variability, what are the predictors? Is it a certain volume?

DR. YADAV: Okay.

DR. ZUCKERMAN: Is it a certain way that this device is used with a team? We like some practical information. The key here is how does one generalize the CHAMPION results to get good results at real-world centers?

DR. YADAV: Okay. Great. Thank you. We'll try to do that.

DR. PAGE: And then, Dr. Patton, you had either two or three issues you wanted a bit more information on, if that could be obtained for us. Would you summarize?

DR. PATTON: One of them was the -- and I think Dr. Cigarroa actually put this better than I did -- is what were the predictors that caused an action to be performed with respect to the PA pressure readings. And, again, this speaks to the generalizability of the results.

DR. YADAV: Sure.

DR. PATTON: As well as the predictors of not responding to elevated PA pressures. The second was how did medications change in the groups over time, which can be lumped into one of the previous questions. And another was more information on the device-related complications.

DR. YADAV: Thank you.

DR. PAGE: That's all clear?

DR. YADAV: Yes.

DR. PAGE: Great. Thank you. Dr. Cigarroa had a comment about the fact that 32,000 pressure measurements were reported, and any further information you can give us in terms of what were the predictors associated with actionable items. Obviously, not every blood pressure report was --

DR. YADAV: Sure.

DR. PAGE: -- acted upon. Is that the crux of what you were saying, Dr. Cigarroa?

DR. CIGARROA: Yes.

DR. YADAV: Yes. And I think these questions are interrelated. We'll try to address them.

DR. PAGE: And, finally, Dr. Lange asked for a sensitivity analysis based on Slide 70, and I think he made it pretty clear what he was asking for. Anything unclear there or does he need to clarify, perhaps, with that Slide 70 back up?

DR. YADAV: Yeah, actually, I am not -- I am thinking about maybe the statisticians have an idea, but I'm just -- you know, I'm not -- we'll work on it, but I'm not sure we fully understand.

DR. LANGE: We can do just one of Slide 70.

DR. YADAV: Okay.

DR. LANGE: Assume all 100 patients, not just 14%, since we don't know -- since the CRF forms weren't filled out appropriately. Just take that bottom group right there, and let's do a sensitivity analysis, and let's assume that that prevented a heart failure or hospitalization and how that would affect the outcome.

DR. PAGE: Great. I think, Dr. Zuckerman, that summarizes the outstanding issues. We have plenty to talk about. I do appreciate the Sponsor keeping their comments as short as they did in terms of the presentation. We'll expect the same from the FDA because we're anticipating brisk discussion after that presentation as well.

We will now take a 10-minute break. So we're running behind, but the 10-minute break to 10:40 and we'll get started. Panel members, I want to remind you not to discuss the meeting topic with yourselves, among yourselves, or with members of the audience. Again, we'll resume at 10:40. Thank you.

(Off the record.)

(On the record.)

DR. PAGE: 10:42. I'm going to call this Panel meeting back to order. I was remiss in not acknowledging Dr. Ohman's outstanding issue. Dr. Ohman, would you just briefly summarize the bit of clarification you were requesting of the Sponsor, and then we'll move on with the FDA presentation?

DR. OHMAN: Yeah. If the Sponsor is here. I don't see anybody. You'll take notes? Okay. So my question had to do with the actual variables in the multivariate Cox proportional model, what they were in the different Phase 1 and Phase 2 trial, because if they're different, that's a different story than if they're the same, i.e., the data is more understandable if they actually are the same that drives those outcomes.

And the other question was the Andersen-Gill modeling, to just provide us more clarity to the Andersen-Gill and the frequency distributions.

DR. PAGE: Thank you, Dr. Ohman. I'm looking at the Sponsor, who looks lonely over there, but the statistician is taking notes and nodding to me that your question was clear and they will work on that over the break. Thank you very much.

We'll now proceed with the FDA presentation. And as before, we have a 90-minute timer and a 2-minute warning at 88 minutes. Please proceed.

MR. QUINN: Good morning. I am Bradley Quinn, biomedical

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engineer and lead reviewer for this PMA amendment. We're here today to discuss the additional data analyzed by CardioMEMS and submitted in response to the previous December 8th, 2011 Panel recommendations and FDA's not approvable letter, dated January 11th, 2012.

The review team includes the following individuals:

Dr. William E. Sanders, a cardiac electrophysiologist, and Dr. Ileana Piña, a heart failure specialist, from the Office of Device Evaluation; Dr. Yuying Jin, a statistician from the Office of Surveillance and Biometrics; and Dr. Shaokui Wei, an epidemiologist from the Office of Surveillance and Biometrics.

This slide identifies the various topics FDA will discuss. My introduction will include the conclusions from the December 8th, 2011 panel meeting, FDA's not approvable letter, and independent third-party audit and the development of the ancillary analyses that are the subject of today's meeting. Following the introduction, I will turn over the presentation to Dr. Sanders.

This slide provides an overview of the Sponsor's device -- since this was previously given, we'll skip forward -- along with the proposed indications for use.

Additionally, the preclinical and animal studies' information has not changed since the last panel meeting.

I'd also like to discuss the regulatory background and history

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associated with the device. This device was presented before the Circulatory Systems Device Panel on December 8th, 2011. During this meeting, FDA identified concerns related to subject-specific treatment recommendations made by the Sponsor's nursing staff to investigation sites. FDA believes that these communications confounded the study data and severely limits the interpretability of the effectiveness data.

This belief was further supported by the Panel and manifested in the voting questions. The Panel voted 9 to 1 that there was a reasonable assurance that the device is safe for the proposed indications. Please note that FDA continues to believe that there is a reasonable assurance of device safety.

The remainder of this presentation will focus on the effectiveness of the device. The Panel voted 7 to 3 that there is not a reasonable assurance that the device is effective for use in the subject population studied.

Finally, the Panel voted 6 to 4 that the benefits of the device do not outweigh the risks in subjects who meet the criteria specified in the proposed indications.

Following the December 8th panel meeting, FDA completed its review of the original PMA and issued a not approvable letter on January 11th, 2012. This letter included two deficiencies that requested additional data to demonstrate that there is a reasonable assurance of

effectiveness for the proposed indications for use and to address potential differences in treatment effect due to gender. The first deficiency also recommended that a new trial be completed that would be designed to minimize or eliminate Sponsor-driven, subject-specific management advice.

CardioMEMS engaged FDA in multiple meetings and submissions to reach a resolution to the issues identified in the Panel recommendations and not approvable letter. The Sponsor continued to follow subjects enrolled in the study and suggested multiple ancillary analyses to assess the device's effectiveness in the absence of nurse communications.

FDA agreed that this approach may be acceptable but identified that these analyses would have limitations that would need to be addressed. These limitations included that this was not a pre-planned or designed study, that not all of the subjects' baseline covariates were re-collected prior to the initiation of Part 2, that population characteristics may be different between Part 1 and Part 2 and between former treatment and former control and Part 2, and that the hypotheses or data analysis plan were not prespecified prior to the collection of subjects' outcome data in the follow-up period. Additional details regarding these limitations will be discussed by my colleague, Dr. Jin.

In addition to the not approvable letter, FDA requested that CardioMEMS engage a third party to perform an audit to identify and verify

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all nurse communications. FDA reviewed the results of the third-party audit and found them to be valid. Dr. Sanders will discuss the third-party audit and nurse communications further in his presentation.

Now for a brief background on the original trial. The CHAMPION Trial of the original PMA study had a mean follow-up time of 15.7 months. It enrolled 550 patients at 64 sites in the U.S.; 270 patients were randomized to the treatment group and 280 patients were randomized to the control group. Treatment group physicians received knowledge of pulmonary artery pressures plus heart failure management based on the standard of care. A majority of treatment subjects were also the topic of nurse communications. Control group physicians did not have access to subject pulmonary artery data, but subjects did receive heart failure management based on the standard of care.

In the original PMA, the primary effectiveness endpoint compared the rate of heart failure-related hospitalizations through six months in each arm. It was determined to be confounded by subject-specific management recommendations contained in nurse communications. The Sponsor had two primary safety endpoints, which the previous panel agreed that the device met safety endpoints and the additional analyses of six months.

The four secondary effectiveness endpoints analyzed at the six-month visit included survival and quality of life. This slide will be used

throughout the presentation and will identify how the Sponsor responded to the two FDA deficiencies in the not approvable letter.

In response to the first deficiency that requested a new trial be conducted, the Sponsor performed additional ancillary analyses that included four longitudinal analyses, a propensity score analysis, and a clinical analysis of the nurse communications. The Sponsor also performed a gender analysis to address the second deficiency. FDA believes that the longitudinal analyses are the most valuable when considering these analyses. These analyses and the results will be discussed in detail by my colleagues Dr. Jin and Dr. Sanders.

This table outlines the differences between the trial periods, randomized groups, and trial components. All subjects received standard of care of heart failure management in Part 1 and Part 2. In Part 1, treatment group had physician knowledge of pulmonary artery pressures plus nurse communications, which was the confounder of the study results. In Part 2, all subjects received physician knowledge, however without nurse communications.

The next slide includes a hypothetical study timeline. It conveys a significant amount of information, but you need not worry. I'm here to walk you through. So I'll give everyone a moment to just take this in. It's a little hard to see, but there's a lot of information up there. This is a hypothetical visual representation of the study timeline for the original PMA

analysis, the additional six-month follow-up, and the continued follow-up period. The information on this slide does not reflect actual patients and is not drawn to scale.

The top set of bars represents the treatment group, and the bottom set, the control group. Each bar represents the progression of a single hypothetical patient through the study and follow-up period. Green represents the availability of subject pulmonary artery pressure data, and red represents the lack of availability. The dotted fill, which are the bars on the left side of the image, represents the timeframe for the six-month primary endpoint.

The vertical line fill, which are the bar segments in the middle of the image, represent the time period post primary endpoint. The solid fill bars on the right side of the image represent the continued follow-up period. Additionally, as noted in the top right, diamonds represent deaths, crosses represent hospitalizations, X's represent inquiries, and stars represent recommendations. Inquiries are generic communications to physicians alerting them about a PA pressure change, and recommendations are subject-specific treatment recommendations.

There were 270 subjects in the treatment and 280 subjects in control groups. The treatment group received physician knowledge of pulmonary artery pressures, and a majority of subjects were the topic of nurse communications. Both groups had standard medical therapy.

Part 1, defined as the period of randomized access, is the original PMA study plus an extended follow-up time past the primary endpoint period of six months. They had a mean duration time of 17.6 months. Following the completion of this period of randomized access, or Part 1, subjects transitioned to a period of open access, or Part 2. The mean duration of the Part 2 study was 13.1 months.

The treatment group from Part 1 is now known as the former treatment group, and the control group from Part 1 is now called the former control group. There are 177 subjects in the former treatment and 170 in the former control. During Part 2, physicians received automated alerts and had access to subject pulmonary artery measurements for all subjects, including both treatment and control groups. It is important to note that nurse communications, including generic communications in subject-specific treatment recommendations ceased prior to Part 2 of the study. Additionally, there is no control arm in the period of Part 2.

For example, the fifth, or the bottom in the treatment group, hypothetical subject had a patient-specific management communication from the Sponsor's nursing staff shortly after enrollment. This was then followed up with a generic inquiry and then another subject-specific management recommendation. Post primary endpoint, the subject had another inquiry and was subsequently hospitalized. This subject then transitioned into Part 2 and continued into the follow-up period.

This concludes my introduction section. Thank you for attendance -- your attention and attendance. Dr. William Sanders will now provide a clinical introduction.

DR. SANDERS: Chairman Page, distinguished Panel, I am William Sanders. I'm a clinical cardiac electrophysiologist and the medical officer for the FDA presenting the clinical results from the PMA amendment of the CardioMEMS CHAMPION HF Monitoring System.

In this section of the presentation, I will briefly review the pertinent clinical aspects of the original trial and discuss the subject populations as well as important design considerations of the new analyses.

The preceding discussion this morning was extremely helpful in pointing out the limitations of Part 1. The focus of my presentation, as well as my colleagues', will be on the new analyses and, in particular, the longitudinal analyses. Thank you.

In review, the inclusion criteria for the original trial were New York Heart Association Class III heart failure and at least one heart failure-related hospitalization within 12 months prior to enrollment. The major exclusion criteria of the original trial was more than one pulmonary embolus or deep venous thrombosis. And it should be noted that left ventricular ejection fraction was not a criteria.

Demographics of total populations entering Part 1 and 2 are shown here. The subjects entering Part 2 were not prospectively reassessed

regarding all parameters. However, the overall demographics of subjects in Part 2 appear to be similar to those in Part 1. The Sponsor has recently submitted additional Part 2 demographic data, which has not been reviewed by the FDA. It is currently unknown to the FDA the variability of timing of the collection of that information with regard to the individual subjects, and it is uncertain the methods used to obtain it.

This slide illustrates the flow of the CHAMPION Trial Parts 1 and 2. A total of 550 subjects were implanted with the device and then randomized 1:1 to either the treatment group of 270 patients or the control group of 280 patients. During the course of Part 1, 93 subjects, or 34%, of the treatment group and 110, or 39 subjects [sic], of the control group exited for the reasons described. During the course of Part 2, 58 subjects, or 33%, of the former treatment group, and 43, 25%, of the subjects from the former control group exited.

Subject demographics with regard to medical history were reasonably well matched in the treatment and control groups in Part 1.

Please note that in Part 1, there were 50 deaths and 7 noncompliant subjects among the 270 treatment subjects; 64 deaths and 6 noncompliant subjects among the 280 subjects. Of the 550 subjects randomized in Part 1, 347 entered Part 2. During the course of Part 2, there were 31 deaths and 10 noncompliant subjects among the 177 former treatment and 21 deaths and 5 noncompliant subjects among the 170

former controls.

Clinically important patient characteristics were not prospectively reassessed at the beginning of Part 2, which started at a mean time of approximately 525 days after the initial demographics were measured.

FDA notes the inherent limitations of evaluating subjects' disposition in Part 2. We believe that bias may have been introduced due to the nonrandom exiting of subjects prior to the onset of Part 2. Ninety-three out of the 270, 34% of the subjects, exiting the treatment group and 110 of the 280, 39%, exiting the control group. This is problematic when evaluating if subjects in Part 1 and 2 are comparable after they exited from Part 1, the group exiting, if patient characteristics between the comparison arms remained balanced in Part 2, and if the risk of future heart failure hospitalization was similar in both groups entering Part 2.

As noted in the inclusion criterion, subjects were required to have hospitalizations in the 12 months prior to enrollment, a hospitalization. At the onset of Part 2, 106, 62%, of the 170 former controls had no hospitalization in the 12 months preceding; 126, 71%, of the 177 subjects in the former treatment group had no hospitalization in the 12 months preceding. Consequently, in Part 2, subjects may not have had the same future risk of heart failure-related hospitalizations that subjects in Part 1 had. Subjects in both arms of Part 2 may have actually been healthier.

FDA has reviewed the causes of all deaths and agrees with their adjudication. During Part 1 and 2, the vast majority of deaths were cardiac in nature. The mortality in the treatment group was 18.5% in Part 1 and 17.5% in Part 2. This similarity in mortality is expected since the former treatment group continued to have access to pulmonary artery pressures.

The mortality in the control group decreased from 22.9% in Part 1 to 12.4% in Part 2. Although the decrease in mortality was expected in the former control group, Part 2, due to the availability of PA pressure data, one would have anticipated the rate be similar to that of the treatment group in Part 1 and Part 2, 18%. The fact that the mortality rates in the former control group is 12.4 versus 17.5 in the former treatment group suggests the possibility of a different patient population in Part 2.

In summary, the results of all the longitudinal analyses that will be discussed should be interpreted with caution, as benefits in the randomization may not have been realized in Part 2. It is unclear whether there is significant differences in the former control and former treatment groups in Part 2 of the study.

The Panel will be asked to discuss, at least comment on, Part 1 and 2 patient populations, whether they're adequately similar, and if not, how that might affect outcomes of the analyses.

Thank you. Dr. Jin is next.

DR. JIN: Hi, everyone. My name is Yuying Jin, FDA statistical

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reviewer for this PMA amendment.

In the original CHAMPION Trial, FDA identified the concern that the device effectiveness was confounded with nurse communication and that there was a statistically significant -- thank you -- treatment by gender interaction. Today I will present further follow-up and a statistical analysis presented by CardioMEMS to address these issues.

FDA asked for additional data to demonstrate there is a reasonable assurance of effectiveness of the CHAMPION HF Monitoring System in deficiency 1. In response to FDA deficiency, the following analyses were performed: longitudinal analysis, propensity score analysis, and the clinical analysis. FDA also asked for additional data to address potential difference in treatment effect due to gender in deficiency 2. In response to FDA deficiency, a gender analysis was performed. We will discuss the longitudinal analysis first.

Let us go over the study design briefly to better understand the longitudinal analysis. The longitudinal analysis used Part 1 and Part 2 combined data. Part 1 study is the original CHAMPION Trial plus an extended follow-up. The average duration time for Part 1 is 17.6 months. There were 270 subjects in treatment arm and 280 subjects in control arm. The treatment group received physician knowledge of PA pressures, and the majority of subjects were the topic of nurse communications. In control arm, physician did not have access to PA measurements, and there was no

nurse communications.

Following the completion of this period of randomized access, patients transitioned to a period of open access, defined as Part 2 of the study. The average duration time of Part 2 is 13.1 months. The treatment group in Part 1 who entered Part 2 of the study was called former treatment. The control group in Part 1 who entered Part 2 of the study were called former control. There were 177 subjects in the former treatment group and 170 subjects in the former control group. During Part 2, physician had access to patients' PA measurements regarding all patients, but patients received no nurse communications.

Before we discuss each longitudinal analysis comparisons and its analysis -- its result, I'm sorry -- I would like to emphasize the study concerns and its limitations. The follow-up study was not preplanned. Not all the subjects' baseline covariates were re-collected prior to the initiation of Part 2. We are also concerned about the change in patient characteristics between Part 1 and Part 2 and between former treatment and former control in Part 2.

This is due to the following two reasons: Subject dropouts were not random, and subject risk profile for future heart failure hospitalizations might have changed. The hypothesis of data analysis plan was not prespecified prior to the collection of subjects' outcome data in Part 2. Due to these limitations, even if the Type I error is preserved,

p-values should be interpreted with caution because Part 2 is not a randomized, preplanned study.

The Panel will be asked to comment on the impact of these concerns and the limitations.

Longitudinal analyses were performed to study Part 1 and Part 2 combined data that involved repeated heart failure hospitalization of subjects over time. Four comparisons were performed to assess the device effectiveness in the absence of nurse communication. The first is the comparison of former control to control. The second is the comparison of former treatment to treatment. The third is the comparison of former control to former treatment. And the last is to compare change in hospitalization rates in control group to the change in hospitalization rates in treatment group. Comparison 1 and 2 here involved paired data as events for patients with dependent in Part 1 and Part 2.

This plot also illustrates the four comparisons. Number one denotes the comparison 1 between control and former control. Number two denotes the comparison 2 between treatment and former treatment. Number three is the comparison 3 between former control and former treatment in Part 2. And number four is the last comparison of change in hospitalization rates. I will go over each of the comparisons in the later slides.

To accommodate different patient follow-up times, recurrent

events of heart failure hospitalizations, an Andersen-Gill model with frailty was utilized in longitudinal analysis, combining Part 1 and Part 2 of the study. A frailty, which is a random effect, was added to the model to address dependence of events for patients between Part 1 and Part 2. In the longitudinal analysis, deaths were considered censored data, and covariates were not considered in this longitudinal analysis.

The first comparison is to compare the heart failure hospitalization rates of former control in Part 2 to control in Part 1. Please note the former control is a continuation of control from Part 1. The objective is to determine whether the hospitalization rate was lower in the former control group than the control group, where former control had physician knowledge of PA pressures.

Based on the results from Andersen-Gill model with frailty, the heart failure hospitalization per patient-year decreased from .68 for control subjects in Part 1, 2.36 for former control subjects in Part 2, who were exposed to treatment. Heart failure hospitalization per patient-year for former control shown in the table was estimated based on the Andersen-Gill model regression parameters and the baseline hazard of empirical control hospitalization rates in Part 1.

As mentioned in the previous slides, when interpreting the p-value shown in the table, we have to be careful because the study was not preplanned, the study has limitation, and preservation of Type I error was

not considered.

The comparison 1 intended to demonstrate heart failure hospitalization rate of former control in Part 2 is lower than the hospitalization rate of control in Part 1. Based on the results of Andersen-Gill Model, providing PA pressure information in the absence of nurse communications seem to be associated with lowering of hospitalization rate. Please note that there are limitations of these comparisons. The study was not preplanned, population characteristics might have changed from Part 1 to Part 2 because subject dropouts were not random, and patient risk profile could have changed.

The second comparison is to compare the hospitalization rates of former treatment in Part 2 to treatment in Part 1. Former treatment is the continuation of treatment from Part 1. The objective is to evaluate whether failure hospitalization rates remain the same in subjects whose access to PA pressure remain unchanged but no longer receive nurse communications.

Based on the result of Andersen-Gill model, the rate of hospitalization was similar for treatment subject in Part 1 and for former treatment subjects in Part 2. Please note that former treatment in Part 2 continued to receive treatment but without nurse communications.

The heart failure hospitalization per patient-year for former treatment and treatment was estimated using a similar approach described

in comparison 1. When interpreting the p-value shown in the table, we have to be careful because the reason mentioned.

Comparison 2 is intended to demonstrate there is no difference in heart failure hospitalization rates for treatment in Part 2 and in Part 1. From the results in the previous table, the reduced heart failure hospitalization observed in Part 1 for treatment seems to be maintained after the transition from Part 1 to Part 2, where the use of PA pressure was continued, but the nurse communication was discontinued in Part 2.

The goal of this comparison is to establish equivalence. Even when we fail to detect a difference between two hospitalization rates, from statistical point of view, we cannot conclude that the hospitalization rates for former treatment and treatment are the same.

Comparison 2 has the same study limitations as comparison 1. Therefore, we need to keep this limitation in mind before making a definite conclusion.

The comparison 3 is to compare the heart failure hospitalization rates of former control to former treatment in Part 2. The objective is to demonstrate that the rates of hospitalizations were similar during Part 2 when both groups were managed in an identical fashion. In Part 2, physician has access to PA pressure but no nurse communication for both former control and former treatment.

As shown in the table, the rate of heart failure hospitalization

for former control is .36 per patient-year. The rate of heart failure hospitalization rate for former treatment subject is .45 per patient-year. Again, p-value here should be used with caution because of the reason mentioned.

Comparison 3 is intended to demonstrate there is no difference in heart failure hospitalization rates between former control and former treatment in Part 2. Based on the results in the previous slide, providing PA pressure information with no nurse communications. The hospitalization rate point estimate of former control is smaller than the hospitalization rate point estimate of former treatment. The heart failure hospitalization rates between former treatment and former control were not shown to be statistically different.

The goal of this comparison is to establish equivalence. Even when we fail to detect difference between two hospitalization rates, from statistical point of view, we cannot conclude that hospitalization rates for former control and former treatment are the same. The failure to detect difference of the hospitalization rates may due to the inadequate sample size or large variability. In addition, because of the study limitation, we cannot make a definite conclusion from comparison 3. The study is not preplanned. There was potential difference in patient characteristics at the onset of Part 2 of the study due to sample no random dropouts and change in subject risk profiles.

The last comparison is to compare the change of heart failure hospitalization rate of control to treatment over the duration of Part 1 and Part 2 study. The objective is to demonstrate that the magnitude of change in hospitalization rates after the transition from control to former control was greater than the magnitude of change in hospitalization rates after transition from treatment to former treatment.

The change in the rate of hospitalization rate from Part 1 to Part 2 for control group is described by a hazard ratio of .52, and the change in the rate of heart failure hospitalization from Part 1 to Part 2 in the treatment group is described by a hazard ratio of .93. Please note that a hazard ratio smaller than 1 suggests a reduction in hospitalization rate. A hazard ratio greater than 1 suggests an increase in hospitalization rate. And a hazard ratio equal to 1 suggests there may have no change.

The ratio of two hazard rates .56 is used to compare two changes. It appears that the change in control is greater than the change in treatment. P-value here should be considered with caution, as the reason mentioned earlier.

The comparison 4 is intended to demonstrate the change of hospitalization rate in control is greater than the change in treatment after transition from Part 1 to Part 2. The results indicated that the change in control group seems to be greater than the change of treatment, control exposed to treatment after transition from Part 1 to Part 2, and in Part 2,

treatment remained unchanged over the study but patients no longer received nurse communications.

Again, we need to consider all the limitations mentioned for all other three comparisons before making a definite conclusion.

This plot of annualized hazard rates presents the results of four comparisons. The left plots shows the results of Part 1 study and the right plot shows the results of Part 2 study. The blue line represents the results for control or former control, and the red lines represents the results for treatment or former treatment.

The annualized hazard rates appear to be different between control subject and treatment subjects in Part 1. The annualized hazard rates difference between former control and former treatment becomes relatively small after all patients received physician knowledge of PA pressure but no longer the subject of nurse communications.

The annualized hazard rates of treatment in Part 1 and Part 2 remain similar, and they seem to have a big decrease in annualized hazard rate for control after transition from Part 1 to Part 2, where they started to receive treatments after this transition.

Please note this plot is different from what CardioMEMS has presented. We believe FDA's plot is more appropriate in presenting the longitudinal results because no adjustment or underlying assumptions were stated here.

This slides shows CardioMEMS annualized hazard rates plots. We disagree with this plot because of the following reason: It is unclear whether merging Part 1 and Part 2 study at 330 day is clinically meaningful. Redefining Part 1 [sic] subject events starting time to the starting time of Part 1 may be problematic, as Part 1 and Part 2 of the study involved different patient management and patient characteristics.

The clinical validity of assuming the cumulative hazard rates of Part 2 to be equal to the cumulative hazard rate of Part 2 at the day 330 is questionable. Therefore, we did not think CardioMEMS' annualized hazard rates plot appropriately represents the longitudinal analysis results. We are prepared to discuss the annualized hazard rates plot in QA session if Panel is interested.

In addition, the Sponsor, CardioMEMS, conducted a series of supporting analyses to complement the longitudinal analysis using the combined data of Part 1 and Part 2: evaluation of Andersen-Gill model assumptions, evaluation of robustness of Andersen-Gill models, longitudinal analyses using individual data, analyses considering competing risk of death, the evaluation of missing data in baseline demographics, covariate-adjusted longitudinal analysis of hospitalization rates using Andersen-Gill model with robust sandwich estimates.

Please note in the covariate-adjusted longitudinal analyses, the covariates were collected only at the start of Part 1 study. And also in

the covariate-adjusted longitudinal analysis, Andersen-Gill model with frailty did not converge with all clinical relevant covariates included. When a subset of the covariates is used, results from Andersen-Gill model with frailty was not consistent with longitudinal analysis.

The second analysis used to address FDA deficiency 1 is the propensity score analysis. The Sponsor assessed inference of CardioMEMS nurse communication on the device effectiveness by performing a propensity score model using the original PMA data. It includes patients from the randomized cohort.

The propensity score analysis assessed a six-month heart failure hospitalization rate between the treatment no nurse communication group and the matched controls. At first, 99 treatment no nurse communication subjects with not subject of a nurse communication were matched with a group of subjects in the control using propensity score modeling.

FDA performed a propensity stratification analysis. It gives an incident rate ratio of .51 with a 95% two-sided confidence interval from .35 to .71. An incident rate ratios smaller than 1 suggest a reduction in hospitalization rate. An incident rate ratio greater than 1 suggests an increase in hospitalization rate. And an incident rate ratio equal to 1 suggests they may have no change.

So both CardioMEMS propensity score analyses and FDA

propensity analysis, based on the stratification, show similar results compared with the controls. Treatment no nurse communication subjects had a reduction in the rate of hospitalizations.

Also, the results from the propensity mentioned in propensity stratification analysis are consistent with the finding in the original PMA study. These results should be interpreted with caution. We believe there's a bias when matching patients between the treatment no nurse communication and the control groups. Subjects placed in the treatment no nurse communications group were not the subject of a nurse communication. These patients might be healthy enough to not receive a nurse communication. The population studied in the propensity analysis is a selected group of device's intended use population.

In addition, even though propensity score analysis can balance observed baseline covariates between two groups, they cannot balance unmeasured characteristics and the confounders.

The above reasons limits the conclusions that can be drawn definitely for the propensity score analysis. Thus, FDA believes that the longitudinal analyses are the most useful in terms of supporting the effectiveness of the device.

