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 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
 MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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April 25, 2012
 8:00 a.m.

Holiday Inn
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

PANEL MEMBERS:

RICHARD L. PAGE, M.D.	Temporary Panel Chair
DAVID J. SLOTWINER, M.D.	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
RICHARD A. LANGE M.D.	Temporary Voting Member
SCOTT EVANS, Ph.D.	Temporary Voting Member
JEFFREY S. BORER, M.D.	Temporary Voting Member
GREGORY DEHMER, M.D.	Temporary Voting Member
JOAQUIN CIGARROA, M.D.	Temporary Voting Member
RALPH BRINDIS, M.D.	Temporary Voting Member
DAVID YUH, M.D.	Temporary Voting Member
KEITH B. ALLEN, M.D.	Temporary Voting Member
JOSEPH J. AMATO, M.D.	Temporary Voting Member
DEBRA GATES McCALL	Patient Representative
BURKE T. BARRETT, B.A., B.S., M.B.A.	Industry Representative
ROBERT DUBBS, J.D., M.B.A.	Consumer Representative
JAMIE WATERHOUSE	Designated Federal Officer

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M E E T I N G

(8:00 a.m.)

DR. PAGE: I'd like to call this meeting of the Circulatory System Devices Panel to order. It's now 8:00 a.m.

I'm Dr. Richard Page. I'm the Chair of the Panel. I'm the Chair of Medicine at the University of Wisconsin in Madison, and I'm a clinical cardiac electrophysiologist.

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

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to PMA P100047 for the HeartWare Ventricular Assist System.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

Mr. Barrett, do you mind if we start with you and we go around the table?

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

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MR. DUBBS: Bob Dubbs. I'm a practicing retiree from south Florida; Patient Representative [sic].

MS. McCALL: Debra McCall. I'm also a Patient Representative from Southern California.

DR. YUH: Good morning. I'm David Yuh. I'm Chief of Cardiac Surgery at Yale University. My expertise is in less invasive cardiac surgery, but I do have some experience in heart failure as well.

DR. ALLEN: My name is Keith Allen. I'm Director of Surgical Research at the Mid America Heart Institute in Kansas City. I'm a practicing cardiothoracic and vascular surgeon.

DR. BRINDIS: Ralph Brindis. I'm the Senior Advisor for Cardiovascular Disease in Northern California Kaiser Permanente, a recovering interventionalist, and have spent time with the National Cardiovascular Data Registry for the ACC.

DR. LANGE: My name is Rick Lange. I'm Vice Chairman of Medicine at the University of Texas, San Antonio, and also a recovering interventionalist.

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

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

DR. DEHMER: Greg Dehmer. I'm with Texas A&M College of

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Medicine and the Scott & White clinic in Temple, Texas. I'm still a practicing interventional cardiologist, and I'm the guy with the bad cold up here.

DR. BORER: My name is Jeff Borer. I'm the Professor and Chairman of the Department of Medicine and Chief of Cardiovascular Medicine at the State University of New York Downstate Medical Center in New York City.

DR. AMATO: Good morning. I'm Joe Amato. I'm a retired pediatric and adult cardiac, thoracic, and vascular surgeon and later on in life received a degree in jurisprudence, a master's of jurisprudence. I'm in Chicago, at Rush.

Thank you.

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

DR. EVANS: Good morning. Scott Evans, expertise in biostatistics and clinical trials, Department of Biostatistics, Harvard University.

DR. SLOTWINER: Good morning. I'm David Slotwiner. I'm a practicing cardiac electrophysiologist at North Shore Hofstra School of Medicine in New York.

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

Thank you.

DR. PAGE: Thank you all.

If you have not done so, please sign the attendance sheets that are on the tables at the doors. This is for the audience.

Jamie Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, is now going to make some introductory remarks.

Jamie.

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member 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 and 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

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

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code 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 a supplement to the premarket approval application for the HeartWare Ventricular Assist System sponsored by HeartWare. The HVAS is an implantable, electrically powered, centrifugal-flow rotary pump with external driver and power sources. It is the

first ventricular assist device that does not require the creation of an abdominal pump pocket. The HVAS is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular 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 208 and 712 of the FD&C Act.

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

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

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.

Appointment to Temporary Voting Status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health,

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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:

Drs. Richard Lange, Scott Evans, Jeffrey Borer, Joaquin Cigarroa, Ralph Brindis, David Yuh, Gregory Dehmer, Joseph Amato, and Keith Allen.

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.

This has been signed by Jeffrey Shuren, Director of Center for Devices and Radiological Health, on April 16th, 2012.

For the duration of the Circulatory System Devices Panel on April 25th, Ms. Debra McCall has been appointed as a Temporary Non-Voting Member. For the record, Ms. McCall serves as a consultant to the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on April 20th, 2012.

Before I turn the meeting back over to Dr. Page, I would like to

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make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, 1378 Cape St. Claire Road, Annapolis 21409. The telephone is (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Michelle Bolek.

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 FDA, please arrange to do so with Mr. James Clark at the registration desk.

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

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

Thank you very much.

Dr. Page.

DR. PAGE: Thank you.

Before we proceed with the Sponsor presentation, I'd just like to mention that public observers at this meeting are welcome and the

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meeting is open for public observation. Public attendees may not participate except at the specific request of the Panel Chair.

The other thing I'll mention is that we have a lot of work to do today. We have an agenda, and I'm going to be working according to the agenda for the time allotment that's been provided to each speaker, and I will ask people to stay on time. I hate to cut you off at the best part of your presentation, so please plan to stay within the allotted time for presentations.

With that, I'd like to proceed with the Sponsor presentation.

Welcome.

MR. GODSHALL: Mr. Chairman, members of the Committee, and members of the Food and Drug Administration, good morning. My name is Doug Godshall. I'm the President and Chief Executive Officer at HeartWare International, Incorporated.

We are here to present data on the HeartWare Ventricular Assist Device, or HVAD, for the use as a bridge to cardiac transplant in patients who are at risk of imminent death from refractory end-stage left ventricular heart failure. The specific indication is supported by the results of the ADVANCE trial, which we will discuss in detail today.

Heart failure is a major public health problem in the United States. Patients with end-stage heart failure are characterized by pronounced symptoms at rest or upon minimal physical exertion, despite

maximal medical therapy. This patient population has a one-year mortality rate of 50%, and the patients in our study had a projected survival of 45%.

Heart transplantation is considered the best available treatment option for these patients. However, there is a substantial gap between the number of patients who need a new heart and the availability of donor hearts. This gap has led to a significant increase in wait time for transplant.

Left ventricular assist devices, or LVADs, are increasingly being used to bridge patients until a donor heart becomes available. Enhanced technology and innovation are essential to patient survival during this extended period of time before a compatible donor is found.

UNOS sets, reviews, and improves transplant policy in order to prioritize patients in need of a transplant. The table here presents UNOS' status and summary definitions.

Each candidate awaiting heart transplantation is assigned a status code which corresponds to how medically urgent it is that the candidate receive a transplant. The higher the status, the more urgent the need.

Status 1A reflects all patients on one or more of the following devices or therapies: invasive hemodynamic monitoring and either single high-dose IV inotropes or multiple inotropes at any dose, mechanical support with device complication and mechanical support for more than 50 days, or

on continuous mechanical ventilation.

Status 1B reflects all patients not listed as 1A, who have been implanted an LVAD or RVAD, or are on intravenous inotrope support.

Those patients listed as UNOS Status 2 reflects all other patients actively listed for transplant, and UNOS Status 7 shows all patients listed but on hold for transplant.

There are few LVADs approved for use in the United States today, and those that are approved have limitations. There's only one continuous-flow LVAD approved in the U.S., the HeartMate II from Thoratec, and while a very good technology, it accounts for essentially all the commercial implants, which severely limits options for treating clinicians and their patients. While we acknowledge our own limitations, the HVAD does provide meaningful clinical benefits not offered by other devices.

The existing devices either have durability limitations or, at minimum, require mechanical bearings to drive their impeller, which the HVAD does not. Our integrated inflow cannula reduces procedure time and the need for onsite assembly of the device.

The very small housing enables the device to be implanted in the pericardial space in every patient, thus eliminating the need for the surgeon to create a pocket within the patient's abdomen to hold the pump, as is required with other devices. This is clinically important as a 3% event rate of abdominal pump pocket infection was reported for the HeartMate II

by Pagani et al. in 2009, and these are extremely challenging cases to manage.

The small size of the device also enables clinicians to treat patients who cannot tolerate implantation of a device below the diaphragm due to body size or other factors within the abdominal space. At 50% the displaced volume and half the weight of the most frequently used device, the HVAD is appealing to both surgeons and patients because it allows a less invasive procedure, which intuitively should lead to reduced infections and bleeding rates.

In addition to benefits delivered by the pump, the system has other features that deliver meaningful clinical value. The locking sewing ring ensures hemostatic attachment to the left ventricle. Our nickel alloy driveline did not fracture once during this bridge-to-transplant trial and has proven to be substantially more durable than alternative designs.

The architecture and software in our controller and monitor has improved ease of use for both patient and clinician by providing clear written text-to-diagnostic information instead of symbols to remember. The patient is constantly informed as to the status of their device. For the clinician, accurate flow estimation and availability of high fidelity waveforms enables them to identify and manage problems earlier.

HeartWare has developed the HVAD to deliver unique benefits over the current options and provide clinicians and patients a valuable

alternative to what is presently on the market.

The following is a brief video which provides an overview of the HVAD system.

The HVAD is a very small pump, at 55 cc displaced volume, but it provides up to 10 liters of flow. The integrated inflow cannula and small pump size enable the system to be placed in the pericardium above the diaphragm. Commercially available devices in the U.S. require a pump pocket in the abdomen, as simulated here by the shadow.

To implant the pump, the surgeon first attaches a proprietary sewing ring. A hole is then created inside the sewing ring using a custom-fit coring tool. The pump inflow is then inserted into the ventricle and is secured inside the sewing ring. The outflow graft is then attached to the ascending aorta, and a strain relief around the graft prevents kinking of the graft itself.

When the pump is turned on, blood is pulled into the system from the ventricle. The hydrodynamically suspended impeller rotates at a constant speed and continuously perfuses the body. The pump is connected to a controller outside the body by the thin, durable driveline. The controller is connected to two power sources at all times, either two batteries, as shown here, or a battery and an AC or DC adapter.

The HeartWare device has been implanted in approximately 2,000 patients worldwide. Approved in Europe in January 2009 and approved

in multiple other jurisdictions since, the product is, as of the end of 2011, one of the two most widely used ventricular assist devices outside the United States, accounting for nearly half of the international VAD implements in the last year.

The small size of the HVAD has made it possible for the device to be implanted in pediatric patients as young as six years old. There have been over three dozen pediatric patients, including six in the U.S., under compassionate use.

Even more impressive, the low profile of the device makes it possible for the surgeon to place two in the same patient, one for the left ventricle and one for the right ventricle, which enables them to treat patients that suffer from the extremely challenging condition of biventricular failure. There have been nearly 70 such cases performed globally to date.

We plan to pursue both pediatric and biventricular indications in hopes of addressing these underserved patient populations, following approval for the bridge-to-transplant, or BTT, indication we are discussing today.

Our next generation pump will be entering the clinic later this year, and at one-third the size of the HVAD, it should further reduce the invasiveness of the surgical intervention.

Today, along with presenting data from our ADVANCE trial, we plan to address the FDA's major concerns. We appreciate these concerns and

would like to provide further clarification for each of these issues. While we acknowledge that there exists some missing data, in particular, right atrial pressure values, and recognize that this created a question for the Agency regarding the interpretation of the data, we have performed sensitivity analyses to confirm that the imputation of missing data did not bias our primary endpoint outcome or assessment of safety of the HVAD. We will provide evidence to show that treatment and control arms are comparable and will address FDA's concern regarding patient severity of illness in the two arms.

Neurologic events and thrombus rates are clearly concerns for both the FDA and HeartWare. We will review results of the mitigation strategies to date, as well as proposed mitigations that will be implemented in a post-approval study. We will also discuss FDA's concern with adverse events classified as "other" and show that all events were classified and adjudicated properly.

To add additional clarification to these issues, we will present both data from our trial as well as data captured during our continued access phase, or CAP.

With this background in mind, I would like to review the outline for our presentation and introduce today's presenters.

Dr. Mark Slaughter, Professor of Thoracic and Cardiovascular Surgery at the University of Louisville and co-principal investigator of our

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study, will describe the ADVANCE trial study design and efficacy results.

Dr. David Hathaway, Chief Medical Officer for HeartWare, will present safety results. Dr. Francis Pagani, Professor of Cardiac Surgery at the University of Michigan, will present our training and post-approval commitments. And I will return for brief concluding remarks.

We also have several additional responders joining us today who have extensive experience in this field. Dr. Keith Aaronson, Professor in the Department of Internal Medicine, and Medical Director of the Heart Failure Program at the University of Michigan, and co-principal investigator of the ADVANCE trial; Dr. Richard Bittman, who is an independent statistical consultant to HeartWare; Dr. Jeffrey LaRose, Chief Scientific Officer at HeartWare; and Dr. David Naftel, Professor of Surgery and biostatistician at the University of Alabama at Birmingham, and co-principal investigator of the INTERMACS registry.

Thank you. And I'll now turn the presentation over to Dr. Slaughter.

DR. SLAUGHTER: Thank you.

Mark Slaughter, Professor of Surgery at the University of Louisville, and a co-principal investigator for the ADVANCE trial. And HeartWare did pay for my travel to today's meeting.

During my presentation I will review the ADVANCE trial and specifically discuss the design, control group, primary and secondary

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endpoints, the study conduct, and patient population. Then I will move into effectiveness results.

The study objective was to evaluate the safety and effectiveness of HVAD in patients listed for cardiac transplantation with refractory, advanced end-stage heart failure.

The study design was a multicenter, prospective, non-randomized two-arm study comparing HVAD to the concurrent registry control group with the primary endpoint being non-inferiority to the control. The secondary endpoints were evaluated and will be presented using descriptive statistics.

HVAD key inclusion criteria specify that patients must be at least 18 years of age at enrollment; have a body surface area, or BSA, greater than or equal to 1.2 m²; have severe advanced heart failure, New York Heart Association Class IV as determined by the study sites and investigators; and the patients had to be listed for cardiac transplantation; either UNOS Status 1A or 1B; and the HVAD was to be implanted as bridge-to-transplant.

There were many exclusion criteria, all of which were listed in the briefing book. But the main ones which we'd like to mention today were no patient could have cardiothoracic surgery within 30 days of enrollment; they could not be on any previous ongoing mechanical circulatory support other than intra-aortic balloon pump; those patients with acute cardiogenic shock from a large myocardial infarction within 14 days of implant were not

included; patients predicted to have severe right ventricular failure and most likely needing an RVAD were also excluded at the time of screening; it was required that patients be able to tolerate antiplatelet and anticoagulation therapies; patients deemed to have irreversible organ dysfunction, such as end-stage lung, liver, or kidney diseases, were also excluded.

Subsequently, the analysis study population consisted of 160 consented patients. Within this group there were 17 patients with consent who were screen failures, and three patients were implanted for emergency use, leaving an intention-to-treat, or ITT, population of 140 patients. All 140 patients were also evaluated for safety and labeled the safety population.

There were three patients who had pre-specified major protocol violations, which dictated that they were to be excluded from the per-patient protocol population. One patient had elevated liver enzymes, another had elevated total bilirubin, and the third participated in another investigational study, yielding 137 patients in the per-protocol population meeting all criteria.

FDA recognized the benefit of having a more dynamic, contemporaneous comparator for newer VAD devices than the previously used performance goal, which was derived from somewhat dated literature. In agreement with the FDA, the INTERMACS registry was used as the control group. ADVANCE was the first bridge-to-transplant trial using contemporaneous VAD patients as a control arm.

INTERMACS is the national registry supported by industry, FDA, and NIH, for mechanical circulatory support for durable devices. Currently, over 132 hospitals participate in this voluntary registry, and over 6,700 patients have been enrolled.

The control group consisted of a group of patients receiving an LVAD, who met pre-specified criteria for inclusion, and were also entered into INTERMACS during the enrollment period of this trial.

Data provided to HeartWare from INTERMACS included all patient demographics as specified in the study protocol, as well as medical history and success or failure outcomes.

This was a bridge-to-transplant trial, and the contemporaneous controls were identified from INTERMACS registry patients prospectively entered between August 2008 and February 2010, the same time period as the trial enrollment. Patients who had received a ventricular assist device as their first VAD implant, who were currently listed for transplant, and who were greater than 18 years of age defined the pool of available control patients from the registry, a total of 544 patients.

The exclusion criteria of BSA equal to 1.2 m^2 , creatinine greater than 5 mg/dL, and patients on dialysis or ventilator support within 24 hours of implant were then applied to this pool to give a control group of 499 patients for comparison.

It was understood by HeartWare and the FDA that HVAD and

INTERMACS control groups may or may not prove to be comparable. A pre-specified analysis of baseline characteristics involving logistic regression and propensity scores determined how the two groups would be compared.

The key output of the model was the C-statistic, a measure of success in predicting group membership. Three scenarios were pre-specified, depending on the treatment and control group comparability. Based on the calculated C-statistic of 0.65 and having at least five patients per propensity score quartile in both treatment and control arms, the two arms could be compared after stratification, consistent with Scenario 2 of the pre-specified protocol.

The primary endpoint was defined as success at 180 days, which is alive on the original device transplanted or explanted for recovery and alive 60 days post-removal.

Given the inherent uncertainty of the INTERMACS success rate and the likely systematic differences between the INTERMACS and HVAD patient cohorts, HeartWare and the FDA agreed upon a 15% non-inferiority margin.

Key secondary endpoints included secondary effectiveness endpoints of overall survival, quality of life, and functional status, and secondary safety endpoints, which were incidents of serious adverse events and unanticipated device events, as well as incidents of device malfunctions. Our safety endpoints were compared to reference studies, and no formal

statistical hypotheses were tested.

The study itself, like most prospective studies, had a clinical events committee who independently adjudicated a specific and defined set of adverse events and a data safety monitoring board that monitored the ongoing safety of subjects at regular intervals. The data in the database was monitored to source documents, and there was site training on implant techniques and device management post-implant to ensure consistency between the multiple sites.

With the study design in mind, I will now move to study results. I will first review the patient populations, including patient demographics and cardiovascular history, and then move to endpoint results.

As you can see, comparing HVAD to the control indicates no significant difference between the two groups. In the treatment arm the average age was 53 years, which was consistent with all other previous bridge-to-transplant trials. The majority of patients were male and Caucasian, at approximately 72%. The body surface area was about 2, and 25% had prior cardiac surgeries.

As we mentioned earlier, the HVAD and control groups are similar regarding demographics, except for the INTERMACS patient profiles, which I'll expand upon shortly.

When we look at the etiology of the end-stage heart failure, it is consistent with previous bridge-to-transplant trials, that is, approximately

40% were ischemic in origin, and about 46% were due to idiopathic cardiomyopathy or an unknown etiology. After that, other patients show less frequent but anticipated origins of heart failure.

I will now review the trial's primary and secondary endpoints. As mentioned, the primary endpoint was success at 180 days. This was defined as alive on the originally implanted device or transplanted or explanted for recovery.

Here we see the non-inferiority of the HeartWare intention-to-treat population compared to the control group. When excluding the three major protocol violations from the safety cohort, the trial still achieved its primary endpoint of success at 180 days, with an even narrower upper confidence limit.

It is important to note that the upper confidence limit of less than 5% is well below the 15% non-inferiority margin.

Here we're presenting competing outcomes over time for each of the endpoints. The Y axis shows the proportion of patients in each group. The X axis shows the days post-implant. The table shows the number of patients at each time point at risk for an event. The white line represents all patients alive on the original device. The green line shows patients who received a transplant. The magenta line, representing success, is a sum of those alive on device and those patients who received a transplant.

In prior U.S. studies, more patients received a transplant at six

months than were supported on a device at six months. In the ADVANCE trial, more patients were supported on a device than transplanted at six months, which reflects the increasing wait time to receive a transplant.

The yellow line represents device exchange, and the blue line represents death on the original device.

Our primary endpoint of 90.7% success is non-inferior to control. The highest previously reported success in a pivotal cohort of a controlled bridge-to-transplant trial was 79%. Now, when we look at both HVAD and control competing outcomes, we can see similarity to the 180-day endpoint.

The outcomes are also similar to 360 days between HVAD and control. The percent of patients transplanted is similar, although patients in the control arm were transplanted earlier. Device exchange is slightly lower in the control patients, but survival was higher in HVAD patients.

FDA agreed that the study met the trial's primary endpoint of non-inferiority. However, they questioned if the inference of non-inferiority would've persisted if the proportion of INTERMACS profile 1 and 2 patients in both study arms were equivalent.

The INTERMACS patient profile is a method to rank patient severity of illness. INTERMACS 1 distinguishes the sickest patients and INTERMACS 7 those less ill. As you can see, the largest difference between the HVAD and control appears to lie with INTERMACS patient profiles 2 and 3.

The small difference in profile 1 distribution is due to a limited number of patients in this profile.

Here we show the results by INTERMACS profile, and as you can see, the results are similar in both arms of the study.

As previously noted, there was a difference between the percent of HVAD and control patients in the INTERMACS 2 and 3 profiles. The non-inferiority primary endpoint outcomes in the HVAD arm did not correlate with the relative sickness of the patient at baseline. This lack of correlation is best reflected when we review the INTERMACS 1 patients, those most ill, who experienced a 100% success in the treatment arm, a success higher than the remaining less ill patient profiles. Furthermore, there's no noticeable difference in outcomes across the spectrum of INTERMACS patient profiles.

In this table, you see the percent of population in each INTERMACS profile, and the last row in the table is the percent success within each arm.

Here are the associated proportion of patients with an outcome of success as shown in parentheses. The FDA questioned whether the inference of non-inferiority would've persisted if there had been equivalent distribution of patients in INTERMACS profiles in both arms of the study.

To answer this question, a simulation was performed on the HVAD group. In this simulation, the 140 HVAD patients were redistributed to

match control arm proportions across all INTERMACS profiles. The success rate by INTERMACS profile in both treatment and control were maintained, and the success rate was recalculated using the simulated distribution. The results indicate a simulated success rate of 90.3% for HVAD, still comparable to the success rate of 90.1% for control.

We would also like to discuss the FDA's concern that the missing data on right atrial pressure, or RAP, may have added an increased amount of bias to the propensity score analysis. We will demonstrate that the missing data did not, in fact, bias the results of the trial.

Here you see again the primary endpoint using right atrial pressure, RAP, imputing the median for missing values. The second column shows the weighted difference of success for the primary endpoint. To address concerns about missing right atrial pressure data, we've created propensity scores using two additional analyses.

In the protocol, investigators were given the option of selecting either right atrial pressure or central venous pressure, since they are clinically equivalent. Therefore, we incorporated CVP, central venous pressure, and right atrial pressure with imputed median for missing values. When incorporated, 51% of the patients are represented, comparable to the 56% of patients with a right atrial pressure value that are represented in INTERMACS. This analysis continues to show non-inferiority.

Next, we excluded right atrial pressure as a covariate from both

treatment and control in the propensity score analysis. Once again, in this analysis the upper 95% confidence interval was less than 15%, showing non-inferiority of a high significance, with a p-value of less than 0.0001.

Now, turning to secondary endpoints, the pre-specified secondary endpoints were overall survival and quality of life improvement as measured by the Kansas City Cardiomyopathy Questionnaire, or KCCQ, and the EuroQol of life five dimensions, or EQ-5D. In addition, we used a six-minute walk test as an objective measurement of functional cardiovascular capacity.

Our first secondary endpoint is overall survival on the device at 180 days. Shown here is a Kaplan-Meier plot comparing HeartWare to the control. The table shows the patients alive at each time point who are also at risk for an event. The results were 93.9% survival for HeartWare's safety population, compared to 90.2% for control.

Here we review the survival of patients extended to 360 days. The survival estimate for HeartWare was 90.6% and 85.7% for control.

As a secondary endpoint, quality of life was assessed by several different measures. The KCCQ is a validated, 23-item, self-administered instrument that measures five clinically relevant domains of health status from the patient's perspective: symptoms, quality of life, self-efficacy and knowledge, physical limitation, and social limitation. The individual scales are combined into an overall summary score, where the higher score the better.

A minimal clinically important difference is a five-point change on the 100-point scale.

At baseline, 128 of 140 patients were able to take the KCCQ. Twelve patients were unable to take the test due to medical debilitation. At six months, 74 of the 88 patients alive on device completed the test. In blue are all patients at baseline and follow-up who completed the questionnaire. The 70 patients who had completed the questionnaire -- sorry. The 70 patients who had both baseline and six-month data are shown in green and had a 31-point improvement at six months.

While we understand that these 70 patients are not inclusive of the entire population, they do correspond to patients who are on HVAD therapy continuously for 180 days, and they do show an improvement in quality of life.

A similar analysis was performed with the EQ-5D. The EQ-5D is a self-administered standardized instrument rating patients' overall health. This assessment includes a visual analytic scale assessing health utility on a scale of 0 to 100.

In blue are all patients at baseline and follow-up who completed the questionnaire. When we examine the 72 patients who had both a baseline and six-month evaluation, shown in green, the baseline score was 40 and the six-month score was 70. As with the KCCQ, this 30-point difference was substantial and clinically relevant.

Finally, we examined the changes in the six-minute walk test, a functional evaluation of physical improvement. As previously shown, all patients at baseline and follow-up who completed the test are shown in blue. Shown in green are the 74 patients who completed the test at both baseline and six months. The difference was 150 m or a 160% improvement in exercise capacity. Although the assessment of quality of life and functional data is limited, it is relevant and clinically meaningful. Notable improvements can be observed in those patients that have measurements at both baseline and month six.

In summary, this bridge-to-transplant trial with HVAD met the 180-day primary endpoint of non-inferiority with a p-value of less than 0.0001. Overall survival was greater than 90% at 180 days, demonstrating a significant benefit to patients with end-stage heart failure waiting for transplantation.

ADVANCE achieved the highest success of any bridge-to-transplant trial to date. We have shown through simulation, imputation, and other analyses that the overall success was maintained despite the absence of some baseline data.

With respect to quality of life, there was not data for all of the patients at each time point. However, with over 80% of the evaluable patients having data at both baseline and month six, the results show meaningful improvement.

I will now turn the presentation to Dr. Hathaway to review safety results.

DR. HATHAWAY: Thank you, Dr. Slaughter.

I'm David Hathaway, a cardiologist and Chief Medical Officer at HeartWare.

Prior to reviewing the safety data, I would like to describe how adverse events in the ADVANCE trial were captured and adjudicated. Safety events were recorded by the investigator according to 17 specific INTERMACS-defined adverse event categories. An 18th INTERMACS category is called "other" and is defined as any adverse event that did not meet one of the INTERMACS-specific categories but was considered by the investigator to be clinically significant. Events were also characterized as serious or non-serious.

All INTERMACS-defined events in the 17 specified categories, plus the serious adverse events in the INTERMACS-defined "other" category, were sent to the clinical events committee for adjudication. Unanticipated adverse device events were also adjudicated by the CEC.

There was a 97% concordance between the principal investigator's determination of adverse event classification and the CEC adjudication of that classification.

With regard to the 17 INTERMACS-defined adverse event categories, the most common adverse events reported during the 180-day

primary endpoint period were bleeding and infection. Bleeding events were especially common during the perioperative or 0 to 30-day period. Infections were distributed more evenly over the course of the trial, occurring both pre- and post-discharge. Neurological events tended to be biased towards the perioperative period, and I will discuss these events in more detail in just a moment.

Arrhythmias were more frequent in the first 30 days, and the remaining INTERMACS-defined adverse events, such as right heart failure or hepatic dysfunction, were also more common during the perioperative period and declined after this time, similar to reports from previous VAD trials.

Now, we acknowledge the Agency's concern regarding the INTERMACS category of "other." Because of similar concerns and the novelty of this aspect of the INTERMACS classification system, we performed an analysis reviewing all INTERMACS "other" events to ensure that no serious events were lost or misclassified. In this review we determined that any event meeting criteria for an SAE, such as multi-system organ failure or post-procedural hemorrhage, mediastinal hematoma, and so on, was triaged with high fidelity to the CEC for adjudication, as were UADEs and deaths.

All of the INTERMACS events defined as "other" are listed in your briefing book and are coded by the MedDRA system. However, there the listing includes both serious and non-serious events.

So here is a summary of the most frequent events that remain

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after the serious "other" events are extracted and sent to the CEC for review. Overall, 174 events were not adjudicated because they were not listed as serious.

The 104 most frequent events are summarized in this table. None of these met INTERMACS-specific definitions and none were judged to be serious by the four major criteria, namely those events that result in death or are life threatening, those that require surgical intervention, those that result in permanent disability, or those that require hospitalization or if the hospitalization is unduly prolonged.

Note, there were 19 cases showing non-serious neurocognitive results. Additionally, since the NIH Stroke Scale and modified Rankin score, or MRS, were performed on all patients at each scheduled visit, this ensured no stroke events were overlooked or misclassified.