The gender analysis was performed to address FDA deficiency 2. The original PMA analysis noted a statistically significant treatment by gender interaction. In order to examine whether the

treatment by gender interaction was driven by early deaths in the control group females, the endpoint of deaths or first heart failure hospitalizations were analyzed using a Cox proportional hazard model over Part 1 and the full duration of Part 1 plus Part 2.

To demonstrate the robustness of the findings, Sponsor also analyzed the endpoints of recurrent heart failure hospitalization or deaths over Part 1 and over full duration of Part 1 and Part 2 using Andersen-Gill model with robust sandwich estimates, Andersen-Gill model with frailty, and using the negative binomial regression.

As highlighted in the table, when considering a p-value of .15, there was some evidence of treatment by gender interaction in the competing risk analysis. FDA typically used a p-value of .15 because the analysis is usually not powered appropriately for interaction. The models that have evidence of treatment by gender interaction include Andersen-Gill model with frailty for Part 1, negative binomial regression for Part 1, Andersen-Gill model with robust sandwich estimates for Part 1 and Part 2, and GEE negative binomial regression for Part 1 and Part 2.

In addition, the results of Andersen-Gill model with frailty for female are shown in the table. The hazard ratio under Andersen-Gill model was in the point of hospitalization for Part 1 and Part 2 combined data is .61. Only this result was presented in CardioMEMS presentation.

The hazard rates for Part 1 study and Part 2 study concerning

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the endpoints of hospitalization or deaths are close to 1, which indicates there may be no hospitalization reduction for female treatment groups. Hazard ratio estimates along the p-value suggested limited heart failure hospitalization benefits in women.

The Panel will be asked to comment on these results.

So the longitudinal analyses results show that the device appears to be associated with reducing heart failure hospitalization rate if the study limitations were not considered. However, there are important study limitations precluding us from making a definite conclusion. The follow-up study was not preplanned. Not all patients' baseline covariates were re-collected prior to the initiation of Part 2. Patient characteristics might have changed between Part 1 and Part 2, and between former treatment and former control in Part 2 due to subject nonrandom dropouts and change in subjects risk profile. Lastly, the hypothesis and data analysis plan were not specified prior to the collection of subjects' outcome data in the follow-up period. First of all, the gender analysis adjusted for deaths shows some evidence of treatment by gender interactions, and subgroup gender analysis shows limited treatment effects in females.

So this slide concludes FDA's statistical assessment. Thank you.

DR. SANDERS: It's certainly good to be back, and I'm

Dr. William Sanders. In this portion of the presentation, I will focus on the

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clinical significance and limitations of the data analyses provided by the Sponsor.

Again, although I'll be discussing results from Part 1 as background, I'd like everyone to kind of focus on the results from Part 2, particularly the longitudinal studies. Specifically, I will comment on data provided regarding each of the following: the nurse communications, propensity score analysis, longitudinal analyses, gender analysis, as well as some additional clinical observations.

Shown in this slide are nurse communications during the first six months. Total, in the treatment group, which was comprised of 271 patients -- excuse me -- 270 patients. Of those, 171 were discussed in nurse communications. A total of 260 communications with 531 recommendations for medical regimen changes occurred in the first six months of the trial. Many of the communications contain more than one recommended change. The number of concordant changes in medications within eight days of nurse communication was 85, or 16%.

Shown in this slide are nurse communications during the entire randomized access period. A total of 425 communications with 850 recommendations for medical regimen change occurred during this time. Again, multiple communications had more than one change recommendation. The number of concordant changes in medications within eight days of nurse communication was 128, or 15%.

Two cardiologists, as you've heard, working independently, evaluated all nurse communications identified by the third-party audit. These cardiologists determined that nurse communications which resulted in change in medication -- medical regimen of subjects consistent with the protocol were appropriate. That definition resulted in only 3% of all nurse communications being deemed as inconsistent with protocol recommendations for drug alterations.

Based on their analysis, utilizing historic hospitalization rates for drug therapy trials, the cardiologists concluded that the treatment effect of nurse communications was 2% or less in reducing hospitalizations. In addition, analysis was performed, including all regimen changes, even though consistent with the protocol. The cardiologists, using the same methods, found the nurse communication would result in less than one hospitalization reduction in the first six months and two for the entire randomized access period.

The FDA reviewed the third-party audit results as well as the Sponsor's clinical analysis plan. FDA feels the most valuable portion of the analysis is confirmation that no nurse communication containing any subject management recommendations were made during Part 2 of this trial. The FDA believes it's difficult, at best, to accurately estimate how many heart failure-related hospitalizations were avoided due to nurse communication.

The FDA has limited comments with regard to concordant and

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nonconcordant medication changes within eight days of nurse communications for the following reasons. We respectfully differ with the Sponsor in that any intervention in treatment group by Sponsor involving correspondence that suggest alterations in medications, regardless of whether these are alterations consistent with the protocol, FDA feels has potential to introduce bias. The protocol was designed to assess the physician's ability to utilize PA pressure information and not the capability of the Sponsor's nursing staff to monitor and correct physician-directed therapy or the lack thereof.

In the propensity score analysis, matched datasets were given to an independent third party for outcome analysis. Dr. Jin has discussed the propensity score analysis, and I would like to highlight the following. Based on matched data generated from the propensity score model with all covariates, the minimum reduction in rate of heart failure-related hospitalizations was 34%. In addition, all other models generated similar findings.

All analyses performed utilizing propensity score models are consistent with device effectiveness. FDA remains concerned with selection bias associated with these analyses. Those patients not receiving nurse communication may represent a healthier population and consequently did not require any intervention.

The total number of hospitalizations and heart failure-related

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hospitalization rate per patient-year during the entire period of randomized access are shown in this slide. In contrast to the original trial with a six-months' endpoint, the full randomized access period had a mean follow-up of 17.1 months. There were 180 and 279 hospitalizations in the treatment and control groups, respectively. The hospitalizations per patient-year were 0.48 for the treatment group and 0.68 for the control. This information is presented for comparison purposes, but again, it's important to note that the effectiveness data of the original PMA, which was presented at the last panel meeting, was found confounded by subject-specific treatment recommendations made by the nurses employed by CardioMEMS for the treatment group subjects.

During the random access period, the absolute risk reduction in the portion of subjects that experienced at least one heart failure-related hospitalization was 8.6% and 7.7% at 12 and 24 months, respectively.

With that as background, the FDA believes that the longitudinal analyses, which I won't present now, provide a more appropriate evaluation of effectiveness data that is free of confounders previously noted.

I will focus on three specific comparisons, and you've heard all of them several times. The first comparison is the comparison of the former control Part 2 to control Part 1. The second is the comparison of the former treatment Part 2 to treatment Part 1. The third, comparison of the former

control Part 2 to the former treatment Part 2. The FDA believes these are particularly relevant in assessing clinical effectiveness in the absence of nurse communications.

Data interpretation. This is important to note that these analyses are considered ancillary. As you have heard from our statistical colleagues, although the p-values are presented along with the results, these should be viewed with caution due to the limitations previously noted.

The first two comparisons of the longitudinal analysis are best illustrated here with the actual number of hospitalizations and heart failure hospitalization rate. The first comparison of former control Part 2 to former control Part 1. The comparison of the hospitalization rates between former control Part 2 and former control Part 1 was an attempt to assess whether the PA pressure information in the absence of nurse communication led to a lower hospitalization rate. If lower hospitalization rates for treatment groups observed in Part 1 were primarily due to the use of PA pressures to guide therapy, one would expect the hospitalization rate in the control group subjects to decrease after transition from Part 1 to Part 2.

As shown in the table, the rate of hospitalizations decreased from 0.68 per patient-year for the control subjects in Part 1 to 0.36 per patient-year for former control subjects Part 2.

The second comparison is that of the former treatment Part 2 to treatment Part 1. This analysis was an assessment of whether knowledge

of PA pressures was responsible for the observed reduction in the rate of heart failure-related hospitalizations in the treatment group during the entire course of Part 1 and 2. If the effect on hospitalization rates observed in Part 1 treatment subjects was primarily due to the use of PA pressures, then continuing the use of PA pressures to drive treatment decisions and discontinuing nurse communications in Part 2 should result in a maintenance of the reduced hospitalization rate in the treatment group as they transition from Part 1 to Part 2. This indeed was the case.

The rate of hospitalization was similar for treatment subjects, 0.48 hospitalization per patient-year in Part 1, and for former treatment, 0.45 hospitalizations per patient-year Part 2.

Based on these findings, the impact of the treatment was a reduction of hospitalization rate by 0.2 to 0.32 per patient-year. The number needed to treat to prevent one hospitalization in a year period was approximately 3 to 5.

As noted on the previous slide, comparison 1 above shows the hazard ratio when former control hospitalization rates during Part 2 are compared to those of the original control group. The hazard ratio was 0.52.

Again, as illustrated in the last slide, comparison 2 compares changes in the hospitalization rates of former treatment in Part 2 to that of the original treatment group. No difference was expected and none was observed. Comparison 3 indicates that once all subjects were treated with

the knowledge of PA pressure, there was no difference in the hospitalization rates in the groups.

In summary, the results of the longitudinal analyses are as follows. There was a reduction in the heart failure-related hospitalization rates from control Part 1 to former control Part 2. No difference was seen in hospitalization rates between treatment Part 1 and former treatment Part 2. No difference was observed in the hospitalization rates between former control and former treatment in Part 2. The impact of the treatment was a reduction in the hospitalization rate of 0.2 to 0.3 per patient per year. The number needed to treat to prevent one hospitalization was approximately 3 to 5.

Study limitations. Again, the FDA notes that these results should be interpreted with caution due to several factors. These are ancillary. There's potential inequality in patient characteristics in the total populations in Part 1 and 2, and there's potential inequality in the patient characteristics between control and treatment arms at the onset of Part 2 as well as the nonrandom subject dropout. However, of the analyses performed, the FDA views the longitudinal analyses as the most compelling and pertinent to the question of effectiveness. With deference to the limitations, the findings in the longitudinal analyses are consistent with device effectiveness.

The Panel will be asked to comment on the longitudinal

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analyses with regard to the device effectiveness and risk/benefit profile in light of the limitations noted.

Thank you for your attention.

DR. ZUCKERMAN: Gene, don't you have gender analysis results?

DR. SANDERS: Thank you. Pardon me. Sorry. We'll continue on. My fault. I wanted to end a little early. Rick's been encouraging me to get going here.

DR. PAGE: You've got plenty of time. Thanks for your efforts.

(Laughter.)

DR. SANDERS: Yes, indeed, gender analysis. The results of the gender analysis were evaluated with regard to .05 during the Sponsor's analysis. And as you've noted from our statistical analyses, we used a 0.15 margin for -- thank you, thank you, appreciate it -- 0.15. However, as previously noted, the p-value of 0.15 commonly used by the FDA for assessing treatment by gender interaction, there was some evidence of treatment by gender interaction in multiple models.

There appears to be limited treatment effect in hospitalization rate reduction in females. The FDA is unclear if this is due to the small number of women, 151 in the second part of the trial, and few events, 38 in the second part of the trial, or if it's due to poor efficacy among women. The FDA finds no obvious reason why the therapy should not be equally

effective in women. FDA believes that clarity should be sought by continuing to evaluate treatment effects in women in a proposed post-approval study if the device is recommended for approval.

As noted, the Minnesota heart failure questionnaire was used to assess general well-being of the subjects at six months and was a secondary endpoint of the original trial. At six months, a quality of life benefit was noted, and it was reassessed at 12 months during Part 1. The lack of significance at 12 months may be due to fewer number of subjects continuing in that period of the randomized access.

Freedom from death was examined over the entire randomized trial, Part 1 of the trial. Despite a marked reduction in hospitalizations in the treatment group, survival was not significantly different in Part 1. Since heart failure patients who do not experience hospitalizations would be expected to have better survival, the reasons for this outcome remains unclear and warrants further evaluation.

The Panel will be asked what, if any, of these issues should be addressed in the post-approval trial.

In summary, the absolute reduction of the proportion of subjects that experienced at least one heart failure-related hospitalization was 8.6 and 7.7 at 12 and 24 months, respectively. The impact of the treatment was a reduction of hospitalization rate by 0.2 to 0.32 per patient-year. The number needed to treat to prevent one heart failure-related

hospitalization was approximately 3 to 5. Despite the marked reduction in hospitalization in the treatment group, survival was not significantly different over Part 1.

In conclusion, the aggregate results are consistent with the device effectiveness. These analyses have limitations which may have biased results. The gender analysis is less clear with regard to device effectiveness in women, and there's been no new safety data presented that changes the safety profile of the device.

Now I am going to leave you, so thank you.

DR. WEI: Good morning. I'm Shaokui Wei, epidemiologist in Division of Epidemiology, Office of Surveillance and Biometrics. Today we'll talk about the post-approval study that has been proposed for the CHAMPION Heart Failure Monitoring System submitted by CardioMEMS. The presentation is based on the principles of the outline submitted to the FDA on September 23rd, 2013.

Before we talk about the post-approval study, we need to clarify that the discussion of a post-approval study prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

The plan to conduct a post-approval study does not decrease the threshold of evidence required to find the device approvable.

The premarket data submitted to the Agency and discussed

today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

Here are the two general principles and rationales for the post-approval study. The first is to evaluate device performance and the potential device-related problems in a broader population and over an extended period of time after premarket establishment of reasonable assurance of device safety and effectiveness.

Second, post-approval study should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of reasonable assurance of device safety and effectiveness.

Through review of the premarket data, FDA has identified the following postmarket concern on the recommended post-approval study conducted to exam. The first, long-term safety and effectiveness. In the IDE study, only 246 patients completed average of 30 months of follow-up. And as these patients were highly selected in order to meet other study criteria, so there is a need to evaluate long-term safety and effectiveness in the broader patient population.

Second, benefit/risk for the patient subgroups. The IDE study shows that in the female patients, limited effectiveness was observed in Part 1 and Part 2 of trial. So the long-term performance analyses by gender should be conducted. The other subgroup is patient demographics including left-ventricular ejection fraction, ischemic etiology, and without ICD and the

CRT-D may also be warranted in designing a post-approval study.

Third, subject compliance with device use at time progress.

The increased rate of subject noncompliance during the clinical trials raises a question of whether subjects will continue to comply with the device use requirement at the time of progress follow implantation. So FDA believes that subject compliance with device use should be assessed in post-approval study.

Fourth, effectiveness of the training and education program.

Treatment at community hospitals may vary from academic hospitals. Therefore, FDA believes that there is a need to evaluate the training and education program and compare the result between the device and the patients for the academic or community hospitals.

Now I will present an overview of Sponsor's proposal, followed by our assessment. The Sponsor proposes to conduct a prospective, multicenter, single arm study to evaluate long-term safety and effectiveness. The primary safety endpoint which will be examined are freedom from device- or system-related complications (DSRC) and the freedom from pressure sensor failure over two years in study compared to the unspecified objective performance criterion taken from the CHAMPION Trial.

The primary effectiveness endpoint is heart failure hospitalization rate over one-year in study compared to the unspecified performance goal (PG) derived from a one-year heart failure hospitalization

rate observed in the treatment arm of the CHAMPION Trial Part 1, plus non-inferiority margin, as stated by the Sponsor.

The secondary endpoint including heart failure hospitalization rate or death rate at one year, patient compliance over the course of the study, and the mortality rate at follow-up intervals of 6, 12, 18, and 24 months.

The study will also include a subgroup analysis and a training evaluation. The proposed sample size will be approximately 1,200 patients. And at least 35% enrollment patient will be women, or enrollment will continue until 420 women are enrolled. The study will take three to five years to complete, with two years of follow-up.

Now I would like to move onto the assessment of the post-approval study proposal. The proposed safety endpoint of freedom from DSRC or freedom from the pressure sensor failure over two year compared to the objective performance criterion used in CHAMPION Trial. The OPC used in CHAMPION Trial Part 1 was as follows. The freedom from the DSRC at six months, greater than 80%. Freedom from the pressure sensor failure at six months, greater 90%. However, the observed CHAMPION six months event-free rate was substantially high with the DSRC at 98.6% and the freedom from the pressure sensor failure at 100%.

Please note that the OPC used in the CHAMPION Trial was for the six months follow-up, not for two-year. FDA does not believe that the

OPC used in the CHAMPION was appropriate for the evaluation of the safety endpoint in the post-approval.

The Panel will be asked to comment on the appropriate performance goal of the evaluation of the two safety endpoints.

The primary effective endpoint is heart failure hospitalization rate over one year in study compared to the PG derived from a one-year heart failure hospitalization rate observed in the treatment arm of the CHAMPION Trial Part 1 plus additional performance margin. The heart failure hospitalization rate in the treatment arm was 0.48 per patient-year, as calculated by FDA. However, additional performance margin was not specified by Sponsor.

The Panel will be asked to comment on the appropriate performance goal for the evaluation of the one-year heart failure hospitalization rate.

Subgroup analysis. At least 35% of enrollment patient will be women or enrollment will continue until 420 women are enrolled. And the subgroup analysis will be conducted by gender. However, the Sponsor did not justify if the proposed sample size for women is sufficient to have the power to detect a clinically meaningful difference.

Should the device be approved and the post-approval study be required, please discuss the following with respect of a post-approval study:

First, whether two years and one year are appropriate lengths

of follow-up over which the safety and the effectiveness hypotheses should be tested, respectively.

Second, what are the appropriate performance goals for evaluation of the two safety endpoints?

Third, what is the appropriate performance goal for evaluation of the one-year heart failure hospitalization rate?

Third [sic], whether other effectiveness endpoints should be included as a secondary endpoint?

Fourth [sic], whether a specific effort should be made to study device effectiveness by gender.

This concludes my presentation. And now Mr. Quinn?

MR. QUINN: Thank you.

Just would like to mention before we conclude that the subject of nurse communications was extensively discussed at the last panel meeting and to remind the panelists that the primary reason for today's meeting is to discuss the Part 2 ancillary analyses.

With that being said -- oops, oh, we switched -- thank you very much for your attention, and we look forward to answering any questions you may have.

DR. PAGE: I want to thank the FDA for a very clear and concise presentation.

At this time, we can ask Panel members if you have any brief

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clarifying questions for the FDA and specifically any issues that we need to potentially address later in the afternoon. Keep in mind that the Panel will be able to address questions to the FDA during the Panel deliberations in the afternoon.

I see Dr. Borer first.

DR. BORER: Yeah. Really a very minor point. In Dr. Jin's presentation on Slide 31, I guess it is, you said that the majority of patients were subject to nurse communications. I think technically that's correct, but our concern was with regard to nurse communications that recommended a change in medication. And my understanding was that that was the minority, small minority of patients. So what have I missed here?

MR. QUINN: Thank you for your question. I'll turn that over to -- everyone's reaching for the mike.

DR. ZUCKERMAN: Dr. Sanders, why don't you respond?

DR. PAGE: Turn on your microphone, please, Dr. Sanders?

MR. QUINN: Yeah, press --

DR. SANDERS: Thank you. The majority of the patients did receive nurse communications, and there were recommendations for medical regimen changes in the ones that were noted on our slide. Of those, of the number of communications, there were -- I've got the exact -- you know, I think that's slide -- it's at the beginning of my presentation of the -- okay, on slide, I guess, 66, that's the first six months. And these were actual

recommendations, and these were from the majority of the patients that received them. So only 99 patients didn't receive nurse recommendations out of the original cohort of 270. So the vast majority had nurse recommendations.

UNIDENTIFIED SPEAKER: Can I help or not?

DR. PAGE: This is the time for the FDA to be answering any questions that we have.

Dr. Blumenstein?

DR. BLUMENSTEIN: So let me try to understand this -- the statement of indication that we've seen from the Sponsor does not mention nurse communications.

MR. QUINN: The indications for use statement?

DR. BLUMENSTEIN: Yes. And so the clinical trial was done with a product that included nurse communications. So we're being -- I'm trying to figure out what we're being asked to do. We're being asked here to do something about assessing whether the product should be approved without nurse communications even though that's the way it was evaluated based on analyses that were done on convenient samples following the trial?

DR. ZUCKERMAN: So, Dr. Blumenstein, excellent question. Let me take a stab at answering that. As noted, during the FDA presentation, the first trial, the so-called CHAMPION Trial, or Part 1 of this presentation today, was a randomized trial confounded by nurse communications. From

the FDA's perspective, we'll never know how much confounding, bias, et cetera, was there, and that's why Dr. Sanders specifically on the slide made that point.

However, as you pointed out, today we're here to look at a diagnostic device. The labeling for this diagnostic device should theoretically allow a physician to use it without a nurse at the Sponsor's site. Consequently, the Sponsor has given us several additional analyses that Dr. Sanders and Dr. Jin have gone through in detail. And we'd like the Panel to really discuss whether with these additional analyses one can use this diagnostic device effectively for treatment, as you said, without the interaction of a nurse. And it's really important to note that FDA agrees with the Sponsor audit that in Part 2 of this presentation, we have no evidence that there were nurse communications. That's why both Drs. Sanders and Jin would like us to concentrate more on the Part 2 analyses than continuing to look at Part 1.

DR. PAGE: And I'll just mention that in the earlier session, in part and in response to the Sponsor's presentation, we went into some detail on intervention by the nurses, how much, what effect it had. That's not what we're here to be discussing. So this afternoon, that's not -- I'm going to steer our discussion around the new data that we have available, not looking back at the original randomized trial, but looking at the subsequent analyses, including the longitudinal analysis, which is what the

FDA is putting out there as being the best data that we have.

So any further information about nurse communication, at best, is slightly reassuring to some people here, but we're not going to be rehashing that trial. Is that consistent with the expectation of the FDA, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, that's a wonderful summary and would really help the FDA by focusing on the comment that you just made, Dr. Page.

DR. PAGE: Thank you.

I saw Dr. Cigarroa had his hand up, and then I believe Dr. Lange. But I'm going to ask one specific question for Dr. Sanders just so I'm clear. Your presentation was very clear, but on Slide 79, you give what I see as a compelling number, the number needed to treat. I believe you made it clear which analysis provided that estimate of number needed to treat. Could I have Slide 79, please?

DR. SANDERS: Yes, that is correct. Yes, that is the correct number. And this is based --

DR. PAGE: Right. And which analysis --

DR. SANDERS: This is --

DR. PAGE: I believe it was the control to Part 2, previous control?

DR. SANDERS: Correct. It's Part 2 compared to the --

DR. PAGE: So analysis number one that you're hanging that specific number on; is that correct?

DR. SANDERS: Correct.

DR. PAGE: Great. Thank you.

Dr. Cigarroa?

DR. CIGARROA: Just a point of further classification along -- clarification, Dr. Zuckerman and FDA, there were, apart from the concerns about nursing communication during the randomized trial component, there were some concerns raised by FDA regarding some statistical issues and comments about observed variance being larger than observed mean that led to potential over-dispersion that might have overestimated effect. Are we to censor all aspects of concerns that were raised about the randomized trial and only focus -- or are we permitted to get points of clarification that might have subsequently led to subsequent clinical events or lack of events during the open phase that is Part 2?

DR. ZUCKERMAN: Great question. What Dr. Cigarroa is referring to is if we go back to Part 1, the original randomized trial, with certain patients, they may have had multiple heart failure events. And consequently, during the first panel discussion, there was some interesting statistical discussion as to what is the optimal model for looking at recurrent events and figuring out a hazard ratio.

That being said, that's an interesting statistical discussion, but

from the viewpoint of the Agency again, we would like ideally, and certainly the Panel can always disagree, that we hierarchically weight the data and are more interested in your analyses of the new data, their pluses and minuses. Certainly, you know, with that original estimate, it can vary somewhat from the randomized trial. But I think we would assume that the hazard ratio is less than 1 and leave it there. That ideally should not be the focus of our discussion today, as opposed to the new analyses and the modeling of these analyses.

DR. CIGARROA: Thank you for the clarification.

DR. PAGE: Dr. Ohman?

DR. OHMAN: I have a bridging question from Phase 1 to Phase 2, and that has to do with the competing risk. Obviously, there is numerically a higher mortality in the group that had the control therapy, making it difficult to assess the primary endpoint adequately because of the competing risk.

So have the FDA looked at the mortality and the cause of mortality in the four different groups that we have, the four quadrants in original and randomized trial and the longitudinal trial, to ascertain if the mortality -- the mode of mortality is different, number one, and number two, is it gender-specific differently. So it gets to the gender question in a different way.

DR. JIN: So that's a great question, so let me get back to your

first questions. So there are a number of deaths over the course of the Part 1 and Part 2 study. We did look at analysis addressing the competing risk of death, which is in the supporting analysis. In that analysis, we performed -- the Sponsor would look at the Cox proportional regression with endpoints of death or hospitalization rate. Also, we look at the Andersen-Gill model, with endpoints that count for both hospitalization rate and events. But unfortunately we did not look at, you know, mortality rate of specifically the survival free deaths over the longitudinal analysis.

DR. ZUCKERMAN: So, Dr. Ohman, that's a great question, and perhaps during lunchtime, the Sponsor wants to also handle a potential answer to your question for the afternoon session.

DR. JIN: So in response to your second question about your gender analysis, we did have a look at the gender subgroup analysis for female and males, and the results is presented in one of the slides. There were limited effects for females, and there seems to have been a hospitalization reduction for males.

Is that clear?

DR. OHMAN: Yeah, I did see that. The question is what was the mortality? You showed the overall events, but what was the mortality component of that?

DR. JIN: Okay. So I think Sponsor will help us answer the question.

DR. PAGE: Thank you. I saw Dr. Lange, Dr. Somberg, and Dr. Blumenstein.

You do not have a question, Dr. Lange? Then Dr. Somberg.

DR. SOMBERG: Thank you. Two questions. One is, to continue the gender discussion for a moment, the -- I was left with the -- I think the Panel was also -- that the FDA still has a concern about if there's less of an effect in females. Have you done an analysis on potentially how that is affected by etiology, because in this study, both people with preserved ejection fraction and low ejection fraction are included. Was there a difference in outcome -- were more females having preserved ejection fraction and maybe less amenable to the therapies? Was that looked at? And my second -- you want me to do the -- just leave that and --

DR. PAGE: Why don't we take them one at a time?

DR. SOMBERG: Okay. That's best.

DR. JIN: So, unfortunately, that analysis was not looked at.

DR. SOMBERG: Is it possible for the Sponsor to address that issue if the FDA doesn't have that data?

And the second thing is I think going on what Dr. Zuckerman was asking us to focus on is the longitudinal study, and the big question is, is that a real difference with the monitoring and without the monitoring in the second open phase of the study? And I noticed there's a good number of dropouts. There's a good number of people, as you say, had a mortality.

There are -- and it's not a homogenous continuation of all the people in the study.

Have you looked at a sensitivity analysis sort of like, as other people have asked, with the worst-case scenario, because you sort of made a conclusion, and the Sponsors definitely made that conclusion that there's a difference. But my question is, is does that difference hold up when you say the people who have dropped out, not continued, and didn't -- for all the noncompliance issues, et cetera? And the other consideration is if they all went against the outcome, what would happen?

DR. JIN: So, again, you know, we look at a series of supporting analyses performed using different models. So the purpose of using those models is to assess the robustness of the finding of the longitudinal analysis. So if I can show you the slides -- can you go to Slide 113?

MR. QUINN: 113, please?

DR. JIN: Okay. So we evaluate the robust Andersen-Gill model, so a series of those supporting analyses was done, including Poisson regression, negative binomial regression, and Wilcoxon rank test, and a nonparametric bootstrap method.

So one way we evaluated robustness is to perform those analyses. The Sponsor performed those analyses. So also the way of handling this, I mentioned also we -- the Sponsor performed a competing analysis, treating those deaths as events. I think it can be think of one kind

of sensitivity analysis, you know? In that case, we were just considering all the deaths to be events.

DR. SOMBERG: I think I understand what you're saying, but another approach would be to say that there are two arms, one that has the monitoring and makes use of it and the other one that doesn't. Is there a significant difference between the two? What happens if you say that all those people who died, there was -- you assume that they're in the study and they had no benefit from the monitoring, all those people who dropped out were in the study and had no benefit? Could you do that?

DR. JIN: Could you repeat it again for your question?

DR. SOMBERG: I'm not sure.

(Laughter.)

DR. SOMBERG: Instead of repeating it, try a different way. When you're doing this type of analysis, you're looking at different possibilities of outcome, and you're assuming what if, right? What if this, what if that. So I'm just saying that when you do your longitudinal comparison, if you put in everybody who's no longer in the study because they died, they dropped out, the physician removed them from the study for one reason or another, all those people, put them in but give them in the group that has the monitoring intervention actively utilized and compared them to the other groups, they don't work in the monitoring and they do work in the active group such that you would try to equalize it and see if

there's a difference still.

DR. SANDERS: I could just comment briefly on that. The difficulty is that that's really Part 1, and the open access is what you're talking about. What we're focusing -- you know, still you've got nurse communication. When you have two arms that are randomized in the first part of the study, that's where that question could maybe be addressed in exactly the manner you're putting it, but when you give open access to both arms and both are receiving it, which is the longitudinal data that we're looking at forward, that becomes more difficult, if I understand the question.

DR. JIN: So if I understand the question, I think what you are talking about is the censored data. So patients who exit data, they were either lost to follow-up, they died, or they did not compliant to the protocol. So those patients in the longitudinal analysis after they have those incidents, their results were no longer in the longitudinal analysis. Okay. So we will not know what's the hospitalization risk for them after that.

So, again, you mentioned the competing risk, because in the competing risk, we adjust for patients who died because there are quite many patients who died. Because of death, they lost follow-up, they are no longer in the trial. So, in that instance, we had analysis called competing risk analysis to account for it.

So we just treating -- you know, the deaths, the sensitivity

analysis, we think those deaths are events, so the analysis will count the deaths as events and use that information in the longitudinal analysis. I hope I --

DR. PAGE: And I think this will be worthy of discussion during our Panel discussions.

Dr. Blumenstein, did you have a comment and question?

DR. BLUMENSTEIN: Well, it seems like what we have here is a hoist it on your own petard moment. The randomized clinical trial has been shown to have an effect, and part of the effect results in patients not going on to Part 2. And so therefore you, by definition, are defining the groups in Part 2 as being different. And so how can we feel confident that we're comparing interventions when we have something that defines a different sample of patients in the various arms that we're comparing. Have you -- I guess the lack of measurement of covariate on entering Part 2 is a big problem. And has there been any effort at all to try to figure out whether you're comparing kumquats and potatoes or whether you're comparing apples and pears?

DR. AGUEL: That's a great question. And it's really at the crux --

DR. ZUCKERMAN: Dr. Aguel, just identify yourself for the transcriptionist?

DR. AGUEL: Felipe Aguel, Branch Chief of the Cardiac

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Electrophysiology Devices Branch at FDA.

That really gets to the crux of the question regarding the limitations or potential limitations of the analysis that we're looking to discuss here today. The Sponsor did go back and collected additional covariates after the fact once they were alerted to the concern based on FDA's Executive Summary, but FDA has not had the opportunity to review those. There are questions regarding how missing data was treated for those additional covariates that were collected as well as the timing of the collection of those covariates. So some of the covariates were collected up front, and we have those. We don't have all of them. The ones that were collected after the fact we haven't had a chance to review.

So, again, this is exactly the topic that we would like discussed today. If you look at the numbers of the longitudinal analyses, they all seem to be pointing in the same direction and are quite consistent, but the question is how important are these limitations that have been pointed out in the FDA presentation?

DR. ZUCKERMAN: So, in summary, Dr. Blumenstein, you've asked an excellent question. The Sponsor has some preliminary response to your question that they can try to give after lunch.

DR. PAGE: And, Dr. Zuckerman, is it possible that there can be any further, at least, if not analysis, then description of concerns that the FDA has with regard to the two populations that are left in the Part 2 of this

trial? Would that be possible to provide the Panel?

DR. ZUCKERMAN: Sure. I think we can only indicate that we haven't seen what the Sponsor is doing and have limited knowledge of what is the methodology by which they've obtained additional covariates. But, Gene, do you want to add?

DR. SANDERS: I think that's the whole point. We just haven't had an opportunity to look at it. They were -- once the Sponsor was alerted, they made a best effort to get some of that data, but that hadn't been reviewed.

DR. PAGE: So we have what we have, and we're not getting any more in the next hour. Fair enough?

Dr. Cigarroa?

DR. CIGARROA: Just like some guidance from FDA on how to look at the clinical outcomes that have been reported. We basically have a run-in phase and then an open-label phase where PA pressures are available. Give me some guidance on the FDA's position on the percent rehospitalization and percent death during the open phase as having simply been an association with having the PA pressures available in the absence of any knowledge as to how that data was utilized, and that is in the absence of being able to see changes in medications. We know in the Part 1 aspect, the percent changes in diuretics, the delta of 50% versus 23% in the addition of nitrates to the baseline data. So I know event rates, but give me some

guidance on causality versus association and what the FDA's position is on this.

DR. SANDERS: As you've noted, there were 32,000 alerts given. There were only 1,400 changes, and that's about 4% in response to alerts. It's hard to correlate that although -- we don't have specific -- as you pointed out, we don't have -- there wasn't a study done specifically to look at how that impacted the -- the medical change impacted the PA pressure. So it's in each individual studied over time. That would be useful information.

DR. ZUCKERMAN: So, Dr. Cigarroa, to summarize, I think you're going to have to give us advice as well as the other members, clinicians around the Panel. But the goal here is that you'll need this afternoon to put together multiple pieces of data. And, certainly, the original randomized trial has an effect of confounding. We don't know how big it is, and that's why with the original FDA letter, we did not conclude that there is a reasonable assurance of safety and effectiveness.

On the other hand, you will be able to cull out some hemodynamic data according to what you just asked. The Sponsor will give other data that will hopefully allow you to extrapolate to some of the other scenarios that we're talking about. But we would just recommend that you do it cautiously and deliberately, but that's really your charge this afternoon.

DR. CIGARROA: Thank you.

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DR. PAGE: I see Dr. Jeevanandam, and then we're going to be adjourning for lunch.

Dr. Jeevanandam?

DR. JEEVANANDAM: I just got a question about Slide 50, right, so if we are not -- if we're going to concentrate on the open label component of this and not look at the original randomized component, if you look at Slide 50, you know, there is a decreased hospitalization --

DR. PAGE: Can we have Slide 50?

DR. JEEVANANDAM: 50. All right. If our mission today are we're going to look at Part 2 and not look at Part 1, the results are very different, right, because the patient populations are very different. The ones going into Part 2 are different than the ones going into Part 1. In Part 2, there's no difference in hospitalization, and in Part 1, there is a difference in hospitalization. So you have to look at both, I think.

Well, you're raising a very important issue that we're going to be discussing as to what we can make of these data, and the four analyses that have been put forward to us, we need to consider what, if any of those, we find compelling given the limitations that have already been discussed.

DR. AGUEL: Felipe Aguel, FDA. You're right. We can't ignore the results from Part 1, because by definition, the longitudinal analyses are a comparison of Part 2 results in the control group to Part 1 results in the control group. The key here is that the control group itself was not subject

of nurse communications, so we believe it's not subject to that bias. The part that we don't want to focus on is the randomized control study in Part 1 where we're comparing the Part 1 treatment group, which was subject to nurse communications, to the Part 1 controls. So it's not entirely accurate that we're asking that we ignore Part 1. We're asking that we not focus on the nurse communications aspect that confounded Part 1.

Thank you for that clarification. Does that help,

Dr. Jeevanandam?

DR. JEEVANANDAM: But how do you pull that out of this data, though? I mean --

DR. PAGE: Well, that's what I look forward to discussing with you after lunch.

(Laughter.)

DR. ZUCKERMAN: So, Dr. Jeevanandam, I think there's one statement in the FDA summary that'll hopefully help the Panel members. It is important to consider the totality of effectiveness data presented. Although each analysis on its own has its flaws and limitations, we'd like you to look at the consistency of results to see if you can extrapolate as to whether this device has appropriate effectiveness.

DR. PAGE: Thank you, Dr. Zuckerman.

With that, we have either one or two bits of work over lunch.

Dr. Ohman, would you just summarize your issue of competing risk and make

sure that although this was the FDA's session, that's actually a question that we're asking the Sponsor to help us out with?

DR. OHMAN: Yes, so the question is the mode of mortality in the Phase 1 and the Phase 2 and how that influenced competing risk. The second part of that question is really relating to the gender issue, where the competing risks appear to be greatest.

DR. PAGE: And, Dr. Somberg, did you have one issue that was going to be analyzed, or were you satisfied that you have what you're going to have?

DR. SOMBERG: I don't think I'm ever satisfied, so the issue that the Sponsor might be able to address and might target some of the FDA concerns is with gender difference, was there a difference in the type of heart failure between men and women that could impact on that? And I still think you can do a sensitivity analysis, because what you're doing is you're comparing the initial randomized study controls where there was a nurse intervention to what happens when now there's just monitoring. But there's groups that come in or -- I'm sorry -- there are people who are left out, put them in to the -- to that second cohort and see if they all have hospitalization outcome if you still have a significant difference.

DR. PAGE: And there was one outstanding issue Dr. Lange wanted to mention.

DR. LANGE: If the Sponsor on their Slide 28 and 34, which is

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the randomization part, if they can prepare that same data for the open label -- open access. Thank you. Over lunch.

DR. PAGE: Is that question clear? I'm looking -- it looks like Sponsor understands the question.

So with that, we will adjourn. We're going to take a 45-minute lunch break. We will reconvene at 1:15. I just want to remind the Panel members not to discuss the meeting topic during the break, among yourselves or with any member of the audience. And we will reconvene at quarter after. Thank you.

(Whereupon, a lunch recess was taken.)

AFTERNOON SESSION

(1:19 p.m.)

DR. PAGE: It's now 19 minutes after 1:00. I'd like to resume this meeting.

We'll now 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.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: 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, 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 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 a 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.

DR. PAGE: We've received two requests to speak. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate recording of this meeting. Each speaker will be given 10 minutes to speak, and at nine minutes, you'll see the yellow light.

The first is Diana Zuckerman, Ph.D., President of the National Research Center for Women and Families.

Dr. Zuckerman? Is Dr. Zuckerman in the hall? I don't see Dr. Zuckerman or any appointee from her group.

We will proceed on with our second speaker, Michael A. Carome, M.D., Director, Health Research Group. Is Dr. Carome here? Welcome. I hope I said that right.

UNIDENTIFIED SPEAKER: We had one problem with the slides. It'll take, like, a minute to download them.

DR. PAGE: Sorry for the delay. We'll get that up as quickly as possible.

(Pause.)

DR. PAGE: Do we have reason to think we're going to have the slide up shortly?

UNIDENTIFIED SPEAKER: Probably 30 seconds?

DR. PAGE: Thirty seconds. Thank you.

(Pause.)

DR. PAGE: There we go. Thank you. Welcome, Dr. Carome.

DR. CAROME: Good afternoon. I'm Dr. Michael Carome, Director of Public Citizen's Health Research Group, testifying on behalf of myself and Dr. Sid Wolfe, the founder of our group. We have no financial conflicts of interest.

In December 2011, Public Citizen testified before this Panel, strongly opposing approval of the CardioMEMS system primarily because the design and conduct of the single pivotal clinical trial evaluating the device had multiple features that created readily apparent sources of bias concerning the effectiveness endpoints favoring the experimental group. A majority of the voting members of this Panel reached a similar conclusion. In particular, on the question of whether there was a reasonable assurance that the device was effective, seven members voted no and three voted yes.

In January 2012, the FDA issued a not approvable letter to the Sponsor, requesting additional data demonstrating that there was a reasonable assurance of effectiveness for the device. The Agency appropriately recommended that a new prospective clinical trial be conducted to assess the effectiveness of the device.

CardioMEMS, unfortunately with FDA agreement, instead opted for a series of post hoc ancillary analyses of data from a subset of surviving subjects enrolled in the original pivotal clinical trial. These analysis

have numerous limitations and flaws that undermine their validity, and they are not an adequate substitute for a well-designed prospective randomized clinical trial. The new data presented by the Sponsor fail to provide sufficient evidence to conclude that there is a reasonable assurance that this first-in-class permanently implanted medical device is effective.

For the randomized pivotal trial, the primary effective endpoint was the rate of heart failure-related hospitalizations through six months. Secondary effective endpoints are shown here.

While statistically significant differences were seen in each of the prespecified primary and secondary endpoints as well as many other supplemental endpoints, the absolute difference between the treatment and control groups for several endpoints, such as days alive without heart failure hospitalization, were relatively small. Also, there was no statistically significant difference in mortality outcomes between groups over the duration of the study.

Several features of the design and conduct of the study created readily apparent sources of bias in favor of the treatment group. Thus, it is highly plausible that the difference seen in the effectiveness endpoints was due in large part, or even entirely, to bias rather than the device itself. The most prominent and egregious source of bias in the pivotal trial were the subject-specific treatment recommendations provided to individual site clinical investigators by nurses employed by the Sponsor for

treatment subjects only.

However, other important sources of bias were apparent. The single-blinded study design. This was one feature of the study design contributing to bias that was unavoidable. Nevertheless, clinical investigators aware of each subject's group assignment may have been influencing decisions regarding medical therapy and whether to hospitalize a patient, both of which could have directly affected primary and secondary endpoints.

Also, per protocol, clinical investigators at each site were encouraged to consult with the national PIs "to optimize the success of medical management of PA pressures." Apparently, no such encouragement for consultation was provided with respect to the medical management of control subjects whose care might have been enhanced had the clinical investigators consulted with the national PIs with the same frequency as the treatment group.

Finally, there was an unbalanced content in frequency of telephone contacts between the investigators and treatment subjects versus control subjects. The protocol included scripts for telephone contact with the subjects in both study groups. The scripts were identical except for subject-specific medication adjustments that occurred in the treatment group in response to PA pressure data. Whenever a telephone contact occurred with a treatment group subject, a control subject was randomly

selected to receive a matched phone contact. These were not comparable study interventions because treatment subjects received telephone contacts that were based on contemporaneous subject-specific clinical information, i.e., PA pressure information, 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 subject was slightly higher than the mean number per group in the control group.

Bias is very insidious and can influence subject's actions and -- investigators' actions and judgments. Once the study is completed, it is impossible to prove how much of a difference between the groups resulted from bias and how much from an actual difference between the intervention being tested. In this case, multiple features of the pivotal trial created readily apparent sources of bias and prevent any valid conclusions from being drawn about the effectiveness of the CardioMEMS system.

With respect to the ancillary analyses, the Sponsor conducted multiple ancillary analyses of longitudinal follow-up data from subjects who had been enrolled in the randomized trial and had survived and not dropped out. During this follow-up study, pressure data from the device was made available to the physicians for all subjects. A number of comparisons were made to assess effectiveness, including those listed here.

Although the results of these analyses consistently suggest that access to the CardioMEMS pressure data reduced heart failure hospitalization rates, several factors highlighted by the FDA undermined the validity of these analyses. In particular, FDA noted the following. These analyses are considered ancillary, not primary analyses, because no study success criteria could be defined a priori and because the study was not originally designed with these analyses in mind. Caution should be used when interpreting the results because the study is not powered for these analyses, multiple analyses were conducted on the same data, and preservation of Type I errors were not attempted.

Thirty-four percent of treatment group subjects and 39% of control group subjects randomized into the pivotal trial did not enter the follow-up Part 2 study. Bias in the ancillary analyses may have been introduced due to the nonrandom exiting of subjects prior to onset of Part 2. The clinically important covariates were not collected at the beginning of Part 2, which started a mean of approximately 525 days after the baseline covariates were measured.

It is possible that the values of some important covariates changed between Parts 1 and Part 2. Using Part 1 baseline values for these covariates in the proposed combined data analysis approach may not be appropriate. Furthermore, because of the lack of covariates at baseline of Part 2, FDA was not able to determine if the subjects in Part 1 and Part 2

were comparable after subjects exited from the duration of Part 1, if important covariates between the comparison arms remained balanced in Part 2, and if subjects in Part 2 still met the trial inclusion/exclusion criteria.

FDA also noted it is not possible to evaluate whether the difference in clinical outcomes in the ancillary analyses may be confounded with differences in the subject populations.

Finally, datum differences in mortality between Parts 1 and Part 2 for the treatment and control subjects was also presented. Although a decrease in mortality was expected in the control groups due to PA data availability in the former control group, one would have expected the rate to be similar to the treatment groups of Parts 1 and Part 2, approximately 18%. The fact that the mortality rates in the former control group is 12.4 versus 17.5% in the former treatment may suggest a difference in the patient populations in Part 2 of the study.

On this last point, we believe it's inappropriate for FDA to suggest that a decrease in mortality was expected in the former control group subjects due to PA data availability in light of data from the pivotal trial showing no evidence of a mortality benefit in subjects in the treatment group.

Even if these analyses were valid, we agree with FDA's current view that the clinical significance of any reduction in heart failure hospitalization is less clear. This is particularly true given the absence of any

survival advantage and the apparent lack of sustained quality of life benefit at 12 months in the treatment group in the randomized pivotal trial.

In conclusions, Public Citizen strongly recommends that the FDA should not approve the PMA application for the CardioMEMS system because: one, the design and conduct of the single pivotal clinical trial evaluating the device have multiple features creating readily apparent sources of bias with respect to the efficacy endpoints in favor of the experimental group, thus preventing any valid conclusions from being drawn regarding the effectiveness of the device; number two, every ancillary analysis had serious limitations and flaws that prevent valid conclusions from being drawn about the effectiveness of the device. And as a result of one and two, there is 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 the risks related to implantation of it.

Public Citizen urges the Committee to recommend that the FDA again disapprove the PMA for this device until a well-designed randomized clinical trial without the aforementioned biases is conducted. It is our view that the FDA conclusion presented in the December 2011 meeting is still valid. The CHAMPION Trial does not provide an unbiased estimate of the effects of the device. It is not clear what, if any, effect in this study is due to the device itself. Further, the effects of the device in a real-world setting is unknown.

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Thank you for your attention.

DR. PAGE: Thank you very much, Dr. Carome.

Is Dr. Diana Zuckerman in the hall?

(No response.)

DR. PAGE: Is there anybody else who wishes to address the Panel at this time? If so, please come forward to the lectern and state your name, affiliation, and indicate your financial interest.

I see no one coming forward.

Does the Panel have any questions for the lone speaker during this segment of our meeting?

(No response.)

DR. PAGE: I see none.

So with that, I'll pronounce the Open Public Hearing to be officially closed. We do appreciate the public coming forward and presenting their perspective, and we will proceed with today's agenda.

At this time, we're beginning the Panel deliberations.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

We had a number of questions that I don't want to get bogged down on today in terms of statistical nuance, but I'd like to ask the Sponsor

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first to come forward with any responses to the questions that we put forward earlier in the day.

DR. YADAV: Thank you, Dr. Page. We appreciate the number of questions asked by the Panel, and we have done our best in the limited time to try and answer them. We did take to heart your directions at the end and Dr. Zuckerman's directions to focus on the Part 2 longitudinal analyses in the limited time that we have.

I would like to start by noting the clinical analysis plan conducted by Dr. Packer and Dr. Lindenfeld, a very time-consuming, labor-intensive exercise where they reviewed every single nurse communication and all the medication listings. So we do want to acknowledge the amount of effort and rigor they put into it.

But ultimately, at the end, it is an expert opinion, and it is meant as a clinical analysis, not a statistical analysis. And the intent between us and the FDA was to provide a clinical context and sort of just statistical analyses to give you a sense of comfort that two eminent, expert clinicians, who also are very experienced in clinical trials, looked at every single communication and can give you their conclusion and feeling about these. So that is the intent of them. It is not meant as a statistical exercise. That being said, I would like to acknowledge the tremendous amount of work they put into it.

If I could have Slide 1, please, we'll try to address your

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questions. A key question is about the covariates. And Dr. Packer did cover this, but there was a lot of material, and I just want to reiterate it. There were 26 covariates in this clinical trial, and they're listed here. Ninety-one percent of them, of all the possible values, and it's like 3,000 possible values, were updated for the start of Part 2. Now, so you're seeing the listing here.

If we go to the next slide, please? And these are the actual values at the start of Part 2. All of these were updated in the PMA amendment, i.e., they were given to the FDA.

The next slide has the remainder of the covariates, and everything that has an asterisk on it was updated after the PMA amendment submission, and so the FDA has not reviewed it. But that should give you a flavor for -- of the 26, 19 had been updated already, and the remaining 7 have been updated subsequently. And what it shows you is that the covariates are comparable at the start of Part 2 between the two groups.

Next slide, please. I will come back to covariates in a second. And this relates to the point that Dr. Packer made. We can also think about this in terms -- I think Dr. Somberg raised this issue also -- how about the people who exited? Were they similar between the two groups, or were they different? And I think as he has shown you, looking at a number of characteristics related to outcomes, they are similar. The people who left the control group and the people who left the treatment group are similar in terms of proportion, in terms of duration, in terms of mortality, in terms of

noncompletion due to things other than mortality, and the rate -- I think most importantly, their rate of hospitalizations is similar in the two groups. So there are exiters. They're balanced between the two groups. And, thus, what you all -- it fits in with the covariates that we just showed, indicating balance between the two groups at the start of Part 2.

Next slide, please. And then, further, I can't recall who asked this, but I think Dr. Ohman asked about the competing risk of death in the longitudinal analysis, and that was performed as part of the sensitivity robustness analysis, and this slide highlights in yellow that when death is added to the model for the first longitudinal analysis comparing former control to control, there is still a significant reduction over the course of the trial. The former control is lower than control, and I'll show it -- it was done for every longitudinal analysis, but in the interest of time, I'm just going to show you this one and number four.

Next slide, please. And we see similarly for number four, adding death does not alter the treatment effect that we see going into Part 2 for former control. And this is the change in control. We compared the change in the control group versus the change in the treatment group to try and account for unknown longitudinal confounders. We see the change is far greater in the control group than the treatment group, because they have the new introduction of pulmonary artery pressure information.

Next slide, please. I'm going to turn it over -- I think several

people -- I think Dr. Cigarroa and Dr. Patton had questions; Dr. Yuh I think actually had a question in this area, too. Help us understand the relationship of these medication changes which we showed you to the pressures and how did this interact. So I think Dr. Abraham is going to address some of these.

DR. ABRAHAM: Yes. And, actually, let me have a slide down for a moment because I want to start off with a few sort of broad comments. And I am going to address at least three or four questions that were asked regarding usability of the system and pressure, in particular, and how medication changes affect pressure and what pressures do leading up to and following hospitalization. So I've got a series of a few slides to address those questions.

But I think it's important to reiterate or to make clear something that Dr. Adamson said early on in the formal presentation, that the approach here is one of stability management rather than crisis management, so patients whose pressures were substantially elevated at baseline, our goal by protocol was to lower those pressures into or toward a target range provided that no untoward effect occurred, such as hypotension or syncope or pre-syncope or worsening azotemia, and then to maintain it there. And if patients started off with lower pressures, then the job was to maintain it there. So this really is an exercise in stability management, not crisis management, and in that regard, it's the sum total of

medication changes and pressure lowering that influences outcome. We don't see there being a 1:1 relationship between a single medication change and avoidance of a hospitalization.

And what you'll see -- I'm going to start off with a case example, so we could have the slide up now, because one of the questions, I think, from Dr. Yuh was, you know, is there a clear relationship between change in medications and change in pressure. And I'm going to show you some aggregated data as well, but I thought that this case was instructive and really speaks to how the system is used.

So here you can see a patient who at baseline has elevated pressures, PA systolic, diastolic, and mean pressures are elevated above 25 mmHg. The goal for PA mean was to try to get this below 25 mmHg, if possible. And the investigator chose initially to increase the dose of a vasodilator in an attempt to lower the pressures.

Now, I also want you to note the timeframe shown on this slide, the dates shown on this slide, because this also is indicative of this approach to achieving and maintaining stability rather than managing crises. You'll see that the management of this patient unfolds over several weeks, not over several hours or a day or two. So the investigator increases the dose of the vasodilator in an attempt to meet the study goal of lowering the pulmonary artery pressures. And what you see over the ensuing three or four weeks is that pressures don't come down. They actually stay about the

same or even trend upward a little bit more. And the investigator now decides to increase the dose of a diuretic. And then gradually over the next few weeks, the pressures start to fall so that at the end of this tracing on the far right-hand side of the slide, the PA diastolic pressure has now fallen below 25 and the PA mean pressure is nearing that goal.

So this is a simple example, a single example of sort of how this is used, the approach to maintaining, achieving and maintaining stability. And I think it does show in a single case example how some medications can result in a response to PA pressure, here specifically the diuretic, but it does also show that those responses are not always acute responses. They manifest over some period of time. Sorry for the feedback.

The next slide answers specifically, or is specifically responsive to the request for the same data that was shown by Lynne Stevenson from the COMPASS Trial. So this is the exact same representation but now using CHAMPION Trial data. So what we're looking at here are the average PA mean pressures prior to heart failure hospitalization and then seven days afterwards. You can see depicted on the horizontal axis the timeframe is six weeks, four weeks, two weeks, one day before hospitalization, and then seven days after. And you see a pattern that is identical to what Lynne showed you from data from the COMPASS HF Trial. Pressures gradually rise over weeks preceding a heart failure hospitalization, and as we would expect in the setting of management of acutely decompensated heart failure in the

hospital with the aggressive use of IV diuretics, those pressures fall back to, or even in this case on average slightly below, where they started at six weeks over a few-day period of time.

Next slide. The next slide is responsive to Dr. Cigarroa's question although only --

DR. PAGE: Before -- Dr. Abraham?

DR. ABRAHAM: Yes?

DR. PAGE: Thank you, but before we go on, I just want to ask Dr. Yuh whether that's getting --

DR. ABRAHAM: Okay.

DR. PAGE: -- to his question.

DR. ABRAHAM: Can we go back to the prior slide?

DR. PAGE: Because I think his question was response to alert for pressure as opposed to response to hospitalization, but Dr. Yuh?

DR. YUH: I recognize the limitations you had in terms of the data that you had to accrue in a short period of time. But I think what you're telling me is giving me the information that I think I need to know.

DR. PAGE: Thanks, Dr. Yuh. Sorry for the interruption.

DR. ABRAHAM: Thank you. No problem.

So let's go on to the next slide. Now, I know that Dr. Cigarroa asked specifically for a quartile analysis. We just don't have it or didn't have sufficient time to put that together. But what we do have is a dichotomized

analysis based on baseline pulmonary artery mean pressure and the effects in both the treatment and control group on area under the curve pressure over the first six months of the study.

So remember all patients had a right-heart catheterization at baseline, so the dichotomized variable here, if PA mean pressure less than or equal to 32 or PA mean pressure greater than 32 is on the basis of that baseline right-heart catheterization in all patients, treatment and control. And then we're looking at the area under the curve change in pressure over the first six months of randomized access.

And what you see here, which I think is not surprising and somewhat reassuring, is that patients whose pressures were not seen to be elevated or terribly elevated at baseline did not have a reduction in pulmonary artery pressure, whereas those pressures whose mean PA pressures started at above 32 mmHg had their pressures lowered. And those in the treatment arm, those who had knowledge of pulmonary artery pressure throughout that six-month period of follow-up depicted on this slide had a significantly greater reduction in PA pressure than those in the control arm. Okay.

DR. PAGE: Dr. Lange?

DR. LANGE: I'm having a hard time knowing what AUC under the curve is, so can we put that in millimeters of mercury?

DR. ABRAHAM: I can -- it doesn't translate exactly because,

remember, as you saw from the earlier case example, you know, pressures go up, pressures go down. Some patients start with low pressures that need to come up, and some patients start high and they need to come down. And we learned this lesson actually from the COMPASS HF Trial that simply looking at pressure at baseline and at six months was relatively uninformative. It's what's happening the entire time in between.

So then what we're looking at here is essentially the cumulative, you know, reduction in -- or the net reduction in pulmonary pressure over that six-month period of time. So we essentially add all the ups and all the downs for each individual patient, and you draw an area under the curve of pressure change from baseline.

DR. LANGE: That area under the curve is a product of height times the length, one of them being millimeters of mercury, the other's time of day. So if you divide that by 180 -- essentially, that's what you've done is you've given me -- I can get a mean pressure from that just by dividing that by 180? It goes up and goes down, but what you're showing me is an area under the curve, so over the course of six months, if you divide that by 180 days, it would be the mean pressure change, would it not?

DR. ABRAHAM: Yeah, that's right, yeah. Yeah, okay. It's about a 3½ mm reduction in the treatment group with PA mean at baseline over 32. Okay? Okay. Yes?

DR. CIGARROA: And were these primarily all in individuals who

had a PVR of less than two Wood units --

DR. ABRAHAM: Yeah, I --

DR. CIGARROA: In your baseline demographics, I think the average was 1.8, so I would imagine that the majority of these individuals did not have an elevated PVR?

DR. ABRAHAM: I don't know actually, haven't looked at that. We can try to get that data together. Jay, do you know?

DR. YADAV: I don't know off the top of my head, but there are a few patients with high PVRs, like 4 or 5, but the mean is as you indicated below 2, but there were -- I know there were a few patients that I remember noticing did have PVRs of 4, 5, 6.

DR. CIGARROA: Thank you.

DR. ABRAHAM: Okay. Let's go on to the next slide, because again, I think this just builds on the answer, also may add some additional information relevant to Dr. Yuh's question as well.