Thus, after additional review, we are confident that adverse events in the 18th INTERMACS category of "other" were appropriately triaged and that SAEs such as major bleeding strokes or infections did receive CEC adjudication.

Now, I would like to discuss neurological events in greater detail.

The numbers of stroke events were presented on the Y axis in this figure, and the percent of patients who had an event are shown in the bars. Fourteen strokes occurred in 13 patients during the primary endpoint

period. There were 10 ischemic and 4 hemorrhagic strokes; 70% percent of ischemic and 75% of hemorrhagic strokes occurred during hospitalization.

Four hemorrhagic strokes were reported during the primary endpoint. Three of the four subjects died, and the fourth subject recovered with an MRS of 5, indicating severe disability. Two of the three deaths were neurological, and one occurred in the setting of multi-system organ failure, or MSOF, and was determined to be a contributing factor.

Ten ischemic strokes were identified. With respect to disposition of these strokes, 4 of the 10 were ultimately transplanted, 3 were alive and transplant eligible, and 3 were alive and not transplant eligible. Thus, 7 of the 10 patients were transplanted or transplant eligible at 180 days.

With regard to the MRS parameter, 7 of 10 patients also had an MRS of 2 or below during the recovery phase, signifying non-disabling outcomes for their strokes. The MRS distributes the stroke patients from 0 to 6. Zero indicates no sequelae and 6 signifies death. The majority of patients here received a 2, meaning they were able to look after their own affairs without assistance, but unable to carry out all previous activities.

Now, the Agency notes a higher level of perioperative neurological events than reported in the literature, so we'd like to review this in more detail, focusing first on ischemic events.

In this graph, the percent of patients who had an event is

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presented on the Y axis. Six of 10 ischemic strokes occurred within the first 48 hours of implant in the bridge-to-transplant cohort.

We recognize that implant technique could contribute to these intraoperative or early perioperative ischemic events. Therefore, we addressed this by instituting user retraining to ensure adequate device de-airing and blood clot evacuation. This training was initiated in December of 2009, near the end of the BTT trial but before continued access enrollment actually began.

The incidence of the early ICVAs dropped fourfold in the 110 CAP patients, from 4.3% to 1%, and this may be attributed to the training that I described and the user experience.

We also note that the overall incidence of ICVAs declined in the CAP patients, from 7.9% to 5.5%. This, too, may reflect both retraining and user experience. But there is an additional factor that appears to be changing the ICVA incidence.

Here we looked at the perioperative ICVA rate over time. The bars from left to right are (1) the original BTT cohort, the continued access patients alone from April 2011, and the total continued access cohort as of September 2011, in response to the FDA deficiency letter. And last are patients who received pumps with sintered inflows, also contained in the FDA deficiency response.

We observed a steady decline of ICVAs over time, and another

encouraging observation, summarized in the appendix of your briefing book, is the potential effect of inflow sintering. Now, these results were early and only looked at 28 patients who had 30 days of pump exposure. However, there were no perioperative ICVAs in patients with sintered inflows and only a 3.1% incidence in those CAP patients with non-sintered pumps.

The number of patients receiving sintered inflow pumps has more than doubled since this preliminary report, and we remain encouraged by the trends.

Hemorrhagic strokes remain another important area for investigation and improvement, and we're working on mitigating those now.

Next, we will evaluate the potential risk factors for hemorrhagic stroke in patients within both the bridge-to-transplant and the continued access cohort. That includes the 140 bridge-to-transplant patients and 110 continued access patients. We will also show the same risk factors in the total population of 250 patients.

Of the patients who had hemorrhagic strokes, the mean arterial pressure, MAP, was 87 mmHg, and 54% of those patients had a MAP greater than 90, as compared to the total patients who had a mean blood pressure of 77 mmHg. In addition, 54% of hemorrhagic stroke patients were septic, and the overall incidence of sepsis in HeartWare patients was 12%.

The proportion of patients on greater than 81 mg of aspirin a day, who experienced hemorrhagic stroke, was similar to the total

population. The hemorrhagic patients and overall population had similar use of aspirin above 81 mg. The mean INR in hemorrhagic patients was 2.3, while the full cohort of 250 patients had a mean INR of 1.8.

So as reported in the literature, elevated mean arterial pressure and sepsis are significant risk factors for hemorrhagic strokes, and this preliminary data suggests that mean arterial pressure may be the most significant factor for our patients. Based on this initial assessment, we are conducting more rigorous multivariate analyses of risk factors for stroke, and we'll use these results to refine our post-approval guidelines.

I will now turn to deaths occurring in the trial.

Six deaths occurred on the original device during the primary endpoint period. Two deaths were due to hemorrhagic strokes, two were classified as multi-organ failure, one was cardiovascular in origin, and one subject died from hepatic failure. Two patients also died after device exchange. Of the six that occurred on original device, two were adjudicated as device related by the CEC.

Now, I'd like to turn to device malfunctions.

There were 26 events reported by investigators as device malfunctions in 20 patients during the primary endpoint period. All reports of device malfunction were managed medically or by replacing or repairing the appropriate component postoperatively.

We acknowledge with FDA that device exchange is an

important issue when assessing the device's safety and effectiveness, and we've developed mitigation strategies to reduce thrombus as a cause for this exchange.

This table lists those pump exchanges that involve pump failures. We have divided pump exchanges into three broad categories: procedural, thrombus, and "other."

Procedural cases are those that occur within three days of implant, and more recently, as we have discovered, many occur considerably later, depending upon positioning of the pump inflows at the time of implant.

In some cases where a rise in serum-free hemoglobin is observed, thrombus is the most likely secondary cause of pump malfunction, and the source of thrombus is believed to be retained clots that are incompletely removed from the left ventricle at the time of implant. This occurs early in the experience of users and may be due to difficulties in cleaning the ventricle. Early procedural cases are amenable to surgical retraining.

True thrombus cases are identified pre-exchange by power spikes on controller log files and a rise in serum-free hemoglobin, or post-exchange by organized fibrin identified in the pump or on the impeller. In the two thrombus cases summarized here, both patients had sub-therapeutic INRs and were on no or low-dose antiplatelet therapy. Late pump thrombus cases almost always present with sub-therapeutic

anticoagulation.

The case listed in the "other" category was exchange for high power but did not have elevated lab values or post-explant pathology findings consistent with a thrombus event.

From investigation of both procedural and thrombus cases, we identified consistent patterns that led to the current classification system. This, in turn, has enabled us to devise mitigation strategies. Therefore, based on our experience, we emphasize the following five clinical principles to our users: first, clean the ventricles thoroughly, and this is addressed through our training program; create smooth coring through the sewing ring; avoid routine use of post-op vitamin K; follow recommendations in the instructions for use for anticoagulation; and finally, if tolerated, treat the early signs of thrombus with heparin and an antiplatelet regimen such as Integrilin or Tirofiban.

Since our first clinical implant in 2006, we have learned a great deal about the risk factors for thrombus and have subsequently implemented mitigation strategies. In our initial international CE mark trial shown in the blue bar to the left, we learned how to more consistently manufacture and manage the pump. Following international approval, our clinicians were able to build from that trial experience and refine anticoagulation strategies in a real-world setting. This led to a decline in pump thrombus rates of incidents from 12% in the original trial to roughly 2% post-approval. The rate has

continued to decline since the introduction of sintered inflow cannulas a year ago.

Here in yellow we show U.S. investigators benefited from the experience of their international peers. During the initial U.S. BTT trial, the incidence of thrombus was half the rate of the international trial. The incidence in the U.S. has further declined from 5.7% in BTT patients to 1% in the initial CAP cohort.

As described in detail in your briefing book, the pump thrombus exchange rate was sustained below 2% by continued adherence to the anticoagulation guidelines.

Turning now to unanticipated adverse device events. So one unanticipated adverse device event, or UADE, was reported during the course of the clinical trial. This event consisted of erosion of an intercostal artery due to friction between the pump and the chest wall. At least two features noted in discussion with the investigator were a large left ventricle and, second, a small chest cavity. The use of PTFE sheets mitigates the problem by preventing direct contact of the HVAD with the chest wall. Training on device placement has also been sufficient to prevent this type of UADE.

Three additional UADE types have been reported during the continued access phase. The first type was electromagnetic interference between the HVAD and an automatic implantable cardiac defibrillator, or ICD. This was characterized as noise in the baseline that was detected by the

sensing lead and reported as ventricular tachycardia.

Mitigation in two cases required adjustment of sensitivity. However, in the other case, the sensing lead was deactivated and replaced with a second lead positioned higher on the right ventricular septum. Combinations of sensitivity adjustment and lead replacement completely eliminated the problem in these patients.

While 85% of the patients in our study have an AICD, the incidence of interference appears to be low. So far, in our database we have 3 reports in 332 patients.

In the second UADE, the tunneling tool for placing the driveline was forced through the abdomen into the stomach. This was an unusual adverse event, and we retrained the site and investigators, and this has not occurred since.

The last UADE was contamination of the connector with blood, resulting in electrical faults. So internal nicks on the outer layer of the sheath may occur during the surgical procedure, allowing blood to enter and migrate down the driveline in the space between the inner and outer layers of the sheath. To prevent the blood from exiting into the connector, the two layers were sealed together at the entry to the connector, and an internal stricture or dam was applied to prevent egress of blood in the event of an internal nick. This has prevented any additional contamination events of this kind.

So, finally, for context, we present our adverse events along

with those from key reference studies for the HeartMate II LVAD, as this is the most commonly used FDA-approved ventricular assist device available.

It is important to note that we were not able to match all of the reported terms in our trial to the published literature.

So here is a brief overview of the trials. The HeartWare trials include the bridge-to-transplant trial, or BTT trial, with 140 patients and 89 patient years of device exposure, and the HeartWare continued access phase, or CAP, with an additional 110 patients. When BTT and CAP are combined, we present a total of 250 patients and 174 patient years of device exposure.

There was one pivotal clinical trial for the BTT indication for the HeartMate II device. This trial evaluated 133 patients with 62 patient years of device exposure, and we refer to it by the first author of the publication, Miller et al. For reference to the HVAD BTT pivotal trial, this is juxtaposed to the HeartMate II pivotal trial of Miller et al.

The HVAD bridge-to-transplant plus continued access data was juxtaposed to the reference by Pagani et al. that summarized the HeartMate II results with continued access patients. This group consisted of 281 patients and 182 patient years of device exposure. There was considerable overlap in investigative sites, and criteria for classifying adverse events were similar. Although this type of analysis has limitations, it provides a context for HVAD adverse events.

So here is a forest plot that summarizes the HeartWare BTT

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adverse events. The horizontal lines are the confidence intervals around each adverse event rate. This plot compares the BTT cohort to the combined BTT plus CAP data shown in green. As you can see, there is high concordance in each category. There's a tendency for some AEs to be lower in the BTT plus CAP cohort compared to the BTT cohort alone. This shift reflects a learning curve and training effect that is observed in the continued access phase with the HeartMate II device as well.

Once again, the HeartWare bridge-to-transplant results with confidence intervals are displayed. But this time we add the HeartMate II pivotal trial published by Miller et al. as reference.

A number of adverse event areas appear quite different, while others are similar. Given that Miller et al. was the first large trial for a continuous-flow device, it makes sense that the novelty of the device would present some challenges and, of course, event rates are not directly comparable. However, overall, the adverse rates are similar between these two pivotal trials for the bridge-to-transplant indication.

Here, the HeartWare BTT plus CAP results are summarized, and the horizontal lines are confidence intervals around the combined cohort AEs.

Finally, we add the HeartMate II continued access study by Pagani et al. to the plot for reference purposes. We make no quantitative assessment other than to say that event rates for AEs, as reported, are within a similar range. The relatively low rate of sepsis and reoperations for

bleeding in the HeartWare cohort is a notable observation.

And as a final note, I would also like to point out that the Kaplan-Meier survival for continued access yields similar survival results at 180 days. Survival consistently greater than 90% at 180 days has been observed from the original CE mark trial until today. We've confronted many challenges, but with every challenge, we've worked aggressively to identify root causes and develop strategies for mitigating and reducing adverse events.

Early perioperative and overall ICVA rates have fallen from 7.9% to 5.5%, and pump exchanges for thrombus have similarly decreased from 5.7% to 1%.

Bleeding events and infections are already lower than reported, but we continue to look for ways to reduce these events as well as decrease strokes and exchanges.

So to summarize the safety data, reference studies from controlled clinical trials suggest similarity in the kinds and frequency of adverse events.

Seventy percent of ischemic stroke patients recovered functionality and were transplanted or transplant eligible at 180 days. The evidence shows that the ICVA rate is decreasing, and we now have plans for further intervention with hemorrhagic strokes.

Pump thrombus events tend to occur in patients who have

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suboptimal anticoagulation. Mitigation strategies have continued to reduce this adverse event.

Reviewing data from both our bridge-to-transplant trial as well as our CAP cohort, the HVAD has an adverse event profile that supports its safe use for bridge-to-transplant patients, which is the indication we are seeking today.

Thank you. I will now turn over the podium to Dr. Francis Pagani.

DR. PAGANI: Thank you, Dr. Hathaway.

I'm Francis Pagani, Professor of Cardiac Surgery at the University of Michigan. I'm co-principal investigator of HeartWare's ENDURANCE trial and the NIH and HeartWare-sponsored REVIVE-IT trial. I'm not paid by the Sponsor, and I've paid for my own travel to today's meeting.

I'd now like to discuss HeartWare's training and post-approval plans.

HeartWare currently provides a multifaceted training program. Clinical training consists of five parts to ensure adequate preparation prior to the use of the device: surgical training, on-site staff training, initial implant support, continuing education, and evaluation.

Surgical training is provided to sites through either isolated pig hearts or animal implants. In addition, a surgical preceptor is always present for the animal implants.

Today, on-site training of hospital personnel is conducted by HeartWare clinical specialists, to include classroom and hands-on instruction. HeartWare clinical specialists and technical support staff provide several days of on-site support coinciding with the initial clinical implants. In addition, they arrange regular continuing education to support staff proficiency and target a center's particular needs. Finally, HeartWare also assists sites in developing educational criteria that may be used in staff development.

HeartWare continues to study the HVAD, and to that end, they have already enrolled patients in a randomized controlled trial, called ENDURANCE, for destination therapy. This is the largest randomized controlled trial ever taken in VADs and will compare the HVAD to the HeartMate II device.

Four hundred and thirty-seven of the 450 patients have already been enrolled and randomized in a two-to-one fashion in this trial. The first patient was implanted in 2010, and the trial should complete enrollment within the next month.

The primary endpoint of this trial is survival, free of disabling stroke at two years. HeartWare is also tracking other secondary outcomes of clinical interest, including bleeding, infections, device failures and device malfunctions. In the next few months, HeartWare will apply for continued access to the destination therapy protocol.

By early 2013, HeartWare plans to launch a randomized

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controlled trial of the MVAD, their miniature ventricular assist device, against the HVAD. HeartWare's MVAD is one-third the size of the current HVAD. This study protocol for this trial will be submitted to the FDA this fall.

In addition, HeartWare will gather real-world data of the HVAD through the proposed post-approval study by using the INTERMACS database and comparing the IDE trial results to post-approval results.

HeartWare has also requested access to the line item data from INTERMACS so that they can compare the HVAD data against other approved VADs.

This study is proposed to be multicentered, prospective, and controlled, utilizing patients entered into the INTERMACS registry. The first 155 HeartWare patients will be compared to 155 contemporaneous INTERMACS patients as well as to HeartWare's pivotal PMA cohort of 140 patients and HeartWare's continued access patients.

The primary endpoint will be survival at 180 days on the originally implanted device. Secondary endpoints for this approval trial will include the collection and assessment of rehospitalizations, INTERMACS-defined adverse events, quality of life measures, functional status, and device malfunctions. This real-world experience will provide valuable incremental data to the controlled studies ADVANCE and ENDURANCE.

There will be additional exploratory analysis of patient subgroups and, importantly, HeartWare plans to evaluate the learning curve

at new sites, which is expected to show improvements in performance in response to training over time. With appropriate training and instruction of HVAD users, improvements in patient care are expected. By conducting a post-approval study, HeartWare will be able to monitor real-world events and the effectiveness of their training program. The current program proposals are in draft stage as negotiations are currently in progress with the Agency and INTERMACS.

Thank you. I will return the podium to Doug Godshall.

MR. GODSHALL: Thank you, Dr. Pagani.

The ever-lengthening wait time for transplant is resulting in an increasing need for mechanical support to keep people alive and well as they wait for a donor heart. And, unfortunately, as the heart failure population grows, this need only increases.

The entire HVAD pump is surgically placed in the pericardial space, avoiding the necessity for an abdominal pump pocket, which usually requires a much larger incision. The elimination of the abdominal incision is expected to reduce surgical trauma, reduce operative time and complexity, as well as expand the treatable population.

The purpose of this study was to evaluate the safety and effectiveness in patients listed for cardiac transplantation with refractory advanced heart failure and risk of death.

The trial met the primary endpoint of success at 180 days with

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high significance, demonstrating non-inferiority to the control. Secondary endpoints helped to further substantiate device performance. Additionally, both quality of life and functional capacity showed noteworthy improvements versus baseline following implant of the HVAD.

The HVAD has an adverse event profile that supports its safe use for a bridge-to-transplant patient and has adverse events that are similar in frequency to the most recent controlled trial data. In cases of bleeding and infection, HVAD safety data shows lower rates relative to historical norms based on the literature.

Overall neurologic injury rates were not materially different from those reported in monitored trials. Survival following ischemic stroke was 80%, and of those who survived, approximately 70% demonstrated meaningful levels of recovery and have gone onto long-term support or transplant. Ischemic events are declining, and we're also focused on diminishing hemorrhagic strokes.

The considerable decrease in exchanges in general, and for thrombus in particular, will continue to be monitored in the post-approval setting to ensure the improvement continues.

In order to assess the clinical benefit of the HVAD, Professor Wayne Levy of the University of Washington entered the pre-implant parameters of our patients into the Seattle Heart Failure Model, which is used to predict survival in heart failure patients. Our patients, if left

on optimal medical therapy, as shown here in yellow, had a 45% one-year projected survival and less than 60% at six months. In our ADVANCE study, shown here in blue, our patients had a 94% survival at six months.

Our clinical trial sites have done an exceptional job for their patients, achieving remarkably consistent results in this bridge-to-transplant population, whether it be in our U.S. pivotal or CAP cohorts, shown here in green, or our international trial, represented in magenta.

This substantial survival benefit over medical therapy speaks to the importance of bridge-to-transplant as an alternative for patients and the HVAD as an alternative option for them.

While we acknowledge that there is risk involved with this therapy, it is important to recognize that there are significant complications from the disease state itself, as well as inherent limitations of current therapies. We hope you have seen in today's presentation that we acknowledge FDA's concerns and have worked diligently to address them.

ADVANCE is the first controlled bridge-to-transplant trial in the United States to achieve survival of greater than 85%, and with 94% survival, our results clearly demonstrate effectiveness.

The data presented today indicate that the benefits outweigh the risks in this patient population with refractory end-stage heart failure in need of transplant. HVAD offers unique features that benefit both the patient and the physician, with the potential of treating a more diverse

patient population.

Based on the totality of evidence, it is HeartWare's belief that physicians in the United States should have the option to offer HeartWare's left ventricular assist device to the rapidly growing heart failure patient population, just as their peers do around the world.

Thank you for your attention. We're now happy to take your questions.

DR. PAGE: I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel at this time have brief clarifying questions for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during the Panel deliberations in the afternoon. So now, these are factual clarifying questions.

Dr. Somberg.

DR. SOMBERG: Thank you, Dr. Page.

I have two questions for the Sponsor, from their presentation. One, if you could turn to your presentation, page 16, the top panel. Help me understand this better.

The pivotal study uses the 180-day endpoint, but we all know that a transplant takes -- a wait for transplant is usually much longer than that. So I'm very interested in the numbers at 180 and 360. Am I correct, is that the bottom number, the number of patients in the pivotal study that go

out to 180 days is how many patients?

MR. GODSHALL: So Slide 16 was that? I'm sorry.

DR. ZUCKERMAN: I think it may be Slide C-31.

DR. SOMBERG: I said C-31.

MR. GODSHALL: C-31. Thank you very much.

DR. SOMBERG: It's on page 16 of your handout.

MR. GODSHALL: Oh, thank you. Yes, to describe the structure of this slide, I would like to bring up --

DR. SOMBERG: Well, I don't need the structure. I just need to the number of patients.

MR. GODSHALL: Right. So the number of patients at the time that this competing outcome slide was constructed was the number of patients at risk at those different time points when the data was captured.

DR. SOMBERG: Okay. And my second question is you presented a number of different compilations of the pivotal study and then the access study, et cetera. But to be able to make a judgment on risk versus benefit, I personally, and maybe other panelists too, need a comparison of the adverse side effects from your intervention versus your putative control group. So in the registry.

So do you have slides comparing bleeding for the pivotal control study, the intervention, versus the INTERMACS registry, for bleeding, infections, stroke, and exchanges at 180 days? At the time of your pivotal

efficacy. I haven't seen that data presented side to side.

MR. GODSHALL: Right, we were not granted access to the control arm adverse event data. First of all, it was not pre-specified in the protocol, and secondly, due to confidentiality issues, INTERMACS was not able to provide adverse event data on the control population for our trial.

DR. ZUCKERMAN: Okay, this is an important point. If Dr. Somberg could continue on that, I'd like to make a statement.

DR. SOMBERG: So when you planned the study, and this is the pivotal presentation study and you had the putative control, the INTERMACS registry, you had assurance that you could obtain the adverse events and then you couldn't, or you had no intention from the beginning to provide the adverse events? I'm confused on that.

MR. GODSHALL: Yeah. So perhaps bringing in a bit of a historical perspective on how we arrived at using the INTERMACS control, because there is novelty to using a registry as a control arm.

In 2007, when we first started discussions with the FDA about commencing this study, there were no continuous-flow devices approved in the United States. In fact, Thoratec came to this Panel for approval of the HeartMate II in November of 2007 and they were not able to -- they did not succeed in hitting their primary endpoint, although they did receive approval or a recommendation for approval.

But as we were at that very same time looking to structure our

pivotal trial, we were left with a situation where the Panel asked for future VAD trials to compare themselves against contemporaneously enrolled patients for a primary endpoint comparison, and yet it was unclear how we would be able to conduct a randomized trial, given that the HeartMate II, at that juncture, was not approved and it was unclear how we would be able to generate a randomized control.

The INTERMACS registry enrolls all patients from all the VAD centers that use commercial devices in the U.S., and as we and the Agency evaluated the INTERMACS database at that time, it was clear that we would be able to, we felt, structure a control arm comparing a primary endpoint against INTERMACS.

But given that the INTERMACS registry collects data differently, adjudicates data differently, it is a voluntary registry, it was decided at that time that comparing adverse events would not be an appropriate comparison, given the substantial difference in the way that the data would be collected and adjudicated, and that we would do comparison or we would just review our adverse event profiles versus compare them against INTERMACS.

DR. PAGE: Dr. Zuckerman, would you like to clarify further?

DR. ZUCKERMAN: Yes. I think Mr. Godshall has reviewed the situation well, but the bottom line is that Dr. Somberg indicates an important point. It would be ideal if in the future or for any post-approval studies, if

INTERMACS, being a national registry, were truly available to supply both adverse event and effectiveness data.

Now, as part of the FDA Executive Summary, I would like the Panel members to look Appendix B, which is page 54, and they can look at some of the reasons why the INTERMACS committee has not allowed a company like Mr. Godshall's access to the AE data.

But I also see Dr. David Naftel in the audience, a co-principal investigator of INTERMACS, and maybe he can say a few things also about what is the INTERMACS perspective at this point.

Dr. Naftel.

DR. NAFTEL: Thank you, Dr. Zuckerman.

My name is David Naftel, and I am a co-PI for INTERMACS and a Professor of Surgery and Biostatistics at the University of Alabama at Birmingham. And I am consultant to HeartWare for today.

So let me review just a little bit of the history. When HeartWare first came to us when we were brand new, we had only been running for about a year, we were absolutely thrilled for the opportunity to be a control group. One of the primary goals of INTERMACS is to move the field forward, and we're very anxious to help in any way we can.

I want you to remember that INTERMACS is a collaboration of NIH, FDA, CMS, all of the companies that make approved devices, and all the hospitals that implant these devices.

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So when we had the opportunity to be a control group, we were excited by that, but we also are well schooled in the principles of clinical trials. So we looked very carefully at exactly what they asked of us, pre-specified in a statistical analysis plan, and that was that they asked INTERMACS to be a control group for the effectiveness endpoint. They also had inclusion/exclusion criteria for us that matched theirs. We were very careful to not turn over the entire dataset to HeartWare. It's just good practice to not have any possibility of bias in selecting patients.

So once we all agreed, the executive committee of INTERMACS and HeartWare and the FDA, on exactly what INTERMACS would provide and that did not include adverse events, then we, as you can imagine, pulled the trigger and pulled out the 499 patients. And we made it a point that we did not want to engage in any data mining, any ad hoc analysis. We wanted to be the purest representation or imitation of a clinical trial.

And there is a second point, that indeed we have almost 7,000 patients now, 30,000 adverse events, so adjudication is not possible. We do have a medical event committee with many people you'd recognize, Dr. Acker, Dr. Jessup, Dr. Kormos. They reviewed the major adverse events of death, device malfunction, bleeding, neurological dysfunction, and infection, and they reviewed those for internal consistency. We do not have access to the medical records, so it's not an adjudication committee. So I don't want to undersell what we do, but I certainly don't want to oversell it.

So where are we today? It is definitely our plan to do everything we can to provide adverse events in the future. To do this in a very protocol-driven structured way, we plan to do that. And then, I think while I have the podium, I do need to talk about the post-approval study because this is essential to that.

DR. PAGE: Dr. Naftel, we might -- if you can do this in a very concise way, we have a lot to do here today.

DR. NAFTEL: Okay. So as you notice, we're under discussions for the post-approval study, and nothing has been finalized with INTERMACS, but we'll do everything we can to provide the data that they need. And certainly we always provide the data for devices manufactured by a company for their patients. The other arm we still have to discuss.

Thank you.

DR. PAGE: Thank you for those clarifying comments. And I think this might bear further discussion later on in the day as well.

Having sat on that panel that reviewed the previous LVAD, it's quite gratifying, actually, to see INTERMACS being functional and helping us. This is a work in progress, and I think in the future we may want to be able to look at both safety as well as efficacy.

If we can move on -- and by the way, I thought the explanation in the letter from INTERMACS was clear, and at this point we have what we have.

That being said, let's move on to other clarifying questions. I saw Dr. Borer, then Dr. Amato, then Dr. Cigarroa.

DR. BORER: Thank you.

My question has to do with the adjudication of events. Let me put this in context. I thought this was a very interesting and a very useful study with impressive data. But like most device trials, the number of patients included and the number of outcome events was relatively small. And the adversity, in order to determine the benefit-to-risk relationship, has to be as precise as it can be, understanding that the patients that you studied were at death's door and we do expect some of them are going to have problems, device or no device, effective device or no device.

But on your Slide C-25, you note that there was a clinical events committee that provided independent adjudication, and that's true. As I went through the data that were submitted to us, though, it appears that that events adjudication committee changed many times, its personnel changed many times, and there appeared to have been important disagreements among the committee about how to adjudicate events.

Now, that can happen, and all of us have sat on adjudication committees and, you know, everybody doesn't always agree about everything. But it seems that here the issue of what was a stroke and what wasn't a stroke was an important part of the disagreement and that the inconsistency of the committee, because of its changing composition,

frequently changing composition, may have contributed to this problem.

So I need to understand better how the events adjudication committee actually is structured, why it changed so often, how it worked and how precise the adjudication of strokes was. The fact that there was or wasn't a difference between the adjudication committee determination and the investigator's determination doesn't mean anything to me. I'm looking to the adjudication committee to give me a number that I can bank on.

MR. GODSHALL: I will bring our chief medical officer, Dr. Hathaway, up to speak to that, and he will address both the adjudication committee evolution as well as address your question about neurologic events.

DR. AMATO: Being a new member of the Panel --

DR. PAGE: I'm sorry.

DR. AMATO: I'm sorry.

DR. PAGE: We've got to take questions in order, please.

DR. HATHAWAY: Okay, thank you, Dr. Borer.

So I will start by, first of all, just describing the clinical events committee very quickly and talking -- then I'll mention what the changes were. I'll say a few words about concurrence among the committee and then say a word or two about the strokes.

So, in its original composition, we had one chairman and two reviewers. Each event went to two reviewers or a member of each review

team, as we'll discuss in a minute. If they agreed on the adjudication, it was complete. If they disagreed, it went to the chairman.

And there were three major issues that they had to vote on. One is did the event meet the INTERMACS definition of an adverse event? Number two, did it meet serious criteria? And then, finally, was the event assessed as related to the device or not? So the amount of agreement or disagreement depended upon which one of those adjudication criteria were used.

Now, if we can look at the changes that occurred in the committee, this summarizes those. The CEC changed during the period of time to the primary endpoint. In July 26th of 2010, the chairman of the CEC actually moved over to become the chairman of our DSMB for destination therapy, and one of the CEC members that was somewhat challenged in terms of his workload elsewhere was replaced.

And then in August, around August 23rd, after the last patient and last visit, we had quite a backlog of adverse events that had not been adjudicated, and five CEC members were added to the review team to create two separate teams of two each and -- or three and two, rather. And then subsequently, on October 31st of 2011, the CEC reverted back to one chairman and two reviewers. So there were some changes.

Now, I would say something about concurrence on assessment of events. So there was very good concurrence between the CEC and the

investigators on a critical thing, which was the identification of adverse events falling into one of the INTERMACS-specific categories. And, in fact, there was actually 97% concurrence there, and in only 3%, or 17 cases, did they not believe that the event met the protocol definition.

So what I'd like to do actually is then talk about the stroke issue so that we can understand that a little bit better, and I'd like to look at the -- there were series of -- I believe, in your briefing book, we don't talk about a post hoc analysis, and I'll tell you why that came about and explain that we really don't disagree with the Agency. We just brought up some issues that we thought were worth some consideration. There were five cases. I'll start out by describing those cases.

Oh, please. Yes. I apologize. Okay, I'm sorry.

So there were four cases that we were interested in. One, at first there was the case of Patient 2712, and there was a misunderstanding on our part. The CEC adjudicated it most appropriately. The Agency picked it up. This patient had an ICVA and a TIA, period. So there's no disagreement; there was mis-adjudication, and there's no misunderstanding on that point.

We raised a question, though, about Patient 005-003, who was adjudicated as two events, an ICVA and a CVA, and he presented with a stroke in the distribution of the right middle cerebral artery with petechiae hemorrhage. Over the next two to three days, it evolved into a full hemorrhagic stroke. So we simply raised the question of whether it was one

event or two. But because it was sent as separate events to the CEC, they appropriately adjudicated it as two events, so rather than seeing it as a combined event.

We've reported it faithfully and included it in all of our calculations, and we're not disagreeing with the Agency. We're just raising it as a question of whether that might've been two -- a single event rather than one.

Patient 000-504 presented with symptoms of what sounded like a stroke, but they resolved in less than 24 hours. He had a CT scan with no evidence of acute injury, and the site referred to it as a TIA. And we felt that that probably wasn't a stroke. But we, again, included it in all of our calculations and counted it as an ICVA, but we bring it up as part of this post hoc analysis.

And then, finally, the one area where I think we do disagree is on Patient 027-001. This patient developed an anisocoric pupil and was confused after being removed from the ventilator two days after implant. He was hyperglycemic. He had serial head CT scans that showed no acute injury at all, other than some old lacunar infarcts. He had a history of hypertension, and his EEG suggested that he had diffuse metabolic encephalopathy. He was never diagnosed or adjudicated by the CEC as a stroke or TIA.

And I think where the misunderstanding between the Agency and the Sponsor developed is that, in the original PMA, when I wrote the

summary, I included him as a neurologic injury and with an asterisk said that the patient didn't have a stroke. So perhaps you'd like to have some other -- but there was no CEC adjudication of that patient as a stroke at all.

So we don't think there's really -- we think the CEC did a very good job. I went back and reviewed their -- after the database was locked, and reviewed their adjudication records and also the other events, just to be sure that there were no misclassified neurologic events or strokes, and we feel comfortable and confident that we reported them faithfully.

DR. BORER: Thank you.

Can I just follow up with one question based on what Dr. Hathaway said?

DR. PAGE: Yes, you can follow up.

DR. BORER: Thank you, David. That was --

DR. HATHAWAY: Sure.

DR. BORER: -- very useful. You said something, though, and I notice it here as well, that in the materials it was strange to me. The CEC determined whether an event occurred, what kind of event it was, which is what CECs usually do, and then whether it was related to the device or not.

DR. HATHAWAY: That's correct.

DR. BORER: That's not my usual experience. My usual experience is you do the body count and you see which way the numbers fall, and the DSMB determines whether this is meaningful or not. So I wonder

why you chose to do it this way.

DR. HATHAWAY: I could only say that, of course, we had a DSMB that reviewed all of our safety and efficacy data. I would have to say that a charter was written, a charge to the CEC included those things. It could've gone the other way, but the decision was made to allow the CEC to make those three adjudications, whether it was serious, whether it was device related based upon not only the data that was collected in the trial, but they, of course, could request any additional information as a package to make those determinations.

And then, of course, because it was new and INTERMACS was new to everyone as a classification system in a pivotal trial, it was important for us to make sure that the CEC and the sites were in agreement, and there was a very high degree of agreement, which was a good thing. So it was a matter of personal choice and precedent for the Sponsor, and we believe that, overall, the process worked well.

DR. PAGE: Thank you.

Dr. Amato, you've been very patient.

DR. AMATO: Thank you.

Being a new member of the Panel, I'm almost embarrassed to bring up a blatant absence of surgical technique. I've been a surgeon for 40 years, and both with my adult colleagues and with my trainees in pediatrics, the question always remains at the end of the surgery, is do you close the

pericardium or do you leave it open?

Most of the time I close the pericardium. If I can't close the pericardium, then I use GORE-TEX or polytetrafluoroethylene or perhaps the new surgical -- the new biological barriers.

The pump is a beautiful little pump, and it's gorgeous. The technique is wonderful, and putting it in is nice. But it's an added volume to the pericardium.

Now, if you have a patient in failure, cardiac failure or cardiac enlargement, it would seem to me that if you close the pericardium primarily, you're going to have an absence of good function. If you leave it open, then when you go back in to take the pump out, you're faced with adhesions and you're faced with other problems that can exist, bleeding, et cetera. In only one slide do you mention one patient in which there was erosion, and you used GORE-TEX to close the pericardium.

The question is do you leave the pericardium open all the time? Do you close the pericardium primarily? Do you close the pericardium with a material of some sort? And if not, why, et cetera?

I just apologize for this, but I think that this should be an intricate part of your discussion on how to place the pump in.

Thank you.

DR. PAGE: That's a very good question.

MR. GODSHALL: I would like to bring up Dr. Slaughter, who has

trained virtually every surgical site in the U.S. for us at HeartWare.

Dr. Slaughter.

DR. SLAUGHTER: Thank you. Mark Slaughter.

So you bring up a very interesting topic, and I would say that, as a rule of thumb, for most adult cardiac surgery for coronary bypass valves, things like that, nowadays the majority of surgeons would not close the pericardium. So it certainly is not the routine for sort of regular heart surgery.

The other issue that I think immediately is easy to answer and address, though, is in this case it was about 30%, that 30% of the patients are redos, so the pericardium is not there. There's nothing you could close anyway, and the initial dissection may be somewhat prolonged and difficult to start with.

So I guess the issue is, once you do have everything sort of out and you're ready to put it in and you've done your bypass, then what do you do? And I would say, as a rule of thumb, it varies from center to center.

Part of the issue is that, once again, these are very sick patients with multi-system organ dysfunction. They've generally been in the hospital for up to a week to two weeks with indwelling lines in an ICU. The reason I bring it up is they're at very high risk for infection. And at some point it will come up, and I think it's one of the highlights here, that the infection and sepsis rate was very low compared to previous experience.

But it is an issue because you already have some foreign body, and the answer is do you want to put more GORE-TEX, more foreign body in there on top of your drains that are a source of potential infection?

I personally do not close the pericardium. I open the pericardium widely to the left, near the left phrenic nerve, so when I'm done I let it lay over the right ventricle. But is it closed? Does it meet the other side? The answer is no.

Various other centers do different things. Some people try using the CorMatrix to try and re-grow pericardium. Some will use PTFE. But as a rule of thumb, I would say it varies from center to center. It does not affect the long-term results, and although they reduce sternotomies, it certainly may make it a little bit more difficult. It has not added a significant risk to the reoperation, which we could certainly see when we look at outcomes for transplanted and whatnot.

I think the issue that you're also alluding to, though, is in most of the patients, when you put the VAD in, they get better, so you get reduction in left ventricular volume and size. The right side comes along for the ride, so it decreases. So you have less of a chance of it being distended and stuck on the sternum.

The issue is the outflow graft, and the HVAD is uniquely designed such that the outflow graft, though, lies in the pericardial well, not beneath the sternum and not in the way for reentry and out of danger's way.

DR. AMATO: Thank you. I think that resolves a lot of your problems, but it just seems to me that, especially if you put a pump in the right side and the left side, that you're going to have increased volume in a heart that is already deficient, and it would seem to me that leaving the pericardium open is the answer to the problem.

However, when you're dealing with long range, two months, three months, a year, going in for a transplant, it would seem to me that you would find difficulties in meeting the sternum and the heart and the pump together, and it brings up problems that I think should be addressed a little more clearly.

DR. SLAUGHTER: Mark Slaughter once again.

So I can certainly reflect on my own and a few others' experience. But in a bridge-to-transplant within this trial, there's essentially zero perioperative mortality, meaning that there were no mortal injuries on reentry. I've taken out multiple pumps and transplants and have a zero incidence of injury. So although it's a theoretical concern, I think nowadays it's become much less of an issue.

DR. AMATO: Granted mortality, but what about morbidity, sir?

DR. SLAUGHTER: Yeah, the same. We actually took a pump out last week, because the option is -- I don't want to draw on this too much, but there are other options also. You can take it out through a subcostal incision. You don't have to do a sternotomy. You clamp the outflow graft, so for a

recovery, which would be the perfect example because that would be the patient you worry about most, so you have a 30-year-old patient with a dilated cardiomyopathy, you put the device in, and it turns out nine months later, they recovered.

So there is the issue of morbidity and mortality. You can take it out through the left subcostal incision, they go home in four days, and they usually require no transfusion. So although it's a theoretical concern, it really has minimal impact.

DR. PAGE: Thank you.

Let's move on to Dr. Cigarroa.

DR. CIGARROA: Two questions. One is now more of a comment, as it reflects Dr. Borer's questions regarding the clinical events committee. So first the comment.

Given the unique methodology of this trial utilizing INTERMACS as a concurrent control for comparison, and the inability to utilize adverse events, given how INTERMACS is structured, I too am concerned about the changing composition of the clinical events committee and the number of individuals on the clinical events committee, given that there is no comparison group for that. So that's now more of a comment. So just to reiterate that issue.

The question now is number of patients who were screened as opposed to the number that were enrolled, and in that screening process,

number of individuals who may have been excluded because of concern for thrombus in the left ventricle or left atrium.

MR. GODSHALL: I will bring up Dr. David Hathaway again to speak to the screening. I don't know that we have specifics on the patients screened out for left ventricle thrombus. I don't know if we have that data.

DR. HATHAWAY: So I will answer that question first. I don't believe we have that data. There were patients who were screened and consented, who were discovered to have thrombus in their left ventricle and that was removed at the time of implant. I'm not aware that any patient was ever excluded for that reason. It would have to have been determined by echocardiography, and to get real high resolution pictures, I would imagine it would have to have been a TEE. But, again, I'm not aware of any patients who were excluded for that reason.

DR. CIGARROA: So just a follow-up on that. It would be nice to have, potentially, that data, given that many of the events occurred in the immediate perioperative period during which the increased flow through the left ventricle and left atrium occurred.

DR. HATHAWAY: Yes. This could be multiple answers. So I guess I will try my best to give you short answers, and we may want to discuss this, I'm sure we will want to discuss this further.

So let me say just a bit quickly about the screening and process. There were 273 potential patients that were identified, 113 patients who

were screening failures but were not consented. And this was a little problematic for a short period in the trial. We had 17 patients who were consented before the screening process was completed and were subsequently discovered to be screening failures.

Now, we have additional data because we followed them out to six months to look at what their outcomes were, and I can present that if you'd like to see it. And there were three patients who qualified under the compassionate or emergency use indication, leaving us ultimately with 140 patients who did receive an implant.

So just if I may make just a couple of comments about the screening process. It was somewhat heterogeneous. I believe we mentioned that we did have some issues with some of our monitoring. We felt that the screening logs were not up to date, as complete as they should've been. But the screening process was a single consent.

There was not a two-consent process that we currently have for our DT study, where we have consenting for screening and then consenting for randomization or inclusion in the trial. And that turns out, we think, to be kind of important because it's hard sometimes to complete the full screening process without having access to information that might require -- that might involve some patient confidentiality or agreement to participate.

So the best bet that we had was to look at standard of care

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assessments for screening at the investigator's discretion. So sites very likely knew their BTT patients' status. They certainly knew if they were 1A or 1B and were able to identify common screening failure reasons. And there were some -- there was variability in the standard operating procedures for doing screening at these sites.

Now, if we could talk about the 17 patients who were consented early, prematurely, but were not implanted, I would say -- maybe I'll just move on to this. Yeah.

So we did follow them up. They had multiple -- I'll show you the next slide. They had multiple inclusion/exclusion criteria that would prevent their enrollment, and there were some insurance denials, withdrawn consents and, at least in one case, a physician decision not to include the patient.

At six months, this is what became of the 17 patients. Twelve out of 17 received a HeartMate II, one an AbioMed, two were transplanted, and one continued on medical therapy, two patients died, and we -- if they were included as part of our intention-to-treat cohort, the overall success rate would've been 94.4% as opposed to 90.7%.

So we sort of looked at it both ways. We didn't include that in our primary analysis, but I thought you would be interested in seeing that.

DR. PAGE: Dr. Cigarroa, does that answer your question?

DR. CIGARROA: It addressed aspects of it.

DR. PAGE: Okay. Keep in mind that we can discuss the ramifications of these concerns later, more appropriately.

MR. GODSHALL: And if helpful, Dr. Aaronson thought he might be able to address the specific question on perioperative ventricular thrombus, if the Chairman is interested in that perspective.

DR. PAGE: Do we need to do that now, or perhaps you could put together something for after lunch?

MR. GODSHALL: Yeah, it's a clinical perspective, but we can discuss it later.

DR. PAGE: Okay, thank you.

Dr. Lange had a question and Mr. Dubbs after that. And Dr. Yuh and Dr. Allen. So let's make these concise questions for clarification and concise responses by the Sponsor, please.

DR. LANGE: Three concise questions. One is related to the Appendix K, which shows the SAEs that are assessed as related to the device. There are a number of patients noted that have intra-cranial hemorrhage or ICVA or had the device exchanged that don't appear on this SAE.

Those numbers would be Patients 011-002, 005-004, 002-002, 001-005, 001-008, 003-001, 010-002, 006-004, 017-206, 027-010, 034-005, 006-003, 011-007, 006-007. So if we could figure out why they're -- with the issues, why they're not listed as an SAE.

MR. GODSHALL: I'm sorry. I believe your question was not

device related versus --

DR. LANGE: They're neither listed as a serious adverse event nor related to the device.

DR. PAGE: Dr. Lange, may I suggest that you give those numbers and we address those after the lunch break.

DR. LANGE: Correct.

MR. GODSHALL: Thank you. I didn't write that fast. I appreciate it.

DR. LANGE: Just for the record, I'll give it to you.

MR. GODSHALL: Noted.

DR. LANGE: Two other questions. One is related to the quality of life issue, and that is there are a number of patients that were able to consent for the procedure but were not able to fill out a quality of life questionnaire. So if you could give me some insight into that.

And the last question is related to the training program. There are isolated pig hearts and animal implant and there's a surgical preceptorship, and then in the information submitted by the Sponsor with regard to the surgical preceptorship, it says, with this option, there will be an experienced surgeon who would travel to clinical sites.

So just clarify whether that's an option or whether all sites have a clinical surgeon, experienced surgeon, come to the site for the first several implants.

MR. GODSHALL: We have training. And, again, most of the training has been done at Louisville with Dr. Slaughter. It's a full session for the entire staff at the center, inclusive of the surgeons. So at Louisville they undergo surgical training, procedure training, device management training.

The on-site training is not generally done by a preceptor attending the case, the first cases at the new center. Most of these clinicians -- well, really all of our clinicians have experience implanting VADs in the United States. So it is a training on the technique of implanting our VAD versus the new experience implanting any VAD, and therefore the observation based on our experience in Europe and in the U.S. has been, if they attend the training sessions conducted by the likes of Dr. Slaughter, intensively training and follow-up support by our clinical specialists, that that has yielded a very short learning curve for the center.

DR. LANGE: So they actually scrub in with Dr. Slaughter and participate in a surgery?

MR. GODSHALL: In the animal lab and, when possible, they attend procedures that he has, but it's hard to predict exactly when you'll have a procedure.

DR. LANGE: Thanks for the clarification. And with regard to the quality of life?

MR. GODSHALL: For quality of life, I'd like to bring up Dr. Keith Aaronson to speak broadly about the various quality of life elements

of the study.

DR. AARONSON: Thank you.

DR. PAGE: Just so I'm clear, Dr. Lange, your concern wasn't the results of the quality of life. Your concern was specifically how you can obtain informed consent and the patient is unable or, for whatever reason, the quality of life questionnaire could not be filled out. Was that your question, Dr. Lange?

DR. LANGE: Yes, sir.

DR. PAGE: So we're not discussing the issues of quality of life. It's just an explanation of how they could consent and not fill out the forms.

DR. AARONSON: Thank you for the clarification. I understand your question, Dr. Lange, and I think if you look at the prior bridge-to-transplant trials, you'll find the same issue was extant there as well and is less so in the destination therapy studies.

At our own center that disparity doesn't exist, and all I can say is that at some centers, with patients who are really extremists, it's felt to be, I presume, an excessive hassle for them. And while we're obviously very focused on getting all of the clinical trial information we'd like to get, that's not absolutely universal.

DR. LANGE: So presumably these patients, as a part of the informed consent, are informed that they'll be identifying quality of life issues?

DR. AARONSON: And lots of other things.

DR. LANGE: Okay, thank you.

DR. PAGE: Thank you.

Mr. Dubbs.

MR. DUBBS: I'm looking at C-27, and it may be that I missed the explanation or I don't understand the percentages, but for the demographics of patient participation in the trial, it says that 72% are male, and I just wondered why it's such a high percentage of males as opposed to females. And then the other part is similar as to race, white versus black.

MR. GODSHALL: First, as Dr. Aaronson just noted on the quality of life, this is consistent with prior VAD studies. What's important to note, however, is that -- and I have some data on the potential for females. Our population is defined by patients listed as Status 1 or 1A by UNOS, and the fact that only 26% of the people on UNOS are females, our potential pool of populations is somewhat constrained by the percent of people on UNOS. We can't include people who are not UNOS listed.

So the fact that in our study we actually saw the highest percent of women enrolled to date, with 28% versus the UNOS registry of 26%. And I have here some references from prior studies with 21% and 24%.

We've actually seen in our subsequent extended CAP experience an increasing percentage of females. But at the end of the day, unless the UNOS registry distribution changes, we probably will not see a

material increase above the 30% rate for females. Although certainly it is attractive for our clinicians, that our device is so small, given that, on balance, the females tend to be smaller than males.

In terms of the race distribution, I don't think other than we take the people that come in our centers are broadly distributed across the country, so they're not concentrated in areas where you would be biased towards Caucasians versus non-Caucasians. It just was the way the patients arrived, and it is not dissimilar to prior studies either.

MR. DUBBS: So maybe it's my unsophistication, but would we then have to consider the differences, male/female, black/white, in terms of the effectiveness of the device? Are we extrapolating that because 72% of males achieve a specific result, that females would as well?

MR. GODSHALL: I would be more comfortable having Dr. Aaronson speak to --

DR. PAGE: Well, actually, Mr. Dubbs, perhaps Dr. Evans would like to briefly comment on that, but we'll have time to discuss issues of whether this population represents the potential commercial population later.

Dr. Evans, you have a brief comment? Okay.

Let's move on to Dr. Yuh.

DR. YUH: I know we're running a little bit behind, but a quick question on your insight on the missing data. You explained that some

significant amount of right atrial pressure CVP covariate data was missing and went to as much length as you could to try to compensate for that and suggested that that did not have -- introduce a bias in your analysis.

Were there any other missing data of significance, in terms of the amount of data, and did that give you some concern as to the quality of the overall data collected for the study?

MR. GODSHALL: As with many studies, we didn't have perfect data collection. We actually upgraded our monitoring capabilities because we recognized that we had an opportunity to further improve training at the sites and improve data collection. But we did not, either in the original monitoring or in post-monitoring, as we improved data collection, retrospectively and prospectively, we did not identify other important variables that would've negatively or positively biased the outcome.

DR. PAGE: Thank you.

Dr. Allen.

DR. ALLEN: As a transplant surgeon, I'm interested in the practicalities of how I might use this device and what you learned while the trial was going on. The way your device works with its magnetic levitation of the impeller, it's very afterload sensitive.

I was intrigued by your slide looking at the arterial pressure and its potential effects on results, as well as anticoagulation. Clearly it, from the Panel pack, appears that early on in your trial there was not very good

attention paid to anticoagulation. Your average INR was well less than what you would normally propose.

Did your statistician or your investigators do an analysis on, specifically, stroke rate and pump thrombosis as it relates to, over the course of the trial, lowering your mean arterial pressure, thus decreasing afterload as well as increasing your INR, which based on your Panel pack you were doing?

MR. GODSHALL: So we have recently been paying a great deal of attention to mean arterial pressure, as was included in Dr. Hathaway's presentation, because we now have enough time and events to be able to evaluate whether or not there is a correlation. So that is a process that's underway. We're conducting multivariate analysis right now.

It does appear, at least on a purely trend basis, that mean arterial pressure is correlated or at least -- well, not correlated. It looks like there's a higher on-balance mean arterial pressure for hemorrhagic strokes, which is not a surprise. We have not done an assessment of mean arterial pressure as it affects pump function. I don't know if that is your question.

DR. ALLEN: Your device is clearly impacted by elevated arterial pressures because of how it functions, and I know it'd be an important analysis to do going forward. I would think you would already have that analysis, based on the completion of the trial.

MR. GODSHALL: Well, what I can do is I can bring up

Jeff LaRose, who invented the pump and is a computational flow dynamics expert, and he can probably speak quite succinctly about the effects of pressures on the pump.

DR. ALLEN: I guess I'm more interested if you have the data. I understand how the pump works, so you don't need to clarify that for me. I'm just interested if you had that piece of data because I think it'd be important and helpful for you.

MR. GODSHALL: Thank you.

DR. PAGE: So is there an analysis that you're requesting to see whether the Sponsor has the data available to present to use later?

DR. ALLEN: It doesn't sound like they do, but they presented data that showed higher hemorrhagic stroke rates with higher mean arterial pressures. Obviously during the course of the trial you've collected what your mean arterial pressures are. You did an analysis, at least in our Panel pack, where you showed that at a certain time point when you paid more attention to anticoagulation and maintaining higher INRs, things seemed to get quite a bit better.

MR. GODSHALL: Right.

DR. ALLEN: Did you do a similar analysis with paying attention to mean arterial pressure and afterload?

MR. GODSHALL: We are digging into mean arterial pressure aggressively now, as we've seen improvements on thromboembolic

complications, which received a great deal of attention from our investigators. We now feel like we have the opportunity to turn our attention to further refine, and we expect it will be continuous adjustment to get things just right, just as really every VAD on the market is always trying to figure out what's the optimal anticoagulation regimen, and we will continue to evaluate all variables that we have to control, including arterial pressure and anticoagulation.

DR. PAGE: It sounds like that analysis is not going to be available after lunch.

MR. GODSHALL: It's a lot of work, but we're very excited.

DR. PAGE: One last clarifying question from Dr. Cigarroa, please.

DR. CIGARROA: In many trials of atrial fibrillation in which is efficacy of antithrombotic therapy, both efficacy and safety, is analyzed, one looks at the percent of time that a patient is within the therapeutic window as it relates to warfarin. Do you have that data for your patients in the active arm here?

MR. GODSHALL: I'll bring Dr. Hathaway to bring up what we do have on that.

DR. PAGE: And, Dr. Hathaway, if you would be able -- I think this is a very important question, and I think anticoagulation is going to be the subject of some significant conversation. So why don't we give you a

little while to put your answer together, and if you can generate a slide, if there are any data you can collect for us, that would be great, and that might help kick us off later on in the day.

DR. HATHAWAY: We'll give it our best shot. That's a good question, and we will give our best shot. I don't know if we'll be able to produce that by this afternoon, but we'll try to do so.

DR. PAGE: Fair enough.

Seeing no hands raised with burning questions, Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: Were you planning on taking a break right now?

DR. PAGE: I am indeed.

DR. ZUCKERMAN: Okay, before we do that, could you summarize with the Panel any assignments that you would like the Sponsor to do during lunch?

DR. PAGE: Thank you.

As I see it, the issue of anticoagulation would be valuable; whether you can give us, in particular, what percent of time patients were in a therapeutic range. And Dr. Lange had a number of specific patient numbers and concerns that at the break he'll be able provide to you that we'd like follow-up on. I believe that covered the two bits of homework we provided; is that correct?

Okay. Well, with that we will break. We are running behind, and I have 10 minutes after, and we will reconvene in exactly 10 minutes at 10:20.

Thank you.

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

(On the record at 10:22 a.m.)

DR. PAGE: Welcome back. Please take a seat. It's now 10:22, and I'm calling the meeting back to order.

It's time for the FDA to give their presentation. And we look forward to a presentation that likewise, as did the Sponsor, and I appreciate it, stays within the allotted 75 minutes. Please proceed.

MS. KAUSHIVA: Thank you. Good morning. My name is Anchal Kaushiva, and I'm the FDA lead reviewer for this PMA of the HeartWare Ventricular Assist System.

First, I'd like to acknowledge the FDA review team, which consisted of the following individuals.

This morning I'll be going over FDA's preclinical evaluation of the device. Dr. John Sapirstein will then present FDA's clinical evaluation. Dr. Cindy Yang will present the statistical evaluation. And Dr. Veronica Sansing will discuss the postmarket study proposal. I will then highlight FDA's main conclusions from our review.

This figure shows the placement and mode of operation of the

device. As discussed by the Sponsor, the inflow cannula is implanted in the apex of the left ventricle and the outflow cannula is anastomosed to the ascending aorta. The percutaneous lead connects to the controller and is shown in the figure. The impeller imparts energy to the entering blood so that it can be pumped to the system circulation.

The HVAD pump uses magnetic and hydrodynamic forces to elevate and rotate the impeller. Both the center post and the impeller contain magnets, and the impeller also has hydrodynamic thrust bearings, and these all contribute to the impeller suspension.

The HVAD pump is the first magnetically levitated LVAD pump. This technology is intended to decrease wear. The HVAD pump is also unlike other VADs in that it can be implanted entirely within the pericardial space, eliminating the need to create an abdominal pump pocket. The HVAD pump is the second continuous-flow rotary pump. This technology ejects a volume of blood, in this case, 50 mL, by the speed of rotation of the impeller and the pressure differential that exists across the pump.

The controller that maintains the LVAD function can be connected to batteries or to AC power. A monitor screen, shown in the figure, is used in the hospital only. Two batteries are also shown in this figure, and these are intended to be carried by the patient at all times.

The proposed indication for use of the device is as a bridge-to-transplantation in cardiac transplant candidates at risk of death from

nonreversible left ventricular failure. The device is intended for use inside and outside the hospital.

According to the Food, Drug and Cosmetic Act, devices intended to be used in supporting or sustaining human life are Class III devices. For such devices, a sponsor must provide data that clearly demonstrate reasonable assurance of safety and effectiveness.

In determining the safety and effectiveness of a premarket approval device, the following relevant factors must be considered: the patient population for which the device is intended; the conditions of use for the device as outlined in the labeling; whether or not the probable benefit of the device outweighs the probable harm it may cause; and the reliability of the device.

The preclinical testing conducted on the device included tests in the categories shown here, including overall system reliability; design and manufacturing; software; electrical safety and electromagnetic compatibility; alarms; animal studies; biocompatibility; sterilization; packaging, shelf life, and shipping; and human factors testing. All preclinical tests were determined to be satisfactory.

Although the final device design underwent all appropriate bench testing, the design underwent several modifications during and after the U.S. clinical study. Some key modifications include the addition of a sintered inflow cannula; a controller and monitor software upgrade;

hardware upgrades to the controller; modifications to the driveline; modifications to the battery pack and charging unit; addition of a shower bag; and addition of an electrostatic discharge shield to prevent electrostatic interference.

Subgroup analyses on these changes have not been presented to FDA for review.

Based in part on the satisfactory preclinical assessment of the original device design, the pivotal U.S. clinical study for the HeartWare Ventricular Assist System was approved under IDE G070199. This was a prospective, contemporaneous control, non-randomized and open-label study. One hundred and forty patients were implanted at 30 centers. This was the first trial to use the INTERMACS registry as a contemporaneous control. And I will discuss the registry a bit more in a moment.

The primary endpoint of the trial was pre-specified and depended on the comparability of the treatment and control groups.