So now we're looking again at area under the curve data in treatment subjects who had heart failure medication changes based on PA pressures, specifically vasodilators and diuretics, as recommended in the protocol, and we're looking at the effects of those medications specifically on the change in AUC pressure. So, again, consistent with the hypothesis, a change and increase in a vasodilator or diuretic seemingly results in a reduction in pressure by this AUC measurement and, again, in the

presentation made earlier is closely related to a decrease in risk in hospitalization.

And then I have one more slide because the FDA has asked us to focus on Part 2 data, and so I do want to reassure the Panel that the effects on pressure seen in Part 1 are, in fact, manifest in Part 2 as well, so there's no new mechanism of action presenting in Part 2. It's the same story from Part 1 to Part 2. So if we look at the change from baseline in PA mean pressure, again using the AUC methodology, in the treatment patients in Part 1 and compare that to the former control patients, the control patients who now have first-time -- their physicians have first-time access or knowledge of their PA pressures in Part 2, you can see that the AUC reduction in pressure is strikingly similar between the two and supports the strikingly similar reduction in heart failure hospitalizations related to the fall in pulmonary artery pressure.

So I hope that that series of slides and our discussion has addressed your questions regarding pressure. If there are any other outstanding points, I'd be happy to try to answer them, but I don't have any other slides at the moment to show you.

DR. PAGE: Thank you very much.

Dr. Yadav, did you have some amplification there?

DR. YADAV: Yeah, we're trying to answer all your questions,

so --

DR. PAGE: Yes, please.

DR. YADAV: Yes, so I --

DR. PAGE: Unless, Dr. Borer, did you specifically want to address one of the slides that was just shown?

DR. BORER: No, it was a slide he showed before, but I can wait until the end --

DR. PAGE: Okay. Go ahead. Why don't you?

DR. BORER: You showed, and we received in our meeting materials, the average ejection fractions at the two different time points, and they're comparable; that's fine. But that doesn't deal with the very important issue that John Somberg raised earlier, which is, is there a differential response in people with HF_rEF versus HF_pEF. Do you have that analysis?

DR. YADAV: Thank you, Dr. Borer. Yes. We have been working on that, and Dr. Adamson actually is going to discuss that with you.

DR. ADAMSON: Thank you, Dr. Borer and Dr. Somberg, very interesting questions. And it turns out that stratification by ejection fraction was a prespecified subgroup analysis in the primary trial.

Before I go to that question, if we go to the previous slide, there was a question about the alerts, and Dr. Page, if I may address this question?

DR. PAGE: Yes, please.

DR. ADAMSON: The automated pressure alerts as well as the PA pressure downloads and database logins in the open access period of this study are shown and depicted in this slide. Obviously, no nurse communications, but the rates per week are comparable to those in the Part 1 of the trial. I don't have the absolute numbers. But let me remind you, or maybe clarify for you because we didn't make that very clear, that a automated pressure alert could be triggered by any of the parameters uploaded from that daily measurement. So it could be PA systolic, PA mean, PA diastolic. Those were initially set at the goal levels of the clinical trial, where we were expecting the investigators to try to reach as a goal.

Now, there was no protocol guidance or prohibition for the investigator to alter those thresholds. And, in fact, some investigators altered them such that they could get alerts every day on patients of interest that they were following. So it's hard to tie a specific action to an automated alert. The point is that the automated alerts were operant in the clinical trial, were manipulatable by the investigator and provided the investigator with a tremendous amount of input as to the patient's ambulatory pressures.

Now, let me address, if I may, just very briefly, the question of the prespecified subgroup analysis of individuals with preserved ejection fraction. Before the trial was designed and implemented, we defined preserved ejection fraction as those who had an ejection fraction greater

than or equal to 40% at the time of baseline enrollment. Those with an ejection fraction less than 40% were considered to be reduced ejection fraction patients.

Now, the average ejection fraction, in the group of 119 patients who had an ejection fraction greater or equal to 40%, was 53%. So this represents a group of individuals whose average ejection fractions were 53%. As one can see with the experience in Part 1 of the trial, the treatment group patients with preserved ejection fraction had a heart failure hospitalization rate of 0.43 in the treatment group compared to a heart failure hospitalization rate of 0.86 in the control group, a significant reduction in the need for hospitalization in this very important group of patients, in fact, a magnitude that was slightly higher than those with reduced ejection fraction, confirming that this approach does indeed have clinical benefit in this population.

Thank you.

DR. PAGE: Thank you.

Dr. Yadav?

DR. YADAV: Thank you, Dr. Adamson. I think Dr. Stevenson is going to address the question directed to her by Dr. Zuckerman regarding characteristics of hospitals.

DR. STEVENSON: First of all, just -- Lynne Stevenson. Just to review, we talked about this morning comparing academic centers to

community centers. To remind you, the CardioMEMS device is a diagnostic tool. It's not a therapy itself. And one might hypothesize that a diagnostic tool in academic centers might be better used because they know what to do with the information. On the other hand, for some diagnostic tools, in fact, it's most helpful in people who don't have quite as much experience. So one wouldn't necessarily know what to expect to see. But as we discussed this morning, we saw a substantial impact in both the academic centers and the community centers, if anything, perhaps slightly larger in the community centers. But clearly reassurance that we see it in both.

Now, we don't have the kind of analysis that Dr. Zuckerman asked us for in terms of the individual variance. We can work on that. Next slide. But what we do have is looking at an analysis of the high enrolling and low enrolling sites. And you can see the majority of sites, 43, enrolled less -- fewer than 10 subjects. And if we look at their event rate in the control arm, shown over on the right, it was .53, so a higher event rate in these low-enrolling sites, which could be due to differences in population, differences in other approaches to this group. But clearly a substantial reduction even in the sites that were relatively low enrolling with less experience, with a 35% reduction. And in the sites with more than 10 subjects, a substantial reduction, but in fact, certainly it was no better in that group.

So I think this gives us some comfort that it doesn't require a large amount of experience to begin to see the benefit of what is basically a

very sophisticated diagnostic tool.

DR. PAGE: Yes, Dr. Lange?

DR. LANGE: Thanks for presenting this. Can I ask about your interpretation of this particular slide for just a second? I would appreciate your opinion about the bottom line. That is, sites that had more than 10 subjects, presumably those that had more experience with heart failure, the control group and the treatment group event rates look very similar, that is, a .09 difference. Otherwise, it's a relative risk ratio of 21.7. But when you look at absolutes, it looks relatively -- what is your interpretation of that?

DR. STEVENSON: Well, in this point, as I say, there are different ways of trying to explain the differences between high-enrolling and low-enrolling sites. In terms of the overall event rate over six months, which is what's shown in that column, it's slightly lower even in the control group, but there's still a significant reduction with the monitoring. I think we need to do a much more granular analysis of the differences in sites, but I think this gives us some reassurance that certainly in -- it doesn't take a great deal of experience because the low-enrolling sites, in fact, did very well as far as a reduction in events.

DR. LANGE: And apropos, it looks like a 21.7% relative risk reduction. Can the Sponsor attach a p-value? I mean, I hate to rest on p-values, because it's post hoc, but it'd be nice to know if it was statistically significant, and if the Sponsor is able to do that, that'd be great. If not, I

understand.

DR. STEVENSON: I'm sorry. I don't think we've done all these detailed analyses with that kind of granularity, but certainly that's something that we can look at in more detail looking at more characteristics than just the site enrollment.

DR. PAGE: Does the Sponsor have any other responses to our questions?

DR. YADAV: Yeah, we're trying to get through the whole list. We're almost done. So then I've got a series of questions by Dr. Blumenstein and the statistical issues, which Dr. Holcomb and Dr. Ogenstad will address, and Dr. Lange had a question about sensor performance, which Dr. Holcomb will also address.

DR. HOLCOMB: I'm Richard Holcomb. I'm a statistician and consultant for the project. The first slide I'd like to present to you addresses the question raised by Dr. Lange with regard to a comparison of the right-heart cath results in the sensor. What this slide up here shows you are results from catheterizations that occurred out to a period of slightly over two years and is a representation of a Bland-Altman comparison in which you are plotting the difference between the two sensors over the average of the two sensors and trying to look for trends with regard to drift in the accuracy and so on over time.

Let me point out a couple of things here. The mean difference

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across this time period was only 1.1 millimeter, so a very low estimate of the bias, the difference between the sensor value and the right cath value.

Neither of them can be assumed to be 100% accurate, so whether or not the difference is reflecting an error in one or the other is unknown with this kind of analysis. The other is that the variability associated with it, and you see here the limits of agreement approximately 2 times 4.6 on either side of that mean bias. That also reflects potential errors in either the sensor or in the right-heart cath evaluation that was done.

The final point on this graph is if you look at the pattern of the differences over time, there's no perceptible drift in the accuracy of the sensor over time, which is, of course, reassuring.

DR. PAGE: Dr. Lange?

DR. LANGE: It's great, by the way. I appreciate this. The Bland-Altman's a great way to display this. I appreciate that very much. So you have a sense of percentage? In other words, if the PA mean pressure is 100, 4 or 5 millimeters doesn't make very much difference. If it's 35, it makes a little bit more difference. And you may or may not have this as a percentage of the -- if you do, that's fine. If you don't, don't worry. I'm not expecting you to --

DR. YADAV: I don't know if we have the slide handy, but we did look at that a long time ago, about that, and the percentage does not -- is so -- at lower pressures, the difference is less, so it doesn't increase --

DR. HOLCOMB: Yes, that's sort of a common characteristic if you're familiar with these in vitro diagnostics is that you sometimes separate the range and have a percentage and an absolute, depending on the range. That has been done, but we can't display it here, yeah.

DR. PAGE: Dr. Blumenstein, I believe, had outstanding issues. Are you going to address those?

DR. HOLCOMB: I am, and I intended to do that if there are no more questions on --

DR. PAGE: I think the Panel is satisfied. That was a very useful graphic. Thank you.

DR. HOLCOMB: Okay. We're now moving into some questions from Dr. Blumenstein. We have answers to perhaps three of the four questions, or maybe four of the five, but not all of them. So let's proceed.

This first display that you see here is a distribution, a frequency distribution, of the length of hospital stay. And the number of days of hospitalization is on the axis at the far bottom. The summary statistics are in the boxes in the upper right-hand corners. You see, in general, just eyeballing this, that the distributions are roughly comparable within the ability of the human eye to see. They have comparable mean values, comparable median values, comparable distributional values, with an excess of events, of course, in the control group, which is the panel on the top.

Now, one sub-question related to this that Dr. Blumenstein asked was whether or not we incorporated any sort of adjustment for the length of the hospital stay into the estimate of the hospitalization rate, and although there were, in most cases, a relatively short hospital duration, so that wouldn't be a factor, there were some that were extended hospitalizations, but the analysis did not take into account a blanking period for risk associated with hospitalization due to being in the hospital.

DR. PAGE: Dr. Blumenstein, did you have any comment on that issue now while we're there, or do you want to save that for later?

DR. BLUMENSTEIN: Well, I'm waiting for the third shoe to drop.

(Laughter.)

DR. PAGE: With that, then we'll proceed.

DR. HOLCOMB: Well, I hope I have at least three shoes, but yeah, go back one. We skipped over this one. This one represents the Kaplan-Meier analysis of the combined endpoint of death or HF hospitalization over the randomized period with the tick marks on the actual graph to give you a sense of the pattern of the censoring, which you can see just visually is not clustered at any particular point in time. You also have the associated logrank statistic with this and our overall results that are indicating that for this composite endpoint, the hazard ratio was .77.

DR. BLUMENSTEIN: No, what I was referring to was the

frequency -- the distribution of frequency of events by arm.

DR. HOLCOMB: That's coming.

DR. BLUMENSTEIN: Oh, okay.

DR. HOLCOMB: Yeah, that's on the next slide. I hope this is what you were looking for.

DR. BLUMENSTEIN: I think so.

DR. HOLCOMB: Yeah. This graph shows the frequency of heart failure hospitalization over the randomized period. On the left on these are the control, the blue, and on the right are the treatment, the orange-colored. And I think what's remarkable about this, potentially, is how many people even over the whole randomized period, if you look at their most common outcome, and that is no event, so there have been comments elsewhere about these distributions. And we're really in a situation where these people are at high-risk for having these hospitalizations, but it's not a guarantee that in any period of time they'll actually experience one.

DR. PAGE: Dr. Ohman?

DR. OHMAN: So if I interpret this -- this is Magnus Ohman -- interpret this figure, if I look at more than one hospitalization, it looks like in the randomized phase, it's reduced by 50% multitude of hospitalizations. Is that an adequate -- am I interpreting this figure correctly?

DR. HOLCOMB: Based on what you see here, the net effect is a

reduction in those multiple hospitalizations -- percentage, yeah.

DR. OHMAN: Which is clinically very significant. Interesting.

DR. HOLCOMB: Any other questions or -- Jay?

DR. YADAV: I'm sorry. Keep going. I'm just sort of -- do you have anything?

DR. HOLCOMB: All issues -- Dr. Blumenstein?

DR. BLUMENSTEIN: That's what I wanted to see. I just wanted to get a good feel for the data so that I could make an assessment of the validity of the Andersen-Gill model and things of that nature and the assumptions thereof.

DR. HOLCOMB: Yeah, a discussion of the Andersen-Gill is forthcoming.

DR. YADAV: Yes, there was a question about that, and Dr. Ogenstad is an expert in this model, so I've asked him to comment on that, and then I think Dr. Packer has one comment, and we're done with our answers.

DR. PAGE: Thank you.

DR. OGENSTAD: So I'm Stephan Ogenstad at Statogen Consulting, and I'm an independent statistician here.

Yes, the Andersen-Gill model, I thought it was valuable to look at it just for a minute. It's a very powerful model. If you look first at the beta coefficient 1 there, which has to do with the treatment group, that is

basically the Andersen-Gill model. What differs the Andersen-Gill model from the Cox proportional hazards model is that there is an indicator telling if the patient is still at risk at a certain time point. Of course, if it's a Cox model, then the patient after death will not keep that indicator variable.

What we have, too, in this model is that we have the beta coefficient 2 and we have the beta coefficient 3. They can then model in which part of the study, if it's in Part 1 or Part 2, that the patient belongs and also can model the transition from Part 1 into Part 2.

So apart from adding on a number of covariates, baseline covariates, in this model, this model actually models what happens when patients transition from Part 1 into Part 2, irrespective of if there is censoring, it takes care of the censoring. Of course, events are of different types as in all kinds of studies, even survival analysis, censoring is not at random. But this is a very powerful model.

What it has, too, it has -- you see the gamma coefficient with the W , the W there is a frailty component, which is a way of looking at this model instead of having covariates, a number of covariates that we haven't measured or haven't even thought about, the frailty picks that up in this model.

We did, and Dr. Magnus Ohman here, he asked about the distributions. And I'm sure he was asking that question very familiar with that there are some uncertainties if we would have some extreme patients

in the study. We looked at that. We modeled this in many different ways. We used sandwich estimators, which is a robust estimator that inflates the variance, so that's the price that you pay for doing this. But we tried this out in many, many different ways. We gave different weights to if a patient would die, a patient transitioned into Part 2. And what is very striking from all these types of analyses that we have done is that the results are very, very consistent.

Any questions?

DR. BLUMENSTEIN: So the model as represented there doesn't have the array of baseline covariates represented?

DR. OGENSTAD: It doesn't have, but we could just hang on a beta 4×4 , which could be a vector of covariates.

DR. BLUMENSTEIN: But did you?

DR. OGENSTAD: We did that, too, yes.

DR. BLUMENSTEIN: Okay. And did you have covariates coming into the model at the time they transitioned from Part 1 to Part 2?

DR. OGENSTAD: That would then be a time-dependent covariate.

DR. BLUMENSTEIN: Yes.

DR. YADAV: Yeah, that's -- and we can pull that slide up again. That was the slide that Dr. Packer showed quickly in the first presentation, where the -- the forest plot with the covariates. If we can get that up, we

can show it to you again.

DR. BLUMENSTEIN: No, I remember the slide, and I remember you saying that. I just -- I didn't see the term for it in this model, so I was wondering -- just clarifying that confusion.

DR. YADAV: I think this is the primary model.

DR. OGENSTAD: Yeah, so --

DR. BLUMENSTEIN: Yeah.

DR. OGENSTAD: -- this is the primary model that doesn't have the array of covariates, but this model can be extended by just hanging on more and more covariates, so that's very easy. It's a generality over this model, and we use that in all types of analyses that we did.

DR. PAGE: Dr. Blumenstein, may I ask you to translate for the rest of us what you're seeing here and your satisfaction with the response that we've received?

DR. BLUMENSTEIN: Well, I mean, I'm satisfied that the Andersen-Gill model was correctly implemented. The Andersen-Gill model allows you to model recurring events, and that's the situation here. The reason that I asked the questions that I did, for example, about the duration of hospitalization and about the number of events, the distribution of the number of events, was that I was concerned about two things. Number one, if the hospitalizations tended to be long, then I'm not sure what an event is because there's a period of time when you're hospitalized and you can't

have an event. And so if, for example, if patients were going in on a mean of 30 days over a six-month period, then you aren't counting events correctly. And I'm still a little concerned about that, but you know, I've seen worse. Let's say it that way.

DR. OGENSTAD: If I could add, what is reassuring here is that, as we have looked before, the distributions of the duration of stay is very, very similar between the two treatment arms.

DR. BLUMENSTEIN: Yeah.

DR. OGENSTAD: So that shouldn't affect too much. It's like freezing the time a bit.

DR. BLUMENSTEIN: Yes. And then if you have lots of patients that only have one event and very few patients that have more than one event, then the question is, well, why use the Andersen-Gill? Why not just use a time to first event, time to first bad thing-type of model? And so I'm --

DR. OGENSTAD: That was something --

DR. BLUMENSTEIN: This is always difficult for a statistician to say it this way.

DR. OGENSTAD: Yeah.

DR. BLUMENSTEIN: I'm disappointed there weren't more patients with more events --

(Laughter.)

DR. OGENSTAD: Yeah, I know. It was actually discussed many

years back with the FDA to use time to first event, and it was decided to use a count model and a count endpoint instead of time to the first event.

DR. BLUMENSTEIN: Right. And so then, so then --

DR. YADAV: There are actually -- I would just -- there are actually a lot of events in this trial, so, you know, there are, I think, 400 events in Part 1 for hospitalizations not counting death, and I think --

DR. BLUMENSTEIN: Well, but, no, it had to do with the number of patients that had more than one event, and so, you know, I would have liked to have seen more. That's always difficult for the statistician to say, but -- and then another issue is on the -- on models like this is what's happening in the underlying disease and is the patient degenerating over time and so on and, therefore, whether that's adequately modeled in these models. In other words, is the event rate considered to be stable over time? So --

DR. OGENSTAD: I actually did --

DR. PAGE: If I may, sir, if I may, I asked Dr. Blumenstein a question, and he's responding to the Panel. If we have more questions, I promise you we'll ask, but Dr. Blumenstein, please continue.

DR. BLUMENSTEIN: Yeah. Right. And you can perhaps respond to that later, but that's not my major concern. So I'm not unhappy about the use of Andersen-Gill. I think I always like to see time to first event anyway because I think it's at least confirmatory and perhaps even more

meaningful if most patients have only one event.

But the real issue is the patients coming into it and the fact that you have groups of patients that are being compared that aren't comparable, and they're not, and they're not comparable because you treated them differently, and you can show me covariates and try to convince me that the distribution of baseline covariates at the time they transition from Part 1 to Part 2 are comparable. And I looked at them, and I don't know. I would want to see some more -- something more convincing than a list of p-values, or whatever.

But the fact is that the patients get into Part 2 because they've been treated in Part 1, and because they've been treated in Part 1, they're different if they survived that. Now, you could make an argument that, well, the patients that survived that and get into Part 2 are comparable, but there's already more deaths in part -- in the control arm in Part 1. And so there's a really confusing and nonrandomized comparisons that are being done here, and that's the crux of the matter.

DR. PAGE: And, Dr. Blumenstein, you're summarizing beautifully, and that's going to be a major part of our Panel deliberations, which don't include the Sponsor or the FDA representatives unless we call on them. In terms of do you have any further questions of the Sponsor regarding this topic, or shall we let the Sponsor continue their response to the questions that we generated before lunch?

DR. BLUMENSTEIN: I'm done.

DR. PAGE: Thank you.

Dr. Yadav, please proceed.

DR. YADAV: I just wanted to add this is a time to first event analysis here, Dr. Blumenstein. Thank you.

DR. BLUMENSTEIN: Yes. I have seen -- I'm sufficiently satisfied with the time to event analyses, especially your survival.

DR. PAGE: Dr. Yadav, before you go on, Dr. Ohman had a comment.

DR. OHMAN: Yes, to build on this whole theme, so what sort of asked for, and I recognized it may be hard to get this at this short notice, but the important thing is that the survivors are survivors. They are going to have slightly different baseline characteristics than the non-survivors obviously. So, therefore, when you come to Phase 2 of your trial, you're bringing in different covariates to your model. And I was interested in the delta of those covariates that were brought into the model because they essentially tell us a little bit how different they are.

And, of course, you can take all your groups and put up the p-values, and they're going to be similar enough because the number of deaths are not that many. But what's really going to drive it is the combination of variables that really drive the deaths. So this could be creatinine clearance; it could be a lot of different things.

I recognize that you may not have that information, and I would totally respect that. That's a very difficult question to ask. But that's really what I was after, to try to address the similarity on a multitude of things as we proceeded into Phase 2.

DR. YADAV: Yeah, I'm not sure how to -- okay. So we'll -- I just -- I had forgotten about the question Dr. Patton had asked about the DSRCs, so I do have another slide.

DR. PAGE: Yes. Please go ahead.

DR. YADAV: If I could have the DSRC slide, please? This is the device system-related complications. So this is a description of those eight events. And what you're seeing here is the adjudication by the Clinical Events Committee, but this is all either possibly or definitely related events. I'm happy to walk you through them, but they're certainly from an interventional perspective, they're very benign sort of things. I'm happy to discuss it further if you would like.

DR. PATTON: This is fine. Thank you.

DR. YADAV: So I think Dr. Packer had a question that he was going to answer. Then we are done with our answers to your questions.

DR. PAGE: Great. Thank you.

Dr. Packer?

DR. YADAV: Thank you.

DR. PACKER: I wanted to just make two points. Can we bring

up Slide 106? 106? Dr. Blumenstein mentioned the point about how one could potentially be comforted by the fact that there's differential exiting of patients. And, clearly, I totally agree with Magnus. The covariates are insensitive to giving that kind of reassurance. We showed them because we had them.

But I think this is particularly informative. This is actually the instantaneous risk of heart failure hospitalization during the course of randomized access in the control group. So you can actually see the fall-off in risk because of the exiting of high-risk patients. And you can see that in the treatment group as well. What's striking here is the sudden drop in risk when there's new access to PA pressures compared to continued access to PA pressures and pretty much the same attrition over time. So if attrition per se was causing a fall in the rate of heart failure hospitalizations, we would expect it to be gradual like this, not sudden like this. So I wanted to make that point.

And just one quick point to Rick Lange's question about the average change in pulmonary pressure. Rick, I think your calculation was about right. In the people with high PA pressures, it's about a 3½ mmHg decrease. What's interesting is how large that is. Because what we've learned is in systemic hypertension trials, 1, 2, 3 millimeters of difference on a population basis is associated with a big reduction in the risk of morbidity and mortality. And we've also learned with PA pressure in heart failure that

a small population-based decrease, 3½ is associated with a rather meaningful decrease in hospitalization for heart failure. And that's why I think when Dr. Yuh mentioned the point about, gee, he would like to see that the PA pressures fell in the control group when they went into the former control group, you saw that they did, and that makes everything hang together.

DR. PAGE: Thank you.

So has the Sponsor responded to all the questions or issues that we had outstanding that you were able to respond to?

DR. YADAV: I think we have done the best we can, and certainly, if we forgot one by accident, please remind us, and we'll see if we have it, but I think we tried to get to all of them.

DR. PAGE: And I believe our questions were all to the Sponsor at that point.

Does anybody on the Panel have any further questions of either the FDA or the Sponsor? I specifically want to recognize Ms. Timberlake, Ms. Mattivi, and Ms. Currier to make sure you have no further questions that you'd like to address now. We will be asking for your comments during our deliberation session. I'm seeing no.

And any -- Dr. Yuh?

DR. YUH: I have a quick question for the Sponsor just as a matter of clarification. For the admissions, the re-admissions to the

hospital, were they -- do you have a sense of what they were driven by? Were they driven by the physicians that were seeing these PA pressures, or were they kind of a grab bag of all types of patients initiated going into the ER on their own? Do you have a sense of that? I know you probably don't have any hard data, but I just wanted to get a sense of who -- what was driving these readmissions?

DR. YADAV: No, thank you. Actually, we do have hard data on that, so thank you. Just we had -- yeah, we did it a little while ago, and we do have it. While the slide comes up, I can describe it to you. So most of the admissions were through the emergency room. And, indeed, it was often not the emergency room of the site. So a lot of these patients live in other small towns and so forth, so they often were at a different ER. So if we can have that slide up, please?

So most people were admitted through the emergency room by non-study physicians. We actually looked at the ER records, and there was not evidence of even PIs calling the patient or the ER doctors. The groups were well balanced in terms of the patients admitted after a study visit, right? I think the actual concern is were people seen in the clinic and admitted preferentially, and that was not the case. And if you look at the difference here over the entire study, it is essentially driven if one looks at -- it is driven by the emergency room difference. And there's no difference for study visits or clinic visit -- hospitalizations following that.

Thank you.

DR. YUH: Great. Thank you.

DR. PAGE: Dr. Jeevanandam and then Ms. Mattivi?

DR. JEEVANANDAM: I had one question I want to follow up to the adverse events. Interested in how many of these patients have pulmonary emboli or pulmonary infarctions?

DR. YADAV: Thank you, Dr. Jeevanandam. That was looked at very carefully by the Clinical Events Committee, and there were no such events.

DR. JEEVANANDAM: Oh, that's pretty good, because in this patient population, you would expect them to have -- I mean, that's 500 heart failure patients.

DR. YADAV: Well, yeah, let me rephrase. There were no pulmonary emboli due to the sensor. There were patients who had the sensors in the left lung, the pulmonary embolus in the right lung, and there were a couple who were in LVAD and transplant who had -- so yes, there were pulmonary emboli but not due to the sensor, as ascertained by the CEC.

DR. PAGE: And, Dr. Cigarroa, do you have a comment with regard to that specific issue? Go ahead, please.

DR. CIGARROA: So certainly not to the -- so the pulmonary emboli were observed at a site in the lung distribution distinctly different

than the sensor but still venous with the manipulation of 11 French sheath that could have caused trauma theoretically and served as a nidus, so how did you make that distinction?

DR. YADAV: Sure, you know, good question. And, again, I showed you the DSRCs, which is all events within 30 days, and then the Clinical Events Committee looked at every such event. And none of the pulmonary emboli were even remotely near the vascular access event.

DR. PAGE: And Ms. Mattivi --

DR. CIGARROA: Thank you.

DR. PAGE: -- did you have a comment or question?

MS. MATTIVI: Actually, if Dr. Ohman had a question related to the same topic. Mine was a little different, and obviously, from the consumer perspective, a bit elementary in context of the rest of the conversation here. But one of the points that you just brought up in terms of we're talking about the sites, I was wondering if -- and perhaps this was looked at in the preliminary studies about rural versus urban sites. I mean, we talked about academic versus non-academic and the amount of enrollment. But I could see this having an impact for rural patients and was wondering if you had looked at that.

DR. YADAV: Yeah. That's a very good question. I don't know if I can get a slide up, but that is something that's been discussed with our investigators. And, you know, we had 64 centers around the country, and

one of the comments they got from our centers that, you know, are in Nebraska and, you know, way out west in rural areas was how it really let them leverage their care network and efficiency. They don't have to see the patient in person. They're more able to efficiently deliver care, because you're right, in rural areas, it is not so easy just to go to the doctor. And what Dr. Stevenson mentioned that most days -- you don't see the patient most days, well, that's even more of a challenge in rural areas, so I think that is a particular attribute of this type of technology.

MS. MATTIVI: And whether that had any influence on patient compliance?

DR. YADAV: Yeah, I think the best we go is show you the community versus academic. I'm not sure how we would define that more precisely than that. And for the academic community, there was no difference.

DR. PAGE: Ms. Currier and then Dr. Ohman?

MS. CURRIER: I have been interested in this question ever since I heard about CardioMEMS, and I saw that on your proportion of who you allowed in the trial, you had some people with pulmonary hypertension, right? And so then my question is whether this device can be used in monitoring pulmonary hypertension. And, furthermore, I'm kind of confused about if you get higher pulmonary artery pressures, how you know whether that's due to heart failure or pulmonary hypertension.

DR. YADAV: It's a good question, Ms. Currier. So we have to distinguish between primary pulmonary hypertension, where it's called PAH, and secondary pulmonary hypertension. So we're dealing here with really secondary pulmonary hypertension. So these are patients who have systolic or diastolic dysfunction, but left ventricular dysfunction, which leads to pulmonary hypertension. So it is not the group that I think you are referring to, which is a different etiology. So this study did not study that population, and I think it would be a topic of interest, but that is not part of this study.

DR. PAGE: Dr. Ohman?

DR. OHMAN: Yeah. When you mentioned that you had covered most of it, this may be an area that you haven't been able to get us the answer today, but I don't want to be remiss of actually the gender analysis that I spoke about, namely, the issue of the cause of death in men versus women during the conduct of this study.

DR. YADAV: No, I didn't forget. And were we able to put together a slide? I don't know if we have a slide. I can tell you off the top of my head that the roughly -- what was it -- can you help me out? What was -- okay, so this is -- these are the --

DR. PAGE: We're not seeking what you're looking at, so --

DR. YADAV: Yeah, I know it just came up. They're very quick. When I turned around, they put it up. So 317, please? So then this is -- now, this is just the data in the first six months. We weren't able to get together

data for the entire randomized access, but this is that seven versus three difference in mortality we talked about in the primary endpoint phase of the study. And you can see in the treatment group, all the deaths were due to heart failure. In the control group, there are four cardiac deaths and three non-cardiac deaths, and we can try to get it for the whole rest of the trial, but this is what we have right now.

DR. PAGE: Thank you.

Dr. Jeevanandam has a question.

DR. JEEVANANDAM: Just one quick question. You know, we looked at admissions and death. How many of these patients went on to get transplanted and LVADs?

DR. YADAV: Yeah. Good question, Dr. Jeevanandam. I think it is roughly 40, 50 patients. Is that correct?

Okay. Here we go. Here's the slide. I was very close. 518, please. So it's 39 patients. And so these are patients getting a VAD or a heart transplant. They're balanced between the two groups. And this is -- we can show -- that's for Part 1 or randomized access. Then we can show you the next slide, please, 519. This is over the complete duration of the trial, Part 1 plus 2, so it's about 66 patients, and they're well balanced between the two groups.

Thank you.

DR. PAGE: Thank you for that amazingly quick response.

DR. YADAV: It's not me, it's the guys in the back --

DR. PAGE: I see the crew back there, and my compliments to them. All right.

DR. YADAV: They're young; they're young.

DR. PATTON: In EP, we follow devices remotely for a lot of patients, but we often have trouble getting them enrolled into our clinic because they don't want to. And I think what we ask them to do for device clinic is a little bit less of an encumbrance. How did you train the patients in this study to do this and help motivate them to continue to do so many pressure readings?

DR. YADAV: Yeah, you know, that's a great question. I'm going to let Dr. Adamson answer that. He was in the study. But just from what I -- when I talk to patients over the course of this five-year trial and met some of them, you know, they were really enthusiastic because they felt like they were participating in their care, and they felt more empowered and less powerless. But, Phil, can you --

DR. ADAMSON: Sure. So that's a good question because, you know, I actually do run lots of EP trials as well. Patients with heart failure have a very significant need to feel secure. And I think one of the ways that this device and monitoring provides them with that is they know someone's looking. There was, in my own personal experience, I reflect what Dr. Yadav mentioned, and that is that patients embraced the concept. They get up and

weigh themselves every day and write it down. They measure their blood pressures. I have patients that measure the amount of sodium they have in their diet by calculating somehow off of labels. So I mean, patients are very motivated especially if they find that they're feeling better and they have a good outcome. And so over the duration of this trial, we had a very high compliance with the daily uploads from home. It was pretty amazing given what we asked of them.

But when you step back and ask what do we ask heart failure patients to do anyway, we ask them to weigh themselves. We ask them to do the other things, take medications three times a day. And they're very motivated because the disease is very bad. And they do get better. And that reinforces them.

DR. PAGE: Thank you.

Dr. Yuh?

DR. YUH: One last question from me for the Sponsor.

Dr. Carome during the Open Public Hearing mentioned that there was a slightly higher rate of physician communication with patients in the treatment arm, is that the case, than the control?

DR. YADAV: Yeah, no, that is not the case, and I think Dr. Adamson mentioned that during his presentation. In fact, we can put it up. Slide 406. This is a more detailed description of what he presented. And, Phil, if you want to talk about it, or it's pretty self-explanatory. It's very

well balanced if you look at all contacts. Thank you.

DR. YUH: That's all I needed to see. Thanks.

DR. PAGE: Great. I want to thank the Sponsor and the FDA for excellent presentations and an outstanding response to the questions that we had.

We're now going to begin the portion of the meeting where we as a Panel will deliberate among ourselves. I want to open the floor to the experts around the table to begin deliberating on any issues that you may have with the data you've heard today, either this morning in the Panel presentations, the discussions with the FDA and the Sponsor, or any of the material you've read in your Panel packs.

I would like to set the stage for the next hour that we're concentrating on the issue at hand and not going through a rehash of the original randomized study. You've heard a number of comments that you may or may not find compelling, but my sense of this Panel and the job at hand for today is that we need to put that aside other than taking advantage of the data that we feel are, especially in the longitudinal study, are potentially valuable, discuss whether we think they are valuable enough -- valid enough for us to come to a conclusion that this device is both safe and effective.

The other thing that I personally am comfortable with is that safety issues have not been of great concern. They weren't of great concern

with the previous panel. So I think what we need to be looking at primarily is efficacy and the balance of risk versus benefit.

So I open this up to the Panel now, and we'll take -- we'll call on each person in the order they raise their hand.

Dr. Weisfeldt?

DR. WEISFELDT: I want to ask the statistically oriented people a question that may just reveal my own naivety and lack of really understanding what -- it's something that's bothering me. Let's say we took -- because in the control group, the hospitalization events seem to, by the curve, have occurred relatively early after entrance into the study. If we just broke the control curve at three months instead of letting it go to six months and then analyzed the control group the same way as you analyze between Phase 1 and Phase 2, would the result be the same as the Phase 1 and Phase 2 comparison, that the control group would, in fact, have a halving of the hospitalization rate, having nothing to do with turning on the pressure? Is my question clear?

Well, what I'm really saying if you just did -- you know, you got Phase 1, and then you got Phase 2 at six months, you just broke it at three months in the control group --

DR. BLUMENSTEIN: Well, I think, if I'm interpreting what you're asking is if you were to make -- to put on a Kaplan-Meier graph, the estimate from the control group in the randomization phase through three

months and then take the -- no, you're -- yes, and then take the first three months when those patients switch --

DR. PAGE: I think, if I may --

DR. WEISFELDT: The next three months.

DR. PAGE: I think Dr. Weisfeldt's asking whether what we're seeing is the natural history of this group.

DR. WEISFELDT: Correct.

DR. PAGE: That has nothing to do with turning this on. And if whether there's any signal looking at the control group during the first six months. Did you see any jump or change in that patient population?

Did I interpret that correctly, Dr. Weisfeldt?

DR. WEISFELDT: Very close.

DR. BLUMENSTEIN: Well, there's, you know, several things that could be done. I mean, I know that you don't want us talking too much about the original trial, but there -- I can't help it. The original trial had as the arm the use of the device plus nurse aid. And then it had as a control arm an installation of something and then all of the things that were associated with that. In other words, they had the little pad and they had the electronics, and they went through all the motions, the control arm patients did.

So in point of fact, the comparison is between what it is in the experimental arm and this kind of an artificial, the patient going through all

the motions in the control arm. So I'm not sure you could ever say the control arm represents natural history of anything because psychologically the control arm patients are going to be going through all the motions.

And I don't know whether that was discussed at the previous time or not. I don't know what implication it has, because I don't treat these patients. But I can't help but recognize that -- and then another aspect of that is the interaction with the physician. The physician is unblinded. The physician deals with those control arm patients in a way that's different than they deal with the patients in the experimental arm. And I don't know how -- what the impact of that kind of behavioral milieu does to the outcome of this. So I don't know about natural history.

DR. PAGE: Well, thank you. And just so I'm clear. When I'm asking for the Panel to concentrate on the analyses that are presented anew today, it's not ignoring the randomized or Part 1, at least for the control arm because that -- we had the analysis, the audit, that there was no nurse intervention in that arm nor in the control or treatment arms in Part 2.

Dr. Zuckerman?

DR. ZUCKERMAN: Dr. Blumenstein, thank you very much for your response to Dr. Weisfeldt's question. And we have lots of limitations in looking at these data. But is perhaps the best way to try to address Dr. Weisfeldt's question to look at FDA Slide 50, where during Part 1, if you look at the solid blue curve, certainly there may be the effect of the heart

failure hospitalization rate as a function of time decreasing somewhat in Part 1. But to address Dr. Weisfeldt's comment, when you go to Part 2, there seems to be a decremental jump instead of a continuous-type curve. Or would you interpret those data differently than I've stated?

DR. PAGE: Was that question for --

DR. ZUCKERMAN: Dr. Blumenstein.

DR. PAGE: Dr. Blumenstein?

DR. BLUMENSTEIN: Okay. I'm going to -- I have to respond to this by stating what I'm going to probably state again and again; I don't know how to interpret this because there's 39.3% of the control arm patients didn't go on to Part 2. And that's a lot. And so I don't know what this means.

DR. ZUCKERMAN: And that's the best response you can give other than there's the decrement and you have a lot of patients who aren't there.

DR. PAGE: Dr. Somberg?

DR. SOMBERG: This is a very difficult situation because there was a flawed study to begin with, and now everything I think that can be done has been tried to be done to ascertain whether there is an effect by this monitoring procedure. It is suggestive that there is an effect, but one of the major caveats we just heard, there's, you know, 39% of people are not there. So you can't reach a conclusion based on fact when you don't have

the fact. So I think there a couple of ways to get out of this. Sort of like a budget impasse, there's a couple of ways maybe to get out of it, none of them pretty and easy.

But one thing is it's been said a number of times that initially, the study looked at a product, looked at a product, the monitor plus the nurse. I'm not sure -- if you didn't want to do a study -- and maybe I'm talking out of turn here, but I always do anyway. So if you didn't want to do another study that obviated the initial study design flaws and you just wanted to get some additional, you know, looked at the data in other ways, and all that -- and it is reassuring to me -- you might say why not just do the product. Why not have the monitor plus -- you know, like the old telemetry we used to do. We have nurses calling, you know, patients or doctors, patients to come in, doctors to take action, et cetera, and all that. So you could have an alert system, and that would I think reassure many people here that then you were labeling it according to the results of the first study.

The second point I would make is, which is outside the lore, but you know, with that said, sometimes you have some dramatic -- let me -- sometimes you have to take action with incomplete data. And we have some dramatic results here. You know, the less experienced the center is -- I was impressed by that slide -- the more benefit you might get. And that suggests that, you know, additional data to those people who don't have all that additional data and don't have people being monitored and have

ancillary personnel to the same extent might benefit here.

So in this case, a controlled, well-designed study looking at pharmacologic therapies, looking at other potential interactions and when to use this would obviate a lot of the concern about having inadequate data before approval. But that's heresy.

DR. PAGE: Dr. Somberg, if I may just get clarification from you on the first point you made where you said might the nurse input be considered part of the device therapy. You're not -- you're suggesting that for a future study? You're not suggesting that that be reconsidered in terms of the dataset we have before us today, are you?

DR. SOMBERG: A panel was convened to advise the FDA. So I'm just -- and also the Sponsor. And I'm just saying if the product, not for a study, but if the label was modified such that -- and the product was changed such that a battery of nurses who advised, watched this and got the reports -- and you could also come up with an algorithm for an automated computer system, et cetera, deliver the same product, that would change a lot of people's concern.

So I'm not advocating a new study, because I think if you were going to do a study, you would want to do the right study, no nurse intervention, this monitoring system versus a non-monitoring system with very carefully prescribed different steps of pharmacologic intervention. But that's a separate study. And you know, we're going from 2010 -- this is

2013. You get a study done. This will be 2018, 2019. So you may not want to do that.

So the alternative is to go back and deliver something, as Dr. Blumenstein pointed out, was the true test of the first study, which is substantiated a lot by the follow-up, but still not taking --

DR. PAGE: You've answered my question. Thank you.

Does a Panelist want to respond to what Dr. Somberg just suggested? Dr. Borer?

DR. BORER: Yes, thank you. I have a slightly different view. I was going to hold this until you formulated the questions, but I don't think that it's necessary to go to the lengths that John is suggesting. We often disagree. You know, there's question. The longitudinal studies are rife with all the problems that people have talked about. There's no question that we can't rule out differential exit bias and all kinds of other biases, but on the other hand, there's no clear suggestion that those actually were problems.

But the way I look at this is just a little bit different. These longitudinal studies are all consistent with one another, and more importantly, they're consistent with the conclusion that would be drawn from Part 1, which is what they were done for. You know, they were done as ancillary studies to see if they would inform us about the correctness or lack of correctness of Part 1.

And were it not for the nurse communication issue, Part 1

might have been approvable. So I'm compelled by my perception that these were all internally consistent, they're all consistent with the initial Part 1 analysis, so they tend to confirm Part 1. They tend to minimize -- in my mind, they tend to minimize the potential impact of the nurse communications by indicating to me, at any rate, that there was a very small number that actually resulted in change. And that suggests that this is probably, probably, maybe not, but probably relatively modest in importance. And, again, absent the nurse communication issue, we probably wouldn't be here today or might not be here today.

The issue of differential mortality in the former control versus former treatment group is something that sort of comes up as a problem here maybe, but to me, it's not. These are relatively small groups of patients, relatively small numbers of events. The absolute differences aren't statistically significant anyway, as I recall the data, and yet the -- and so to me, the differences in the absolute mortality rates are not terribly, intuitively, at least, important. I don't think that would alter what I've said.

I think the ancillary data, the longitudinal studies confirm Part 1, and that makes me feel good about this.

DR. PAGE: Thank you.

I'm interested in other Panelists' perspectives, and I appreciate your getting us back on track to what we really need to be discussing, and that is the longitudinal and other studies that are put forward today. You

mentioned that you're reassured that they are consistent with each other and they're consistent with the initial trial. But we've also agreed that the initial trial had flaws that have been addressed. I don't want to go into whether they've been addressed adequately, because we need to concentrate on the further information.

Yes, sir?

DR. BORER: Can I just add one point?

DR. PAGE: Please.

DR. BORER: What I've just said is relevant to males in the database. We're going to deal with the females in the database two questions from now, but everything I just said is relevant to what I believe happens with this device in men.

DR. PAGE: Well, it's fair game to talk about the gender issue, and I think we should during this hour, but I'll ask for now, just in general, for panelists to comment on whether they see enough data given the issues about whether these two groups are comparable, acknowledging the problems with the data as they are, whether you are leaning toward being compelled to see a benefit here or not. And I've seen Dr. Lange, Jeevanandam, and Cigarroa and Ms. Currier.

Dr. Lange?

DR. LANGE: I recognize that there's a difference in Phase 1 and Phase 2. I'm still at a loss to figure out exactly how to explain it. And I

say that there were 44,000, or 40,000 recordings done 32,000 times; 72% of the time, the PA pressures were elevated. So three out of four days for all the individuals, the PA pressures were elevated, and yet it changed therapy 1,400 times, and I can't figure out whether it changed therapy because the PA pressure was elevated or because every day someone would call and say, gosh, how are you feeling. And when the person said I feel short of breath, you'd say, well, let's treat you.

And so I can't -- it's hard for me to figure out whether it's, in fact, the monitor itself or they just trigger someone to pick up the phone and call every day and say how are you feeling. And when someone describes shortness of breath, they'd treat them before they got to the hospital stay.

And the issue about the patients being very different, apropos to the covariates, remember that to get in the trial, you had to have New York Heart Association Class III symptoms. By the way, a minority of them were on aldosterone inhibitors, which is a little unusual because we know that prevents hospitalizations for heart failure, and 60% of them were on that. But you also had to have a hospitalization within one year. So by virtue of the fact that if you have the device and were followed for a year and you didn't have a hospitalization, you wouldn't even have been enrolled in the trial. So it is a different group, and I'm not quite sure how to deal with that.

DR. PAGE: Thank you, Dr. Lange.

Dr. Jeevanandam?

DR. JEEVANANDAM: I mean, it would come back to the slide that's up there, Slide 50, right? So if we're looking at the Part 2, you would say that you wouldn't approve this device because you didn't have any effectiveness in decreasing hospitalization over control. So it's only by combining it with the first part that you can come up with some indication of efficacy.

DR. PAGE: Just for clarification, Part 2, they were both being treated the same.

DR. JEEVANANDAM: That's right. So if they were both --

DR. PAGE: There is no -- that's the past control in Part 2. They're both being treated identically --

DR. JEEVANANDAM: Um-hum --

DR. PAGE: -- but neither one with nurse intervention. Is that clear to you and the rest of the Panel?

DR. JEEVANANDAM: Yeah.

DR. PAGE: Dr. Cigarroa?

DR. CIGARROA: So just as a point of clarification, we don't know if they're being treated in a similar fashion. We know that everybody has access to the PA pressures. We don't know changes in treatment that would be comparable or not. And that is we don't know the rates of

adjustment to beta blockers, diuretics, whether or not there was a change from 50-something percent to 70-something percent to nitrate. So my point would be we do know that PA pressures are accessible? We have no information on treatment.

DR. PAGE: I'll ask FDA, in your analysis, was there any concern raised over difference in how the previous intervention in the previous control were treated in the Part 2?

Dr. Sanders? That's an important question, Dr. Cigarroa.

DR. SANDERS: Okay. Thank you. As far as treatment, I think it's a good point about the treatment of advanced heart failure with different agents, but as far as the treatment between beta blockers and diuretics itself, there appeared to be no difference in the way they were -- they certainly were approached in the same manner in Part 2 as Part 1.

Now, you could debate the degree and the adequacy of the other agents, but as far as the protocol used for the treatment, they were the same. Is that --

DR. PAGE: I think I understand. Dr. Cigarroa, and then I'm interested in other Panelists as to whether they are concerned that the two groups are treated differently in Part 2. That had not been raised, and I'm not sure where we have evidence that there is difference. But please go ahead and expand, and then I'm interested in other Panelists' comments.

DR. CIGARROA: So it's my understanding that the algorithm

used was similar. Therefore, the advice provided was similar. But what we do know is that at the start of the Part 1 study, that is a randomized, there were 24% and 20%, respectively, on nitrates. At the conclusion, as best I can tell from the data, there were 74% in the active arm and 53% in the control arm. I don't know thereafter if there were similarities and what that might lead to on top of conventional medical therapy. That's my only point.

DR. PAGE: Fair enough. Dr. Borer and then Dr. Lange?

DR. BORER: I think it's a very important point, but those data are knowable, aren't they? There are CRFs that tell you exactly what the patients received. They were followed throughout the trial. So do you have the data about the comparability of the add-on therapies during the Part 2?

DR. PAGE: Dr. Sanders?

DR. SANDERS: I just wanted to make one comment. Part 2 was an open access trial, so whether the physician followed the absolute protocol, the protocol was the recommendations. You had the recommendations there. So that, you know, just to clarify.

DR. PAGE: And those were identical between the two groups?

DR. SANDERS: Right.

DR. PAGE: Right.

DR. SANDERS: Those recommendations were part of that protocol.

DR. PAGE: Right. Dr. Borer?

DR. BORER: Don't we have data about what drugs they got?

DR. SANDERS: From the CRFs, the CRFs were not collected as part of part -- the open access. They were not the same CRFs. The trial ended at six months.

DR. AGUEL: Perhaps I can suggest that the Sponsor might be able to have this -- an answer to this question whether this data is knowable or not. We don't have the data, but the Sponsor may.

DR. PAGE: I think that would be very helpful if someone from the Sponsor wants to come up and address this. But just so I'm clear, Dr. Cigarroa, you're looking at differences in therapies at the time when they entered Part 2; is that right? So I guess the question is are you concerned that they're actually treated differently or they came in as different patients -- different patient populations, which is something that we're going to be discussing more fully?

DR. CIGARROA: Given that shoes were previously discussed, I'm concerned about both shoes. And that is that we have a -- in essence, what we have is we have a run-in phase. We have a differential nonrandomized dropout, and we have different medical therapies in terms of potential dosages and rates of utilization at the conclusion of the case, which may reflect substantial differences in the patients at the start of Part 2 that are not assessed by the covariates that are mentioned. So yes and yes.

DR. PAGE: Fair enough.

Dr. Yadav, did you have a response to the issue of how they were treated after they entered Part 2?

DR. YADAV: Certainly. Let me try. I think Dr. Cigarroa was asking two questions. One is the treatment going into Part 2. And I think what we showed you is that it's very similar to what Dr. Sanders echoed. Now, there may be some subtle differences I think you were getting at. But I think what I would keep in mind is that those would work against the former control group, i.e., you might think the former control group rate would be higher if there were less well-treated in Part 1 because they were not in the treatment group, right? And what we actually see in the longitudinal analysis is that the former control does the same or slightly better than the former treatment group. So that should help you.

In terms of the CRFs or medication changes, they were not mandated in Part 2. We do have some, but they're not comprehensive like they are in Part 1. So we did not formally analyze that.

DR. PAGE: And, Dr. Cigarroa, did you have a follow-up?

DR. CIGARROA: Well, I think that, one, I appreciate the response, and that helps clarify. But I think to Dr. Borer's point, treatment algorithms in the open access were not necessarily required to be followed. And, therefore, the treatment that was administered/received is unknown.

DR. PAGE: Thank you.

Dr. Lange? Microphone, please?

DR. LANGE: Can I go back to the slide that looks at high and low volume centers, because I just want to get the absolute rate, hospital rate, because once you're in the open access, we have a rate that's about in the treatment group.

DR. YADAV: I think what I would point is these are six-month rates versus annualized rates. So here you are seeing six-month rates. Everything else you were seeing were annualized rates. So you can multiply them by two, which would not be an exact way of doing it --

DR. PAGE: I'm sorry. It wasn't clear to me. Are you asking the Sponsor a question, Dr. Lange?

DR. YADAV: I'm sorry. I thought he was.

DR. PAGE: It's okay.

DR. YADAV: My apologies.

DR. PAGE: Or were you asking for us to see the slide to discuss?

DR. LANGE: Just to see the slide put up.

DR. PAGE: Thank you.

DR. LANGE: Thanks. Thanks.

DR. PAGE: I saw Ms. Currier and then Dr. Blumenstein, and Dr. Jeevanandam, actually, before Dr. Blumenstein.

Ms. Currier?

MS. CURRIER: I hope I haven't forgotten how I should formulate this.

Okay. I look at this as a data collection device basically. And so then you have two questions. One is does it do it like they say it should, and apparently it does. And then does the data collect, is that important. And apparently that is what's being argued, whether the hypothesis is correct that these pulmonary pressures have anything to do with the treatment of heart failure.

And if the information that is collected is medically interesting, then I don't care who analyzes it. It could be my cat, you know, because you know, I don't think it's important as far as whether this gets approved or not, because all the time, we get data that gets ignored. Patients complain about it all the time. So I think that's just a reality of our medical system.

But the other point was if this data is not relevant, if pulmonary pressures aren't relevant, then why do, when someone goes in for -- with short of breath, da, da, da, they say have a right heart cath and we'll look at your wedge pressures, we'll look at those pulmonary artery/veins and then do something according to that. And so it seems like in medical practice, people are saying that these are important things to consider.

DR. PAGE: If I may respond, I don't think there's any argument that pulmonary artery pressures may be valuable in certain situations. The

issue is whether ongoing monitoring in this way is going to change outcomes in patients in a large randomized trial. And likewise, what people are struggling with is whether, in addition to that monitoring, there was further intervention that had nothing to do with the device.

Does that help kind of from your perspective, Ms. Currier?

MS. CURRIER: No, because then I want to make a comment.

DR. PAGE: Okay, please, and then we need to proceed.

MS. CURRIER: As a patient, I'd rather have a little goody in my thing than always be getting poked with a right heart cath. And I'd rather know what's going on inside me rather than have to, you know, have these terrible diets and this sort of thing if it's not doing any good. Because you put on these things that are very restricted, and then you don't know that it's doing any good. You say I don't feel any different. So that's my perspective.

DR. PAGE: I very much appreciate you sharing your perspective.

Dr. Jeevanandam?

DR. JEEVANANDAM: So, you know, I want to bring up that thing with PA pressures, right, and this is what Dr. Lange went into as well. So, you know, we see a lot of heart failure patients, and these people had a mean PA pressure of 29 to 30 as a baseline characteristic starting the trial, so that's actually pretty high. And you would want to bring those down.

Those are pretty abnormally high. And then if you look at the data of the patients going into open access -- so theoretically, it's the same group, so you have gone through the treatment process, and now their PA pressures are the same. They're 31. So they've gone through the whole process whether they're control or they are monitored, and their PA pressures haven't really changed. And so --

DR. PAGE: So how do you reconcile that with the data we're looking at?

DR. JEEVANANDAM: That's the question, right? So is there some other reason why they are being kept out of the hospital, and it's not necessarily the PA pressures?

DR. PAGE: Fair enough.

Dr. Blumenstein?

DR. BLUMENSTEIN: Could I ask the Sponsor a question at this point?

DR. PAGE: Yes, please.

DR. BLUMENSTEIN: Yes. Did you do the Andersen-Gill type modeling as a landmark analysis, and that is include only the patients that make it to Part 2?

DR. YADAV: I believe we did. Dr. Ogenstad, do you want to answer?

DR. OGENSTAD: Yeah, the answer is simply we did do that.

DR. BLUMENSTEIN: Could we see the results, please?

(Laughter.)

DR. YADAV: Yes, so -- and I think this helps. If we could put up the slide, please, 165? And this helps to address, I think, the question Dr. Jeevanandam had also -- so if you look at patients who were in both parts, i.e., a survivor's analysis, however you want to think about it, you can see that there is still a significant benefit. So the former control to control rate drops significantly and the number 4 analysis, which Dr. Packer has pointed out as key, which is adjusting for changes, longitudinal changes, is also highly significant, showing a hazard ratio of .5. And then if you -- and the rates are reported at the bottom, but yes.

DR. BLUMENSTEIN: Thank you.

DR. YADAV: Thank you.

DR. PAGE: Dr. Borer, I've got Dr. Cigarroa ahead of you unless this is on that specific topic.

Dr. Cigarroa, please?

DR. CIGARROA: Just to come back to the issue that you raised about the PA pressures, I would imagine that, in part, you have lability to PA pressures, and so I don't know if that second time it's at a point in time and therefore, there's no delta, as opposed to number of episodes in which you have exceeded a threshold, and it may simply be the way the data is being presented.

DR. PAGE: Thank you.

Dr. Borer?

DR. BORER: It was that point that I was going to get to, and I agree completely with what Dr. Cigarroa says. But over and above that, it seems to me that for the population, we don't have the individual moment-to-moment data. But for the population, the PA pressures did come down in the people who had the device in place, and the number of hospitalizations did come down in parallel. To me, that's intuitively very reasonable. I would like to have the moment-to-moment data; I'd like to have the point-to-point. We don't have it. That would help us make the case. But everything I've seen is consistent with pulmonary pressure coming down, patients having fewer events, good thing. So I'm not quite sure I understand where the problem is there.

DR. PAGE: Dr. Milan?

DR. MILAN: So just to add my voice to the discussion here, specifically about the longitudinal analysis comparing former controls to controls, with the dropout that was certainly nonrandom during Part 1 of the trial, I would have expected the patients to do better in Part 2 regardless of whether or not there was new therapy. I think this gets back to Dr. Weisfeldt's question.

So, in particular, I'm curious now that Dr. Blumenstein has asked about the landmark analysis where the patients are removed from the

Part 1, the patients who didn't enter Part 2 are removed from Part 1, whether or not he thinks that that is a legitimate analysis, whether or not those patients are generalizable to the patients who entered the trial to begin with, and sort of how that alters your thinking about this.

DR. BLUMENSTEIN: It doesn't. Those patients just have the same non-comparability issues as any other thing that we've already discussed as being non-comparable. In other words, that would be groups formed outside of randomization. Since I worship at the altar of randomization -- I have to say that at every one of these meetings; it's my own personal thing -- since I worship at the altar of randomization, that's the only way that you get a fully legitimate comparison that's of intervention. And so by doing a landmark analysis, it helps. It helps to know that they did it. But it doesn't really shed a whole lot of light on it.