The primary study treatment group consisted of 140 patients implanted with the HeartWare VAS. The study control group consisted of 499 patients in the INTERMACS registry. INTERMACS is a collaborative effort between the National Heart, Lung and Blood Institute, the Center for Medicare and Medicaid, FDA, and the University of Alabama at Birmingham.

The primary purpose of the registry is to track outcomes of patients who received approved mechanical circulatory support devices in the

U.S. Currently 131 transplant centers contribute patient data to the registry, and as of March of 2012, over 6,000 patients had data entered into INTERMACS.

In addition to these primary study groups, a continued access protocol was approved to allow for expanded access of the device after trial completion in early 2010. FDA has reviewed only limited data from this continued access phase.

I will now hand the presentation over to Dr. John Sapirstein, who will be discussing the clinical trial and its outcomes in more detail.

DR. SAPIRSTEIN: Good morning. My name is John Sapirstein. I'm a cardiothoracic surgeon in the Division of Cardiovascular Devices, and I'll be going over FDA's clinical review of this PMA.

Here's an outline of what I'll be talking about this morning. I will begin with some trial design issues involved with the IDE. I'll review parts of the IDE protocol and the trial execution. I will briefly discuss some of the propensity score methodology that was used, but Dr. Yang will discuss this in more depth after me. Next, we'll go over the primary endpoint results, particularly in relation to the propensity score covariates, and we'll go over some of the adjunctive analyses that FDA requested. Finally, we'll look at the secondary endpoint results, emphasizing some of the adverse event data, the comparison to literature values, and some secondary effectiveness measures.

Now, as you've already heard several times, this was a

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prospective, non-randomized, multicenter study intended to evaluate safety and effectiveness of the HeartWare VAD for bridge-to-transplantation. The Sponsor, as you also heard, is conducting a parallel study of this identical device for the indication of destination therapy. Because this latter trial is ongoing, FDA is not at liberty to discuss its knowledge of that trial's ongoing safety and effectiveness results in this public forum.

This current trial was the first to use the INTERMACS registry as a control arm for a premarketing clinical trial of a VAD. As such, it was to serve as a contemporaneous control alternative to the standard bridge-to-transplantation performance goal. Now, that performance goal of survival at 180 days was developed in 2002 and considered by this Panel during its 2007 deliberations for the HeartMate II bridge-to-transplantation indication.

The performance goal is based upon data published after 1997 and thus represents patients who were implanted with VADs on or after 1993, for the most part. You can see on the graphs here that a separate meta-analysis from the same time period of 2002 was consistent with FDA's performance goal of 65%.

Now, around the time that this Panel was considering the HeartMate II PMA, the INTERMACS was being launched. The registry implemented standardized, prospective data collection and was intended in part to foster appropriate development and regulation of VADs. FDA felt that the use of this constantly updated dataset would serve as a more dynamic,

contemporaneous, and therefore clinically relevant comparator for newer VADs than would the static performance goal that you just saw.

In this way, it would facilitate good trial execution in a small target population that really does need reasonable enrollment periods in order to bring these devices to market. And so the concept was to compare 180-day survival in the INTERMACS registry control arm to that survival in the HeartWare device arm.

Now, the trial had a single primary endpoint of survival to 180 days, and I'll define that term "survival" in just a bit. As you heard from the Sponsor already, the two arms of the trial were compared for comparability using propensity score analysis. And here are the eight baseline covariates that were used in that analysis.

Now, importantly, each of these covariates contributed equally to the propensity score, and there was none of what I would call a clinical weighting of the covariates. This may be relevant to some of the later discussions that we'll have.

Now, because this was not a randomized trial, there was no reasonable guarantee that the two groups would in fact be suitably matched to allow for a direct comparison, and thus there were pre-specified statistical rules for assessing comparability based on the C-statistic, as you already heard and you'll also hear more from Dr. Yang after me.

If the groups were determined to be well balanced or only

somewhat imbalanced, a non-inferiority comparison of HeartWare to the INTERMACS group would take place with the definition of success, as you can see, listed up there. The mathematical hypothesis was for non-inferiority, and the margin was 15%. If, however, the groups were not in fact comparable, then the HeartWare success rate would be compared to the performance goal of 65%.

Now, note that the definition of success in this scenario incorporated a component of transplantability while on the HeartWare device. Those aspects are highlighted in yellow.

Patients who were still with the device at day 180 had to fill one of those two criteria: Either they had to be UNOS status 1A or 1B -- and you saw the UNOS definitions previously, and this connotes the highest priority patient who was also clinically suitable for transplantation -- or if the patient was not 1A or 1B at day 180, then eventually underwent transplantation by coming lock date, that too would count as success. The mathematical equation for the performance goal analysis is shown there. And please remember, that's the lower 95% confidence limit and not the point estimate of HeartWare success that is used for the statistical comparison.

Now, when we contrast the definitions of success that I just described, there may be two ways to look at their relative stringency. First, one might consider the performance goal survival to be a somewhat higher

bar, since it includes that consideration of transplantability. On the other hand, if one looks at a more recent series of results for bridge-to-transplantation -- and what I have here are aggregate INTERMACS registry data -- it seems that in the current era, survival at 6 or even 12 months is substantially greater than 65%. And here it's about 88% at one year.

Now, it's true that this rate of success includes all recipients, including the non-1A/1B patients and patients who have undergone device exchange. So it's not really an apples-to-apples comparison. Nonetheless, the Sponsor did assume group success rates of 82% for its sample size calculations of a non-inferiority hypothesis, and it also predicted that the 78% point success in the performance goal analysis would meet the performance goal endpoint.

Thus, although we are in no way trying to distance ourselves post hoc from the prospectively agreed-upon performance goal, it is probably true that at this time the performance goal has lost some clinical relevance and is not wholly reflective of the current state of practice.

Pre-specified secondary safety and effectiveness endpoints applied only to the treatment arm. Effectiveness involved quality of life and functional status measurements that you can see here. Safety endpoints looked at overall survival rates, serious adverse event rates, and failures or malfunctions of the device.

Now, with regard to the single-arm adverse event analysis, it's

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important to understand that trying to compare collected adverse event rates to a so-called performance goal for adverse event rates is problematic. The published rates of adverse events often use differing definitions of the events. They involve multiple devices, each with their own device-specific rates, and they reflect changing rates over time.

FDA did encourage the Sponsor to consider formal hypothesis testing of the device's serious adverse event rates for this trial. However, the Sponsor did indicate that the lack of formal adjudication for INTERMACS control arm events would render the comparisons invalid. As such, the protocol did exclude comparative analysis.

Nonetheless, our review of the PMA data led us to strongly believe that a comparative safety analysis to the specific INTERMACS patients would be a reasonable adjunct. This is because the two arms of the trial use identical adverse event definitions, the control arm was heavily dominated by one single device, and the arms were enrolled over analogous time periods. As you see from our Executive Summary, the control arm data, however, were not released to either the Sponsor or FDA for our review.

The principal inclusion/exclusion criteria -- you've seen these from the Sponsor -- for both arms are listed. As you can see, in most part, the two populations seem to be similar.

I will point out, though, that the HeartWare treatment arm specifically excluded patients with high right atrial pressure, which is a known

marker of biventricular dysfunction, while the INTERMACS patients did not include an analogous criterion. Also the degree of respiratory dysfunction and renal dysfunction, allowed prior to study enrollment, differed somewhat between the two groups.

Now, these are comparative flow charts of patient enrollment and device therapy. On the left is HeartWare; on the right is INTERMACS. Both studies included patients enrolled between August 2008 and February of 2009. Of the 273 HeartWare patients initially screened, 160 ended up being enrolled. However, as you already heard, the Sponsor determined that 17 of these patients had been enrolled in error and then were removed from further analysis. I'll speak more about these 17 patients shortly.

A further three patients similarly did not meet the inclusion/exclusion criteria and were removed from analysis, except that these patients underwent the HeartWare implantation on an emergency use basis. Thus, the intention-to-treat population consisted of 140 patients.

Three other patients who were enrolled and implanted had major protocol violations, which the Sponsor already mentioned. A further 110 patients were available for adjunctive data under the continued access protocol, but their level of follow-up was incomplete throughout the time of our review.

On the INTERMACS side, you can see the various reasons for removal from potential inclusion in the control arm. Four hundred and

ninety-nine patients constituted the intention-to-treat population for INTERMACS. Two of those patients changed site of care, which resulted in withdrawal from informed consent prior to their meeting the day 180 endpoint.

Now, this is the distribution of patient enrollment among the 30 implanting sites for HeartWare. As I indicated in the last slide, roughly one-half of screened patients were not eligible, according to the protocol, for participation in the trial.

The four high-enrolling centers -- and that comes from the protocol definition of having enrolled more than 10 patients -- they're shown in the blue on the left, and they implanted 34% of all patients. Their screening failure rate, though, was 30%. Two of those four centers, as far as we can tell, had no screening failures.

Conversely, four low-enrolling sites, which are indicated in yellow, who together implanted only about 7% of the devices, generated approximately half of all the screening failures.

The Sponsor also provided FDA with some justifications for these enrollment and screening disparities, but the underlying reasons are not fully evident to us at this time.

Now, in terms of the 17 screen failure patients, FDA reviewed the specific justifications that the Sponsor provided for these screen failures. Remember, these were patients who were enrolled despite exclusions and

then did not receive the device. Generally, we agreed with the Sponsor's justifications, but it's important to note that many of these inclusion and exclusion criteria nonetheless remained present for patients who were still in the trial and were implanted.

The outcome of 17 screen failure patients are listed. The majority received what was functionally the control device, the HeartMate II, outside of the protocol. The three emergency use patients were those patients who signed the consent despite having exclusions and yet did receive the treatment device, unlike the screen failure patients.

I'll also add at this point that, throughout the IDE process, FDA did raise questions to the Sponsor regarding possible differences in investigator equipoise in the context of the number of emergency use and compassionate use requests that the Agency received.

Baseline demographics for the HeartWare patients are listed here. These were typically middle-aged white males, as we've already discussed, with Class IV heart failure. Some of the hemodynamic data, such as cardiac output, mixed venous saturation prior to implantation, seems to suggest a patient cohort that was reasonably well compensated at the time of device implantation.

Now, here are the comparative baseline data for seven of the eight pre-specified propensity score covariates. As you can see, they were statistically similar. Importantly, though, as we've already discussed, baseline

right atrial pressure data were missing for a large proportion of the patients, more so for the HeartWare arm, 80%. The Sponsor did use central venous pressure as a surrogate for right atrial pressure, but even with that the degree of missingness was 49%. Dr. Yang will comment further on the implications that these missing data had for the propensity analysis overall.

Now, INTERMACS patient profile was the eighth covariate, and as the Sponsor has already defined for you, the profile levels. This graph compares the profile percentages in each group. There was a statistically significant difference in INTERMACS patient profile between the two arms, with the control arm having a patient profile distribution representative of more critically ill patients.

In particular, look at patient profiles 1 and 2, which describe the most sick individuals presenting for VAD placement. As you can see, the control arm had proportionately nearly twice as many profile 1 and 2 patients as did the treatment arm.

Therefore, although the propensity score analysis ultimately determined the groups to be only somewhat imbalanced, FDA does believe that this very important covariate, arguably the clinically most important covariate, demonstrated substantial differences.

Returning just for a second to some of the other covariates, it's probably instructive to look at more than just the statistical comparison. In FDA's view, the scatter plots for creatinine, which is on the top, and right

atrial pressure below are clinically suggestive, despite the lack of statistical difference. The control arm does appear to contain a proportion of patients with elevated creatinine and right atrial pressure that's not as readily evident in the treatment arm. You can also see the influence that the necessary imputation of right atrial pressure had for interpreting this covariate.

Now, in terms of trial conduct, here's an accounting of the protocol deviations. FDA reviewed the captured deviations in detail, and their types are listed here, and felt there was minimal impact on overall trial results and interpretability. Notably, most of the deviations occurred under the oversight of the designated contract research organization during the time when most of the implantations occurred.

The Sponsor did acknowledge to FDA that CRO monitoring was suboptimal. And in response to a question of ours, it said that monitoring visit frequency was insufficient to maintain pace with enrollment, training on the protocol required procedures, and follow-up on site deficiencies was ineffectively executed.

So, accordingly, FDA cannot be sure of the impact, if any, for those deviations which were not adequately captured. Or, stated another way, we just can't know the impact of what we don't know.

The clinical events committee adjudicated a high volume of events. Events were adjudicated by two members, with disagreements decided by the chair. Throughout the trial the CEC changed its composition

multiple times, as we've already heard. Overall, two chairs and eight different members participated in the adjudication process.

Since nearly half of the adjudications were not unanimous, FDA is concerned that the multiple persons involved added potential questions of consistency to the reported adjudications, essentially that the adjudications may not have been reproducible over time. Over one-third of the situations in which two members disagreed involved either the designation of the event as serious or the designation of device relatedness.

With regard to adjudication, I do have to point out that the Sponsor, in its reports to FDA, proposed several post hoc mitigations or changes to adjudication of events such as death or stroke, which on the whole for us rendered the interpretability of important serious adverse event rates markedly more problematic. Dr. Hathaway referred to some of those, and perhaps later on we can go into more detail.

The presentation of data by the Sponsor to FDA during the PMA review period also presented us with challenges regarding confidence in the accuracy of the adverse events data. There were inconsistencies between the initial PMA, the major PMA amendment, and throughout the pre-panel interactive review time period. With regard to the latter, three separate adverse event analyses were presented to FDA during that time.

Furthermore, the Sponsor had to update important device exchange and ischemic stroke rates to us, with newly identified events, only

very recently. As a result, while there is agreement in general on the adverse event rates between FDA and the Sponsor, the specific values which we are presenting do differ somewhat.

So these are the results of the primary endpoint hypothesis testing. For the intention-to-treat populations, success rates were 90.7% and 90.1%, and the resulting difference was within the 15% non-inferiority margin, implying endpoint success. The same analysis is shown for the smaller per-protocol cohort below. The p-values here reflect the difference for the test of non-inferiority compared to the non-inferiority margin of 15% based upon propensity score quintiles.

Now, you'll hear more about the propensity score methodology from Dr. Yang in just a bit. For right now, I want to stress that the propensity scoring is essentially randomization after the fact, which means that any two patients with similar scores will, based upon the pre-specified covariates, have similar propensity to receive the treatment in question, which in this case is to have received the HeartWare device.

Furthermore, the higher the score, the higher the propensity to have received the HeartWare device. And this is why, when we look at the distribution of patients in the trial, there are proportionately more HeartWare patients in the higher score region, which is quintile 5, and proportionately more INTERMACS patients in the lower score region, which is quintile 1. And I've highlighted some of those proportions in yellow.

And so bearing in mind that a higher quintile implies a higher propensity to have received the HeartWare device, we can look to see how the endpoint results for the individual quintiles compared.

At the top is HeartWare and below is INTERMACS. The first row is the count of failures and successes. If we look, for example, just at quintile number 4, we see it contained 36% of HeartWare treatment arm patients, yielded 35% of that arm's successes, and contributed 31% of the arm's failures.

Similarly below for INTERMACS, 16% of the patients who were in quintile 4, 16% of the treatment arm's -- excuse me -- the control arm's successes were in quintile 4, and 14% of the arm's failures were there.

If you look over at quintile 1, what stood out for us is that not a single failure for HeartWare is in quintile 1. Yet fully 39% of INTERMACS failures come from quintile 1. Obviously one point that is relevant is that there were very few HeartWare patients in quintile 1. The model demanded that there be at least five, and there were eight. But that doesn't really help to explain the high failure rate observed in the INTERMACS arm.

So there may be something different about quintile 1 or, more generally, there may be some significant limitations to the implementation of the propensity score-based non-inferiority test.

And let me acknowledge from the outset that what I'm going to present right now is a clinically driven post hoc consideration. FDA fully

agrees that the trial met the primary endpoint from a statistical standpoint.

So here are three broad categories of the limitations to the analysis that could affect inferences one draws from the results. First, there is the question of what impact missing data has for the entire propensity scoring, and Dr. Yang will address this point after me.

The next one could ask whether the chosen covariates were the appropriate ones. Clearly, FDA and the Sponsor believed they were at the time that the trial was designed and agreed to. Now, we would like to have the Panel weigh in on the adequacy of those choices.

And third is the question of whether the two study arm samples were sufficiently representative of the patient population for which the device will be used. This third item is what I want to bring up for your consideration right now.

These are plots of the trial's primary endpoint in the context of competing risk for possible outcomes. HeartWare is on the left; INTERMACS is on the right. Summary of success in transplanted or alive with the original device at day 180. And just as an aside, there were not attempts at weaning for recovery in the trial. Those summaries of success are depicted by the black lines at the top, and they show approximately 90% survival, as we already know. And it follows naturally that the failure rate at 180 days are similarly clinically equivalent in the two arms, 9.3% and 9.8%, respectively.

But note that the mechanisms by which patients failed seemed

to differ substantially. Device exchange, which is shown in the orange line, accounted for over half of HeartWare failures, while death of the patients, which is the blue line, accounted for nearly all of INTERMACS failures.

Since baseline INTERMACS profile levels, statistically different between the two arms, has been identified to clearly have an influence on survival, we asked the clinical question -- again, this is post hoc -- whether the importance of baseline patient profile was appropriately captured by the propensity score function, and whether the relative paucity of the sicker patients in the treatment arm -- again, remember 33% level 1 and 2 for HeartWare and 60% for INTERMACS -- whether those differences could affect the clinical inferences of non-inferiority. Stated another way, if there had been better balance of patient profiles, is there reason to think that the failure results would have been different?

So these are the endpoint results, success stratified by patient profile, and at first it would seem that meeting the endpoint did not meaningfully differ across either patient profile or across the two arms of the trial. But if we look at just the sicker patients in profile 2 -- and as we already heard, profile 1 had very small numbers in both arms -- things start to look perhaps a little different.

Now, we see that the day 180 failure rate due to death, again, the blue line, is essentially equivalent in both arms, 8%. Remember, overall, that death as a failure mode for HeartWare occurred at only 4.3%. The

reason is that 50%, approximately, of patient deaths, irrespective of which arm of the study, occurred in patient profile 2 individuals. Furthermore, death, when it occurred, seemed to be a relatively early event, as the graphs demonstrate, especially for the HeartWare patients. And perhaps this is reflective of the impact of patient baseline condition.

Device exchange rates, on the other hand, the orange lines, track similarly to what the aggregate results were; that is, exchange remains more common in the HeartWare group.

So while we are accepting the results based on the propensity score comparison, which I again want to stress we are not disputing, we do want to consider whether matching of this key covariate might have, in essence, provided better power to detect failures in HeartWare on the basis of death.

Thus, FDA does believe that the observed differences in baseline clinical condition of patients could very well have clinically confounded the inference of non-inferiority. And on the basis of these concerns, FDA asked the Sponsor to perform the pre-specified performance goal analysis as an adjunctive analysis.

As you can see, the HeartWare cohort did meet the performance goal endpoint with a 95% lower confidence limit of 72%, exceeding 65%. Fourteen percent of the HeartWare successes under non-inferiority failed in the performance goal analysis, mostly because they

were no longer appropriate transplant candidates by the time of the data lock. In other words, they were status 7.

As I showed earlier, recent literature does suggest that the current bridge-to-transplant 6- or 12-month survival is approaching 88%. And, again, although this definition includes non-1A/1B patients and includes device exchange patients, the INTERMACS control data from the current trial suggests that device exchange is not a common event for the currently marketed and commonly used devices.

So if we assume that the proportion of aggregate bridge-to-transplant VAD patients with non-1A/1B status is similar to what the HeartWare group demonstrated, in other words, 15%, then an updated performance goal comparator reflective of the current state of the art may in fact be approaching 70% or 75%. And perhaps that's a threshold that the present trial would not have clearly met. But once again, we agree that this trial did meet the pre-specified performance goal.

An additional analysis that the Sponsor provided looked at the primary endpoint definition of success without inclusion of UNOS status, and longer term, mainly out to the date of the last patient's day 180 endpoint determination, these results were consistent with the pre-specified endpoint results. Device exchanges remained high in the HeartWare group. Failure by death predominated in the control arm.

The results stratified by gender and body surface area are

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presented here. In general, women seemed to have had similar success to the men. But I will make the observation that the trial did demonstrate a higher death rate for women than for men in HeartWare, as you can see here.

With regard to body surface area, an important design aspect of this device is its relative small size, perhaps making the HeartWare VAD more accessible for smaller patients. However, only one patient with a BSA of less than 1.5 m² received the HeartWare device, and thus inferences regarding the results in small patients are necessarily limited. This will be discussed by Dr. Sansing later on.

Now, focusing on the specific failure events, death was an endpoint failure in six HeartWare patients. The adjudicated cause of death and relatedness are listed here. FDA does feel that at least some of the events, while not adjudicated as definitively related to the device, in fact, it had some substantive causality associated with the HeartWare device.

The two additional deaths listed here occurred in patients after they had failed on the basis of device exchange. These events were not adjudicated. The death events were not adjudicated. But FDA does believe that the signs and symptoms of thrombus in the index pump, though not necessarily causal for the deaths, remain somewhat contributory.

Need for device exchange was the endpoint. Failure for seven patients and their vital status at the 180-day time point is shown here. We reviewed details of each of these device exchanges and believe that all of

them were associated with signs or symptoms of pump or ventricular thrombosis. The Sponsor identified nine additional pump replacements as having been necessary by a date of July 15th, 2011. As of that data, 8 of the 16 patients were with ongoing VAD support. Seven of them were UNOS status 7, and one had been delisted from the transplant list.

Accordingly, FDA disagrees with the Sponsor's supposition that it put forth in the PMA amendment, suggesting that pump exchange was no longer a clinically relevant aspect of the bridge-to-transplantation endpoint.

Despite the comprehensive adverse event definitions called out in INTERMACS and used for the trial, nearly half of investigator-identified adverse events were deemed to be "other." Thirty-six percent of the serious adverse events that investigators reported were "other." The Sponsor reasonably justified the seemingly large proportion of serious adverse events not otherwise defined by the INTERMACS terms.

However, the volume and nature of some of the other events -- and you can see some of the descriptors there -- do raise the possibility that they inadvertently contained INTERMACS events in spite of the CEC's reclassification efforts.

Now, this table represents FDA's best effort at summarizing strokes by the endpoint date. In our estimation, based on the data that the Sponsor provided us, ischemic strokes occurred in 8% of patients, and isolated hemorrhagic strokes occurred in an additional 3%. For the most part,

the effect of stroke in this patient group was severe, in FDA's opinion.

Because the direct comparison to the stroke rate, or any other serious adverse event rate, to the INTERMACS control arm was not possible, the Sponsor selected three published references that it felt could serve as appropriate comparators of serious adverse events. And these comparisons are presented in your Executive Summary.

For the majority of the events, FDA agrees that there was no clinically significant differences existing between the rates observed with the HeartWare device and the rates from the reports, all of which concerned the HeartMate II device.

Now, with regard to the important neurologic event rates, however, we remain cautious about such a conclusion. As mentioned previously, the Sponsor and we do not fully agree on the observed stroke rate in the trial. Notwithstanding this detail, we do feel that the stroke rates in HeartWare patients, in particular, the proportion of patients afflicted with ischemic stroke, are at the very least clinically similar but perhaps even higher than the cited rates with the commercially available device. Look, for example, at the percentage of patients affected with ischemic stroke by 30 days.

I'll also point out that the last reference on the bottom table from Starling et al. reported adverse event data from the HeartMate II post-approval study that used a system very similar in nature to the adverse event

data collection used for the HeartWare trial.

Now, to help with FDA's assessment of key adverse events like stroke, we asked the Sponsor several times for current continued access, or CAP, data. But the information we had was limited to 110 patients with incomplete adjudication dating through February of 2011. Key analytic stroke data are shown here. These are 250 patients from the principal IDE cohort and 110 from the continued access cohort. As best we can tell, it appears to us that the stroke events in the CAP population are essentially unchanged from the primary IDE cohort.

Look, for example, at the perioperative ischemic stroke rate for the combined population. Since we assume that these events represent single events in multiple patients, it seems reasonable to infer that the unchanged percentage of patients affected, approximately 5%, implies that the CAP rate has not substantively improved. And this finding is in the setting, as the Sponsor already indicated, of changes in a surgeon's training and anticoagulation management postoperatively, which was implemented specifically to address thrombus and stroke events.

And this is just a graphic representation of how we inferred the numbers that I just presented. Because it is obviously a somewhat different perspective than what the Sponsor presented, I will note, however, that we are stressing perioperative 0 to 30 days, while the Sponsor appeared to be stressing the 0 to 48-hour stroke rate.

Now, with regard to pump failure, 21 of the 250 combined IDE and CAP patients had this event. That's 8%. Fifteen of the failures necessitated exchange of the device. Over half of the pump failures were due to thrombosis and required device exchange. An additional five thrombotic events were salvaged without exchange using tissue plasminogen activator.

In summary, we infer that the CAP pump failure rate is consistent with what the primary IDE cohort experienced and is most often associated with pump thrombosis. The Sponsor presented data concerning the beneficial effects of sintered cannulae.

Please understand that FDA has not been provided with those data in a way that permits appropriate review by us, and that the numbers involved are certainly too small for drawing discrete inferences.

The infectious event data are shown here, again, with the literature comparisons. The observed perioperative driveline infection rate in the HeartWare device, 3.6% of patients, is a little bit difficult to reconcile with a more favorable longer-term infection profile evidenced by the common closing date. But the longer-term results are probably more clinically relevant in your view and thus, however, we have no major concerns regarding infection profile of this device at this time.

Assessments based on changes in New York Heart Association classification and the six-minute walk tests were generally indicative of functional status improvement while on device. However, these inferences

are limited, since a marked amount of missing data substantially curtailed the ability to perform paired assessments. Also, note is made of the high variability of six-minute walk tests, as indicated by the large standard deviations.

Similarly, the degree of follow-up for the quality of life, the KCCQ and EuroQol testing, limits the inferences regarding quality of life improvement. That said, among patients with paired data at six months, the assessments do support improved quality of life. Acknowledging this, one must also remember, though, that the trial was clearly unblinded.

So, in summary, this was the first premarket FDA trial to use the INTERMACS registry as a contemporaneous control. The trial did meet the primary endpoint for bridge-to-transplantation, but FDA does believe that some considerations may have affected the clinical comparability of the two groups. The trial also met a pre-specified performance goal endpoint, but the result is not as compelling, given the current status of the VAD field.

Safety inferences were complicated by several factors, including a lack of comprehensive access to important safety data, issues regarding trial oversight, and the manner in which adverse event data were presented by the Sponsor to FDA. Three events are of particular note: thrombosis, device exchange, and stroke. In FDA's view, they all do seem to be somewhat interrelated.

Thank you very much. And I'll have Dr. Yang come up.

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DR. YANG: Good morning. I'm Cindy Yang, mathematical statistician at the Center for Devices and Radiological Health, FDA. Because propensity score is used in this PMA, I will present a brief introduction on propensity score analysis.

The basic idea of propensity score methods is to replace the collection of confounding covariates in observational studies with one function of these covariates called propensity score. In other words, propensity score is the propensity of a subject being assigned to treatment A versus treatment B, conditional on observed covariates. In propensity score modeling, the outcome is an event, namely the treatment subject actually received, for example, treatment A or treatment B.

The independent variables are observed covariates and some interactions of various orders. There are many functional forms with propensity score modeling. For example, logistic regression is one commonly used estimation. The clinical outcome variable for the trial, for example, patient survival, is not involved in propensity score modeling.

The purpose of propensity score modeling is to simultaneously balance many observed covariates in two treatment groups. The comparison between the two groups, one received A, the other received B, with a given value of propensity score, is expected to be balanced with respect to all observed covariates used in the model.

Stratification, or also called subclassification, is one common

covariate adjustment based on propensity score and is used in the current trial design. In doing stratification, all patients are ordered based on their propensity scores, then are divided into different subclasses. For example, using propensity score quintiles, the subject can be stratified into five subclasses.

As mentioned before, the goal of stratification is to find subclasses in which the treatment and the control groups have balance. It is theoretically proven that if appropriately done, balance on all covariates within each subclass can be achieved simultaneously.

However, a propensity score model may not always help when key covariates are not observed or are very noisy. Propensity score methods cannot help. If the set of the covariates used in the propensity score model is not the right one, the value of the propensity score methods is of question. In addition, it is not always possible to achieve balance with propensity score methods. If possible, a randomized controlled trial is always the gold standard.

In doing a propensity score analysis, outcome-free design is essential. Here, the outcome means the clinical outcome for the trial, for example, patient survival. An independent statistician who is blinded to the outcome might help in assuring the feature of outcome-free. Before analyzing the outcome data, communication with the FDA on the final propensity score design will document the final design.

I will now present the FDA statistical review of the HeartWare Ventricular Assist System submission. First, I'm going to describe the study analysis plan. I'll then report the study analysis results, followed by a statistical summary.

The study is a prospective, contemporaneous study. Patients from INTERMACS, over the same enrollment period as the HeartWare VAS treatment group, are used as control. A propensity score method is used to evaluate comparability between the HeartWare VAS treatment group and the INTERMACS control group. According to the protocol, C-statistic is used. It is the area under the ROC curve and is intended to serve as a concordance measure of the comparability of the two arms.