DR. PAGE: And, Dr. Blumenstein, I'm afraid we have no altar here, so we need to address the patients we have available. And if I might have Dr. Milan comment and then you comment on the issue of the comparison 1, the previous control to control. We're not dependent on -- because I believe the FDA has put that forward as, if anything, the most compelling of a number of signals that all go the same direction. We're not dependent on comparability between groups. There was no nurse interaction. But clearly the patients who started Part 2 were different from the patients who started Part 1.

That being said, you commented that you would have expected them to get better. Do you see a signal that suggests they got better more than you would have expected if something weren't done? And then, likewise, I'm interested in Dr. Blumenstein's perspective on that and then the rest of the Panel as well.

DR. MILAN: So that's great. In fact, you took the words out of my mouth a little bit, which is I would have expected them to get better whether or not the PA pressure monitoring that was revealed in Part 2 was beneficial or not. And they did get better. And so the question really is did they get more better than I would have thought they should have. It's a matter of degrees.

And then the other issue is the shape of this curve, right? So now it's not a question of whether or not they continued to -- or whether or not their heart failure hospitalization rate dropped. It's a question of how much it dropped and the shape of the curve. And when we're starting to talk about that kind of stuff, I lose confidence in the signals that I'm looking at.

DR. PAGE: Thank you.

Dr. Blumenstein?

DR. BLUMENSTEIN: And you actually raised a good point that I hadn't thought of before. So could we see that landmark analysis up once more for that specific comparison?

DR. PAGE: Sure, if we have that. I don't know which slide that was.

DR. BLUMENSTEIN: They brought it up ad hoc.

DR. YADAV: Yeah, so it's --

DR. PAGE: If you can just identify the slide. Right now we haven't asked for your input on our discussion.

DR. YADAV: Okay. Sorry. Yes, can you put this up, please?
165.

DR. PAGE: Thank you.

Is this the slide you wanted?

DR. BLUMENSTEIN: Yes. Do you have the diagrams that are comparable to those that have been shown by you or the FDA for the rates over time?

DR. YADAV: No, I don't think we do. This is one of the robustness analyses, so we do not have that curve.

DR. BLUMENSTEIN: So what you're showing here is the change in hazard ratio as a result of implementing Part 2, correct?

DR. YADAV: Yes, only in patients that were in Part 1 and 2, yes.

DR. BLUMENSTEIN: Okay. And so what are the -- what is the estimate of the rate in Part 2 for analysis 1?

DR. YADAV: Dr. Blumenstein, that is at the bottom of the

slide.

DR. BLUMENSTEIN: Ah.

DR. YADAV: So this is former control and equal to 170 compared to the same patients in control, so it's .38 in Part 2 and .56 in Part 1 --

DR. BLUMENSTEIN: Right. And so this is --

DR. YADAV: -- annualized rates.

DR. BLUMENSTEIN: So this is using each patient as their own control, more or less?

DR. YADAV: I suppose one could say that, yes.

DR. BLUMENSTEIN: Kind of in a loose way.

DR. YADAV: Yeah, yeah, yeah.

DR. PAGE: So just so -- if you can take us just through that, Dr. Blumenstein. So we're all looking at the same thing. We're looking at the bottom two sets of cells, control to former control, and the control was .56 and the former control is .38 that generates the hazard ratio that we're seeing there of .68. Is that correct? Is that specifically what you were looking for --

DR. BLUMENSTEIN: Yeah.

DR. PAGE: -- and that's answering my question in terms of what's happening with comparison number 1 of the longitudinal analysis.

DR. BLUMENSTEIN: So I haven't whipped out my special

smartphone app scientific calculator, but I think that's the case.

DR. PAGE: And Dr. Zuckerman is nodding his head that we're interpreting that correctly. Let's move on along this line as to whether we're seeing something that, in at least one area, Dr. Ohman, that you might comment on whether you're seeing compelling data or you remain concerned as well.

DR. OHMAN: Well, it's an imperfect experiment, I guess, is the best way to characterize what we've seen. But I'll give you some of my thoughts.

First of all, on the bias issue, it's rather interesting to me because even the patients who actually went into this trial in the first place are biased against it, entire population of heart failure patients. I'm sure if there was a concomitant registry done, and I'm sure the Sponsor will shudder at the thought of that because that would be very complex to do, but the reality is that it's biased on that level, too.

But that helps me because the patients who were in the control arm in Phase 1, they're biased. But they're also biased against the patients who never even got into the trial, so it's just a degree of bias. And to me, many times we do crossover studies. Actually, in certain sections of the Agency, not the device side necessarily, but they do crossover trials. That's sort of the standard approach because there is no other simple way of doing trials like that.

And so this last slide -- and they always pull it down too quickly, but in this slide, this last piece of slide -- that'd be 165 -- it actually describes it very nicely. It's biased, for sure, but the data, when you take that into consideration, the data beyond Phase 1, i.e., Phase 2, is very consistent with the biased information in Phase 1, and therefore, I believe that what we see here is a treatment effect. So that's on the one level.

The second part here, these are sick patients. I didn't realize that so many people went to LVAD transplant. That was a large cohort of the trial. So these are not -- these are patients that are hard to change the mortality on because you essentially go to LVAD, you can't die, at least not easily. So in a way, the best measure of what we're looking at here is recurrent heart failure admissions.

And then the final thing that sort of sticks in my brain, if we look at using Andersen-Gill, and I'm really glad that this was sort of analyzed in multiple different ways, the Andersen-Gill is particularly sensitive to patients that have multiple events. And quite frankly, in practice, the patient will come into the hospital once a year or once every other year. That ain't our problem. The problem are the people who come in over and over again. And when you see in that cohort both in Phase 1, if I remember the slide right, and Phase 2, there is a 50% reduction in the multiplicity of events. Now, that to me is very powerful.

So recognizing that a lot of bias is here and a multitude of

imperfect science, looking at the totality of evidence in multitudes away, biased or not biased, I do believe that there is an effect here that's fairly consistent across the board no matter which way you try to cut the data. That's at least my personal bias.

DR. PAGE: Dr. Borer?

DR. BORER: Yes. I'd like to extend what Dr. Ohman said about mortality. Remember -- Lynne Stevenson's not here anymore, but as she pointed out, you know, this is an assessment of a diagnostic device. It's not an assessment of therapy. Mortality reduction in clinical trials of patients with heart failure has been achieved in several trials where a new treatment agent was measured against placebo on a background of all at that time acceptable therapies. Here, everyone was on all the acceptable therapies. It was just a matter of giving a little bit more this time or that time based on a pulmonary artery pressure. To expect there to be a difference in mortality in a relatively small trial with that kind of design seems to me non-credible. I wouldn't have expected it.

What I would expect, what I would hope, is that the trial could show what it did show, you know, what it seems in general it showed, a reduction in events, in heart failure events, which is a big deal. To expect it also to show a reduction in mortality seems to be in the "too hard" box. I don't think that's reasonable because the trial just wasn't designed to -- in a way that would have made that likely.

DR. PAGE: I see Ms. Timberlake has a comment or question.

MS. TIMBERLAKE: I just want to say I completely agree with Dr. Borer. When -- I'm going to put on my regulatory hat for a second. What the company is seeking is a diagnostic indication. They're not looking for a therapeutic claim. When you look at the indications for use, to me it's an augmentation of your clinical decision points, where you gather that information to make decisions, as changing medication, increasing/decreasing, and that's one point of information.

So in my opinion, what they set out to do was to give a certain range, have the device information relate to the physician, and that physician would use that information to make further clinical decisions. So to your point, it's not so much about morbidity. They are a sick population. But when you look again at the indications for use that the company is seeking, it's truly a diagnostic device. Maybe someday it'll do more with a post-approval study; we'll learn more about further benefits of the device.

DR. PAGE: Thank you very much.

Dr. Somberg?

DR. SOMBERG: I think this is a straw argument. I haven't heard anybody at the table wanting to vote no in the first or the second panel here based on a lack of mortality, Dr. Borer. I think the issue has to do with what exactly is the guidance. It's a diagnostic test. But is it a diagnostic test alone -- and that's why they have the second panel, the second

discussion -- or is it the diagnostic test plus the advice from a panel of nurses in constant calls. And Dr. Lange, I think, said it, you know, very succinctly. Is it because there are just a lot of calls and heightened surveillance, and therefore, people are being identified who all of the sudden have a change in symptoms? Because if the pulmonary pressures are up in all of these people -- what was it, 4,000 or something -- and we only have 1 in 4, 1 in 5 of those acted upon, there's something else there. And how is Dr. Zuckerman going to draft a label for that when that's an unknown factor?

And, you know, I hate to keep raising the unknowns instead of -- you know, I think our Chairman is getting annoyed with me because I keep raising the unknowns, but there are a tremendous amount of unknowns. So I feel the feeling is not that there is lack of a mortality effect. The question is if this was a clear-cut guidance on how to use this data, then I would be very happy to support it. But I think there's a lot of danger here.

I mean, people could be -- all of the sudden when it gets out into general use, be intervening with vasodilators and diuretics for all 4- or 5,000 times pulmonary pressures are elevated, and that may have an adverse outcome. So we have to have that consideration as well.

DR. PAGE: Dr. Zuckerman, did you want to respond?

DR. ZUCKERMAN: You know, this has been an interesting discussion, but I do think one needs to really hone in again on, one, where perhaps Dr. Borer's comments were originally made that -- and I guess

Dr. Ohman also, in that although there are biases and limitations in all these analyses, it is interesting that there's concordance. And certainly FDA is interested in having Panel members look at the totality of data rather than one particular data strand because that's not going to be helpful here.

Number two, just in terms of the hemodynamics, it may be helpful when patients continue to discuss the hemodynamics to look at FDA Slide 21, which does indicate that the mean capillary wedge pressure is kind of right on the border. So it's not surprising perhaps that invasive monitoring might be helpful, although I'm sure there'll be disagreement on that.

But the final thing is that the Sponsor is here today to get a label that suggests, as shown in FDA Slide 5, that the hemodynamic data are used by physicians for heart failure management and to reduce heart failure hospitalizations. So I do think the Panel needs to weigh that again, as they've been doing. Has enough effectiveness data been shown to indicate that heart failure hospitalizations can be reduced with this diagnostic device?

But by the same token, I do think the Panel members need to be realistic. I think everyone here understands that heart failure is one of the most complex diseases that cardiologists deal with, and it's just not a pressure or a vasodilator protocol. It encompasses perhaps those hemodynamic data, a reasonable guidelines protocol, and a sensible

physician. And please remember that part of the mix when trying to think about the benefit/risk equation here and what all these data mean, because we aren't ruling out that sensible physicians will be using this particular device, potentially.

DR. PAGE: Thank you. And the other thing I thought you were going to address, but I will myself, is Dr. Somberg has mentioned a couple times whether this would be labeled or indicated to have this external nurse input, and that's not the case. That's not something we're considering at all today. And, furthermore, the longitudinal study, study 1, never did any patient have nurse intervention before or after the randomization phase. So Part 1 and Part 2 were independent of any input, and we're not discussing any opportunity -- I know you were kind of blue-skying, Dr. Somberg, but in terms of our job today, this afternoon, to give advice, we are taking this as a device used by a physician in a way that the protocol was in terms of the patients in the control Part 2, where there was no intervention.

Is that fair, Dr. Zuckerman?

DR. ZUCKERMAN: That is very well stated, Dr. Page.

DR. PAGE: Dr. Lange?

DR. LANGE: Two things. One is that it would be great if the FDA could limit this device to the use of sensible physicians.

(Laughter.)

DR. LANGE: And the second is I think it'd be great to spend

just a minute talking about the gender issue, and --

DR. PAGE: You know, Dr. Lange, I had not forgotten about that, but that is one of our questions. It's 3:30 now. And I'm wondering whether that would be best addressed when we take it as one of the questions. I'm happy to delay our break and delay our time going into the FDA questions, but I thought it would fit there. Would that be okay with you, Dr. Cigarroa?

DR. CIGARROA: So just a comment and question to the FDA. First of all, no doubt that the device measures PA pressure, and that's stable. Is there precedent for -- and, by the way, no doubt that there's internal consistency during the longitudinal follow-up, as Dr. Ohman eloquently stated. Is there precedent for using longitudinal analyses of patients that may be distinctly different, where we don't know what those differences are to provide approval?

DR. ZUCKERMAN: So Dr. Cigarroa, an excellent question, but I do want to get back to Dr. Lange's excellent comment. He asked is it possible to restrict use to sensible physicians. The way the FDA would address that type of device approval question is not unique to this device. Whether we're talking about corroded stenting, percutaneous aortic valve replacement, or potentially therapies of this type, once an approval is made, we never shut our eyes. And I think there are mechanisms that this Panel can help us to implement rationale dispersion of extremely important

cardiovascular technology. So I'd like you to continue to think about that, Dr. Lange.

DR. LANGE: My major concern was if you restricted it to use to sensible physicians, I'd never get to use it.

DR. ZUCKERMAN: I doubt that. By reputation, you're a sensible physician.

(Laughter.)

DR. ZUCKERMAN: Dr. Cigarroa, I think that you need to again understand the rules of the game for device approval. And thank you for asking your excellent question. Valid scientific evidence, as defined in our Code of Federal Regulations, has a broad definition. And certainly, at the end, Ms. Waterhouse will remind us. But I think it's fair to say that at least 50% of our device approvals occur with looking at nonrandomized data. Certainly, I agree with our Panel statistician that there's nothing like having a randomized clinical trial such that we can be better assured about the potential effect of bias, confounding, et cetera. But it's certainly not unusual for us to be in this sort of situation.

So, again, we're asking your best help as a clinician. You have to put the data together from multiple aspects. As our statistician has wisely reminded us, there are multiple problems here. But it doesn't prevent us from looking at the big picture and trying to do our best today.

DR. PAGE: Thank you, Dr. Zuckerman.

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With that, I'm going to ask that we take a break. Our break is going to be until 3:45, so just under 15 minutes. We're going to start promptly at 3:45. I do remind the Panel not to discuss the issue at hand with each other or with any member of the audience until we reconvene at 3:45. Thank you.

(Off the record.)

(On the record.)

DR. PAGE: I'd like to bring us back into session. At this time, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among Panel members only. Our task at hand is to answer the FDA questions based on the data in the Panel packs, the presentations we've heard this morning and this afternoon, and the expertise around the table. With this said, I would ask each Panel member to identify him or herself each time he or she speaks unless called on to facilitate transcription.

Right now, I will ask Mr. Quinn to read us the first question.

MR. QUINN: Panel Question 1: FDA believes that the results of the ancillary analyses, specifically the longitudinal analyses, may be subject to limitations. Not all subject characteristics were obtained at the onset of Part 2, thereby making it impossible to determine if subjects in Part 2 of the study continued to meet the inclusion/exclusion criteria for the study. Furthermore, potential differences may exist between study groups

as a result of an unbalanced change in subject characteristics over time and because of nonrandom survival bias.

Panel Question 1a: Please comment on the overall validity of the ancillary analyses given their limitations.

DR. PAGE: Why don't you go ahead and read the three, and we'll --

MR. QUINN: All three?

DR. PAGE: -- take them one at a time.

MR. QUINN: Sure.

1b: Please comment on the potential survival bias introduced by subjects exiting the study prior to Part 2; and

1c: Please comment on the death rate being lower in the former control group than in the former treatment group, and consider if this is indicative of population differences between the two study groups.

DR. PAGE: So I'd like to look to the Panel to start off the discussion of these questions all as a group, but let's start with (a), the overall validity of the ancillary analyses given their limitations.

Dr. Borer?

DR. BORER: Yeah, I've already given my answer, but I'll summarize it. There are clearly many limitations, et cetera, et cetera, but given the fact that the longitudinal ancillary analyses are internally consistent, they're consistent with one another, and most importantly, that

they tend to confirm the CHAMPION study results, which is what the ancillary analyses were done for, I think that they are important and valid for men. So that's summary of what I believe.

DR. PAGE: And is that touching on (b) and (c) as well, that --

DR. BORER: Yeah. Yeah, sure. With regard to (b), I think there certainly is potential survival bias introduced by subjects exiting the study prior to Part 2. You know, I can't determine the extent to which that impacts on the results, but again, given the internal consistency of the data that we have, I really don't think -- my intuition is that that does not negate my belief in the validity of the data.

With regard to the death rate being lower in the former control group than in the former treatment group, it may be indicative of population differences, but I think that the difference is relatively small and in a relatively small population with relatively few events. It has no meaning, and it certainly isn't statistically significant.

DR. PAGE: Thank you for kicking that off. And I might suggest that from hearing the conversation today, (b) and (c), I think there are various degrees, but I think everyone has some concerns about both (b) and (c). So primarily, we're addressing (a) here, but feel free to comment on (b) and (c) as well.

Looking around the table, does that sound like a reasonable way to proceed?

And Dr. Blumenstein?

DR. BLUMENSTEIN: So I wanted to go now because I wanted to give the other extreme view.

(Laughter.)

DR. BLUMENSTEIN: So Part (a), the randomized clinical trial is what you would call Level I evidence, that is, level Roman numeral I evidence, because it's based on a randomized clinical trial comparing the use of the device with the supplemental nurse against --

DR. PAGE: I'm sorry to interrupt, but the question in 1a --

DR. BLUMENSTEIN: Yeah?

DR. PAGE: -- is the ancillary analyses.

DR. BLUMENSTEIN: Yeah, I'm getting there.

DR. PAGE: Okay.

DR. BLUMENSTEIN: All right. So you have this Level I. And then what is going on is that what we're asked to comment on is really Level III. And the reason it's Level III is because it's not a designed study. It's a convenience sample. It's observational. And it has no real control over the biasing factors. That is, specifically the patients going into Part B are different, and it's what I referred to before as hoisted on your own petard. If you have a result, that significant result from Part A, then by definition, you're going to end up with different populations in Part B.

And so for that reason, I tend to think that this -- that these

are problems. They're real. And they inform us as to the value of the data.

DR. PAGE: So if I may, from your perspective, (b) and (c) are, as everyone I think is going to acknowledge, that there are concerns there, but to your perspective, those concerns are great enough where the overall validity of the ancillary analyses is in question?

DR. BLUMENSTEIN: That is correct, that it is just further -- it is Level III evidence and therefore subject to all of the problems that are available --

DR. PAGE: If I may press, though, the evidence, we agree, is not what we wish it were, but the evidence we have is what we have. So given the -- your concerns about (b) and (c), does that -- can you just further comment about your overall validity -- your -- as you take it all in, the ancillary analyses, whether given these limitations, whether you find the data compelling or you really don't know what to make of them.

DR. BLUMENSTEIN: I don't know what to make of it because the selection factors that went into the makeup of the patients entered into those analyses are serious and structural. They come from the design of the trial, and there's nothing much that can be done about it. And covariate adjustment, while it's sometimes useful in situations like this, it's seldom useful.

DR. PAGE: Thank you very much.

Dr. Yuh and Dr. Somberg?

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DR. YUH: So the ancillary analyses really is akin to circumstantial evidence, isn't it? I mean, it's not perfect, but it is supportive of a positive signal indicated by the initial study. And it was done in collaboration with the FDA. So taking everything in totality as the FDA is asking us to, I do feel personally that -- I'm satisfied with the ancillary analyses despite the limitations.

DR. PAGE: Thank you.

Dr. Somberg?

DR. SOMBERG: I think it's very problematic, and because of 1c and the difference in mortality of the groups, I think that severely questions the validity. It's convenient to say things are going in the right direction, looks good, these are good guesses. And that may be the case. But there are a lot of pieces of data that don't fit in here, such as a large number of elevated pressures, et cetera. So, therefore, because things are not going in the right direction, it might be that there are biases pushing them in that direction. And that's why we do randomized controlled studies. And I'm not sure how I'm voting at this point, but this Panel question is really very important, and it's very troubling.

DR. PAGE: Thank you, Dr. Somberg.

Dr. Weisfeldt?

DR. WEISFELDT: The question in 1a deals with the validity of all ancillary analyses that were provided to us. And I want to make a point

that one of the ancillary analyses that we saw that has not been commented on whatsoever is the propensity analysis of the 99 patients who did not have nurse involvement versus the 99 matched patients, which showed the same results as the overall initial study. And since that was the reason that the Panel the last time voted against this, was the bias, I think that that, to me, is meaningful data. We have a outside consultant, I think, who validated that the 99 patients didn't have nurse contact. And I'm having trouble not placing that piece of evidence way ahead of the piece of evidence that is getting all of the discussion thus far.

DR. PAGE: Fair enough. Thank you very much. Other Panelists care to comment? Dr. Ohman?

DR. OHMAN: Yeah. I hate to argue with a statistician, but I don't see it as quite as Class III evidence. There's a Class II conveniently by the American College of Cardiology that actually sort of takes into consideration the quality of the data. And if you look at the quality of the data, this is sort of right up there. This is prospective collected information using a protocol that actually has a fairly good criteria to how it should be implemented, and while the biases are there and the issues that we all discussed, I still think that this type of analysis, while not directly informing us, it's the aggregate of data that informs us, not the single component. And yes, randomized trials are the gold standard for what we do. We have a randomized trial that actually is positive, but we're not going to talk about

that, but that's the -- that's I think in the background of all the additional analyses.

DR. PAGE: Thank you.

Dr. Blumenstein, if I may, Dr. Weisfeldt brought up a very important point, that we haven't been discussing the propensity analysis. We focused more on the longitudinal analysis. We've heard two different statistical groups have different perspectives in the propensity analysis. Did you want to weigh in as in terms of I hear that you have concerns about the ancillary studies in general, but of the ancillary studies, do you see that as more or less compelling relative to, say, the longitudinal study of the control in Part 1 and the post-control in Part 2?

DR. BLUMENSTEIN: Well, of course, a propensity analysis is done when you lack randomization as a means of equalizing the groups being compared. To me, the issue with the propensity analysis is that you have identified a subset of patients that may not be represented if -- and so within the framework of the limitations of propensity analysis and the fact that it identifies a subset of the patients, it may not, in fact, be the ones that you really care about. It provides an answer, but it may not be the answer you want.

DR. PAGE: So, again, in terms of as you formulate if you were going to formulate a hierarchy of the more compelling and less compelling, where would you put the propensity analysis?

DR. BLUMENSTEIN: I would put it above the Andersen-Gill modeling of the Part 2 but below the randomized results from the trial.

DR. PAGE: Okay.

DR. BLUMENSTEIN: And if -- I mean, I used to be part of a committee that wanted to inform journalists about how to report randomized clinical trials. I wanted them to use a very large point size when publishing it in the newspaper and a very small point size for anything else. So if you'd like, I'd say maybe 20-point for the randomized clinical trial and maybe an 8-point for the propensity analysis.

DR. PAGE: Thank you for indulging my question.

Dr. Zuckerman?

DR. ZUCKERMAN: Okay. Dr. Blumenstein, thank you again for your excellent comments and anchoring us in clinical trials methodology. And Dr. Weisfeldt's comment is an extremely important one because we really didn't have time to talk about the propensity score analysis. And each of the Panel members will need to weight it when they look at the totality.

One comment I would like to make is that, in contrast to 99% of the propensity score analyses that we do get at the Agency, this one was extremely well done in terms of methodology by Dr. D'Agostino and his group, meaning that there was an independent statistician. And so our main concern is really with the fundamental point that Dr. Blumenstein always reminds us of: Can the propensity score analysis truly represent a

randomized trial? But it's of a higher grade than what we usually see at the Agency, by far.

But getting back to Question 1, Dr. Borer, because this is such an important question, when you're referring to the longitudinal analyses, can you just clarify for the record, FDA Slide 36, are you referring to all four of these analyses?

DR. BORER: I believe I am, but let me go back to Slide 36.

DR. PAGE: Maybe if we can put that up briefly?

MR. QUINN: Slide 36, please?

DR. PAGE: It's the one that shows the four different longitudinal analyses. There we go. Thank you.

DR. BORER: Yeah. Yes. Former control/control -- yes, in fact, I was.

DR. ZUCKERMAN: Okay. And the second point is if you could look at Slide 39, as we all know, there are biases in the longitudinal analysis comparison 1, and therefore, it's sometimes interesting to look at the magnitude of treatment effect versus potential magnitude of bias. Do you want to comment at all on the actual magnitude of treatment effect for this analysis?

DR. BORER: That's really very difficult to do because of the design of the analysis. But if the implication of your question is to segue into Question 2, which is what does this all mean, I will say something about

that if you'd like or you wanted something else?

DR. PAGE: Actually, I think he's asking specifically about this data analysis. Of the four that were shown in the previous slide, FDA has emphasized this comparison number 1 as perhaps being the most robust --

DR. BORER: Yeah.

DR. PAGE: -- because it's one comparison that has a population that never had any nurse intervention.

DR. BORER: Yeah. I mean, I think the best you can say for this, because I don't want to talk about the magnitude, given the design, but I can talk about the consistency. These data are highly consistent. We're not supposed to talk about p-values here, I guess. This is an exploratory p-value, but p less than .0001, this is a highly consistent dataset. So I'm very happy with the fact that this does seem to be a compelling piece of evidence in favor of the device, the use of the device being important in underlying benefit to patients with heart failure.

DR. ZUCKERMAN: Thank you for the clarification.

DR. PAGE: So far, I'm hearing from the Panel some people who are more impressed by the validity and others who aren't. And before I reflect to Dr. Zuckerman my summary, is there anybody on the Panel who has specific comments about these questions 1a, b, and c that haven't already been raised and wouldn't somehow fit within what I'm seeing is a fair variety of perspectives?

Dr. Cigarroa?

DR. CIGARROA: So I think there is tremendous internal consistency. I'm continuing to struggle with understanding how our concerns about (b) and (c) allow me to formulate my final opinion about the (a). So very consistent results across all four in the longitudinal analyses. I thought that the propensity scoring was well done. I'm still struggling with differences at entry of the open phase of patients and how that allows us to comment on validity rather than consistency.

DR. PAGE: Great.

So if I may, Dr. Zuckerman, with regard to Question 1, for 1b and c, I think there's acknowledgment that there is concern both to the potential survival bias by subjects exiting the study prior to Part 2 and the fact that the death rate in the former control group being lower than the former treatment group raises the issue of whether the population differences between the groups are important. So there's acknowledgement of both of those being an issue.

What is not consistent is whether these represent fatal flaws in terms of the overall validity of the ancillary analyses that have been presented. So you have some who are leaning favorably toward the, in totality, taking what we have available to us, and others who feel that the issues in 1b and 1c, and perhaps others, are such that they really don't know what to make of or do not consider the overall ancillary analyses to be valid.

Is this adequate, Dr. Zuckerman?

DR. ZUCKERMAN: That's very helpful. Thank you.

DR. PAGE: Thank you.

We'll now go on. Mr. Quinn, would you please read Question No. 2?

MR. QUINN: Panel Question No. 2: The clinical significance of the results for the device is an important consideration for assessing the benefit/risk profile of the device. The implantation of this device requires an overnight hospitalization, risk of implantation procedures, and some subject discomfort. Based on the results presented, heart failure-related hospitalizations would be reduced by 20 to 32 hospitalizations per 100 subjects per year when the CardioMEMS devices is used to guide heart failure medical therapy. The number needed to treat to prevent one heart failure-related hospitalization is approximately 3 to 5. The absolute risk reduction in the proportion of subjects that experienced a heart failure-related hospitalization was 8.6% and 7.7% at 12 and 24 months, respectively.

Question 2a: Please comment on the clinical significance of the observed treatment effect in the Part 1 and Part 2 analyses.

Question 2b: Please comment on the overall effectiveness of the device and the clinical significance of the results, taking into account the totality of the data presented along with the limitations discussed. Please provide a discussion on all of the key factors that influence your assessment.

DR. PAGE: So now I'm looking to the Panel for commentary on Question 2. Specifically, in 2a, it's coming from the perspective that you are assuming that what we're seeing is real and whether those -- whether the number needed to treat, for example, of 3 to 5 is important enough and worthwhile going through the hospitalization, the cath in the leg. So that's the clinical importance, independent of whether you think risk and benefit or whether you're compelled by the data.

Part b, however, gets more to what we were discussing in Question 1a, I believe. But you might fold both of those in. So if I may, I'll ask the Panel to comment. Dr. Borer already has his hands up, but I will ask for independent of whether you are compelled by the overall ancillary analyses, whether a number needed to treat of 3 to 5, assuming the data were perfect, is good enough to balance with the hospitalization, cath, and the other clinical input that needs to be undertaken for this device to be placed.

Dr. Borer?