Three possible scenarios are considered. When the two groups are considered as well balanced or somewhat imbalanced, the HeartWare VAS will be compared to INTERMACS with appropriate adjustment. When the two groups are not comparable, the HeartWare VAS will be compared to a performance goal instead of the INTERMACS group.

The ITT population for the treatment group includes all enrolled patients who underwent anesthesia for implantation of the HeartWare VAS. The SAF population for the treatment group includes all ITT patients who received the HeartWare VAS. The per-protocol population for the treatment group includes SAF patients who did not have protocol violations.

The INTERMACS contemporaneous control group consists of patients enrolled in the registry who met the pre-specified control group inclusion/exclusion criteria over the same enrollment period as the HeartWare VAS treatment group.

The primary analysis population is the ITT population. Our primary and secondary analyses were to be performed on ITT and the per-protocol populations. Our safety analyses were to be performed on the safety population.

As Dr. Sapirstein stated earlier, there are 140 patients in the ITT population in the HeartWare VAS group. The safety population for the HeartWare group is the same as the ITT population. The per-protocol population includes 137 patients after removing three patients with major protocol violations.

For the INTERMACS contemporaneous control group, there are 499 patients with two patients who withdrew consent being counted as missing data.

For comparison of HeartWare VAS to INTERMACS, the primary endpoint is pre-specified as being survival at 180 days. The hypotheses for the primary endpoint in this case are shown here, where π_{HW} is the proportion of treatment group success rate and π_{INT} is that for the INTERMACS registry control group. The non-inferiority margin is 15%. The Type I error rate is a one-sided Type I error rate of .05.

When HeartWare is to be compared to a performance goal, the primary endpoint definition is different from that when the HeartWare VAS is compared to INTERMACS. The definition of success is listed here.

The hypotheses for the primary endpoint in this case are shown on this slide. π_{HW} is the proportion of successes in the treatment group. The performance goal is set at 65%. The success rate in the HeartWare VAS group would be compared to the performance goal of 65% using a one-sided binomial exact test. That is to say, the lower 95% one-sided confidence limit would have to be higher than 65%.

A logistic regression model is used in the propensity score model. Eight covariates are pre-specified for the model. They are age, gender, BUN, RAP, creatinine, BSA, prior cardiac surgery, and INTERMACS patient profile.

Among the eight covariates, RAP data were missing for 80% of patients in the HeartWare VAS group and 44.5% of patients in the INTERMACS group. According to the protocol, the missing data were imputed by replacing the missing value with a group median. That is, all missing RAP data for HeartWare were replaced with a value of 9.5 mmHg and all missing RAP data for INTERMACS were replaced with a value of 11 mmHg.

This large amount of missing data of RAP makes the validity of the propensity score analysis questionable. The Agency's request to the Sponsor to perform multiple imputations of RAP using regression is declined.

After running the propensity score model, the C-statistic is found to be .65. The box plots of propensity scores for the HeartWare treatment group and the INTERMACS control group are shown here.

Using quartiles, the number of patients in each strata is summarized in the table.

By the pre-specified criteria, it is then decided that the two groups are somewhat imbalanced and the primary endpoint analysis can be performed with adjustment of propensity score stratification. However, the evaluation of the comparability of the two groups should be considered with the totality of the analysis.

To hopefully further reduce bias, covariate balance checking is made using quintiles of propensity scores for each covariate. For continuous and ordered categorical variables, a two-way analysis of a variance model is used. For each of the covariates, the two-way interaction of the treatment and propensity score quintile, as well as the treatment assignment comparison after stratification, were checked. None were found significant, at a significance level of .15, when missing data are imputed with group medians.

For RAP, if only included is the observed RAP in the two-way ANOVA model, the p-value for the treatment effect is .1, but for the treatment by quintile interaction is .7. Evaluation of the true balance of RAP is not possible due to a large amount of missing data.

For binary variables, a Mantel-Haenszel test is used. None were found significant, at a significance level of .15, when missing data are imputed with group median.

Using the primary endpoint definition for comparing HeartWare VAS to INTERMACS, among the 140 patients in the HeartWare VAS arm, 127 are successes and 13 are failures. Among the 499 patients in the INTERMACS groups, 448 are successes, 49 are failures, and 2 are missing. Using quintiles in the propensity score stratification, the upper bound of the 95% one-sided confidence interval of success rate difference is found to be 1.6% on the ITT population and 0.09% for the per-protocol population.

Two INTERMACS patients withdrew consent and thus have missing outcomes. A worst-case analysis was performed when the outcomes for the two INTERMACS patients with missing endpoint data were imputed to be successes, and no marked change in the results was noted.

The majority of the subjects in both HeartWare VAS and INTERMACS arms are males. The effect of gender is analyzed by comparing the primary outcomes for the male and the female patients.

For male subjects, the success rate was 93.1% for HeartWare VAS and 89.9% for the INTERMACS arm. Male subjects seemed to perform better with HeartWare VAS.

For female subjects, the success rate was 84.6% for HVAS and 90.8% for the INTERMACS arm. Female subjects seemed to perform better

with INTERMACS.

A test of the interaction between the treatment arm and gender was conducted using logistic regression. When no covariate was included, the p-value was .15. When the age covariates used for the propensity score model are included, the p-value was .135.

Please note that the trial was not powered for the interaction test.

Using the definition of primary endpoint comparing to performance goal, 77.9% of HeartWare VAS patients reached endpoint successes. The lower bound of the one-sided 95% confidence interval for the success rate was 72%, which is higher than the 65% performance goal.

Using the primary endpoint definition for performance goal, the success rate for males is 79.2%, with the lower bound of the one-sided 95% confidence interval being 71.5%. For females, the success rate is 74.4% with the lower bound of the one-sided 95% confidence interval of 60.4%, which is lower than the 65%. The p-value for male and female differences with a Fisher's exact test is .65.

In summary, the study appears to meet its pre-specified non-inferiority criteria using analysis pre-specified to compare to INTERMACS. However, the evaluation of the true balance of RAP is not possible due to a large amount of missing data. Alternatively, the study appears to meet the performance goal endpoint. Conclusions of the study should be drawn based

on the totality of the data, including both statistical and clinical findings.

I will now hand the presentation to Dr. Veronica Sansing, who will address the post-approval study.

DR. SANSING: Good morning. I'm Dr. Veronica Sansing. I will now present the post-approval study considerations.

Before we talk about post-approval study issues, be reminded that post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to initial establishment of device safety and effectiveness.

The FDA review team identified the following potential postmarket issues for this device. Primarily, the Sponsor should monitor the sequence of the adverse events, such as thrombus necessitating transplants and device malfunctions, including type of malfunctions. For instance, in the premarket study, six out of seven pumps were removed for suspected thrombus; four of these device malfunctions were due to high power alarms. And two transplants occurred as a result of these device malfunctions. However, it was unclear if thrombus preceded the malfunction or if the malfunction preceded the thrombus.

Fifteen strokes were reported in the IDE study. However, there is not data to indicate if these events were device related.

Another important consideration is the long-term device performance while on continuous support. The IDE study assessed survival at

180 days on support or 60 days post-explant for recovery. This short time frame may not capture the full spectrum of adverse events associated with the device. For example, a study showed that mean support time in INTERMACS was 385 days.

The patients in HeartWare's premarket study were consented for five years of follow-up. Continued follow-up of this cohort is needed to better assess device performance.

In the postmarket study, the device is made available to a wider range of patient populations and interventionalist teams. Operators within the IDE study will have had experience in performing these procedures. Therefore, for non-IDE sites, a training program is required to minimize adverse events associated with operators. Although not studied in the premarket cohort, there may be a learning curve associated with device use in the non-IDE sites.

A post-approval study is needed to assess body surface area subgroup performance. The Sponsor believes that the size and implantation technique of its device may make it suitable for smaller patients who would not otherwise be candidates for implantable VAD support. However, the IDE trial only enrolled one patient with a body surface area less than 1.5 m².

The Sponsor has proposed conducting two post-approval studies. First, extended follow-up of the premarket cohort and, second, a newly enrolled cohort study that incorporates evaluation of a training

program.

For the first post-approval study, the Sponsor agreed to evaluate the device's long-term effectiveness through extended follow-up of the premarket cohort. This table presents an overview of the extended follow-up plans within the premarket protocol. This is a multicenter prospective trial.

The extended follow-up patient population will be all IDE subjects on continued support with the HeartWare VAS for more than 180 days. As of August 2010, a total of 140 subjects were implanted, and as of March of 2012, 300 continued access protocol patients have been consented and enrolled for five years of follow-up. Extended follow-up for patients remaining on the device is every six months for five years.

The endpoints are as follows: overall survival; serious adverse events, including neurological and unanticipated adverse device effects; device failures and malfunctions; quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire and the EuroQol; functionality as assessed by the New York Heart Association classification and the six-minute walk test.

Today's review of the second post-approval study is based on the protocol version dated March 15th, 2012. Post-approval Study 2 is a prospective, non-randomized, two-arm registry study of newly enrolled patients implanted with HeartWare to assess safety and effectiveness in non-IDE sites.

Rejection of the null hypothesis for the primary objective of survival would denote non-inferiority of the HeartWare group to the comparison group with a 10% margin, one-sided 5% alpha. However, the Sponsor did not give justification for the 10% margin within the protocol.

The Sponsor states that at least 155 HeartWare patients and 155 comparison patients are to be enrolled for 180 days of follow-up data to detect non-inferiority. The statistical plan for the newly enrolled study will use a Kaplan-Meier survival analysis to assess the primary endpoint of survival, exchange, or recovery. The Sponsor did not provide a plan to conduct propensity score modeling.

The Sponsor has agreed that a learning curve for physician training will be analyzed by assessing the poolability of patient data between IDE sites and non-IDE sites. In addition, the Sponsor has submitted a full proposal for the physician training program, followed by a comparison of adverse events by site types.

Teams of clinicians new to HeartWare will participate in the five-part training program. These sites will most likely be exclusive to the non-IDE sites. However, within the protocol, this is not yet stated. The objective is to describe program compliance and competency by sites and across sites through assessments administered to the teams.

Patient outcomes, as specified in the newly enrolled study, will be described by sites and across sites. Patient-level clinical data will be

collected in the newly enrolled cohort post-approval study and will be used to assess patient outcomes in association with the training program.

Data collected in the study will be reported using summary tables and subject data listings. Descriptive statistics, such as mean standard deviations, will be considered. Though descriptive, statistical comparisons will be made using analysis of variance, Kaplan-Meier, and paired t-test; p-values less than .05 will be noted.

There is no currently updated post-approval plan to evaluate safety signals and long-term effectiveness for the extended follow-up of the premarket cohort.

Within the newly enrolled study there are the following concerns. A 10% margin is proposed to demonstrate non-inferiority between HeartWare and the comparison device. However, no formal justification of the 10% margin was presented within the protocol.

Device malfunction is an issue of concern. In order to clearly evaluate device performance, it is important that the study not only capture device malfunctions but the type of malfunctions as well. Additionally, the Sponsor needs to provide power calculations for the analyses of device malfunctions and adverse events based on the proposed sample size.

HeartWare is intending to use INTERMACS for the purpose of the post-approval study. However, use of this registry has been limited by the inability to assess line data thus far, as previously described by the FDA.

The Panel is asked to consider any additional primary and secondary endpoints that pertain to the post-approval study.

Regarding the training program that will be incorporated into the newly enrolled study, the Sponsor has designed a postmarket training program. However, it is unknown if this program is similar or different from the premarket training program.

In addition, the potential number of sites and interventionalist teams that will most likely participate in this program was not yet stated within the protocol.

I will now hand the presentation over to Anchal for the conclusions.

MS. KAUSHIVA: Thank you. I will now go over FDA's main conclusions from our review.

As you've heard many times this morning, this is the first trial using the INTERMACS registry as a contemporaneous control. Access to patient line data from the registry was not available.

The trial did meet the pre-specified primary endpoint with a 90.7% success rate. However, FDA has the following concerns: the comparability of the treatment and control groups may be questioned from a clinical perspective; higher rates of thrombosis, device exchange, and ischemic stroke were seen with the HeartWare VAS; questions related to data presentation and trial oversight remain.

It is important to note that the success rate did not take into consideration important adverse events.

Although the HeartWare VAS also met the pre-specified 65% performance goal, the performance goal may not reflect current BTT results today.

Based on limitations of accessing patient line data, FDA is interested in a rigorous post-approval study and would like to gain a better understanding of how to maximize use of the INTERMACS registry.

Although the Sponsor provided a post-approval study plan, including a newly enrolled cohort and a training program for clinicians, an extended follow-up plan has not yet been provided.

Thank you.

DR. PAGE: Thank you very much for a very clear presentation.

Does anyone on the Panel have brief clarifying questions for the FDA? Please remember that these are clarifying questions. We will have an opportunity to question the FDA further during Panel deliberations this afternoon.

Dr. Allen.

DR. ZUCKERMAN: Before we start, could Dr. Patel also come up to the red table and just identify herself for the record? She may be answering some of the questions to keep things moving. Sorry.

DR. PAGE: Thank you.

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Dr. Allen.

DR. ALLEN: Thank you.

I appreciate the FDA's very detailed presentation. You know, as a trialist you could've predicted, particularly in retrospective, the challenges of what essentially is used in a non-audited, non-validated, voluntarily reported registry as a control arm.

One simple question. Can you tell me how many patients in the INTERMACS group did not have a HeartMate II? It's a simple question. I'm just curious if we know even that fact about the control group.

DR. SAPIRSTEIN: I don't have the exact number, but if you look at the INTERMACS data -- and certainly the Sponsor or Dr. Naftel can comment on this -- it's vastly overwhelmed. So the large majority, without question, were HeartMate II. But I don't have the exact --

DR. ALLEN: But we don't know those numbers.

The second question. You know, once again, as a clinician I'm interested, very interested in the adverse events. On Slide 49, when you make a comparison of cerebrovascular accidents to published literature, I think that's real important because, as a panelist, I'm going to have to make a decision about safety almost as a standalone trial, a single-arm trial.

But it's interesting, on Slide 49, that the subgroup "other," if you look at HeartMate or HeartWare, "other" comprises very few patients. But when you go across the line, there's a lot of other cerebrovascular events

in the "other" category. When you actually add all of those numbers up, they're pretty comparable between Pagani, Miller, and Starling.

What do we know about "other"?

DR. SAPIRSTEIN: We looked at these references, and again, these references were chosen by the Sponsor. I cannot give you, from the references, discrete incidents of what they were. There were some. There were a total of two, I believe, spinal cord infarcts, one in each of the two trials, the Miller and Pagani. But they were not -- they weren't explicitly outlined to make comparisons for me.

DR. ALLEN: The final question regards, obviously, the comparability of the INTERMACS data with the HeartWare patient demographics, and I'm interested in the FDA's concept of looking at variables between 1 and 7 in the INTERMACS.

As a clinician, it's like looking at the difference between New York Heart Association IIIb and IV. There may be fine lines between an INTERMACS 2 and an INTERMACS 3, that in a self-reported registry, the clinician is more likely -- and I speak from personal experience -- to likely bump their risk up versus, in a very audited controlled trial arm, you're tending to probably be more accurate in your assessment of that. And so I think when you start to -- I'm just curious what the FDA's thoughts are.

When I presented at panels before and you look at endpoints, for example, New York Heart Association class, differences of one class, to

me, are pretty meaningless. So a difference between a 2 and a 3 seems a very gray line.

DR. SAPIRSTEIN: Well, it certainly is a continuum, and it's a seven-point scale instead of a four-point scale for New York Heart Association, so that has to be factored into it. It is, as you say, a voluntary registry, and we can't control the individual's assignment of the profile level. But that is just like when dealing with heart failure trials and New York Heart Association classification, that's the metric that we have.

And the INTERMACS registry has published data that can clearly show discrimination in survival between INTERMACS profile 2 and INTERMACS profile 3. I'm in no way suggesting that the INTERMACS profile 2 patient is a markedly different patient than INTERMACS patient 3, level 3.

But these are the data that we had, and there are data to suggest that there are differences, ramifications, clinical outcome ramifications from the different levels.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I have two questions. The first is I see an inconsistency in the FDA presentation. I wonder if you can clarify it. It may be based on time period and different datasets you're looking at. But on page 44 of 58 in our briefing book, it talks about, in your comment, the six-minute walk test distance is lower with comparable LVAD devices, and

specifically I think the HeartWare had a poorer -- and then, you know, you just presented information where you said they're about comparable. So I wonder if you can first comment on that, and then I'll come back to my second question.

DR. SAPIRSTEIN: I'm sorry, can you say which slide number that was?

DR. SOMBERG: Page 44 of 58 in the briefing book, in the little box that says the FDA. And I think this is important while you're looking at that because there are mechanical physiologic considerations that may be risk. The pump would be affected. But on exercise, it may not be able to increase its output to meet performance, and therefore you would have a limited six-minute walk versus other LVADs, potentially.

So is this something you've picked up early on that went away or, you know, is this a non-observation? You just did say that there was no difference in six-minute walk, is that right, in your presentation this morning?

DR. SAPIRSTEIN: What I said this morning was that when you looked at the data overall from a clinical perspective, bearing in mind the limited paired data that we had, that there wasn't a clinical difference. As far as what's stated here, I'd have to go back and look and see. I'm not quite --

DR. SOMBERG: Okay, maybe you can do that this afternoon, and I don't want to belabor the point right now, but that's an important piece of information, I think, in your -- and maybe the Sponsor also wants to make a

comment on the six-minute walk because their presentation in the briefing book was different than yours.

My other question --

DR. PAGE: Dr. Somberg, let me just interrupt for a second so we can make it clear what we're asking for.

What you're questioning is not whether or not the six-minute walk in the patients for whom the data are available improved. You're addressing the comment in the Executive Summary from FDA that said the six-minute walk distance in patients who had received this device did not appear to be as far as that seen in other reports of VAD-treated patients.

Am I summarizing that correctly?

DR. SOMBERG: That's true. But of course it is possible that that came from the INTERMACS data, from that. I'm not sure what this dataset in 44 of 58 refers to.

DR. PAGE: So maybe after lunch you can clarify with us and perhaps go to the person who wrote that specific paragraph, what was intended.

DR. SOMBERG: Okay. And my second question -- is that okay?

DR. PAGE: Yes. I'm seeing hands raised. Do they have to do with this specific topic? No, okay.

Dr. Somberg, you had a second question?

DR. SOMBERG: Yes.

Maybe for just a moment you can explain to me the reasoning behind the initial discussion of a 180-day endpoint. It's my understanding that 8 to 14 months is the average range, about a year, wait to transplant. So I just wondered why, with the negotiations with the Sponsor and discussion of this type of protocol, the FDA focused in on the primary endpoint at 180 days.

DR. SAPIRSTEIN: Well, I don't know if FDA focused in on it, but there has been a long history with the bridge-to-transplantation indication, essentially agreement among clinicians, sponsors, and FDA that that was an appropriate metric to evaluate how well the device can work as a bridge.

As I alluded to, everyone acknowledges that this is a small population, and we have to balance making the length of the trial, the degree of information that we get from the trial with the practical reality that we need to have the safe and effective devices. And so the six-minute walk -- excuse me -- six months has classically been the time frame for the endpoint.

DR. SOMBERG: Just as a follow-up, I guess. I mean, would you think it would be appropriate to reconsider that since the time to transplant is considerably longer and --

DR. ZUCKERMAN: Okay, Dr. Somberg, we can always reconsider it, but for the purposes of this PMA, I think it's important to understand that these are the data. We need to get a benefit/risk assessment here with these data.

What we're not taking into effect, and perhaps some of the panelists want to know in more detail, is the extensive preclinical and reliability testing that are done with these devices, we are confident that these devices do not break at 181 days in the majority. That's preclinical testing. There are limitations. But it's the grand composite of preclinical testing in a standard time point that allows FDA to make a final assessment.

DR. PAGE: Thank you, Dr. Zuckerman.

I see Dr. Cigarroa and Dr. Amato and Dr. Borer have their hands up.

Dr. Cigarroa, please.

DR. CIGARROA: A question to the FDA. In your presentation, with regards to efficacy and safety, there was a slide that focused on stratification failure by gender.

Do you have any information in that analysis on mode of failure? And any comments on the 95% confidence interval for female at the lower range of 60.5%?

DR. SAPIRSTEIN: Yeah, we don't have those data available from the Sponsor.

DR. PAGE: And perhaps we can involve Dr. Evans in the discussion when we talk about the dataset in its entirety after lunch, as to the meaning of the differences between genders.

Dr. Cigarroa.

DR. CIGARROA: Would the Sponsor be able to provide that data for this afternoon?

MR. GODSHALL: So could you specify what data you would need?

DR. CIGARROA: For female gender, the mode of failure.

MR. GODSHALL: The mode of failure, meaning how many were, for example, alive on the device and not listed for transplant or expired, or we can provide an accounting for --

DR. CIGARROA: Thrombosis, device exchange, et cetera.

MR. GODSHALL: Right. So we would be able to describe it for females. I assume specifically not --

DR. CIGARROA: Correct.

MR. GODSHALL: -- for males. We can provide, by gender, primary endpoint analysis to the performance goal.

DR. PAGE: Great, thank you. We'll look forward to that.

Dr. Amato.

DR. AMATO: I'm going to be like a bear. Can I go to the fourth slide of the first presenter, please? I'm going to insist. I think the pump is a wonderful pump, but I'm going to insist that in the training of individuals, I'm looking at that as though I were looking at the pump going into the aorta and looking at it as though it were an internal mammary artery. I can't possibly conceive that no danger to that tube or cannula has existed or can exist, and I

insist that training of the individuals that are placing the pump in, either more specifically, specified more clearly, or at least change the slide so that the tube is not directly in the mid-sternum area.

Do you have any comments on that? For the FDA.

DR. PAGE: We're querying the FDA right now.

Dr. Sapirstein, do you have a comment as to the nature of the figure and, surgically, whether this is a proper representation of placement?

And, again, right now we're asking questions of the FDA specifically about their presentation. We will discuss the surgical process and any recommendations we give after the lunch break.

Do you have any comments now, Dr. Sapirstein?

DR. SAPIRSTEIN: No. I mean, we do take the Sponsor's assessment that the outflow cannula does pass, as it says, in the pericardial well, away from the midline for reentry. I can't comment if that depiction is wholly consistent with the way --

DR. PAGE: I see Dr. Allen raising his hand, and I want to hear his perspective on this, but I'm going to save the conversation about the surgical guidance, okay, the surgical guidance until after the break. And we'll get to you in a moment.

We have Dr. Borer, Dr. Lange, and then Dr. Allen.

DR. BORER: I thought the FDA presentation was pretty clear, but I do have a question, and it's parallel to Dr. Somberg's question. It has to

do with the non-inferiority margin.

In the presentation you stated that the proposed 10% non-inferiority margin wasn't accompanied by any justification, and that's undoubtedly true. I'm not sure what justification you would provide. The 15% that was used in the initial agreement also, I think, had no justification, at least none that I saw. Clearly, in these protocols, the formal FDA-developed -- I mean, the cardio and renal division that developed the putative placebo idea for non-inferiority trials, that's not possible to apply here.

So I would be interested to know the basis of it. I'm not challenging it any way. I just want to know the basis of the 15%, the selection of 15% as a non-inferiority margin and the potential inappropriateness of the 10%, an even more stringent non-inferiority margin.

DR. ZUCKERMAN: Okay, Dr. Borer, let me just take a first pass at it. You're very correct. For design of non-inferiority trials, one needs to be very cognizant of the delta used for so-called non-inferiority, and we do use the same principles that our colleagues do use in the Center For Drugs, with an additional caveat and that caveat is -- and Dr. Allen can enlighten us this afternoon -- is that, realistically, we're dealing with a reasonably fixed sample size for bridge-to-transplant patients, maybe about 500 per year. So we would all like the smallest delta possible.

But by the same token, we do simulations prospectively with

the sponsor to come up with sample size estimates and trial performance criteria that seem "reasonable." And at the end of the day, there are some problems with that approach, and certainly if we had a sample size that we could generate of 1,000 patients easily, we would be moving in that direction.

So, therefore, it's really incumbent on all of us to look at the actual observed data, the trial execution, et cetera, because even though you can generate, as in this trial, a p-value with lots of zeros and then a one, as you're pointing out, there's a lot that goes into the actual calculation of a p-value, and we don't want to lose that clinical perspective here today. That's one of the reasons why we're here at this Advisory Panel. It's just not about a p-value.

DR. BORER: I mean, that's fine and I understand that, and that's perfectly reasonable. But why, then, would there be some question if the Sponsor wanted to develop a postmarketing study with a more stringent delta? Wouldn't that be reasonable if they believed that they could develop a sample size sufficient to support that kind of --

DR. SANSING: I'm going to clarify your choice of words. It technically is not a problem. It's simply an issue. When we're determining sample size, we look at a delta. The delta must have a clinical justification because, of course, you understand that a delta powers the sample size. If there is no clinical justification within the protocol, an element of the study design is missing.

So we do appreciate the 10% margin, which was also seen in the HeartMate II bridge-to-transplant post-approval study. But, however, as we required within the protocol, clinical justification must be stated. Yes, 10% is less than 15%, so you do have a more stringent thing. However, justification still is required in writing. So there's no problem at that point.

DR. BORER: Thank you.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: Just a couple questions regarding several slides.

On Slide 32, it mentions that 156 of the events were not adjudicated. First of all, if the FDA has any insight into why some events were adjudicated and not, and particularly, if you go to Slide 44, there were deaths that were not adjudicated. That would seem like a serious event that would require that. So some insight on that.

Secondly, with regard to your concerns about the discrepancy between the CEC committee members, did you all do an analysis that if you took the more serious adjudications, if there was a disagreement and it was rated higher with regard to severity and to device relatedness, did that materially change the analysis at all?

Okay. So in other words, it's a very crude sensitivity analysis. In other words, take the highest degree of seriousness and assume it's device related, and does that materially alter things?

On Slide 33, the comment is made that the FDA and the Sponsor disagree on discrete values for some rates. After lunch, if you could provide which rates those are, so we can assess whether they are materially important or not, that would be helpful.

DR. SAPIRSTEIN: As far as the adjudication, I don't believe -- no, we didn't do the type of sensitivity analysis that you just alluded to.

DR. LANGE: Okay.

DR. SAPIRSTEIN: Perhaps I'm not quite understanding what exactly -- the line data for the adjudications don't necessarily go into -- that we have from the Sponsor, don't go into detail of what specific event was characterized. It's a listing of yes/no for agreement, yes/no for device relatedness, and that sort of level of detail.

DR. PAGE: And, Dr. Lange, we need to discuss how the CEC behaved and operated in this trial, so I think you bring up a good point there. The specific question that you wanted to pin down -- and it seems like we ought to be able to have that after lunch -- would be as on Slide 33.

Can you just make up a single slide of the specific rates that there remains some disagreement between the Sponsor and the FDA?

And I imagine, in some of these cases, they can run both ways. But let the Panel decide whether, first of all, these are important issues and, secondly, whether you take it on counting a stroke versus a TIA, for example, how that would affect the endpoint and the frequency of adverse events.

DR. SAPIRSTEIN: I can clarify very quickly for some of them. Or I can do it after lunch.

DR. PAGE: Let's do it after lunch.

DR. SAPIRSTEIN: All right.

DR. PAGE: Thank you.

Dr. Allen.

DR. ALLEN: I'd like to bring up the topic of sintering, and I want to make sure that when I'm voting later, I really understand the device that I'm voting on, because my understanding from the FDA and Dr. Zuckerman, or Dr. Sapirstein can correct me, that sintering was added in the last part of the trial at some point in time. So you have outflow cannula that originally was not sintered, and then it has become sintered.

And while intuitively I agree with that and that sounds like a great idea, I want to be ensured, from the FDA standpoint, that they're comfortable with that. You know, the analogy would be adding silver to the sewing ring of a heart valve. Intuitively that sounds like a very good idea, but it had disastrous consequences.

How does the FDA feel about that?

DR. SAPIRSTEIN: As I said, we have not formally been provided with the sintering data in any comparative manner. The only information we have is what was in your Executive Summary from the Sponsor, and our review of that shows that the numbers of patients involved was very small. I

think it was --

DR. ALLEN: I think it was 25.

DR. SAPIRSTEIN: In terms of in the continued access protocol, the number was -- I think there may have been one patient in the IDE trial. In the continued access protocol population, the number four, I think, or something along those lines, and then there were other patients.

DR. ALLEN: I guess you understand my concern about this, because if we're voting what was in the 140 for the IDE, but yet the device that's going to be marketed isn't what was in the IDE --

DR. ZUCKERMAN: Okay. So Dr. Allen --

DR. ALLEN: That's what I'm asking.

DR. ZUCKERMAN: -- this is a great question that you're posing. I would suggest that the Sponsor prepare a reply to your question. We will need to talk with the Sponsor because some of their reply may not have been provided to FDA, as Dr. Sapirstein has noted, and we will need to note what we do know in the PMA for the record. But thank you for bringing up this point, and I think the Sponsor will be doing some homework during lunch also.

DR. PAGE: And I might ask the Sponsor also to respond to what I'm sensing is a bit of frustration in terms of FDA requesting information and not receiving it. So not now, but at lunch perhaps, if data might have been available to us today regarding sintering, why those data -- and frankly, the

data need to come through the FDA, so both FDA and the Sponsor have a chance to analyze and digest the data -- why we don't have those data available today.

Were there other questions?

Dr. Slotwiner.

DR. SLOTWINER: Yeah, I just wanted to ask a question about the two groups and the INTERMACS profile levels and that discrepancy in how many patients were in the sickest levels in the study group. And I'm curious because I guess, going forward, the INTERMACS is likely to be the reference point.

Does the FDA believe that it could be some clinical bias that investigators used in enrolling the study group, or is there a way to try to even the groups out in future ways?

DR. SAPIRSTEIN: Well, I think there probably will be a way to even it out. That's partly why we're asking the Panel to consider this. We are just, for right now, making the observation that we saw and are wondering if it may have had an impact on the data results that we saw.

The first part, you were asking about the number of --

DR. SLOTWINER: Well, I'm just trying to understand what may have caused the discrepancy and whether it may have been selection bias or identification bias by the investigators, into which category they go.

DR. SAPIRSTEIN: I don't know if it's investigator bias,

necessarily, because it was pre-specified to make sure it was an independent individual to assign the INTERMACS profiles. So we have confidence in the numbers that the Sponsor has provided for the INTERMACS profile levels.

As was mentioned previously, though, the question of, I suppose, what's the confidence of the profile levels of the voluntary registry is something for the Panel to consider.

DR. ZUCKERMAN: So, Dr. Slotwiner, in a nutshell, FDA is bringing up this important subject, but we're really looking for expert Panel advice. For example, I'd like you, after lunch, to ask your colleague Dr. Allen and others, what other covariates should potentially be in the model to make it more valid. Dr. Evans, to your left, may want to talk about the actual methodology that we use because these are areas of concern for the Agency.

DR. PAGE: Great. We are at the lunch hour. I have two brief questions from Dr. Lange and Dr. Cigarroa.

Dr. Lange.

DR. LANGE: Briefly. If the FDA, after lunch, will tell us, in light of the destination trial, what's going on, how will that change your postmarketing study. In other words, you're going to have durability from this device as a destination. So let's consider that when you're talking about your postmarketing. I'd like to find out how --

DR. ZUCKERMAN: Yeah, I wouldn't assume that would change it at all.

DR. PAGE: And Dr. Cigarroa. Dr. Cigarroa is hungry.

(Laughter.)

DR. PAGE: It's time to break for lunch. I want to remind the Panel members that none of our discussions over lunch amongst yourselves or with anybody else will be regarding the topic at hand today. We'll reconvene in an hour. Less than an hour from now. Exactly at 1:00. Please take your personal belongings with you. If you do leave them in the room, the room will be secured, and as such you can't get back in until 1:00.

Dr. Zuckerman.

DR. ZUCKERMAN: Okay, before we break, and I know everyone is hungry, does the FDA team believe they have all of the questions that were posed by the Panel?

Dr. Page, do you want to just summarize?

DR. PAGE: Yes, to summarize, thank you.

Six-minute walk data and the statement in the Executive Summary; the issue of gender and the failure mode, to the Sponsor; the CEC, on Slide 33, the discrete disagreements that FDA has; and finally an analysis from the Sponsor regarding the sintering and how that affected -- how many of the devices we're looking at had the sintering.

Does that summarize it adequately? Okay, thank you.

DR. ZUCKERMAN: I think so, unless any other Panel comments. It looks good.

DR. PAGE: We're adjourned.

(Whereupon, a lunch recess was taken.)

AFTERNOON SESSION

(1:04 p.m.)

DR. PAGE: It's now four minutes after 1:00, and I'd like to resume the Panel meeting. May I have the attention of all the panelists?

We'll proceed now 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.

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 that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this

meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you very much.

We have seven speakers and in an order that I think has been provided to you. We're providing five minutes to each speaker. If you have less than five minutes of text to say, that's fine. If you have more, please stop at five minutes.

(Laughter.)

DR. PAGE: We'll start with Nancy Ann Pecar -- and I'm sorry if I said that wrong -- as representing a HeartWare device recipient.

Welcome, ma'am.

MS. PECAR: My name is Nancy Pecar, and my husband is Joseph. I am a thankful recipient of the LVAD technology produced by HeartWare. My surgery was performed on February 2nd, 2011, and at the time I was 71 years old.

Prior to the HeartWare LVAD implantation, I had been a heart patient, HF/CHF, for 21 years. My original diagnosis was a viral cardiomyopathy in 1991. My cardiologist's care and concern for my treatment was taken seriously from day one.

It was predicted that a lot of medications would have to be

given and altered to treat the current symptoms. In addition, I received two ablations and, I believe, seven cardioversions. A heart catheter tube was also part of the ongoing treatments. Eventually, a pacemaker and then an AICD were implanted.

It became quite clear in 2011 that the medications were not meeting my needs at that time. My husband, Joe, and I feel very fortunate that our cardiologist knew of the LVAD technology and the team of Dr. Boyce at the Washington Hospital Center. It was suggested that we proceed immediately with the necessary preliminary testing to see if I would be a candidate for this equipment. The answer being yes, we proceeded with the implant.

I will also note at this time that, in addition to everything else that was going on, I was slammed pretty hard with a case of pitting edema, and that was sufficiently taken care of at that time.

I will admit that this event was not an easy one, but we had faith and trust with those that were responsible for this event, and that trust was well placed. We tried to be educated on this new HeartWare technology and believe we were well taken care of.

As an aside, I would like to tell you that for about two years before the LVAD surgery, I had been treated as having a platelet deficiency, ITP, and 12 years for Type II diabetes with oral medication treatments. Since the HeartWare LVAD implant, all meds for the diabetes and ITP have been

discontinued.

I am a good patient and follow all directions. Our doctor's staff has been very faithful to us. I have had for quite a while a philosophy that if you have a medical problem and you look for somebody to help you take care of it and you go to them and you pay them, you better follow what they say.

(Laughter.)

MS. PECAR: My husband, Joseph, and all of our children and 11 grandchildren are grateful for my recovery and ability to live a pretty normal life.

The one thing that bothers my husband, Joe, a bit is the fact that while I was in the middle of all of this, I would order Christmas gifts, et cetera, and recite by heart over the phone my credit card number, including the expiration data and security code. That is a habit I should really consider giving up now that I can physically walk the malls again.

We traveled to Michigan for a Pecar family reunion last July, only four and a half months after surgery. We received from the medical staff excellent information and help and also about going to deal with the TSA. That was no small task.

We live a good life. All of our children and grandchildren live in the area, so we are able to attend sports events, birthday parties, and routine gatherings; what fun.

I thank you for giving me the opportunity to share my life

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before HeartWare and after. We are very thankful for all that has been done for us, and especially our church family of approximately 12,000, who had us on the prayer list through this whole event. We are truly grateful that the HeartWare technology was available to us.

Please strongly consider making this equipment available to those who will be given a new chance for life at its fullest.

Thank you.

DR. PAGE: Thank you very much, ma'am. We really appreciate your sharing your story with us.

I'll assume that there aren't questions or comments from the Panel, but please interrupt me if that's not the case. Otherwise we'll move on to Carlo Brunori, also a HeartWare device recipient. I hope I said that correctly, Mr. Brunori.

Welcome.

MR. BRUNORI: Thank you for this opportunity. Again, my name is Carlo Brunori. I'm a 73-year-old retired wildlife biologist. I am a recipient of the HeartWare LVAD back in November of '10, and it has been an obvious lifeline for me. I was very active as a wildlife biologist. I learned the outdoor enthusiasm and conservation since I was 12 in Pennsylvania and hunted all of these years. So it became my vocation and avocation.

Again, I was always very active. I did environmental review for wildlife and covered the whole state. I was very active. I'm a vegetable

gardener. I have a small 20-tree orchard, so I am very active in that regard. I am back doing it in moderation.

Again, my life depends on being active. I'm not a person who can just lay around. So, therefore, without the LVAD, the results would not be too good.

When I had the heart attack in October of '10, I went to Washington Hospital Center, and they tried medication and the whole regimen, but there was too much damage to the left ventricle, obviously, and it wasn't pumping enough blood to the aorta, and I was building up with fluids. I had four lung taps for fluids.

So the result was, Dr. Boyce said, you have two choices. Here's the two booklets on LVADs. Which one do you want? That was a shocker, but I knew I had to do something because the alternative wasn't too good.

Again, I am back active in the garden. I am still hunting, and a highlight of the last year, on December 2nd I killed my seven-point buck. So I am active in environmental groups, conservation groups, Turkey Federation, Ducks Unlimited, and do my own wildlife work. I plant wildlife food up on my friend's farm. So it's a part of living again and living it as good as you can.

My dad used to have a saying: You can rust away faster than you can wear away. And that's very true. I never had a chance to ask him, was that his original thought or did he pick that up along the way? He died back in '99, so it was a little late. But that was a very good expression, and I

took that to heart.

Again, with the LVAD, I think we need more equipment of this type. We need more research and experimental needs. As far as the LVAD, it's an excellent device. I've had no problem with it. I live a near-normal life. And with the Baby Boomers coming right behind me, I think we know we're going to have to prepare more for this and heart implants where needed and feasible.

So, again, after all of these years, I am still doing what I like to do and thankfully for the help of the LVAD.

In closing, I'd just like to say that I'm very active, like I said. I'm still a member of my professional wildlife society, as a retired member of the Maryland and Delaware chapter. I am a member of the Maryland Anne Arundel County Forestry Board, so I try and keep active and participate and give back to my community in many ways.

Therefore, all I can say is I am here because of the LVAD, I am active because of the LVAD, and I can only say that hopefully we're going to move onward and upward.

Thank you.

DR. PAGE: Thank you, Mr. Brunori, for sharing your life experience with us. We appreciate that.

MR. BRUNORI: Okay, thank you.

DR. PAGE: The next speaker is DaKeia Williamson, a HeartWare

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device recipient.

Welcome, Ms. Williamson.

MS. WILLIAMSON: Thank you. Good afternoon. My name is DaKeia Williamson. I have no financial relationship with HeartWare. I am pleased today to take this day off from work to share my personal experience with my HeartWare LVAD.

Back in 1999, one week after childbirth, I had coronary artery dissection, and I was doing well on meds until about the beginning of 2010, when my heart muscles had become very weak. I was in and out of the hospital.

I was implanted on 5/19/2010. Before I was given the choice to become implanted, I was gravely ill. My symptoms of heart failure were getting worse. I started losing all of my energy, no appetite, and my weight had dropped from 130 pounds to 114 pounds. I was pretty much a living couch potato on my mother's sofa. At one point I had no more will to live. It was a nightmare not being able to do anything with my two children.

The heart failure team of Dr. Boyce and others at the Washington Hospital Center spoke to my family about the LVAD and suggested that I receive the HeartWare due to my petite frame. My family was nervous, but I just wanted anything that will make me feel better.

After the surgery I had a few complications from clotting, but once that was resolved about a month after receiving my LVAD, I began to

feel like myself again.

I remember taking my younger daughter to the movies for the very first time in months and seeing my oldest daughter off to college, two of the things that I thought would not happen because of my end-stage heart failure. Now, I work full time, I'm pursuing my B.S. in information systems, and raising my two daughters.

My weight is now back up to 140 pounds, and I feel great. I love how I can conceal my LVAD in my cute purses and go throughout my day doing most of my activities, and no one will ever know that I have it unless I make them aware. I am so grateful for HeartWare because it gave me my life back, and I hope that others will be afforded this opportunity.

Thank you for allowing me this time to speak.

DR. PAGE: Ms. Williamson, thank you so much for sharing your story with us.

MS. WILLIAMSON: Thank you.

DR. PAGE: And as I calculate it, you're almost at two years for having the HeartWare?

MS. WILLIAMSON: Yes, that's correct.

DR. PAGE: Thank you.

The next speaker is Sergeant Major John Thomas, who is also a device recipient.

Welcome, sir.

SGM THOMAS: Thank you for this opportunity, Mr. Chairman and members of the Panel. I am six months post-heart transplant. My name is Johnny Thomas, and I'm from Miami, Florida.

HeartWare provided for my travel here, and I am not a stockholder in the company, nor have I been compensated for my time. I'm here today because I want to share my personal experience with the HeartWare ventricular assist device.

I assume that many of you have been challenged throughout your life's journey as well, and when it comes to day to day, tenacious people believe they can make it alone. And I've altered that mindset now, that we cannot live in isolation. My story addresses the issues accentuating the need for other people in our lives.

As a proud retired Army sergeant major, after 24 years of service, I've had several tours in Southeast Asia, Vietnam, and as a fitness poster soldier for the United States Army recruiting program, there is nothing that would not give greater pleasure than to just talk about myself.

(Laughter.)

SGM THOMAS: Since the age of 18 my life has been a huge challenge. In battle I received a gunshot wound to the chest, knife injuries, a loss of kidney, myocardial revascularization, five open heart surgeries. Perseverance is the word. Overcoming the worst things in life, even with many of life's setbacks, many struggles were overcome with mental

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toughness.

Once diagnosed with heart disease, I felt like life had pushed me in a corner and I didn't know where to go. I could surrender or fight. And life experiences taught never to give up. And after 20 years living with a diseased heart, the physical challenges were too great. Weighing over 235 pounds, I received my heart, and that would not have happened without HeartWare's ventricular assist device.

Following the implant, life improved gradually, and I could walk and move about again without difficulty. Over 14 months passed without any issues. My body responded normally to the appendage, and I was comfortable with the device.

Then the new heart call came in. Initially I turned it down. Surprised by the call, I experienced momentary anxiety. I knew what to expect with HeartWare, and it's accepted my new norm. But my better judgment told me that the HeartWare ventricular assist device was a bridge to a heart and not the heart.

God located that special heart for me, and my responsibility was to wait, and that's where HeartWare's device served its major role in sustaining life, life with quality and dignity. I've never been lacking in motivation as a heart patient, nor have I ever been obese, lethargic, or too weak to care for my health. What I was lacking was time. The LVAD provided me with time until I received a heart.

And paraphrasing the words of Vince Lombardi, there's only one way to succeed, and that is to give it everything, and I have. I believe that HeartWare adheres to the same standard.

Committee members, as you deliberate, I ask you to embrace the words of Coach Lombardi. Because I live, I give you a visual reference of tangible success.

Thank you.

DR. PAGE: Sergeant Major Thomas, thank you so much for sharing your experience with us.

The next speaker is Martin Struber from the University Heart Center, Leipzig, Germany.

DR. STRUBER: All right. My name is Martin Struber. I'm a cardiothoracic surgeon from the Leipzig Heart Center, which is the largest heart center in Europe. I used to work in Hannover Medical School before, and all of the slides and data you will see now are from Hannover.

As a disclosure, my travel expenses have been covered by HeartWare. I'm a consultant to HeartWare and also the primary investigator on the pilot trial. I'm not a stockholder, and my time is not being compensated.

I'm happy that you allow me to speak here and give you a bit of a European perspective to it, and I'm here because I feel strongly that this technology should be made available to patients in the United States.

So my first -- move this forward. It's not working forward. Yes, it's not working.

DR. PAGE: As we're getting that taken care of for you -- I'm sorry for the delay and this will not cut into your five minutes. I will hold you to five minutes. I let the last speaker go on a little bit longer, but I wasn't about to stop him.

(Laughter.)

DR. PAGE: For a number of reasons. But I will hold our physician presenters to their five minutes.

Thanks.

DR. STRUBER: That was our initial experience with the international study group, and nobody knew about the HeartWare device. We were doing the pilot trial with international centers, and that was the initial outcome with a two-year follow-up and 80% survival, and we were quite impressed by their survival rate and also by the lack of adverse events in this first cohort of patients that ever had been treated with the HeartWare device.

We learned on the way that we had in our Hannover experience, in the 6 of 90 initial patients, a pump thrombosis. Two of them were early, and we think they were attributable to remaining thrombus that were not removed at the time of implantation. So we surgeons learned that at the time of implantation, we have to look for remaining thrombus in the

heart chambers. Four of these patients were at late pump thrombosis.

And what we learn from this photography, and you see human hearts at the time of transplant, on the left side is the HVAD device and there is a thrombus formation around the inflow cannula. And on the right side you see a HeartMate II device where the sintered surface is covered with fibrin to prevent thrombus formation. And therefore we advised the company to change the inflow to a sintered inflow cannula. And what we learned is that in about 52 patients that are personally implanted with an HVAD device since May 2011, we had no single case of pump thrombosis anymore.

In Germany we have the unique situation that we have a long waiting list for heart transplantation and not many heart transplants. But we have unrestricted access to a lot of ventricular assist devices, and we have no restrictions in reimbursement. Therefore, we put in about nine pumps per million population, and we expect 800 in the last year; 325 of those were HeartWares.

And the question is, why does HeartWare gain such a robust market share? The reason is, in my opinion, the versatility of the device. This is the approach we use now as a minimally invasive thoracotomy to implant the device.

We also were able to start using the device as a biventricular support device. You see the first successful case here ever done with biventricular HeartWare, and out of this experience our colleagues in Berlin

published, last year, their first 17 cases of biventricular support using the HVAD device. And we presented, last week, our first 15 patients with biventricular HVAD device on the international conference in Prague. So it seems that this experience of more than 30 patients now will become a future option for biventricular failure.

We took this also further to use this technology as a total artificial heart. For example, in this patient whose heart was destroyed by myocardial infarction, so we used two HVAD pumps as a total artificial heart, and you see this gentleman walking around waiting for a heart transplant.

So I'll leave you with this last picture here of our smallest patient, seven-year-old boy, three days after implantation of an HVAD device, having ice cream with a happy mother and also a happy doctor.

And I'd like to thank you for your attention.

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

Our next speaker is --

DR. SOMBERG: I have a question.

DR. PAGE: Dr. Somberg would like to ask a question.

Dr. Somberg.

DR. SOMBERG: Do you have any data for the European experience on the adverse effects, specifically stroke in the HeartWare versus the alternative? If you say you have a number of other devices, how does it compare? Do you have any hard numbers you can share with us?

DR. STRUBER: We did a commercial registry, and we looked at a few patients comparing to the HeartMate II, and we could not find any difference in the stroke rate. So we're looking at the real-world scenario at about a 3% stroke rate, 2 ischemic strokes, and 3% hemorrhagic stroke per patient year. They were all the numbers in Europe.

DR. PAGE: Thank you.

Our next speaker is Dr. Shashank Desai from Inova Fairfax Hospital.

DR. DESAI: I would like to thank the Committee for allowing me to speak. So my name is Shashank Desai. I'm actually the medical director of the heart failure transplant program. In this country that also includes the LVAD programs. I'm a cardiologist and not a cardiac surgeon. I have been an investigator for the HeartWare study in this country. I have also been on the speakers bureau for HeartWare, but I've not been paid to come testify or to travel.

I wanted to give you a little bit of experience of sort of what happens at a U.S. center and how and why we think that approval of this device would be of benefit.

So we're an 833-bed hospital in the suburbs of Washington, D.C. There are only two hospitals in the suburban metropolitan area of Washington, D.C. that actually implant LVADs and transplants, and in most of those two centers we serve a seven million population, understanding that

the heart failure population incidence is about 2.3% in the United States all together. Both hospitals in this area, especially at Fairfax, did transplants back from '86 and LVADs since 1990.

But this is sort of what the real world looks like in the United States at any one of our centers, and on the bottom I've actually put our transplant volume in blue, and up top you can see that there's a variety of different VAD devices that have been implanted at Fairfax Hospital. And over the course of the last three years, in purple is HeartMate II and in red is our HeartWare experience under the study. And what I can tell you is that this is sort of the denominator with which I sort of present to you our experience and how we make decisions.

So we looked back at our complication rate, and I realize that that's probably one of the biggest things that we're looking at here, and just to sort of say to you that thrombosis hemolysis is a complex issue in our world. It is difficult to identify who is thrombosed until you actually open the pump up and look inside. There's a variety of different things that we look at, including the pump powers, including the patient outcome, including the echocardiogram, and we use a variety of different anticoagulation strategies. And as Dr. Struber said, in our international meeting, every hospital has its own cocktail of how to treat it.

So in our case we've actually had six patients where we've used one anticoagulant with a TB3A inhibitor. We've had two patients that we've

treated with heparin, and we've had three pump exchanges. And this is our 2011 experience. I gathered this for your perusal. And, again, we are not seeing that HeartWare is significantly different from our currently FDA-approved device as well.

Our driveline infections have been about equivalent, understanding that our denominator of HeartMate II is significantly more than HeartWare. We've been able to treat most of these patients, and in this country, patients do get transplanted for a driveline infection.

This is our experience, and I think that what I would say to you is that over the 20 patients that we've implanted over the course of the last three years, 17 of them have been for left ventricular assist devices. And we've used all kinds of reasoning, as other investigators have, of patient size, cavity size, appropriateness of one device versus the other, and I think we could get into an hour-long discussion on how we're making decisions. I don't think that's completely known yet.

However, we have used three different devices, and I think this is where the game changer is, as Dr. Struber said, the fact that we can implant an intra-ventricular device into the right side. We implanted one patient that had L-transposition where the RV was actually the systemic ventricle. We have also implanted two biventricular assist devices, and that is actually what I'd like to highlight here.

I think the difference in LVAD technology is there. I think that

there will be significant differences over the course of time that we will learn. But I think, right now, the biggest game changer is exactly this.

So these two patients, they're both in their forties, and they both have the same disease, sarcoid cardiomyopathy. The guy on the left presented in cardiogenic shock with liver failure and kidney failure. He got put on ECMO, and he received a HeartWare biventricular, one in the right side and one in the left side. He made a remarkable recovery. Discharged 40 days later and has not been readmitted since December and is now walking a mile and a half. He's returned back to work. He's a personal trainer and is back to personal training. He's waiting for a heart transplant.

We had the same situation earlier this year with another individual, the same age, same disease, and he had much less complications and was able to get an FDA-approved intra-corporeal BiVAD, and he spent almost 330 out of the next 336 days in the hospital.

So I would culminate really with the fact that there are going to be different characteristics between centrifugal pumps, between pumps that are actually implemented inside the ventricle. As Dr. Struber said, I think that there are possibilities of a variety of different implant techniques, and as the implant techniques get better, the complications get better. It means that cardiologists are able to refer these patients. Patients that sort of feedback to us talk about smaller and lighter components, talk about the ability to plug into a wall and externals.

So I will leave it there.

DR. PAGE: Thank you very much.

DR. DESAI: Thank you.

DR. PAGE: Our last scheduled speaker is Edwin McGee, Jr.

Dr. McGee is Surgical Director of Heart Transplantation and Mechanical Assistance at Bluhm Cardiovascular Institute.

Welcome.

DR. MCGEE: Thank you. As has been stated, I'm Ed McGee. I'm a cardiac surgeon at Northwestern Memorial Hospital in Chicago, where I'm the surgical director of our VAD and transplant program. I'm a consultant for HeartWare in terms of surgical training, but I think it's important to understand that I received no compensation for the travel from Chicago to this meeting.

And I'm attending today without compensation, as I think this FDA panel meeting regarding approval of the HeartWare HVAD is a critical fork in the road in the treatment of patients with advanced heart failure, which I think is arguably one of the most pressing public health issues our society faces.

My practice centers on caring for patients with mortal heart failure. Since 2008 I've implanted 131 continuous-flow VADs either as a bridge-to-transplant or as long-term destination therapy.

While vast improvements have been made in the field of

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mechanical assistance in recent years, we are still not where we need to be in terms of morbidity profiles and outcomes. It's important to realize that none of the currently available devices, be it approved or under trial, are problem-free.

Since 2009 I've implanted 42 HeartWare HVADs as part of the ADVANCE and ENDURANCE trials. In my opinion, the HVAD is the most reliable and least morbid ventricular assist device currently available. It is well engineered and easy to implant. It is easily prepped and assembled with standardized mechanical connections. The fact that the implant is not nuanced and is easily prepped, and the pump is easily prepped, it standardizes the operation and minimizes user variability. The pump rests on the heart in the pericardial space and does not require creation of an abdominal wall pocket.

The HVAD provides effective support and is incredibly safe to implant, with an operative mortality of 1.6% in the ADVANCE trial, which was less than that reported for isolated aortic valve replacement in a recent report from the Society of Thoracic Surgeons' database, by Brown et al., in the *Journal of Thoracic and Cardiovascular Surgery* in 2009, volume 137, page 82 through 90.

The size of the HVAD allows it to be easily placed in small patients and women. Additionally, the HVAD has demonstrated, as you have seen, that it can provide effective support for the right ventricle, with

mortality rates superior to the Thoratec PVAD and SynCardia Total Heart, which are both cumbersome and loud and require multiple cannulae and/or pneumatic lines that exit the body.

I have personally implanted and managed successfully two such HVAD BiVAD patients and along with many in the field consider the HVAD to be the state of the art of BiVAD support.

The driveline of the HVAD is extremely durable and resistant to damage. We are finding that driveline failure is a frequent cause of pump replacement with the HeartMate II. I have not experienced that issue with the HVAD. The fact that the HVAD driveline is flexible also allows for freedom of placement of the exit site either out of the abdominal wall or through an intercostal space.

The driveline of the HeartMate II, due to the pump configuration, must at some point traverse initially the right upper quadrant of the abdominal wall. I have successfully replaced HeartMate II pumps that have developed complex right upper quadrant infections with HVADs, as the HVAD driveline facilitated tunneling away from the septic side of the abdominal wall.

Additionally, the flexible driveline of the HVAD and the fact that no pocket is required makes it feasible to treat patients who have had multiple abdominal surgeries, those with ventral hernias, and those that have external ostomies. This will be a more commonly encountered problem as

our VAD population ages and has more comorbidities when we get more into DT.

The HVAD is not perfect. Like all continuous-flow LVADs, it requires therapeutic Coumadin and an antiplatelet agent for anticoagulation. The HVAD provides an accurate flow estimation and, more importantly, it provides useful pump parameters that assist in patient management when a problem arises. This is not always the case with the HeartMate II.

We are familiar with driving cars with modern diagnostic computers. When we have a problem with the antilock brakes or some other component, the car's computer alerts us of the issue before the brakes fail. The added safety provided by the onboard computer, I would argue, makes driving safer. In that regard, managing a patient with an HVAD is like driving a modern car. When a problem occurs, you can accurately diagnosis the issue and manage it.

While work remains to be done with system improvements, the HeartWare HVAD is a quantum leap forward in the field of mechanical assistance.

Thank you for your time and consideration.

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

Does anyone else wish to address the Panel at this time? If so, please come forward to the podium and state your name -- oh, I'm sorry. Go ahead, Mr. Dubbs.

MR. DUBBS: Can you tell us the statistics of the length of time your patients have had the device, from the minimum to the average to the maximum?

DR. McGEE: That is a very complex question, and it depends on a lot of factors, including body size, blood type. Usually they range around six months to a year to get transplanted. I think the 180-day mark has certainly been a historic time point used by all VAD approval trials for bridge-to-transplant, but that probably needs to be revisited as we move to more long-term support that we're seeing with more people being listed and actually changing the UNOS allocation policy that occurred in 2006. So it made getting hearts harder.

MR. DUBBS: You mentioned that some of your patients are not going to have transplants but will retain the device for a long term?

DR. McGEE: Those are the patients in the DT trial, yes.

MR. DUBBS: And what is long term? I mean, is that years?

DR. McGEE: For the --

MR. DUBBS: You have patients that have had the device for years?

DR. McGEE: Yes. Yeah, and the DT endpoint is two years.

DR. PAGE: Just to clarify, DT is destination therapy, although we're not addressing that here. These are patients for whom the device is placed without any anticipation that they would be eligible for a transplant.

DR. McGEE: My longest bridge patient in the ADVANCE trial was approaching two years.

MR. DUBBS: And have there been any complications over that longer time period, with the device functioning properly?

DR. McGEE: No, I've not run into any late -- I mean, of course, we've had the usual complications that you see with all support. But actually the fellow that had the pump for two years, we managed without any coagulation for six months because he had an AVM and GI bleed. But I have not had any late complications other than, you know, in this patient supported over a year.

DR. PAGE: Thank you again.

Does anyone else wish to address the Panel at this time? If so, please come forward and state your name, affiliation, and indicate your financial interest.

(No response.)

DR. PAGE: I see no one coming to the podium, and as such, I now pronounce the Open Public Hearing to be officially closed.

Before we proceed, I want to thank each of the speakers. I especially want to thank the four patients who shared their personal stories. Quite frankly, you inspire us and you confirm the importance of the work we're doing here today. So, again, thank you for joining us and sharing with us your personal history.

Now, we'll proceed with today's agenda. We're going to now begin Panel deliberations. Although this 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 they speak. This helps the transcriptionist identify the speakers. During the next hour or so, we'll open up the floor to questions for both the Sponsor and the FDA.