DR. BORER: Yeah. The answer is yes, it does. Reducing heart failure-related hospitalizations by 20 to 32 per 100 subjects per year, and I'll assume that that number is correct -- it may not be obviously, may be off a little bit, but that is phenomenal. I mean, that's really fantastic. That would be a tremendous benefit. And that benefit is cumulative. It's not just this year. It's again next year and again the year after that. The risk against

which it's being measured is a one-time-only risk, seems from the data we've seen to be rather modest. It may be annoying, but it's modest, and it's once. I just don't see an issue here. If you can reduce hospitalizations that way, everybody needs to remember that if you have one hospitalization, you've markedly increased your likelihood of having another hospitalization for heart failure as compared with if you didn't have a first hospitalization. If you have a second, you're that much more likely to have a third, and you're much more likely to die. So the fact that you could reduce hospitalizations to that extent, I think, is a very compelling piece of information. So I think that I'm favorable about this. I think the clinical significance is high.

DR. PAGE: Thank you very much.

Dr. Patton?

DR. PATTON: Admittedly, I'm still struggling a little bit with this. The numbers look fabulous, as put in your question. But I'm still trying to figure out how a device that had 44,000 transmissions, 32,000 of which were alerts that resulted in 1,400 medication changes, was the reason why we see this enormous clinical change. And so I'm still not quite sure how to make sense of that data.

DR. PAGE: So I guess, if I may press you, what I was asking is if you assume that the therapy was responsible for 3 to 5 hospitalizations one way or the other -- I think you're getting more toward 2b --

DR. PATTON: That's true.

DR. PAGE: But in terms of 2a, the clinical significance of assuming the data are valid and one has to go through what one has to go through to place the device, do you find a clinically significant result in the 3 to 5 number needed to treat in terms of hospitalization in this patient population?

DR. PATTON: Absolutely.

DR. PAGE: Thank you.

DR. BLUMENSTEIN: Can I ask a question?

DR. PAGE: Dr. Blumenstein?

DR. BLUMENSTEIN: Where exactly did the 3 to 5 come from?

DR. PAGE: I believe I asked Dr. Sanders that when he presented it, and that was based on analysis number 1 of the longitudinal studies. Dr. Sanders is nodding his head. And just to remind the Panel, analysis number 1 was the controls going to post-control, Part 1 to Part 2. Is that correct?

Dr. Cigarroa?

DR. CIGARROA: With the assumptions you stated, very positive number needed to treat, an impressive number.

DR. PAGE: Thank you.

Dr. Jeevanandam?

DR. JEEVANANDAM: I think it's you have to differentiate this as was explained earlier as a monitoring device, so you're monitoring a PA

pressure, and it's effective in monitoring a PA pressure.

I think that the sobering thing here is that it's not really taking care of heart failure, right, because your PA pressure is still up, you have incidence of mortality that's significant, you have instance of transplants and LVADs and everything else that doesn't seem to change between control and treated patients. So as a monitoring device, it's fine. Is it affecting heart failure? Other than just admissions, we don't have any functional improvement in these patients, and we don't have really any long-term outcome improvements. But as a monitoring device, I think it's effective in monitoring PA pressure.

DR. PAGE: And would you say that the 3 to 5 number needed to treat is a clinical relevant outcome, assuming, that is, related to this device?

DR. JEEVANANDAM: I mean, you know, a patient is undergoing a procedure to -- you know, it's interesting from a society point of view. You're looking at three to four patients to decrease one hospitalization. It would be interesting to reverse that and say, okay, if you're a patient, right, what is the chance that you're going to have a decreased hospitalization because you have this device. And we have, you know, some signal that it's less. But I don't know if I'm a patient I'm going to go through the discomfort of having this and a product in me if it's not really going to hurt my heart -- it's not going to affect my heart failure but it's

going to affect only my admissions.

DR. PAGE: Fair enough.

Dr. Borer wanted to comment.

DR. BORER: I just want to make one point. Val, I'm not sure why you say there's no functional improvement based on the treatment that's given based on the device, because my recollection is that the Minnesota Living with Heart Failure Score improved by five points, which is not trivial. It was significant at six months, not significant at a year, but the power to see a significant difference wasn't present at a year at the magnitude that was seen. And yet the point estimate difference was identical. So, you know, it seems to me that that suggests that if you act on the basis of what you saw with the device, people actually do feel better. It's not just that they don't go into the hospital as frequently, which is a big deal, but they actually feel better, too, I think.

DR. JEEVANANDAM: I mean, to me, a function efficacy -- and that's not what we're discussing here. We're discussing effectiveness of this device for PA pressure, but in terms of functional improvement would mean, you know, decreased mortality, decrease need for LVAD, decreased need for a transplant, and something else, like a six-minute walk or a VO_2 that's gotten better. I mean, for all you know, we could be drying these people out, and they could be -- you know, they could be fatigued, and actually their six-minute walks could decreased. We don't know. We don't have that

data. So that's why I say -- you know, when you look at a heart failure patient, to me, function is as important as just a PA pressure.

DR. PAGE: Thank you.

Dr. Yuh?

DR. YUH: Yeah, certainly, the significance of the treatment effect is definitely impressive. I think, though, the device is exerting its effect in ways perhaps different than the Sponsor had intended. And to varying contributions, it puts a spotlight on the heart failure patient. I think, truthfully, that heart failure cardiologists may use it in a way as a crutch or assurance to treat outpatient heart failure more aggressively. And it may actually give heart failure cardiologists the confidence not to admit a patient because they know what the PA pressures are. They don't have to wonder what it is to admit the patient for a right-heart cath.

So I think even though perhaps the fine-tuning of PA pressures may not be borne out in the data that we see, the effect, the end effect, I think, is still significant.

DR. PAGE: So, Dr. Zuckerman, I want to hear what Dr. Lange says before I address you.

Dr. Lange?

DR. LANGE: I don't want to leave Dr. Patton out or hang her out to dry. We're assuming that this catheter somehow affected the therapy. 31,000 times it didn't. 31,000 times, there was an elevated PA

pressure, and there was not change in medical therapy. So, again, I'm not convinced that the device did anything. Whatever happened in the study did something, but I'm not sure it was the device.

DR. PAGE: Thank you, Dr. Lange.

Dr. Blumenstein, did you have another comment?

DR. BLUMENSTEIN: Yeah. I always feel like I have to be negative about everything I hear.

(Laughter.)

DR. BLUMENSTEIN: And believe it or not, I'm not particularly happy about it. But on the other hand, since that is my role, the quality of life analysis, I didn't say anything earlier, but I really don't like it. And I'm talking about Sponsor Slide 41. And, again, we have the missing data issue. And the Sponsor chose to use last observation carried forward in order to make that comparison. So I'm not so sure that that's a valid analysis because last observation carried forward doesn't capture the trajectory of a patient getting worse. And a higher score, in this case, is worse.

DR. PAGE: Great. Thank you.

So now, Dr. Zuckerman, with regard to Question 2, the Panel generally believes that the specific question put before us, and not unanimously, but generally is in agreement that the number needed to treat in terms of 3 to 5 to reduce one hospitalization per year, and their suggestion that that is a durable effect after the -- through the one

hospitalization each patient has to have to have this implanted. The feeling is that that's a clinically important outcome assuming it's true.

In terms of (b), you're hearing the same divergence of perspective as to confidence that the device is indeed responsible for the outcome that's suggested by that number needed to treat.

I should also comment that you did not ask about the quality of life. That was brought up. Some Panel members are more interested in a suggestion of improved quality of life, but Dr. Blumenstein pointed out the difficulties in interpreting those data.

Is this adequate?

DR. ZUCKERMAN: Yes, that's very helpful, but I want to make one comment. The original quality of life data analyzed by the Sponsor are actually on Slides 39 and 40 by the Sponsor and are consistent with, I believe, Dr. Borer's comments. On the other hand, I do want to recognize that Dr. Blumenstein has told us that the additional re-analysis performed by the Sponsor to get a nice p-value probably isn't very helpful. But Dr. Borer's comments were a little bit different, and they're really referring to Slide 39 and 40 of the Sponsor.

DR. PAGE: Thank you.

So with that, we'll move on to Question 3.

MR. QUINN: Panel Question 3: The gender analysis seems to show no heart failure-related hospitalization rate reduction in females

during Part 1 and during combined Part 1 and Part 2 study.

Please comment on the findings of the apparent lack of a decrease in heart failure-related hospitalization rate in females and whether it is appropriate to study this result further.

DR. PAGE: So I'm looking to the Panel to speak up.

Dr. Somberg?

DR. SOMBERG: Well, I originally thought it had to do with preserved ejection fraction versus low ejection fraction. That's been a hypothesis killed very quickly. And thank -- you know, that's good to get that out. I do think there is a gender difference. It may be due to the small sample size. It might be due to that this device has some benefit by, as Dr. Yuh said, making people -- making physicians more attune to the patient and more confident that they can -- because they know the pressures, et cetera, they don't have to admit the patient. For whatever reason, there seems to be a gender difference. It should be investigated in the future. It is of concern, but this is really a sub-issue compared to the major ones that we've discussed.

DR. PAGE: Thank you.

Dr. Borer?

DR. BORER: Yeah. I agree with John about the difficulty with the gender issue. In fact, that, to me, is the rub here and has to be handled separately. I'd refer back to Lynne Stevenson's comment about weight

management with a scale. I thought that that was going to be fantastic, that all we'd have to do would be to prescribe a bathroom scale for everybody with heart failure and, wow, the admissions would go down. And then the two trials were done, and it turned out not to be true. Totally unexpected. It turned out not to be true. So there had to be an explanation. And an explanation was given. And maybe it's right and maybe it's not right.

I think that this situation with the women in the trial is quite parallel. The data just aren't there. There wasn't any benefit. Maybe it's due to small numbers, lack of power to see something. Maybe it's due to this; maybe it's due to that. But the data just aren't there.

So I do think that before the device could be approved for use in women, we'd have to have data. And I personally -- not to jump too far ahead -- think that that requires the post-approval randomized study in women. I wouldn't approve it for women. That's the way I look at these data.

DR. ZUCKERMAN: Okay. Dr. Borer, those are very important comments. So as we move forward, can you and other Panel members specifically also look at two important FDA slides: Slide 82, which actually shows the numbers for both men and women and the qualitative or quantitative results; and also look at Slide 59, which shows multiple interaction analyses. Half of them are positive; half of them are negative.

DR. BORER: Right. The interaction, to me, the interaction

analyses are very important. This Slide 82 to which you refer is one in which, if I remember correctly, we were talking about not just hospitalizations for worsening heart failure, but also including deaths, you know, and the data there for women aren't terribly impressive. The curves seem to be a little separate, but not very impressive. A lot of suggestion of interaction with gender and results. I just don't find those data compelling in terms of efficacy, and I would want more data before I would say this should be done in women.

DR. PAGE: I'm looking to the other Panelists. Does every Panelist agree that this gender issue is so great that they would be uncomfortable if they were approving, approving as a group?

Dr. Blumenstein?

DR. BLUMENSTEIN: Yeah, I'd like to note that what you're seeing up here on this particular graph is what we statisticians call a quantitative interaction, not a qualitative interaction. That is, there is a hint of benefit in both men and women as opposed to one having a hint of benefit and the other not having a hint in the other direction, for example.

So I don't know if that's true for the other slide that we saw for all those analyses. I would assume it probably is. Quantitative interactions are not nearly as serious as the qualitative interaction, where things go in the opposite direction.

DR. PAGE: And if I may pursue this a little bit more with you,

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Dr. Blumenstein, because I can speak personally that I am less troubled by the gender interaction. In Slide 59, we talked about p-values and .05, or whatever, but to get into this analysis to raise concern was a .15, so basically, looking for some sort of potential interaction. And what we have here is four of those encircled analyses being less than .15, and the rest being greater. So from your standpoint, if I'm understanding you correctly, are you as concerned that there's a signal that this doesn't work for women or is the Panel overly concerned about that issue?

DR. BLUMENSTEIN: Actually, my comment was that even if there was a significant quantitative interaction, then I wouldn't be so concerned. So the fact that someone uses a criteria of .15 and finds a few analyses that meet that criteria, that only -- I assume that means that it's -- only that there's a quantitative interaction that has met the criterion that is not -- and I'm assuming. Again, I haven't studied it, but I'm assuming that none of these are representative of a qualitative interaction, that is, the effect going the opposite direction.

DR. PAGE: I think that's the case. I'm looking to the FDA as to the -- as to whether this was going in a different direction. It was just a lower magnitude in a sub-analysis group, and that's why I was surprised by the level of concern that's raised.

DR. BLUMENSTEIN: Well, I'm looking at the estimates, and they're all -- they all have the same sign, so I'm assuming they all are

qualitative rather than mixed qualitative and quantitative.

DR. ZUCKERMAN: Dr. Blumenstein is correct. Thank you.

Perhaps there's a bigger treatment effect in men, but they're both going in the same direction. That's been our interpretation.

DR. PAGE: Dr. Ohman, and then Ms. Timberlake?

DR. OHMAN: Yeah. So this is the area that I was concerned about, and the challenge here is the fact that we're underpowered quite a bit. We have relatively few women. What is interesting to me, though, is that when you looked at Part 2, we actually have proportionally more women, maybe 9% more, so there is actually -- and that is where, with all the issues we talked about already, but that's actually where the treatment effect, if we can say that, given the fact that it's a crossover type of design, is greater. So this is one area -- and I know we're going to talk about that later, where I would encourage to think about sort of in the post-approval type of work to try to understand this disconnect a little bit. And I would hope that one can provide much more data on many more women than what we have today, because this is clearly inadequate to draw much conclusions one way or the other.

DR. PAGE: Thank you very much.

Ms. Timberlake?

MS. TIMBERLAKE: I just want to point out, you know, this is in the gray area, but the data is heading in the right direction, and I would hate

to see FDA contraindicate women for the use if they do eventually approve the device, and perhaps thinking about a caution or informed consent development that the patient and the physician share together. And then two words, post-approval, to get more data around this issue.

DR. PAGE: Thank you very much.

Dr. Borer, your light's on right now. Did you have a further question? Any other comments?

Dr. Lange?

DR. LANGE: Unfortunately, because of the small sample size, as everybody's mentioned, what it looks like is there could be a 50% benefit; there could be a 40% harm. So we just -- you know, I wouldn't want to say that, gosh, it's headed in the right direction, and I just think we don't have enough data, and I'd be concerned about using it without more data.

DR. PAGE: Thank you.

Dr. Patton?

DR. PATTON: When the Sponsor provided the information about the mode of death, it was interesting. Although the numbers were tiny, so I'm speculating a lot, there was an excess risk of sudden death in the treatment group in women, which is unusual, since women have a lower risk of sudden death than men in the heart failure population, if I'm remembering correctly.

DR. PAGE: And what implications does that have for you?

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DR. PATTON: The Sponsor is telling me that I'm remembering them reverse. Okay.

DR. PAGE: Maybe we can --

DR. PATTON: Maybe we could put up that slide.

DR. PAGE: Yeah, remind us which slide that was. My recollection was there were less deaths -- there seemed to be less deaths with the treatment group than the control, but less benefit in terms of hospitalization, and those two could have counterbalanced, but that's just my recollection. We need to see the slide. Are we working on the slide?

DR. YADAV: They're trying to get --

DR. PAGE: It was one of the slides that you presented first off, wasn't it?

UNIDENTIFIED SPEAKER: It was ancillary. It wasn't in the --

DR. PAGE: Okay.

DR. ABRAHAM: So the numbers were three heart failure deaths in the treatment group -- there it is.

DR. PATTON: So I transposed it in my head, the control and the treatment. Thank you.

DR. PAGE: So what we had was seven deaths in control, three in treatment that was put forward on this slide. Okay.

Any other comments?

(No response.)

DR. PAGE: So, Dr. Zuckerman, with regard to Question 3, there is a spectrum of concern. There's certainly -- I think there's concordance that we know less about women, and what we do know appears to be less of a significant treatment effect, although the treatment effect is at least seeming to go in the same direction as the men. At the very least, this would need to be analyzed in a post-approval study if approval were to be recommended today.

Is this helpful?

DR. ZUCKERMAN: Yes, it is, thank you.

DR. PAGE: Thank you.

We'll now read Question No. 4. Mr. Quinn?

MR. QUINN: Panel Question 4: Given the device's safety profile, the totality of the evidence regarding effectiveness, and the clinical significance of these results, please comment on the benefit/risk profile of this device.

DR. PAGE: I've gotten a sense from a number of the members of the Panel, but has anybody had a chance to give their perspective, or otherwise, I might like at least a positive and a negative perspective to be put out there for us.

Dr. Ohman, would you care to give your perspective on a risk/benefit profile?

DR. OHMAN: Yes. So the risk profile was obviously very much

deliberated at the last meeting, so not so much today, but the benefit part, I think we've looked at many various ways of defining benefit, biased or unbiased, or slightly biased, more biased, and I see it weighing sort of in the scale of the right level, i.e., more benefit than risk, although risk in this situation may actually pertain also to the risk involved with what the physician does with the data, which is obviously one of the pieces we've discussed on and off.

DR. PAGE: Fair enough. May I have a contrary perspective, just for the record? Dr. Milan?

DR. MILAN: So we met almost two years ago to review this original randomized portion of the trial, and I think we all agree that there was a signal there for benefit in the treatment group, and the question was it seemed to be entangled with this nursing intervention. And now there've been a series of post hoc analyses that are meant to help us disentangle the intervention of the -- or the contribution of the nurses.

And what I have to say about that longitudinal analyses is that I still have serious issues with the validity of those analyses mostly because of the 39% dropout -- I'm talking about just comparison number 1 -- a 39% dropout in the patients entering Part 1 versus Part 2, which makes it very difficult for me to draw any meaningful conclusions about how those patients did in those two parts of the study.

And then the propensity score, I agree that those data are

interesting to look at. I'm troubled by the idea that we would use a minority subgroup of the entire entering population to try and assert an indication for the entire 270 patients who were -- who entered that part of the trial.

So, finally, my only other point I want to make is that many people are saying, oh, the data are pointing in the right direction and it's plausible and we should just let the totality of the evidence push us in that direction, and I want to return to the Lange/Patton argument, which is there were a lot of alerts, very few of which seem to have been acted on, and how do we know that it was really that -- the PA data alerts that made those patients better or whether it was some other aspect of this clinical intervention that made the patients better.

DR. PAGE: Thank you.

Dr. Blumenstein?

DR. BLUMENSTEIN: Well, with respect to the rate of heart failure-related hospitalization in the trial that included the nurse assistance, you have benefit, and since you have almost no risk, then you have a ratio that's almost infinite. So as far as using this device with nurse assistance, yes, it's favorable. I'm being sarcastic.

(Laughter.)

DR. PAGE: Thank you. But would you -- since you did raise your hand, do you want to give any other perspective without sarcasm as to your perspective on the data as you see them in terms of weighing risk and

benefit?

DR. BLUMENSTEIN: Well, if you believe that you can delete, based on the analyses that have been done, that you can delete the nurse assistance, then yes, you have that, but I would go one step further and say that I'm still somewhat troubled by the fact that there's no survival difference. And I know that people have said, well, it wasn't designed for that, and so forth, and I can see that argument, that is, that you are really talking about device performance as opposed to clinical utility when you say that. But the point is that for patients to undergo all this trouble to get this device and go through the motions of having measurements and sleep on a funny thing and so forth, or whatever it is they do with that device, I'm not convinced, and so I -- that there is a long-term benefit with respect to survival.

DR. PAGE: Thank you.

Dr. Patton?

DR. PATTON: I think I'm probably hampered a little bit by not having been present at the prior panel meeting, but I have noted that there's been a lot of reference to this device as being very, very safe, and certainly, the Panel vote last time was that the device was very safe. But I am -- I did notice that the complication data were limited to the 30-day data and maybe a six-month, although I'm perplexed about why we don't have any more longer-term data on complications from the device, if even that

there aren't any, which would be interesting to know.

DR. PAGE: Does anybody on the Panel have any perspective on longer-term complication data?

Dr. Zuckerman?

DR. ZUCKERMAN: So perhaps the Sponsor can clarify to respond to Dr. Patton's good point.

DR. YADAV: Thank you, Dr. Zuckerman and Dr. Page. The safety slide was for the entire trial. There were eight device system-related complications in the entire trial, and they all happened in the first 30 days.

DR. PATTON: Oh, I'm sorry. I misunderstood that you -- that it was the 30-day -- okay, all right.

DR. YADAV: Yeah, they just -- they all were in the 30 days, but that is the entire study.

DR. PATTON: Okay. Got it.

DR. PAGE: Before we summarize, may I just ask Dr. Lange or Dr. Patton, who -- I don't remember who first raised the very important issue of so many bits of data with relatively few interactions, and help me understand how you would differentiate these bits of data from, for example, hourly blood pressure readings in a unit or daily blood pressure readings from a patient who's wearing a monitor. I don't know how to count the number of recordings you get in a 30-day or a 7-day blood pressure monitor recording or something like that. So help me understand how the

fact that there were less interventions relative to a number -- really big dataset, if you will, and the whole jargon these days is big data. Most were not intervened upon, but how is -- help me understand how that's different from a lot of different blood pressure measurements in a clinical scenario, where you don't act on most and you act on trends?

DR. LANGE: Your point's well taken. Again, 40,000 measurements. In fact, there were 30% less in Part 2, but it didn't change the outcome at all. So less measurements, 30% less measurements in Part 2, and it didn't change anything at all. So the real question is what prompted these medications change, because there were 32,000 blood -- excuse me -- pulmonary pressures that were elevated. Three-fourths of the time it was elevated. And, well, maybe it wasn't the blood pressure measurements at all. Maybe it was somebody calling up and saying, hey, I noticed your pressure is up, how are you feeling. And you say, well, I'm short of breath. Well, gosh, we need to increase your medications. So that's my concern. And, unfortunately, you can't capture that on the data that the Sponsor gave you, and so that's where part of the rub lies.

DR. PAGE: Thank you. Thank you.

DR. LANGE: Furthermore, there was no relationship to change in medications and hospitalization. That's what the Sponsor said. So if there is a relationship between number of measurements, medication changes, decrease in heart failure hospitalizations, but it didn't follow up, so --

DR. PAGE: Dr. Borer?

DR. BORER: Yeah. As I understood it, the 40,000, 30,000, whatever, was alerts, which is a pressure passing a certain threshold. And the stimulus to action, I think -- and your analogy to a 24-hour ambulatory blood pressure monitoring device, I think, is a very good one. You know, you have 30% of the measurements may be out of range for that portion of the day. Do you jump in and increase the drug? Well, the issue here is an alert means you've passed the threshold. When you act perhaps -- and we didn't get the data; I agree with you -- a clinician looking at the data requires a trend for passing not just a threshold that's set by the manufacturer but a threshold that's set by clinical judgment, which may be much higher.

So I think it's hard to look at the number of alerts and say, hey, why didn't somebody interact unless we actually have the data about why they didn't react to it. But it doesn't trouble me quite so much because I think of it just the way, Richard, you mentioned it, the analogy being the 24-hour ambulatory blood pressure.

DR. PAGE: Thank you, Dr. Borer.

Dr. Zuckerman and then Dr. Ohman?

DR. ZUCKERMAN: Okay. This is a really important question and key points brought up by Drs. Lange and Patton. Perhaps the Sponsor, Dr. Yadav, could clarify a moment what we're talking about from the Sponsor's perspective to help us really get to the heart of the matter here.

DR. YADAV: Thank you, Dr. Zuckerman.

I'm sorry. There seems to be some confusion on this point, and perhaps we didn't do a good job of explaining it. There were virtually identical number of patient contacts between treatment and control, and I think Dr. Abraham or Adamson showed that slide. It was 6.5 in the treatment group and 6.4 in the control group, or vice versa. Here is it.

DR. PAGE: In all fairness, I don't think the issue is between treatment and control.

DR. YADAV: Yes.

DR. PAGE: It's in treatment, there are so many alerts, but how do we know that the alerts --

DR. YADAV: Okay. Yes --

DR. PAGE: -- had anything to do with the intervention?

DR. YADAV: Absolutely. So that was one part of it. And the second part is the relationship. I think Dr. Borer, I think, pointed out that this was -- you could think of it as notifications. Alert may be too strong a word. And the physicians had the discretion -- Dr. Borage (ph.) is not here, but he told me one time that, you know, he set his really low, so he could get alerts all the time. So there's discretion in that. Remember the alerts are triggered by any component. So you could get three alerts for one reading, and that's up to you how you want to set that.

One way to think about it is physicians logged in three times

per week on average. They logged in three times per week to look at the trend. Remember alerts are points in time. As Dr. Zuckerman pointed out, they're points in time. People look at trend data, and that happened three times a week. So they logged in three times a week, on average, and they made one medication change due to PA pressure on average. So three logins per week, one PA pressure per month. And that led to the treatment effect.

Hopefully that gives some perspective.

UNIDENTIFIED SPEAKER: Not really --

DR. LANGE: Thanks, Jay, I appreciate it. There were 27,000 logins. 27,000 logins.

DR. YADAV: Well, it's good to have the denominator.

DR. LANGE: So there are 27,000 logins.

DR. YADAV: Right.

DR. LANGE: There's 1,000 change in medications. And apropos to what Joaquin, or Dr. Cigarroa, mentioned is unfortunately we don't know what triggered that. In other words, we don't know --

DR. YADAV: Well, no, you do actually. As we reported to you, the physicians, the investigative sites filled out a CRF where they indicated why they made the medication change. And so that is not correct. There were three logins per week leading to 1,400 medication changes, or one medication change per patient. It is important to have the duration,

obviously, and the number of patients. We could have had 50,000 patients. So, you know, I think it's important to have the denominator in place.

DR. LANGE: That's an interesting concept, because if what caused the physician to give the medications was an elevated PA, and it was elevated 75% of the time, I'm even more confused.

DR. YADAV: Remember, remember the hypothesis, and maybe Dr. Abraham could just --

DR. PAGE: Actually --

DR. YADAV: I'm sorry, I'm sorry.

DR. PAGE: Was there still an outstanding question from Dr. Lange or Dr. Zuckerman to the Sponsor --

DR. YADAV: Well, I just wanted to complete my answer.

DR. PAGE: Otherwise -- I understand, but this is our deliberation period, so you need to let us go on, please.

DR. YADAV: Sure.

DR. PAGE: Dr. Lange, did you have any further comments?

DR. LANGE: No, sir.

DR. PAGE: Dr. Ohman?

DR. OHMAN: Yeah, I mean, this is -- the really hard part here is the disconnect between physiology and events. And maybe the best way -- and this is why I really liked this Andersen-Gill approach, because it gets into multiplicity of events. You will recall that figure -- I'm not going to

ask them to pull it up, but you remember that the majority of triggers were in no events or one event, which means that that's just noise out there. It's really the action is in the multiple events piece, where we haven't seen exactly what the triggers and what led to changes there, but in that group of patients with multiple events, that's where it really made a difference.

So I think the challenge is sort of linking the pieces going forward. And when you have so many patients with triggers that never get hospitalized, it gets really hard to understand. But for some patients, those with multiple admissions or whatever, they seem to have some signal that helps. Maybe that's the best way I can see it.

DR. PAGE: Thank you for that perspective. I'm going to try to wrap up here for Question No. 4.

Dr. Zuckerman, the Panel is somewhat divergent in terms of the risk/benefit analysis, as per previous questions. There is concern with regard -- in some of the group with regard to whether the device is really responsible for any positive clinical outcome. And, likewise, others are more compelled. Without going into further detail, is that satisfactory for you at this time?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Thank you.

We'll now go on to Question No. 5, addressing indications for use.

MR. QUINN: Would the Panel be agreeable to me not reading the indications for the second time?

DR. PAGE: Yes, I think that's a very good idea.

MR. QUINN: Panel Question 5a: Considering the demographics of the patient population studies, please discuss whether the proposed indications for use are appropriate.

Question 5b: Additionally, please discuss whether there are additional subgroups of patients that should not receive the CHAMPION device.

DR. PAGE: So I'm going to just put something out there for discussion, and that is patients who have been hospitalized for heart failure within the previous year. This trial was designed several years ago, and our heart failure experts may or may not want to confirm that hospitalization in heart failure patients is something that's a bit of a moving target in terms of whether patients are hospitalized or defined as being hospitalized or observed. So I'd like us to at least consider whether that is the operant definition for these patients.

But also please comment -- and Dr. Borer, you've got your hand up -- as to whether you believe the indications are appropriate and whether there is any subgroups for which you're concerned -- you would not allow indication.

DR. BORER: Yeah. I don't think that the overarching definition

here is terrible, and I certainly wouldn't argue with the outset with following the trial in which people who were hospitalized -- who had been hospitalized during the preceding year and therefore at the highest risk or at particularly high risk receive the device until more evidence is available that might allow an extension of the indication.