But first what I'd like to do is address the homework that we left for the Sponsor and the FDA to deal with over lunch. So I'll first ask the FDA -- excuse me -- the Sponsor to come forward. And I know you have a series of answers put together, and I'm fine with you proceeding in the order that you wish, just as long as we get to each of the questions that we gave you before the lunch break.

MR. GODSHALL: Thank you very much.

DR. PAGE: State your name, please.

MR. GODSHALL: Doug Godshall, with HeartWare.

DR. PAGE: Thank you.

MR. GODSHALL: Apologies.

If it would be acceptable, I would actually like to do some of the Agency's homework first, because we agreed that addressing the six-minute walk test may be more efficient for the Sponsor to do.

DR. PAGE: As you wish.

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MR. GODSHALL: Okay.

DR. PAGE: As long as it satisfies the Panel.

MR. GODSHALL: Okay, so I would like to bring Dr. Keith Aaronson up to review the six-minute walk test data when utilizing the same methodology as was used in the Pagani paper.

DR. AARONSON: Keith Aaronson, University of Michigan. If you could put up Slide MD-40 for me, please. Thank you.

So there are a number of papers in which results of the six-minute walk test for the HeartMate II have been shown. And, in fact, I'm co-author on two of them, and there's actually four different methods. I think this is actually the most informative.

So on the top here we show subjects, all of whom walk. There's no imputed values at all at both baseline and six months and had a distance reported. And as you can see, there's not very many patients in either study for whom we have that information. There are 25 out of 140 patients in the HeartWare study, and you see the 260 at baseline and 338 at six months. There are even fewer, 14 patients out of 281 patients, in my colleague's paper, and you see the distance there, 201 and 368. But, again, very small numbers to make comparisons and clearly very selected.

On the bottom we have a different comparison, and this is all patients who did not walk at baseline. So this is a much larger group of patients, didn't walk for any reason, but who did in fact walk at six months.

What we're showing you here is their six-month. All of them didn't walk at baseline. All of them had six-month measurements. A much larger, I should say, group of patients.

So there are 30 such patients in the HeartWare group who walked 333 meters, with a standard deviation of 125. In the Pagani paper -- again, that's the HeartMate II pivotal BTT trial plus the first, less than half, I believe, of the continued access program. They walked 326 meters and a somewhat larger standard deviation of 232 in 95 patients.

So I think if we examine this, I think what we're left with is imperfect data but no sense that there's any substantial difference between six-minute walk distance with these two devices.

DR. PAGE: Thank you.

I believe this was Dr. Somberg's question, and it had to do with what was in the Executive Summary. FDA, are you satisfied with this response? Great. I'm seeing a nod, so thank you.

MR. GODSHALL: The next question, unfortunately, which I think was an interesting one regarding INR, we do not have the data to answer your question, but we are very interested in trying to mine our data to learn that ourselves because I think that was a good question.

DR. PAGE: Can you summarize the question for us?

MR. GODSHALL: Well, you would be better equipped to summarize your question, I think, than I would.

DR. CIGARROA: So the question was in reference to how efficacy of antithrombotic therapy, I think, key in both safety and efficacy, in minimizing the potential risk for formation of thrombi that may be associated with thromboembolic phenomena, is reported in the A-fib dataset, and that's percent of time that individuals are at therapeutic INR levels.

DR. PAGE: Great. Thank you, Dr. Cigarroa. We'll look forward to knowing that answer sometime in the future, but we will not have that information today. Is that correct?

MR. GODSHALL: Correct. We will be able to discuss anticoagulation, et cetera, which I'm sure we will, but we do not have it measured in the same way.

DR. PAGE: The Panel will discuss anticoagulation a little bit later.

Thank you.

MR. GODSHALL: The next slide I would like to bring up is the clarification from Appendix K that Dr. Lange raised. If you could bring up that slide. AA-6. Thank you. And I would like to bring Dr. Hathaway up to discuss this. I believe we have the information that you're looking for.

DR. HATHAWAY: So, Dr. Lange, this Appendix K actually, I believe, is the site-reported as serious and device related. And if you could just remind me of your question again, I'd like to give you more information.

DR. LANGE: From the material we received, Appendix K had a

list of events that were described as serious and either possibly or probably --

DR. HATHAWAY: Yeah.

DR. LANGE: -- were related to the device. Yet there were a number of adverse events which did not appear in supplement K.

DR. HATHAWAY: Yes.

DR. LANGE: I was wondering how to clear up that discrepancy.

DR. HATHAWAY: And unless I'm mistaken, I believe this table has been clarified in six additional -- and these would be the events that were adjudicated by the CEC.

DR. LANGE: So in other words, these were not in the resolved items in supplement K, but should have been?

DR. HATHAWAY: Well, the original one was events as reported by the site. So what we're showing you here are those events that are also reported by the site but adjudicated by the CEC as well.

DR. LANGE: What you're saying is these other events --

DR. HATHAWAY: Yes.

DR. LANGE: Yeah, I guess I'm still somewhat confused.

DR. HATHAWAY: Okay.

DR. LANGE: And I may be confusing myself.

MR. GODSHALL: Perhaps let me back up one slide to AA-7, about process, and then I think I can explain the difference. So if we show AA-7 here.

So, again, as Dr. Hathaway described, the events in Appendix K are as site reported, not as adjudicated. And the sites have an option to describe the site as -- the incident as not related to the device, but then there's a qualifier where they can say it's either procedure related or patient condition related. So if somebody has a bleeding event from the implant of a device, the site might say it's not device related, it is because of the procedure of putting the device in.

It then gets sent to the CEC, and they see that it is how the site has described it, and if they agree that it is not related to the device but is because of the procedure, they might concur. They would concur. On the other hand, if the site believes it's either unlikely related, it's possibly related, probably related, or related, then the CEC would opine on whether they agree or disagree with that relative relatedness. The CEC does not determine the degree of relatedness. It's just a yes/no vote. So if they believe as one would expect.

So if we go back to AA-6, what the CEC then did is received the specific patients you asked about and of the -- I believe it was 14, whatever that number was. They moved six over -- two, four, six, seven over to become now device related. So the CEC overrode the site's view and said that they were actually device related, where the others they agreed were not device related.

DR. LANGE: Thanks for that clarification.

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MR. GODSHALL: The next area of discussion was sintering, and what we'd like to do is have Dr. Slaughter walk through just a brief tutorial on the technology so there's some common appreciation for this technology that is used widely on really every VAD now implanted in the U.S. And then we will -- as well as some of the surgical implant techniques that were being asked about earlier, and then we'll share some data that we very briefly reviewed with the Agency and recognized that the Agency has not had line listings or full review, but it hopefully will provide some additional beneficial information about what we're seeing with sintering in our trial.

So, first, I'd like to bring Dr. Slaughter up.

DR. SLAUGHTER: Thank you. Mark Slaughter again.

Oh, you pulled them up, okay. Actually we're going to start with A-11.

So to quickly answer Dr. Amato's questions and the others too, so far, previously, you've seen sort of basically artist's renditions and diagrams. So these are some operative photos.

Can you put it up? Sorry. There we go. Sorry.

So just very quickly. So the idea, as was pointed out, predominantly still in the United States, it's done through a median sternotomy per essentially instructions for use and protocol.

Next slide, please.

And then, as has been described, the sewing ring is placed on

the apex. At this point, then, the punch is made and the inflow cannula is inserted.

Specifically, your question is regarding pericardium and placement. Many of these patients, the left pleural space does need to be partially opened because it's not an invisible device. As you implied, it does occupy some space, maybe around the sides of the heart or some other anatomic configurations, and you still need to make accommodations. But you can see it's within the sort of pericardial left pleural space, out of the way.

And then specifically the outflow graft. So it's oriented such that you can rotate the device, point the outflow graft so it's below the pericardial reflection there. You can see it's in the pericardial well and way out of harm's way. Some programs still may put something over it, but certainly it's not necessary and in no way lies beneath the sternum, as was in the previous, sort of, artist's rendition.

This is one more, then. Just as you're getting ready to close, you can see the heart is still quite large. It would require a lot of foreign material to try and cover it.

And one last photo, once again just for the outflow graft. It was asked. Here you can see it once again, well out of the way, on the greater curvature of the ascending aorta. And I think also, as another unique feature, being a smaller graft, you can see there are three patent bypass

grafts, the aortic cannula. So in those areas we have limited real estate.

There is a potential real advantage with the smaller outflow graft.

Next. Can we keep going?

And actually our public speakers probably addressed this just as well or better. But along the way and up until now, and then also Dr. Allen has sort of suggested, this was the only device at the time that did not have sintering, actually, and as has been pointed out, without sintering, the LV apex is the area of greatest stasis in these very large dilated hearts. You then put suture in the apex, which renders them sort of further impaired. So you have this possibility of developing a rim of thrombus that can migrate up and then get in the cannula.

And then, when you subsequently sinter it, what happens is the sintering allows tissue in-growth. You get a pseudo-endothelial layer. It eliminates that area of greatest stasis. You get rid of that ring thrombus that I just showed you in the previous ones. And this is also why we do think, with time and greater experience, particularly, some of these late ischemic strokes you will not see because you don't have that thrombus present in the LV apex any longer.

Thank you very much.

DR. PAGE: Thank you. Stay up for just a moment, please.

I want to have a discussion about the surgical technique, and we're going to do that after we hear from the Sponsor and the FDA in terms

of homework over lunch.

But I believe the question was how many of the devices were sintered in the group that we're looking at, and what is the device we're approving? We're looking at the data from the trial, but somewhere along the trial, I guess, very much toward the end there was a major change. So do we have data regarding the patients in the continued use? So I guess the question, as I understood it, were how many of the patients, of the 140, had sintering?

DR. SLAUGHTER: Yes.

DR. PAGE: And what is the outcome of the sintered patients subsequent to that time? And I finally asked the other question, and that was how come the FDA didn't get the data on that?

DR. SLAUGHTER: I will refer to Mr. Godshall for the last part.

So within the pivotal trial, the 140 patients, there was one patient that received a sintered inflow cannula and has had no issues. Since that time there's been a total of 62. Two were pump exchanges, so a pump that had to be exchanged. A sintered inflow cannula was inserted. And then there were 60 primary implants. Within that total of 62, there has been one pump exchange for a procedural issue and, to date, no thrombotic events.

And I'll let Mr. Godshall address the issue of availability of data.

DR. PAGE: Thank you.

Just to clarify. So the 140 that were given in terms of

determining approval, one of them was sintered and all the rest were not sintered?

MR. GODSHALL: The data you've seen today has only been smooth inflow cannulas.

DR. PAGE: Except for one?

MR. GODSHALL: That was a patient that -- we introduced sintering last summer. Last May was the first implant with sintered inflows. And so it was an early bridge-to-transplant patient who had a late pump exchange that went to --

DR. PAGE: I see. So all 140 were primary first implant, a smooth inflow.

MR. GODSHALL: Correct.

DR. PAGE: Thank you.

MR. GODSHALL: Correct.

So on the broader topic of data, if you would like to discuss your question about data.

DR. PAGE: Yes, please.

MR. GODSHALL: Okay. As we play back in time, the discussions we were having with the Agency, we received -- we submitted our filing in December of 2010. We received a deficiency response in May of 2011 and forwarded our response to that deficiency in early October of 2011. And inclusive in that response, we asked the Agency if we could use some of our

continued access data to address aspects of their concern, and we included continued access and pivotal trial data to attempt to address their questions.

We then had a series of discussions in January of this year about whether or not we would be going to panel, and the Agency indicated that they would potentially be able to have a panel as soon as April, where we are now, and during the discussion we were asked, well, do we, the Agency, have all of your data? And we were under the impression that the data that they had was the data that we would be using, and the prospect of getting all the data monitored and adjudicated and in the kind of condition that would be satisfactory to Agency and Panel, we realized would take us a couple of months. And, in fact, the data is now ready, and it's going into the Agency this week in the form of our annual report.

And as a company, when we looked at the data that we have, we felt confident that it addressed between the pivotal patients and the 110 patients in the CAP cohort that the Agency had. And particularly given the consistency of results that we keep seeing in our different trials, that for us waiting another potentially three or four months to get the data, to then have a panel in July or August to have data that looked a lot like the data that we have presented did not seem like a practical option if it was a similar -- if the data was going to be similar, which our data has traditionally looked very similar from different time points, with the caveat that we recognize that there was not a great deal of sintering data and it had not come up as a major

issue.

And given the clinical feedback from our customers, where they have used sintering on every single patient with every HeartMate II, I know it was described as a major change. Our customers think it's a major benefit but not a major technical change. Now, that's our customers' perspective, not the Panel's perspective, I recognize.

What we do have for today is we do have data on our sintered patients through 30 days, because they started implanting in May, so the robust set of data is our 30-day sintered data. That's also when a bad thing would happen. If there was an adverse tissue reaction, once the tissue grows into the sintered region and endothelializes, late reactions are not likely. So we can compare 0 to 30-day data on the 62 patients versus the 0 to 30-day data on sintered patients, if the Panel is interested in that.

DR. PAGE: I think we would be interested in seeing that. But just to clarify, those are data that have not been seen by the FDA prior to this moment; is that correct?

MR. GODSHALL: I think Dr. Zuckerman had about a minute and a half to look at the slides.

(Laughter.)

MR. GODSHALL: That might be a stretch, actually.

DR. PAGE: He's a quick study, but I'm not sure that quick.

DR. ZUCKERMAN: That is correct.

DR. PAGE: I think it would be valuable for us to see those data, if they can be presented quickly.

MR. GODSHALL: Very well. What I would like to do is first bring up from our core slides the original presentation, our adverse events, just for context on the adverse events presented by Dr. Hathaway, which includes the 0 to 30-day event rate with smooth pumps. So I would be looking for the adverse event table in the safety section. And then I'll have Dr. Hathaway speak to the events in the smooth pumps versus the sintered pumps.

DR. PAGE: And we don't need a long discussion of these data because, in fact, we need to see what we can see, but them not having been vetted by the FDA as such, we need to be able to move on and discuss what has to be seen as a lack of data at this point, or at least limited data.

So do we have the slide up?

MR. GODSHALL: Yes.

DR. PAGE: Great, thanks.

MR. GODSHALL: So as you see in this slide, this is the original PMA dataset just for context, in terms of the percent of patients, focused on the 0 to 30-day rate.

And if we look at the next slide, that looks at the next set of events. Very, very similar to other VAD studies.

If we then pull up the AA-21, we see in this adjudicated dataset

that has been presented to the FDA -- and I know there are areas of particular interest, and I'll get to stroke on the next slide. But you'll see that the percent of patients is quite modest, including reoperation for bleeding is quite low, and that occurs in the first 30-day period, generally.

And then the next slide, where we've been speaking of stroke quite frequently, to date, in our 62 patients, we don't have any strokes in the 0 to 30-day period and we've discussed the improvements or our perception of an improvement that we've been seeing in the ischemic -- the perioperative period for ischemic strokes. We do know of two hemorrhagic strokes that are in the midst of adjudication. So while everything else on this list is adjudicated, we want to make sure that we weren't -- that the Agency was aware of those two events as well. They are nearing adjudication, as far as we can tell.

DR. PAGE: Dr. Allen, turn on your microphone.

DR. ALLEN: The two hemorrhagic are -- there's not two additional out there.

MR. GODSHALL: Right, we have two which we put on the list, even though everything else --

DR. ALLEN: They're in the process of being adjudicated.

MR. GODSHALL: Everything else is adjudicated, but we felt, knowing in the back of our heads about this unfortunate outcome for the patients, it would be inappropriate not to put it on the list.

DR. PAGE: So this looks like about a 3% hemorrhagic and a 0% ischemic stroke at 30 days for the 62 patients in the CEC.

MR. GODSHALL: Yes, which I am certain is too good to be true forever. I'm sure we will have 0 to 30-day --

DR. PAGE: We understand the limitations of the data.

MR. GODSHALL: Yeah. So these are 62 patients on sintered pumps.

DR. PAGE: Let me open this up to the Panel. Any comments or questions on this presentation? Okay, great. Any other questions that we've left unanswered, or other homework?

Oh, Dr. Lange.

DR. LANGE: We didn't address this, in terms of the protocol for anticoagulants or antiplatelets with the original study. And is it the same for the sintered-treated patients?

MR. GODSHALL: A very good question. To date, it is the same. Given that we've only had one exchange in our sintered patients, in the 62, and it was not for a thrombus event, and anecdotally, as our friends in Europe are telling us that they're seeing, as Dr. Struber indicated, a notable decrease in their practice, it is giving us an opportunity to contemplate a slightly lower regimen going forward. But it's too early to make any changes. The combination seems to be working well, so we'll continue assessing.

DR. LANGE: Could you just review that protocol, what the

antiplatelet/anticoagulant protocol is for the patients that received therapy?

MR. GODSHALL: Yes, and I'll bring Dr. Hathaway up to discuss our anticoagulation approach.

DR. HATHAWAY: Sure. Just very quickly, it's an INR of 2 to 3, and we recommend starting at 325 mg of aspirin, but adjusting downward if needed. Some sites do aspirin resistance testing and some don't. We're going to reevaluate this very shortly, in light of some of our sintering data.

DR. PAGE: Thank you.

Dr. Allen.

DR. ALLEN: I just want to be clear because what you're telling me is not exactly what I'm reading, nor is what I'm hearing out on the street, because you started off with antiplatelet therapy, a baby aspirin a day, correct? And your current recommendations are that you should go to a full-strength aspirin, 325, and you absolutely should run an INR of 2 to 3. I'm not aware of anybody being told or any data that suggests that sintering now, all of a sudden, says you can use reduced anticoagulation.

DR. HATHAWAY: No.

DR. ALLEN: I just want to be real clear publicly about --

DR. HATHAWAY: Yeah.

DR. ALLEN: -- this point.

DR. HATHAWAY: So the current recommendation in our protocol and in our instructions for use is an INR of 2 to 3 and a starting dose

of aspirin of 325.

DR. ALLEN: Yeah, from Richard's standpoint, because the protocol and some of the data on the issues were with a lower dose of aspirin. I'm trying to help you, actually.

DR. PAGE: It's a very important topic, and I don't think we're finished discussing anticoagulation for the day.

Dr. Lange, did you have another comment?

DR. LANGE: So, again, just to clarify. So the patients that had thrombus and/or device exchange, since there was no aspirin, these were all protocol deviations?

DR. HATHAWAY: Okay, in those cases where patients were on no aspirin, there could've been two reasons. Either they were the 0 to 48-hour patients immediately post-op, so they wouldn't be on aspirin and that would've included a few in the stroke category and also in the procedural category, if thrombus was a complicating factor. And there were a few patients who had GI bleeding or some other indication or reason to discontinue their aspirin for a short period of time.

DR. PAGE: Mr. Godshall, did you get to answer all of the questions that you heard us ask of you?

MR. GODSHALL: Those are all the questions I remember you asking. Were there --

(Laughter.)

DR. PAGE: I had one more, I think.

Dr. Cigarroa.

DR. CIGARROA: And it may have been addressed, and forgive me if you did. A follow-up question to the anticoagulation. Rick, are we going to spend more time on that, or can I follow up on a statement that they made?

DR. PAGE: Yes, I think we should, as a Panel, discuss anticoagulation in a little while.

DR. CIGARROA: Okay. Did you comment on the mode of failure for women? It was one of the items.

DR. PAGE: I think that was asked of the FDA.

DR. CIGARROA: Okay, sorry.

MR. GODSHALL: Well, we can --

DR. PAGE: Let's have FDA answer that, since that was part of their homework. And if that doesn't suffice, we'll call you back up.

MR. GODSHALL: Very well.

DR. PAGE: I'm sorry?

UNIDENTIFIED SPEAKER: I think the FDA suggested that the Sponsor was going to get that information.

DR. PAGE: Was that the case? People at the FDA, are you planning on answering that, or you were giving it? Okay, you're still on.

(Laughter.)

MR. GODSHALL: Thank you, I think.

DR. PAGE: You're welcome.

MR. GODSHALL: Recognizing first that the female population is a smaller sample size of transplant-listed patients and would be a smaller sample size within our study as a result, as it will be in any bridge trial, we do have data regarding the outcome for the females per the performance goal assessment.

So as noted earlier, there are 39 females, and 29 of the 39 females achieved the primary endpoint of success as defined in the performance goal, which again is listed as status 1A or 1B or transplanted or having the device removed for recovery of the myocardium, which did not happen in any of the patients. There were 10 of the female population that did not achieve success. Four of those 10 were on the original device, not listed 1A or 1B. They were listed status 7, which is essentially being on hold. And one was active, meaning status 2, but not 1A or 1B.

Of note, there are patients, such as Sergeant Thomas, who don't necessarily want to get transplanted or sites that choose to put people off of the 1A or 1B status and list them as status 7. So it doesn't necessarily mean that they were not eligible for transplant. They just were not 1A or 1B at the time.

There were three exchanges, two for thrombus and one for right heart failure exchanged to BiVAD, and three of the patients died. There

were no strokes in this population prior to the 180-day endpoint.

DR. PAGE: And you don't have any further data on the status 7, the nature of the status 7? Because they can be bad or good.

MR. GODSHALL: It is difficult. There is a pattern where we had three sites that -- in the broader population on performance goal, we had three sites that enrolled 11% of the total patients in the cohort, and they were responsible for 44% of the performance goal failures in total. So we had 18 total performance goal failures of people who were on the original device but not listed as status 1A or 1B.

And so almost all of their patients were successful and alive, one had been transplanted, and yet they were failures by the performance goal because they were listed as status 7 and it's -- one of my colleagues, clinical colleagues, would do much better at describing bridge-to-decision versus bridge-to-transplant and strategies on managing time on the 1A or 1B status list, if that would be of interest.

DR. PAGE: I don't think we need to go into that level of detail. Thank you.

Dr. Yuh.

DR. YUH: Yeah, two questions to the Sponsor. One is, before you made the alteration in terms of sintering of the inflow cannula, were there any preliminary studies to look at the natural history of the neointimal -- neo-epithelial growth to that, other than the post-transplant explantation

view of that? For example, how would you know that that neo-endothelium wouldn't propagate and create a pannus into the inflow tract?

MR. GODSHALL: I'll bring up Jeff LaRose, our chief scientific officer, to discuss our preclinical testing, which sintering was introduced to actually eliminate that propagation that we observed clinically. But we, of course, had to test it preclinically to satisfy ourselves ethically and the Agency, obviously, with data before we entered the clinic.

DR. YUH: A second question just so -- it may be addressed by the same person. Did you do any antibody profiles on the patients with these devices in, in terms of alloantibody reactivity PRAs, because these are bridges to transplantation and noting that there is an incidence of sensitization in patients with long-term LVADs.

MR. GODSHALL: That is not going to be Jeff that will respond to that, but I'll see if we have that information.

MR. LaROSE: Hello, I'm Jeff LaRose, Chief Scientific Officer.

So what we did in the preclinical testing is, of course, we did animal studies. We looked at actually several different lengths of sintering. We did GOP studies to ensure that, at least in the animal model, it was safe in order for us to bring it into the clinical trial. So we did look at the progression as far as up to 90 days, but that was it. So nothing further from there. But none of the animals had progression, other than the smooth interface that was shown here and submitted to the FDA, as far as part of the design

change.

MR. GODSHALL: And I'll have Dr. Slaughter answer the PRA question.

DR. SLAUGHTER: Mark Slaughter.

So PRA was prospectively collected as part of the protocol, and there's no difference compared to any other device used currently and did not alter transplantation.

DR. PAGE: Dr. Amato.

DR. AMATO: I want to thank Dr. Slaughter for his very specific explanation of the surgical technique for the implantation and explantation.

I'm wondering if I could ask Dr. Struber from Leipzig and Dr. McGee whether their techniques are similar in their training of implantation and explantation, and have they had any other difficulties not already presented in that regard?

DR. PAGE: Bram, in terms of bringing back speakers from our open public comment, I have no problem with that, as long as it's not breaking any sort of protocol.

DR. ZUCKERMAN: No, it's fine. And I know that they'll be brief and to the point.

DR. PAGE: Yes, they will definitely be brief and to the point.

(Laughter.)

DR. PAGE: And we are going to hold -- I'd just like to hear their

comments. We're going to have a discussion about surgical technique once we hear from FDA answering their questions.

Go ahead, sir.

DR. STRUBER: We use the standard technique, as has been described by Mark Slaughter, just the same way, and then we modify it, with growing experience, to a more minimally invasive approach with smaller thoracotomies. That was our way of evolution.

DR. PAGE: Great. Is it Dr. McGee who is --

MR. GODSHALL: No, I think he had to go to Poland.

DR. PAGE: I think he's gone. We will have a discussion about the surgical technique.

So I want to thank the Sponsor for being very responsive over lunch in terms of our questions and for having put together a very nice presentation and a very clear presentation this morning. Thank you.

Let's move on to the FDA. And we had a number of questions, and I'll allow you to take them in the order that makes most sense for you.

MS. KAUSHIVA: Thank you.

I think the Sponsor --

DR. PAGE: Please state your name.

MS. KAUSHIVA: My name is Anchal Kaushiva.

The Sponsor had addressed the first question regarding the six-minute walk, and Dr. John Sapirstein will be discussing the second question,

which was on the discrepancy rate of the adverse events.

DR. PAGE: That was Slide 33 that specifically we'd asked for more clarification, the discrete values for some rates.

DR. SAPIRSTEIN: Well, we'll try to find the slide that we had and make it a little bit easier, the reference with the differences in discrete rates. And that was referring predominantly to two events. The first was the ischemic stroke rate.

Hang on one second, and I'll try to get this.

So in our review of the stroke rate, we found ultimately that there were 11 patients. Now, this was based on information that we got from the Sponsor. These are obviously small numbers, so the individual numbers do become important. The Sponsor did represent to us that one patient, which was 027-001, did have an ischemic event, and the Sponsor re-contacted the CEC chair to reconsider that. And based on that interaction between the Sponsor and the former CEC chair, the Sponsor came back and decided that this individual was not an ischemic stroke. It was a metabolic encephalopathy.

Concurrent with this, the Sponsor also reclassified another patient, 027-012, as having had metabolic encephalopathy. And this is all information that the Sponsor gave to us serially. So it became very confusing to us to know exactly what the discrete stroke rate was. Up until approximately one month ago there were two other ischemic stroke rates

that the Sponsor identified to us.

So ultimately we needed to fix on the specific number. We had general agreement that it probably comes down to disagreement on one patient, of whether or not that individual had an event or not, which is why in my slides I was representing that, while the Sponsor gave an event rate of 7.1%, I think we calculated it as 7.9%. And that's sort of obscuring, perhaps, the forest through the trees because it doesn't really change our overall view of the ischemic stroke rate, which is what is shown on this slide here.

Based on the data, with the CAP data and on the IDE data, we do believe that the stroke rate was about the same when we did our calculations. We did note that, in the Sponsor's presentation, at one point they were referring to 11 ischemic strokes, and then there was an accounting also of 10 ischemic strokes. So this is what the main rate confusion was. I don't think it markedly affects the deliberations of the Panel.

The other rate difference concerns device exchange associated with thrombus, and there was one patient who underwent a device exchange in the early postoperative period after the index pump and underwent a biventricular pump placement instead.

When we reviewed those patient narratives, we saw that there was what I called signs or symptoms of thrombus. I'm not saying that that was the only event precipitating the switch. It clearly wasn't. It was probably biventricular failure. But nonetheless it was there, and the Sponsor chose to

not consider that as being in any way thrombosis related. From a conservative standpoint, we would've said that that was in some fashion related.

And finally a little bit of difference on rates concerns the adjudications of deaths. While we are in no way trying to retrospectively change what the adjudications of death by the CEC were, we're not as convinced that some of the events, such as multi-system organ failure after a hemorrhagic stroke or even a hemorrhagic stroke that was in some way related to a fall, was wholly divorced from the presence of this device.

So those were the three types of event rates.

DR. PAGE: Thank you.

In terms of other issues that I had left to discuss were the issue of women, gender, as it applies. Were you preparing anything more for us, or shall we take that up among the panelists?

DR. SAPIRSTEIN: No, we were actually deferring to --

DR. PAGE: Okay.

DR. SAPIRSTEIN: -- the Sponsor on that.

DR. PAGE: Fair enough.

First of all, does the Panel have any other questions with regard to follow-up that we received? Or otherwise, not seeing any hands raised, I'm going to move on to a discussion of the surgical technique.

Dr. Amato has pointed out concerns. There isn't a lot of

information there, and I'm interested. We have three cardiothoracic surgeons here on the Panel. I'm interested in others' comments about the issue of pericardium and how one deals with that and where one is putting the outflow.

Dr. Amato, did you have any other comments, or do you want to reframe the issue? And then I'd be interested especially in the surgeons commenting on this.

DR. AMATO: I thank Dr. Slaughter for explaining the technique, and I was just curious as to, in all implantations, whether it be an artificial heart or a heart, there is always some difficulty when you enter the pericardium and exit the pericardium, and I was just wondering whether there were other things that we had not talked about in regard to the implantation and explantation.