But the part that I have some difficulty with is the functional Class III. That is a clinical definition. It's a subjective judgment. And I can see some difficulties there. When people come into the hospital and a device like this probably would be most often applied as you're walking out the door of the hospital, so to speak, during a hospitalization, people are tuned up. Somebody who came in Class III might be Class II by the time they left. Does that mean they shouldn't get the device? Somebody who came in at Class IV might go out at Class III, but the fact that they were -- spent some important time, substantial time in Class IV, does that rule them out? I have some difficulty with that. I don't think that that's solvable by a discussion here today, but I think that if this is approvable, that the FDA and the Sponsor have to sit down and make a set of operational definitions that are perhaps easier to use than just functional Class III.

Also, the issue of preserved versus low ejection fraction seems not to be an issue here, but the definition was an ejection fraction of 40%. Today, perhaps that isn't the ejection fraction that would be the cut point for HFpEF versus HFrEF. And so some thought has to go into that.

It's not that I think that the overarching definition here is bad. I think it needs some detailing in a label before it is -- before the label is finally written and the indications are finally defined.

DR. PAGE: Thank you. Earlier you had said that you would not consider this approvable for women without a randomized study. Are you still feeling that way?

DR. BORER: Yes. I would have some difficulty with that.

DR. PAGE: Thank you.

Dr. Weisfeldt and then Dr. Lange.

DR. WEISFELDT: Infants. I don't know that there's been an exploration of small children. Is it adults only or is it --

DR. PAGE: I believe this has only been studied in adults.

DR. WEISFELDT: So I mean I -- I don't have any trouble with large children, but I am a little concerned about infants, actually, with heart failure.

DR. PAGE: So thank you. So the issue of pediatrics -- defining this as non-small child and some further negotiation on that.

Dr. Lange and Dr. Cigarroa?

DR. LANGE: My hat's off to the Sponsor and the FDA for trying to pin a population down a little bit, because remember, the inclusion criteria was they had to have heart failure for at least three months, be on ARBs or ACE inhibitors for at least a month, beta blockers for three months,

and still be Class III at that point. So apropos to your point, Jeff, I think that there are ways to help identify that population so it's not overused.

DR. PAGE: Thank you.

Dr. Cigarroa?

DR. CIGARROA: So with regards to 5b, I, too, have concerns about women, given the number and the fact that it was underpowered. And, secondarily, I would also add a comment about pulmonary vascular resistance. Given the entry criteria in the 1.8 Wood units in which I think that if --

DR. PAGE: So help me understand. You would add the indication, something about pulmonary vascular resistance?

DR. CIGARROA: Under the additional subgroups that should not receive the CHAMPION device, I think individuals with an elevated pulmonary vascular resistance should not receive the device.

DR. PAGE: Thank you.

Dr. Lange?

DR. LANGE: Again, just a point for the record and what the Sponsor -- make sure that they didn't take people that had a BMI over 35, or if they did, that the diameter from the posterior back to the pulmonary was not more than 10 centimeters, because you can't record a pressure. So that would be a subgroup I would eliminate.

DR. PAGE: So in the interest of time, Dr. Zuckerman, the

indications for use generally are seen as reasonable. Issues for further negotiation and discernment would include the heart failure class. Clearly, patients move from one class to another and would not want to be ruling in and ruling out inappropriately. So some sort of operational definitions.

In terms of subgroups, there still would be at least some concern about preserved ejection fraction. Patients shouldn't be too big or too small based on the experience of the trial. So small children, certainly, and BMI or the distance between the pulmonary artery and the back being 10 centimeters, as pointed out by Dr. Lange. Likewise, Dr. Cigarroa mentioned that patients with high pulmonary vascular resistance, these might be contraindicated.

And, finally, there remains some concern about women. We've already, I think, heard from the group. There are some who feel that perhaps they would not be included in the indication at all, but at the very least, I've heard consensus that that would need to be established with a postmarket approval -- postmarket study if the approval were to be recommended and given by the FDA.

Is this helpful?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Great. We'll move on to Panel Question No. 6. The labeling is in all of your Panel packs. I'm looking for big picture. Dr. Borer, your microphone is on. You're not asking a question, are you?

DR. BORER: I'm sorry.

DR. PAGE: I'm looking for high-level concerns about labeling.

Otherwise, that's something that's negotiated after Panel. Are there any high-level concerns about the labeling?

(No response.)

DR. PAGE: Dr. Zuckerman, I'm not seeing any high-level issues regarding labeling. Is this satisfactory?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Thank you very much.

And now we'll move on to Panel Question No. 7. Mr. Quinn, do you want to read us Question 7, maybe in an abbreviated fashion? We can read the first paragraph.

MR. QUINN: Question 7a: Whether two years and one year are the appropriate lengths of follow-up over which the safety and effectiveness hypotheses should be tested, respectively.

7b: What are the appropriate performance goals for evaluation of the two safety endpoints?

7c: What is the appropriate performance goal to evaluate the one-year heart failure hospitalization rate?

Question 7d: Whether other effectiveness endpoints should be included as secondary endpoints.

And lastly: Whether a specific effort should be made to study

device effectiveness by gender.

DR. PAGE: So I'm looking for commentary from the Panel. I see Dr. Somberg has his hand raised.

DR. SOMBERG: Certainly, for gender, but I think this surmises that there's no control arm, and I don't think a single-arm study is appropriate given this level of confusion about the endpoints.

DR. PAGE: So I'm going to keep us on task here, and we are working in an environment where we are assuming it's been approved and now we're commenting on the post-approval study.

Is that what you want from us, Dr. Zuckerman?

DR. ZUCKERMAN: Correct.

DR. SOMBERG: And that's exactly my response is if it's approved, I still think a single-arm study is inappropriate.

DR. PAGE: Fair enough. Noted.

DR. BLUMENSTEIN: I concur.

DR. PAGE: Dr. Blumenstein -- Dr. Zuckerman, in terms of additional post-approval randomized studies, can you comment on the FDA's perspective on that?

DR. ZUCKERMAN: That's usually unusual, but the Sponsor has a large control dataset that would be available for propensity score analysis, Dr. Somberg, to compare, for example, two-year heart failure hospitalization rates. You're looking for a reasonable control?

DR. SOMBERG: In this situation, if one assumes that the risk and the benefit is such that you approve the device, and you do not have a concomitant control, three to five years after the other dataset, you will never have a true answer to how best to utilize the data this device provides to optimize current patient care. You will have some sort of point estimate of what it does, and then you will say you will have to compare it to historic data, and you will be rehashing this once again not at this forum, but in the AHA/ACC type forums.

DR. PAGE: I'm going to keep us on task in terms of assuming a post-approval that's not a new randomized trial.

Dr. Borer?

DR. BORER: Yeah. I would agree with you. I don't think a new randomized trial is needed for the primary indication. I do think it's going -- you know, if what I said before is correct and people agree, and we don't have data about efficacy in women, then I think that's a subgroup that probably should have a randomized trial. But for the -- but for men, I don't think that's necessary, and I do think that questions can be answered with the dataset -- the large control dataset that the company may have.

Remember we're not talking about a therapy here. We're talking about how to use data in therapy, and that's a little bit different. But there are other parts of this question.

(a) Whether two years and one year are the appropriate

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lengths of follow-up for safety and effectiveness hypotheses. I would say post-approval, two years for effectiveness. We're talking about a population with a relatively limited lifespan, so two years, even though relatively short, is okay in this group for effectiveness. For safety, yes, I think that's fine, because we just haven't seen anything past 30 days.

One of the appropriate performance goals for evaluation of the safety endpoints, there was some discussion in the materials about how it no longer should be 80% and 90% for the two safety criteria. I don't see why. It was good enough two years ago. Why is it not good enough now? I think that we may want to get more information, and we may want to see it longer -- that's the key -- to make sure that there's durability of safety. But I don't think there's any particular reason to change the safety performance goals.

What is the appropriate performance goal to evaluate the one-year HF hospitalization rate; it's in the "too hard" box for our discussion here. I think that's going to be a separate discussion for the FDA.

And other effectiveness endpoints? To me, they're not relevant. The effectiveness endpoints are hospitalizations and mortality, and that's it. And you're really looking at the effect of a treatment based on a test, so I don't think looking at other things is really particularly important.

Specific effort made to study the device's effectiveness by gender? I've already said I think it is necessary to look at women

separately --

DR. PAGE: Thank you. I'll ask Dr. Ohman to comment.

DR. OHMAN: So couple of points here. Well, one of the challenges is using a control that is quite old now. By definition, the trial has been going for a while. So I would recommend that actually you -- instead of actually putting the device in immediately, but to have a run-in phase and use that run-in phase prior to the device insertion as a control, active control arm, because in that way, you can actually define it much better, and you can know much better about the current control.

I think it's very important that actually we have a better understanding of the signal -- I call it the Lange/Patton rule here now -- of understanding what is it that drives the signal here, and there's lots of data that can be derived from that as a sort of secondary analysis. And then, of course, the size of the gender component has to be large because there's a lot of uncertainty there. And whatever large is, I'll leave that to the FDA to decide.

DR. PAGE: Dr. Lange?

DR. LANGE: I would agree with my colleagues is that a control -- a historical control for women doesn't cut it. You can do it in a run-in phase or a randomized control, and if you say we can't do it postmarketing, then just approve it in men and then do the randomized control. I mean, there are ways to get it done, but I think what we're telling

you is we're uncomfortable with that.

And the only reason I would suggest maybe doing safety for a little bit longer than two years is with the ASD devices, putting in intracardiac metal devices, we see erosions occur a little bit later. So I might just say just carry the safety out just a little bit longer, looking to see whether it causes problems inside the pulmonary artery.

DR. PAGE: So two years would not be long enough, from your perspective, for safety?

DR. LANGE: Yes, sir. I would go for at least -- I'm sensitive to the fact that these people aren't going to live 10 years, so I would say take it out for three or four years.

DR. PAGE: So, Dr. Zuckerman, in the interest of time, because we have significant work to do still, I'd like to cut our conversation with regard to Panel 7 short. You've heard a number of perspectives in terms of, first of all, the issue of safety perhaps being longer, the appropriate performance goals, certainly, as rigorous as was expected, but I think there might be other opinions that might say since .8 is a very low bar, and if we saw .85, I'd worry about that, frankly, so perhaps at least at .8. The appropriate performance goal at one-year hospitalization rate, that would take some work. The other effectiveness endpoints for secondary endpoints we haven't really had a chance to discuss at any length. And, finally, the effectiveness by gender, a fairly strong perspective of concern about the

effectiveness in women has been raised. I don't think that's shared by the entire Panel, but we'll need to see that when we end up taking a vote.

Is this helpful, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Thank you.

So now it's time for FDA and Sponsor summations. The Panel will hear summations, comments, and clarification first from the FDA, and you have 10 minutes. You'll have a one-minute warning.

DR. AGUEL: Good afternoon. My name is Felipe Aguel, and I'll be giving a very brief FDA summation given where we are in the afternoon and amount of time we have left. We've heard today that -- we've heard multiple ancillary analyses that were presented by the Sponsor, done by the Sponsor, to address the questions in a not approvable letter that was sent a couple of years ago after the first panel meeting that was held on this device. The efficacy and the merits of each of those analyses were discussed along with the limitations of each. I think it's been recognized that the limitations are important, but there was a variety of opinion regarding whether those limitations render the ancillary analyses invalid.

There was a very interesting discussion regarding the causality of device used and the treatment effect observed. We saw that there were, in Part 1 of the study, there were 44,000 readings, 32,000 alerts, and that resulted in 1,400 medication changes based on PA pressures.

We've heard a very good discussion regarding the gender effect, the fact that it's a quantitative and not a qualitative interaction that was observed. It was suggested that this should be studied in a post-approval study in larger numbers and using a randomized control trial or at least a concurrent control in the post-approval phase should the device be approved.

All in all, FDA believes that there was a notable consistency in the results, but the limitations discussed are significant.

Regarding the clinical significance, the number needed to treat that was discussed is certainly impressive that makes the assumption that we can rely on the numbers to begin with.

So, all in all, what I would ask is that the Panel consider the totality of the data. Some Panelists expressed the opinion that they believed the propensity score analysis was more compelling. FDA believes that the longitudinal analyses are also compelling. I think there's a variety of opinion there. All in all, we need to look at all of the data, including the Part 1 results, the analyses that we saw and discussed in detail today, along with all of the limitations as you vote on the three voting questions.

Thank you.

DR. PAGE: Thank you very much. I'll now call on the Sponsor, who I must commend for working very hard to present the data that we needed, and look forward to your final comments. We give you 10 minutes,

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and you'll have a yellow light at nine.

DR. YADAV: Thank you, Dr. Page. I will not take up that much of your time. I appreciate your indulgence with our presentation today.

When we started working on this problem back in 2001, there was a great need in heart failure and prevention of heart failure hospitalizations. Certainly, in 2013, that need has not decreased. If anything, it has increased. It has become more of a public health issue. It has become a notable problem for Medicare, and certainly readmissions have become even more critical.

What we have shown you today is six years of clinical data and 1,200 patients years of follow-up, so a substantial dataset. Hopefully you are reassured that not only heart failure hospitalizations, which have a significant impact on patients in terms of disease progression, but also all-cause hospitalizations -- you know, we're not increasing some other cause of hospitalization. That certainly gives me a lot of comfort. All-cause hospitalization and death are markedly reduced either in the randomized trial or over the full duration of the longitudinal study.

I would also note that the causes of admission -- the route of admission is through the emergency room, which is not through the clinic. And that was the difference -- that is the entire difference in the hospitalizations.

I would clarify the connection between the readings and the

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effect size. It is important to keep the denominator in perspective. So there are 270 patients in the primary endpoint period. There is six months, 24 weeks. So one can do the math. And if you adjust for that and you look at the log -- so I think the question is what are physicians responding to. And, certainly, they could be looking at the alerts, but most likely, they're looking at the trends when they log in, because remember, the alerts don't give you trends. That's just one reading. In fact, it's one component of a reading. It's systolic, diastolic, or mean. When they log in, they're looking at the trends, and they did that about three times a week on average. And they made about one PA pressure-based medication change per month. So that is the connection. And that led to the decrease in hospitalizations of 36 hospitalizations at six months or 97 during randomized access over 17 months or 118 for all-cause hospitalizations.

As you have heard from the FDA, from Dr. Stevenson, these are very large effect sizes. They're comparable to the drugs that we use for heart failure. They're very, very meaningful.

You've heard a number of analyses, and the nature of science is that no experiments are perfect. I certainly know that as a basic scientist in my training and certainly as a clinician. And we learn from every experiment that we do. The randomized controlled trial wasn't perfect. We have worked hard to give you additional data, a number of additional experiments, and we have learned from that experiment. And our steering

committee and our principal investigators have learned from that experiment. And we're giving you additional information.

And certainly in science, we look at concordance of multiple experiments. None of them are perfect. If all of them show us stuff that works together, then we're more likely to think that we're getting the nature of reality because these are all approximations of reality. And I think the fact that you have seen a randomized control trial, which despite its limitations was highly positive, you have seen a clinical analysis by two independent, eminent clinicians who read every single e-mail who did not think they were influential, you've seen a propensity analysis in the patients who were never the subject either of an inquiry or recommendation -- they're truly isolated -- and the effect size is very similar. And I think the similarity of effect size, they should also be compelling. They're not that different. They're very similar.

And then -- and the propensity analysis, as Dr. Zuckerman pointed out, was conducted by an independent statistician, Dr. D'Agostino, Jr. Further, you don't just have one longitudinal analysis. You have four distinct longitudinal analyses, all four of which met their prespecified hypotheses. That seems unlikely due to chance.

Yes, longitudinal analyses are all affected by patients who exit. That is part of that. And the analytic techniques used accounted for that. Further, we showed you the landmark analysis asked by Dr. Blumenstein,

which is only in patients who were in Part 1 and Part 2, and the treatment effect is still present. It is very similar quantitatively and statistically significant.

Regarding women, the study, like many cardiovascular studies, has too few women. That is clearly a problem in cardiovascular trials and something that we're all trying to address. Certainly, the post-approval study that we've proposed would have a very large number of women, would have at least 30, 40 percent women. I think it is important to note, as Dr. Blumenstein pointed out, this is a quantitative interaction, not qualitative. The women, the treatment women did not do worse. As an interventionalist, we have lots of examples in cardiovascular medicine where the women actually do worse. That's not the case here. The women who were treated with the device did the same as the men. The control women, due to play of chance, did -- had an unusually low event rate we think is due to the competing risk of death. And when we show you the competing risk of death analysis, there is no treatment by gender interaction, by the prespecified model, the Cox model, for competing risk analysis.

In summary, I think the risk is exceedingly small. Indeed, I would say with some pride that this device sets a new standard for risk for implantable cardiovascular devices. It is incredibly safe. And that is not accidental. It has to do with the design. We could have made a titanium machine sensor like we have all seen, and you would have not seen this

performance. We created an entirely new technology, which is very current, very reliable, very durable. It does not require repeat procedures for patients, which I think is a key point that Ms. Currier made. These patients have many, many procedures. This device gives them a chance not to have multiple right-heart catheterizations.

The risk is exceedingly low. You have seen a very large clinical benefit any way you slice it -- you can look at the randomized trial, you can look at the longitudinal analysis, you can look at propensity. It is 3 to 5 patients needed to prevent a hospitalization per year, as Dr. Borer pointed out. That's incredible. That is as good as anything else we do in medicine. You saw that the benefit is true in small hospitals, big hospitals, academic, community. So it does not appear to be a very complicated device to use. Certainly, that can be addressed further in a post-approval study.

So I appreciate your time today. I think there is a great need for this device. I think we have shown you compelling data from multiple points of view and multiple analyses over a very long period of time that all come together and demonstrate a high clinical utility and benefit for this device.

Thank you.

DR. PAGE: Thank you, sir.

So with that, I'd like to turn to our non-voting members for comments prior to our taking a vote. I'd like to ask Ms. Timberlake, our

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Industry Representative; Ms. Mattivi, our Consumer Representative; and Ms. Currier, our Patient Representative, if they have any additional comments.

Ms. Timberlake first.

MS. TIMBERLAKE: I just want to thank both FDA and the manufacturer presenting today. Overall, based on what we've discussed today, that there is reasonable assurance for -- that the device is safe and effective in use and that the benefit does outweigh the risk, I would like to see the device not contraindicated for females, and that the additional analysis could be handled in the post-approval requirements.

DR. PAGE: Thank you very much.

Ms. Mattivi?

MS. MATTIVI: I'd also like to thank FDA and the Sponsor for really great presentations and discussions of the data. I think consumers were well served by the discussion here today, and I'm excited that technology is moving us towards something to provide a more reliable signal to reasonable physicians other than a talking bathroom scale.

(Laughter.)

DR. PAGE: Thank you.

And, finally, Ms. Currier?

MS. CURRIER: Yeah. So when I was sitting there reading my Panel pack and being frustrated about something in my own health, I came

up with a bumper sticker, which was "Test, Don't Guess." And I figure that was a good one for this particular device. And it's a way, I feel, that there's just an awful lot of pain for the patient not knowing what's going on, you know, and this device would let the physician figure out whether their medications are working and not see it three months later. Oh, it's not working. Try this. So that's what I like about it. Thank you.

DR. PAGE: Thank you very much. And I'd point out that our three non-voting members of the Panel have been tremendously constructive today, and we really appreciate your efforts on our behalf as we have deliberated the issues here that we're now going to proceed on with a vote.

We are now ready 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.

Ms. Waterhouse will now read three definitions to assist in the premarket approval application voting process. Ms. Waterhouse?

MS. WATERHOUSE: 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 a 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 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 directions for use and warnings against unsafe use, will provide clinically significant results.

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 reasonably 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. PAGE: The Sponsor has proposed the following indication for use statement:

The CardioMEMS CHAMPION HF Monitoring System is indicated for wirelessly measuring and monitoring pulmonary artery, or PA, pressure and heart rate in New York Heart Association Class III heart failure patients who have been hospitalized 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 CardioMEMS CHAMPION HF Monitoring System is used by the physician in the hospital or office setting to obtain and review PA pressure measurements. The CardioMEMS 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. Ms. Waterhouse will go through the voting procedure with us.

MS. WATERHOUSE: Panel members, please use the buttons on your microphone to place your vote for the following three questions.

Voting Question 1 reads as follows: Is there reasonable

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assurance that the CardioMEMS HF Pressure Measurement System is safe for use in patients who meet the criteria specified in the proposed indication?

Please place your vote now.

(Panel vote.)

Voting Question 2: Is there reasonable assurance that the CardioMEMS HF Pressure Measurement System is effective for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

Voting Question 3: Do the benefits of the CardioMEMS HF Pressure Measurement System for use in patients who meet the criteria specified in the proposed indication outweigh the risk for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

DR. PAGE: We're waiting for two more votes.

MS. WATERHOUSE: For Voting Question 1, all of the Panel members voted yes.

DR. PAGE: And for the record, that's 11.

MS. WATERHOUSE: Keep it up, Question 2. For Question 2, Dr. Somberg voted no, Dr. Lange voted no, Dr. Ohman voted yes, Dr. Yuh voted yes, Dr. Jeevanandam voted no, Dr. Weisfeldt voted yes, Dr. Milan voted no, Dr. Patton voted no, Dr. Blumenstein voted no, Dr. Borer voted

yes, and Dr. Cigarroa voted no.

For Voting Question 3, Dr. Somberg abstained, Dr. Lange voted no, Dr. Ohman voted yes, Dr. Yuh voted yes, Dr. Jeevanandam voted yes, Dr. Weisfeldt voted yes, Dr. Milan voted no, Dr. Patton voted yes, Dr. Blumenstein voted no, Dr. Borer voted yes, and Dr. Cigarroa voted no.

So for Voting Question 1, the Panel voted 11 to 0 that the data shows reasonable assurance that the CardioMEMS HF Pressure Measurement System is safe for use in patients who meet the criteria specified in the proposed indication.

On Voting Question 2, the Panel voted 4 yes, 7 no that there's reasonable assurance that the CardioMEMS HF Pressure Measurement System is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 6 yes, 4 no, and 1 abstain that the benefits of the CardioMEMS HF Pressure Measurement System outweigh the risk for use in patients who meet the criteria specified in the proposed indication.

DR. PAGE: And I just want to confirm with the Panel that all your votes are correctly recorded. We actually had a no vote -- a positive vote on 1, a no on 2, but a positive on Question 3. And you all heard your votes.

And at this time, I'd like to go around the room and ask each

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Panel member to discuss their votes. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer. And I'll start over here with Dr. Milan.

DR. MILAN: So I voted that I thought the device was safe but that that there was not a reasonable assurance of its effectiveness. And I believe that the ancillary data presented here were not valid or convincing, and I think that the appropriate approach is what the FDA originally recommended, which is a properly performed randomized trial.

DR. PAGE: Thank you very much.

Dr. Borer?

DR. BORER: I voted yes for all three questions, though as I said several times, I am concerned about the use of the device in women with the currently available data, but that's not the way the questions were worded. I think that the ancillary studies were very helpful in clarifying the utility of the original randomized trial, and based on that, I think this is an approvable and probably very useful device.

DR. PAGE: Thank you, Dr. Borer.

Dr. Blumenstein?

DR. BLUMENSTEIN: So I voted yes for safety and no for the two efficacy-related questions. I didn't feel that the additional analyses clearly demonstrated that the device could be used without nurse

assistance, based on the fact that there was a lack of experimental structure in the data analyzed.

DR. PAGE: Thank you.

Dr. Patton?

DR. PATTON: I had the unusual vote. I voted yes for safety and I voted no on effectiveness, because I wasn't completely convinced by the data. But my third vote, which was a yes, was because I felt like the device was very effective in doing what it was intended to do as a diagnostic device, and the risk profile was so low that I felt like there was a good chance that this could be clinically useful.

DR. PAGE: Thank you, Dr. Patton.

Dr. Lange?

DR. LANGE: Yes. I voted yes, no, and no, and for the same reasons that Dr. Milan mentioned, so I won't prolong it.

DR. PAGE: Thank you.

Dr. Weisfeldt?

DR. WEISFELDT: Yeah, I voted yes for all, and the reasons were what I've said already. The propensity analysis, I thought, was stabilizing with regard to the efficacy aspects of the device. And I think that's it.

DR. PAGE: Thank you very much.

Dr. Yuh?

DR. YUH: Yes. I voted yes for all three questions. You know,

although -- and I'm not surprised with the split in the vote on Question 2, but to my eye, I did feel it was an effective monitoring device that did facilitate closer monitoring of these very difficult patients for heart failure cardiologists, and so that's what the rationale for my vote was.

Thank you.

DR. PAGE: Thank you very much.

Dr. Somberg?

DR. SOMBERG: Well, I thought the device was safe like everyone else did. I thought there was certainly a consistent trend to support its efficacy, but there were really a lot of unknown questions. And I couldn't say the data was valid to support that. So I voted no for 2. I abstained on the third on because -- and my vote would be changeable if the -- if some time in the future we would have data in sets with a controlled trial. But without a controlled trial, just a registry, we will never have it, so therefore, I could not vote affirmatively. So I leave it to the FDA to make a decision on whether we're going to see this approved, see this not approved, and if we see it approved, I think it should have certain comparisons. Not a repeat of the first study, but a modification of it looking at other aspects and have an appropriate comparator especially with gender.

DR. PAGE: Thank you very much.

Dr. Cigarroa?

DR. CIGARROA: So for Question No. 1, I believe it is safe, and I

think that's consistent with the dataset and is actually a change in how I voted at the first panel meeting.

With regards to Question No. 2, is there reasonable assurance, I voted no, and I have been conflicted about the meaning of reasonable with regards to the scientific evidence given that I am unable to resolve what I believe are the substantial probability of differences in patients at the outset of Part 2 of the study. And that I'm still wrestling with.

DR. PAGE: Thank you --

DR. CIGARROA: And that led to Question No. 3 being no.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Jeevanandam?

DR. JEEVANANDAM: So I was a split voter, too. So I voted yes for Question 1. For Question 2, I think for the indication, in terms of hospitalization, I didn't think that it met reasonable assurance of efficacy. However, the safety profile was good enough, and I think it's an excellent diagnostic tool. And, you know, even if it's not used in this particular indication, there are an innumerable number of heart failure patients that I take care of that I'd love to put this thing and know what their PA pressures are. For LVAD patients, you know, you can actually make a big difference in the PA pressures just by turning that LVAD up. And I think that's why, you know, from a selfish point of view, I'd love to be able to put this in one of my patients and measure their PA pressures. I just got paged for two people

who need right-heart catheters tomorrow who won't need them if you had this sensor in, so that's why I voted yes for Question 3.

DR. PAGE: Thank you very much.

Dr. Ohman?

DR. OHMAN: Thank you. I was consistent in my vote from Panel 1 to Panel 2. So I thought this was yes for safety. I feel that there's reasonable assurance that it's effective mainly because if you look at the totality of information presented today, it actually is very uniquely one -- unidirectional. That is to say, it all is in the same realm. And this, of course, is a field of physiology that we have learned to deal with ever since the ESCAPE Trial many years ago. So I think that we weren't reinventing the wheel here, to a large extent. And, finally, I feel that this type of device could have considerable role in the management of a patient population that we really do not have a whole lot of options for. And, once again, the totality of data presented plus the physiological information from the past is, to me, overwhelming of benefit.

DR. PAGE: Thank you very much.

I want to thank the Panel for not putting me in a position where I had to break a tie.

(Laughter.)

DR. PAGE: If I were to vote, I would vote in the affirmative for Questions 1, 2, and 3. I wrestle with the same issues. I am personally less

troubled by the gender issue, but I think it will need to be studied in the post-approval study if that were to occur.

In closing, I want to thank the Panel for really -- we were dealing with a device that is frankly dazzling in its technological achievement. But this Panel was not dazzled by it and, to the contrary, was rigorous in evaluating the data and very thoughtful in how we approached the problem with the initial PMA and then this time. And I think the overall vote reflects the discomfort all of us have in evaluating this device. But we did the best, I think, with the data that we have available.

I want to thank the FDA and the Sponsors, obviously, for presenting very well. I also want to make mention of the Sponsors group there. I've never seen a group that was able to come up with more rapid data and slides to address our questions, and that really helped us do our job in this relatively long day.

And, finally, I want to thank the federal employees who I think are working for free today for us to be here.

(Laughter.)

DR. PAGE: But I feel like the Panel did a terrific job, and I really appreciate the support.

Dr. Zuckerman, do you have any further comments?

DR. ZUCKERMAN: Yes. The American public was extremely well served today. This was an outstanding Panel, a very difficult topic, and I

really want to thank everyone on this Advisory Panel, and please have a safe trip home. Thank you.

DR. PAGE: With that, the October 9th, 2013 of the Circulatory Systems Devices Panel is now adjourned. Safe trip home, everybody.

(Whereupon, at 5:36 p.m., the meeting was adjourned.)

CERTIFICATE

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

CIRCULATORY SYSTEM DEVICES PANEL MEETING

October 9, 2013

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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