But it was very nicely explained, and I think that I'm satisfied with it. I think the pump is an excellent pump. I was just concerned that in the teaching process of the implantation, that the younger doctor or other doctors that are involved undergo the same teaching process of the same explanation as was given today.

Thank you very much.

DR. PAGE: Thank you.

Dr. Allen, Dr. Yuh, do you have any other comments?

DR. YUH: Only to add that what Dr. Slaughter, you know,

outlined is correct in terms of, you know, our approach in implanting LVADs. The concern amongst most LVAD surgeons, after implantation, is hemorrhage in the early postoperative period and closing the pericardium. At least intuitively, it seems a bit risky in terms of incurring tamponade physiology in the early postoperative period.

And so a solution is oftentimes to open the left well space widely to provide the blood an egress, a round of egress to avoid that. In the absence of surgical bleeding, of course.

So there are other modifications in terms of making pericardial flaps to address the issues that you have circumvented with closing the pericardium and not actually creating a closed space around the heart. But, in general, that seems to be the general practice, and I would be surprised if many heart failure surgeons deviated from that general approach.

DR. PAGE: Thank you.

Dr. Allen.

DR. ALLEN: Yeah, I don't have any issues with how this operation is done. I think it's actually an evolution. Dr. Pagani, Dr. Boyce, who's in the audience, and Dr. Slaughter have done a lot on, you know, teaching other surgeons how to do these VADs, whether it's HeartWare or HeartMate II, and I think you'll continue to see an evolution in surgical technique.

DR. PAGE: Great, thank you.

Other questions? Dr. Cigarroa.

DR. CIGARROA: In terms of the location of placement of the device in the apex, were there any variations where they were placed in for base or anywhere other than where the protocol stated?

MR. GODSHALL: I'll bring Dr. Francis Pagani up to discuss different options of location of placement of inflow cannula, depending on the requirements for different patient body habitus.

DR. PAGANI: Frank Pagani.

To the best of my knowledge, the device was placed at the apex or slightly anterior to the apex, but that is the general position of the placement of the inflow cannula.

DR. PAGE: Okay, thank you.

I have one other question, myself, and that relates to any surgical decisions in and around placement of an ICD. There were a couple, I think, two cases was it, or three, where an ICD needed to be reprogrammed or repositioned because of crosstalk.

So I guess one question is, is that an issue in terms of electrophysiologists as they place an ICD, whether they should try not to go quite as apical as they might with the shocking or sensing lead? And likewise, what has been the experience in terms of normal functioning of ICs? And the final question being, does the patient need an ICD with this device or, if they're in VF, are they perfusing satisfactorily until they get to medical

attention to get external cardioversion?

MR. GODSHALL: I'll bring up Dr. Aaronson to discuss the three AICD questions.

DR. AARONSON: Keith Aaronson. Okay, we're on now. Help me if I miss one of the questions.

So in terms of the ICD issues, it was a sensing lead issue, not the shocking lead.

DR. PAGE: Right.

DR. AARONSON: In terms of what the electrophysiologist should do, I think there's a lot of people in the audience who would be thrilled if the ratio of ICDs to VADs was anything approaching unity. But I don't think anybody expects that electrophysiologists, going forward, will be placing their leads thinking about the possibility that they're going to get -- their patient on line is going to get an HVAD. Certainly there were some patients who needed to have new leads or needed to have a new sensing lead placed because it was a chronic lead.

And the last question I think I missed.

DR. PAGE: The issue of, if a patient is in VF with this device placed --

DR. AARONSON: Yeah.

DR. PAGE: -- are they awake and alert and could they wait to get to medical attention in VF?

DR. AARONSON: Right. So as opposed to the pulsatile devices, so the pulsatile devices are less sensitive to preload and afterload. Certainly we might only see a mild decrease in output, particularly in a patient that was more chronic after the pulmonary vascular resistance drops. With continuous-flow devices, these clearly are preload dependent, and if someone's in VF, their RV is not going to fill their LV and allow the device to function well. So maintaining a functioning ICD I think is important.

DR. PAGE: Thank you.

Did you have another comment?

MR. GODSHALL: I did not.

DR. PAGE: Okay, you can have a seat. Thank you.

It's now the portion of the meeting where we, as a Panel, 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 regard to the data that we've heard today, either this morning at the panel presentations, or the discussions with the FDA and the Sponsor that we've had this afternoon, or any issues in your Panel packs.

We are fairly soon going to be going on to the questions because the questions are really quite comprehensive and deal with a number of the issues that I think have been mentioned. But right now I want to open this up to the Panel.

Dr. Cigarroa.

DR. CIGARROA: So as per your prior recommendation to continue discussing the issue of anticoagulation, interestingly, in looking at one of the slides that compared the degree of anticoagulation in individuals who had hemorrhagic versus non-hemorrhagic strokes and listing of the protocol for antiplatelet therapy as described and a target INR goal of 2 to 3, the individuals who did not have a hemorrhagic stroke had an INR of 1.8, if I remember correctly, which is distinctly different than what I would have expected.

And so the question, you know, I think we need to think about is (1) is that contributing potentially to "safety" or is it increasing the potential for thrombosis, and that is, would have more hemorrhagic strokes if we were in the therapeutic range? A goal. I mean, it's an issue.

DR. PAGE: Great. Other comments regarding this? Is it fair to say that we've heard from the Sponsor that, frankly, the attention to anticoagulation was short of crisp at the early parts of this trial? Panel, do you have concerns about that? We've heard that they changed things in response, in part, to perceived thrombosis issues.

Dr. Somberg.

DR. SOMBERG: Well, I think it is what it is, unfortunately, and we have little data, and there was certainly no exploration of different agents and different antiplatelet agents. So yes, there was -- it is stated here that there was less attention to anticoagulation. I just don't know. You raise a

very good point, whether if you are at goal, you know, counterintuitively you might actually facilitate it because it's a continuous-flow device with hemorrhage, et cetera. There's a possibility of this. Maybe being at two to three is not good, but we have no dose response data on this.

And this brings me to the segue to my concern, is that it's hard to believe, after being on this Panel for, like, 12 years and seeing these presentations, to be in the 21st century and to have a single-arm study that does not have a way to have a comparator so we have some sort of calibrator to know if we're having more strokes or less strokes than what's out there, et cetera, when there are competitors, is very, to me, disappointing.

And it's also disappointing that I seem to feel, especially with the presentations we had in the open session, that there's a lot of data out there, but it's just not presented in a coherent fashion on especially the toxicity, because while there seems to be a trend to say, oh yes, the device works, but I want to know how it works in comparison to a comparator because we have other devices out there, and whenever I say something works, I want to know what cost it has. And the balance is just very hard to get at.

So I'd be very interested to have some guidance from one of my colleagues here and hear how they're going to balance it because I'm having trouble of having this information in isolation, and we talk about one stroke, two strokes, less, more, adjudication, not adjudication. Those are all

non-issues to me.

DR. PAGE: Yes, Dr. Brindis.

DR. BRINDIS: Well, I think Joaquin really raises a great point, and I think we've learned a lot from the A-fib literature about this issue, about TTRs, and the reality is, in the past, we haven't had this type of data and we haven't paid attention to it. I suspect the INTERMACS registry also doesn't have good data related to what the true antithrombotic regimen is, what the TTRs are.

So I think these are right barriers, particularly for all of our implantable devices where the risk of stroke occurs, whether it's percutaneous valves or these, that we need to start collecting this data going forward.

DR. PAGE: For the record, could you define TTR, please?

DR. BRINDIS: Time in therapeutic range.

DR. PAGE: Thank you.

Yes, Dr. Borer.

DR. BORER: Yeah, I think this is a very important issue, obviously, but I think that it was Dr. Sapirstein who talked about the forest and the trees, and I'd like to pick up on that.

We have a trial that involved 140 patients. Eleven percent of those patients, or maybe 10%, had a stroke. All of them were at death's door. I think that's the overarching set of data we're dealing with. I really am

not terribly interested in trying to figure out, after the fact, whether the stroke was due to the device or that the stroke was due to something else or whatever. A worst-case scenario, 10% of the people had a stroke.

The issue of how best to prevent that by anticoagulation, by antiplatelet devices, et cetera, et cetera, it's not going to be resolved even if we had a control group that was contemporaneous in a randomized trial, which would be very, very difficult to do and which obviously was not something the FDA thought was fair or doable because that's not the agreement that was made with the Sponsor. So I think that it's very important to get some more information.

We were disappointed to hear a similar lack of data with regard to the percutaneously inserted valve a few months ago, when there was no standardized anticoagulation regimen and there was a relatively large number of strokes, 6%, in the people who got the valves.

These are things that need to be worked out. But I think what we have to look at here today is whether the benefit-to-risk relationship that we can infer from the data we have, all-cause events, is sufficient to believe that this implement, this device, should be made available to patients.

I'm not disagreeing with the need to have more information about anticoagulation regimens to refine the way we do the work, to improve the odds against stroke, et cetera, et cetera, but I don't think that's our primary issue here today. I think our primary issue here today is to look at

what may be the worst-case scenario, the number of strokes, the number of people, the survival, and to make our best judgment based on that and then suggest that more data be collected. But I don't think that more data is the approvable issue.

DR. PAGE: Dr. Allen.

DR. ALLEN: I think Dr. Borer's comments are very germane. I think what we have to look at is the data that we have and make that risk/benefit analysis in real time. This is the data we have, and we don't have any other. You are going to get data. Panel discussions are going to come in a randomized trial that does a head-to-head comparison down the road for DT. I assume that will come to panel. And so you are going to get some head-to-head data.

But with regard to anticoagulation and solving those issues, whether it's 10 strokes or 11 strokes, I'm not sure it is going to be a deal breaker, at least for me as an implanter and somebody that takes care of these patients. And anticoagulation, despite all the A-fib literature, is an incredibly sharp double-edged sword in these patients.

So while we think anticoagulation is important to prevent some complications, I can tell you, on a daily basis, I manage complications in these patients who are anticoagulated, whether it's GI bleed from AV malformations or hemorrhagic strokes because of acquired Von Willibrand's disease and so forth. So it is what it is, and I think each site has to evaluate

this on a patient-by-patient basis.

DR. PAGE: Fair enough. And I would remind the Panel that we will be talking about approvability, risk versus benefit ratio, a little bit later. Right now we're talking about the anticoagulation, and I think it may have some value to discuss a little bit further, in part, for future trials of other devices, for postmarket trials, if this were to be approved.

I don't know that we saw what the protocol was in terms of -- I know INR of 2 to 3, but was there a rigorous protocol? If it's 2.1 you bump up the warfarin, or was that level of guidance not provided to the investigators? And I'm asking the Sponsor. I think it's of value for the Committee.

DR. SLAUGHTER: Mark Slaughter.

And actually, you know, all of your comments are very appropriate.

So the original protocol recommended heparin in the perioperative period, then starting Coumadin once the patient was estimated, gradually increasing to an INR of around 2 to up to 3 and to start an aspirin. The problem is, as you noticed today, though, some patients are very, very sick; they don't get estimated very soon. It's very hard to follow it. So they were recommendations, and each center was able to sort of apply it as best fit their patients.

So it wasn't rigorously enforced. It has gotten tighter as time has gone on, as you've implied, and you have to individualize on each patient.

As you saw today, we saw a 39-year-old woman who's very small and a 71-year-old woman, and depending on their renal function and other comorbidities, you still have to adjust it within the sort of guided instructions. So no, there are no rigorous sort of protocols or enforcement rules. There are general guidelines to achieve the best balance.

DR. PAGE: That answered my question, thank you.

Dr. Cigarroa and then Dr. Borer.

DR. CIGARROA: Sure. So I fully support and agree with the statement that Dr. Borer made. But one exception is I never know what the worst-case scenario is.

With regard to complications, one of the most dangerous agents that we use is antithrombotic therapy, and especially when we employ it in systems where you can acquire deficiencies. And my only comment would be that the INR level in those who did not have a hemorrhagic stroke was 1.8, simply stating that if we are in a situation and we have very tight control and we're up in the 2.5, 2.8 range, that the complication rates that we see, and particularly the devastating complication rates of hemorrhagic strokes, almost always result in death, may not be what we see in the trial.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, I would certainly agree with what Dr. Cigarroa says, but I think the point that Dr. Slaughter made, and that was

implicitly made by Dr. Allen a minute ago, is very important.

We can provide guidelines or you can provide guidelines. You can't enforce them. These patients are individuals. Each of them has a set of characteristics, and the individual physician has to weigh them. There aren't large groups of data upon which to draw to determine what you should do for this individual, so that even if the guideline is an INR of 2 to 3 and aspirin 325 mg a day, there could be many reasons why many physicians, after thinking long and hard, will determine that the individual patient has to be treated differently.

I don't think we will get data from whatever wonderful trial gets set up next, any Phase IV study that's done. I don't think we're going to learn how to deal with people rigorously because I think it's very difficult to do. And I think we have to keep that in mind when we deal with these anticoagulation issues. The best, I think, that we can hope to do is to provide guidelines based on the experience that we have.

I think Dr. Cigarroa's point is absolutely right on. What would happen if the INR had been a little bit higher than 1.8 in these patients? I don't know. But we're only going to find out by observing. I don't think we're going to be able to enforce some particular target based on what we find by our observations.

DR. PAGE: Any other comments regarding anticoagulation from the Panel?

Dr. Slotwiner.

DR. SLOTWINER: Just I think, with such a small number of patients, it would be wonderful if we could get more information from the INTERMACS registry. I know that it would be burdensome and perhaps impossible to keep track of this level of detail on individual patients, but I think that we're never going to have a large series of these patients. And maybe if we could even just look at a subset of the INTERMACS, prospectively, to correlate, to correspond with future trials, we might be able to get some more solid data on anticoagulation and other factors that we'll be discussing.

DR. PAGE: Great. And we will be discussing the INTERMACS dataset a little bit later as we go through the questions, but you queued that up very nicely for us.

Dr. Lange.

DR. LANGE: With regard to Dr. Borer's and Dr. Cigarroa's comments on anticoagulation and not knowing what to do, oftentimes we don't have all the information we'd like. And so what I'd encourage the Sponsor and the FDA to do when you're considering postmarketing studies is to give enough power to decide what to do to get enough information with regard to anticoagulation and antiplatelet therapy and to collect that data rigorously.

You guys have already alluded to the fact that the CRO was

suboptimal, and so we all regret that. But what I would do is look at the next study, postmarket study, that would get the information that helps to inform us of what to do.

DR. ZUCKERMAN: So, Dr. Lange, those are really good points, and there's been a tremendous Panel discussion here, and certainly the Agency and, I hope, the multiple sponsors in the audience have heard the Panel loud and clear, that we can do better with defining anticoagulation protocols, et cetera, a central issue in this arena. But I do want to point out two things.

One, I think Dr. Allen said it best. We have to deal with the data here regarding benefit/risk. There is an opportunity for a post-approval study, but these are difficult issues. For example, the anticoagulation issue with drug-eluting stents is requiring a 15,000-patient post-approval study. So when we get to that arena, as Dr. Lange points out, there are going to be some tensions between what is doable and what is realistic.

Thank you.

DR. PAGE: Great. And if I can put in just my own comment, and that is that anticoagulation is so important, and I recognize that every patient is different and we need to adjust according to the patient. That being said, doctors have been hiding behind their own autonomy for years, in terms of kind of making up the rules as they go, and we need to be guideline driven, and from my standpoint, the definition of quality is to reduce

variability.

So while patients are different, I think, from my perspective, I'd rather see stronger guidance from the FDA and industry in terms of how to anticoagulate so at least we know how it was done. But that's my own perspective.

Why don't we now move on to the portion where we discuss the FDA questions.

Dr. Evans, are you raising your hand?

DR. EVANS: Well, I would just like to have a bit more discussion on a few issues before we jump in.

First, I'd like to thank the folks at HeartWare and the FDA for all of their hard work in evaluating this important device. I certainly realize the many complexities associated with this evaluation, and I appreciate the dedicated efforts to understand the data.

But I would like to discuss a few issues that arose during my review of the data and in listening to the presentations. And perhaps I could first offer a little bit of background and a few comments about trial design issues and propensity score methodology.

If you conduct a randomized trial, then you have an expectation of balance with respect to all potentially confounding factors, regardless about whether you know about them, regardless of whether you've measured them, regardless if you're 100 years before the medical

profession has thought about it. And it's this expectation of balance that is the foundation for obtaining unbiased estimates of a contrast between interventions or valid tests comparing interventions, and because it isolates the effect of treatment independent from other factors that could be impacting outcome.

Non-randomized studies do not have this expectation because there's no assurance of unbiased estimates. And bias could be induced because treatment assignment can be associated with these other factors that impact the outcome. So estimates from non-randomized studies are subject to this sort of bias that can be induced by these confounding factors.

So propensity scores are used to try to reduce the bias from these potentially confounding factors. But there are some important assumptions and limitations that are associated with propensity scores. First of all, they can only adjust for factors that you know about and that you measure.

And so I think it's important for the Panel and others evaluating these data to think about whether these eight factors that were controlled for, how they were selected and whether we believe these eight and only these eight are the ones that are potentially confounding. And one of these eight, the RAP, had missing data for -- about half of the data were missing, which the magnitude of that missing data is quite large and that magnitude of missingness could have substantial influence on a result.

Some other assumptions associated with this sort of analysis are you need substantial overlap between the groups, and there's sort of a modest overlap. The differences between the groups, with respect to these factors, cannot be too big, and you need lots of data is sort of the other assumption.

Now, at the end of this analysis, after statistical adjustments are made for these imbalances in these eight factors, the question became whether we could show, with reasonable confidence, that the success rate for VAS is within -- is not worse than 15% of that observed in INTERMACS. And this is clearly shown, and it's actually shown with some room to spare.

Now, I think the Panel has to think about whether the issues of the propensity score adjustment is really only partially successful in this scenario and whether 15% is the right question or whether differences should be smaller than that. In this particular case I think it would've been sufficient for even five, which is even better.

Now, my first sentence when I teach clinical trial design is that fancy statistical methods do not save design flaws. So the question is, is there design flaws here? Well, there a few issues, I think, to discuss around that.

First, this is a controlled study for effectiveness, but it's an uncontrolled study for safety and that's particularly -- you know, it's a two-arm study for effectiveness, but it's essentially a one-arm study for safety.

And I think that's, at least for me, concerning in the sense that, as we're asked today whether this device is safe, that evaluation needs context. In other words what's the alternative? It's a relative evaluation. And I, at least, am not able to interpret the data unless there's that sort of context.

Now, I understand that there are concerns for multiplicity, and we certainly want to control error rates, and I'm a statistician and I constantly preach about adhering to pre-specification in the protocol, but I think the need for context in this case actually trumps the concern about multiplicity adjustment and so on. I don't think pre-specification is a reason to avoid a controlled comparison that may be necessary in order to make an informed interpretation of the safety data.

The second issue is that, with non-randomized controls, you certainly need to understand the data quality and the representativeness of the INTERMACS data, not only knowing who's in it but knowing who didn't go in it. How representative is what's in the database, the INTERMACS database?

And, you know, given that this is a voluntary registry -- and in fact, there's some discussion about an ITT analysis. Well, I don't know how to interpret an ITT analysis in the context of a registry control. You are, by definition, excluding non-volunteers. So what do you mean by ITT? You're intending to treat volunteers just as you are anybody else.

So, lastly, I thought it would be worth touching upon the issue

that our practicing retiree, Attorney Dubbs, had mentioned about the gender issue. And I don't know if you could bring up FDA Slide 75. Is that possible?

So there was some discussion about gender issues, and in the trial, of course, and many trials, there's very low power to detect gender differences and the study is not powered to assess within gender effects. That's clear, and most studies are not. And the data are, in fact, somewhat limited in females, particularly for the VAS arm. In fact, they're limited enough -- maybe my numbers are off. It's the gender slide. Yeah, there you go.

So the number of females is relatively limited, and it's limited in such a way that even a couple of females that succeed or fail could change the rates. It's fairly sensitive to just a couple of the female results. And, however, at the bottom there's a test there to figure -- of interaction, and basically that test is trying to answer the question or addressing the question, are there differences -- are the treatment effects, the difference between the VAS and INTERMACS success rates, does that vary between genders? And there's some evidence to suggest that that's the case.

But importantly, in this particular case, not only is there some suggestive evidence that that's the case, that it's also a potentially quantitative interaction. And what that means is that the effect may go in one direction for males and in the other direction for females, and you can see that, you know, the VAS results are better for males, but they're actually

inferior for females.

Now, again, I think the bottom line is you don't have enough females to actually know whether this is a stable result or whether this is due to chance or something else. But I think it's worth noting, and I think the bottom line is we don't have enough data on females, and it's something to consider, say, in a PAS study.

So I'll end there.

DR. PAGE: Thank you very much.

Dr. Borer, do you have a comment?

DR. BORER: Yeah, I'd like to pick up on one comment. I thought those were very important points.

The issue of the lack of the right atrial pressure or the CVP as the alternative, I think, is perhaps more important than we've discussed yet. And let me preface my remarks by saying I don't think it's a fatal flaw, given the other data that we have here.

But we're talking about heart failure. There is no single characteristic as yet that we can measure and report that provides extraordinarily accurate and precise prognostication in patients with heart failure. And there are a group of characteristics, and generally we look at all of them.

But one that's not looked at as it should be, I think, is some measure of right ventricular function. In fact, right ventricular function

probably is prognostically more important than left ventricular function in patients with heart failure. It's generally secondary right ventricular dysfunction that we're dealing with, but sometimes primary, and the reason for that, in part, is that it's hard to measure right ventricular function. There's no simple test that you can use. There are some, and we could talk about it, but this isn't the place. But here in this study, an effort was made to get an index of what was going on, on the right side of the heart. That opportunity was largely missed. It was missed in the registry and it was missed in the trial.

I'm sorry we didn't see more about the central venous pressure, even, since that was the protocol-determined alternative.

You know, the question is raised, are these eight characteristics the right ones? I don't know, and I don't think we're going to settle that here today. I think that's an off-line discussion.

But I would just make a plea not to ignore the measures that allow some index of right ventricular and right heart function to be assessed, because in this particular population it's very important. Again, not a fatal flaw with regard to these data. A lot of other things were measured. I think there are a lot of things we can say. But I think this deserves to be highlighted in this discussion and pointed out to the FDA for their future discussions with the Sponsor.

DR. PAGE: Thank you, Dr. Borer.

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Dr. Allen.

DR. ALLEN: Dr. Borer's comments are pertinent. Although, from a practical standpoint, let me put this in perspective as to why I really don't think that missing data is of any consequence. And the reason it is, is because if you put a left ventricular device in a patient who has right ventricular failure, you will have a very bad outcome.

I have no idea why right ventricular functions, whether it's echo calculated, RV pressures, or central lines, or Swan-Ganz catheter readings, weren't collected in either the INTERMACS or the HVAD study. I guarantee, if you look hard in the medical record, at some point in time every single patient that gets an LVAD has got an echo or a Swan or a CVP line.

But that's not really important because I trust that the investigators and the surgeons and the referring cardiologists that are sending these patients for left ventricular support, we all know how important right ventricular function is.

So the fact that there is potentially a difference of 2 mmHg, 9 versus 11, and that some patients don't have that data, I really don't think that's inconsequential because, in either arm, if you were putting this in patients that have right ventricular failure, the death rate and the complication rate would be exceedingly higher than what we're seeing.

DR. PAGE: Thank you.

DR. ZUCKERMAN: Okay. So the comments made by Dr. Evans,

and in response, Drs. Borer and Allen's comments, are very helpful. But Dr. Lange, could we just spend a few more minutes on fleshing out some of Dr. Evans' comments right now?

DR. PAGE: Is that Page and not Lange?

DR. ZUCKERMAN: Excuse me?

DR. PAGE: You said Dr. Lange.

DR. ZUCKERMAN: I'm sorry, Dr. Page.

DR. PAGE: I think it's okay with Dr. Lange as well.

DR. ZUCKERMAN: I hope I haven't got CVA.

(Laughter.)

DR. PAGE: It's been happening for years.

DR. ZUCKERMAN: If we could put up FDA Slide 67 or if you could just look at Slide 67 in your handout.

You know, Dr. Allen, there were eight variables used. I think you've talked very well from a clinical perspective that massive right heart failure probably wasn't part of this trial, et cetera. But we would like to develop models that better educate us about what's going on so we can do better comparisons.

In addition to these eight variables, as we move forward, would you have selected any other variables, for example, one reflecting serum nutrition or anything else? They're right behind you, or I guess you're seeing them on the screen.

DR. ALLEN: I think this gets to a bigger question, which is the reliability of using the INTERMACS data in this trial. And I'll be very honest and blunt. As a panelist, I'm really not putting a lot of weight when I'm looking at this data in the INTERMACS portion of it. You have to look at it for what it is. It's a voluntary, non-audited, non-validated registry program. We submit data to it.

But I think a lot of the conversation at this table, when we talk about INTERMACS, we're holding INTERMACS up to a level that it's not. It may get there someday, but it is not an audited, validated database.

And so I'm having a hard time coming to terms with this comparator, as Dr. Evans said, not in a bad way, because I think you're going to end up, as a panelist, much like Dr. Borer has already stated, looking at the data that you have and that's it.

DR. ZUCKERMAN: Those comments are very important, Dr. Allen, and I know that Dr. Page is going to be coming around to INTERMACS and how we can best utilize it. I certainly agree with Dr. Page's comments, prior comments, that this has been a big step forward using it as a control. But your comments also need to be considered, and I think they were perhaps lost on Dr. Evans and we can explore it a bit more.

How do we get a core dataset from INTERMACS consisting of bleeding, infection, and stroke, perhaps, as Dr. Slotwiner said, from a subset of hospitals that have the data integrity that you would like to see?

DR. ALLEN: And I think INTERMACS is heading in that direction, but I think that's going to take a long time. It's not the STS database. It doesn't have hundreds of thousands of patients with 30 years or 25 years of background and data analysis. You're looking at a database that has five years of data, 4,000 or 4,500 patients enrolled in it. So it is what it is.

How you're going to ensure that the data that goes from centers into INTERMACS is accurate and, more importantly, how do you validate that and audit it so that the FDA feels comfortable that that's the case, I think those are very difficult and challenging questions.

As I said, the trial that was agreed upon and the ground rules that were set in 2004 or 2005, and you said it a number of times, it is what it is. Those were the rules that were set up. It is the data that we have. We may want more data, but post hoc analysis is fraught with problems, and I don't think that's our charge. We need to look at the data as it is.

DR. PAGE: I appreciate your comments very much. And in terms of this specific Panel's decision as to the HeartWare device, what we have must suffice.

I am impressed by the deliberations that I participated in, in 2007, having made a difference as to what we're seeing now and I'm wondering what we're going to see in 2016 or 2017 if we don't give guidance. So this is an opportunity to think outside the box a little bit.

Bram mentioned the possibility of bleeding, infections, CVA.

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We saw the letter from INTERMACS and indeed safety data were not part of the deal and we were all reminded of them not being available to us for this analysis. But I'm interested in the Panel's perspective of, going forward, what we could hope for or expect from INTERMACS to give guidance so when the next device comes along, we have both efficacy and safety data, if those might be available.

Dr. Somberg and Dr. Brindis both had their hands up.

Dr. Somberg.

DR. SOMBERG: Well, Bram, correct me if I'm wrong. You're asking, are there any other considerations that should be added here for a propensity score, to see if the two groups are approximately equally matched, as opposed to the other question Dr. Page brought up, is the --

DR. PAGE: I think you can ask both questions.

DR. SOMBERG: Okay.

DR. PAGE: But if you like --

DR. ZUCKERMAN: That's correct.

DR. PAGE: -- we can compartmentalize and first ask the Panel, are there any other specific factors that should be in a future propensity score analysis? Other than the eight that were chosen, what would you like? So let's talk about that in just a few minutes and then talk about the INTERMACS of the future and how it would inform a future panel discussion on a future device.

DR. SOMBERG: Well, I think it would help if we had more complete data at any of these points. That's the first thing. But the thing I think that might be of interest but is somewhat speculative, and I'd like to hear my colleagues, is a BNP or pBNP level. And that may be, how should I say this, well, hemodynamic is pretty useful too, so a CVP or right atrial pressure. But it's a number, it's demonstrable, and you may be able to understand the severity of the heart failure in the two groups.

DR. PAGE: Dr. Brindis and then Dr. Borer.

DR. BRINDIS: Yeah, I don't know the answer to this, Bram, so I assume that's why we're all trying to learn together. I looked at our risk model and related it to PCI mortality in the NCDR, appreciating that totally different population. So I actually like your idea about -- certainly age is huge. But I like the idea, maybe, of some sort of idea of nutrition, like maybe a serum albumen marker because it's easy to collect and may be helpful.

And I also wonder if, again, this is a harder piece of data to collect, an understanding of, you know, significant lung disease, whether we can actually have a marker there because that could be -- it's an independent marker within the NCDR registry.

DR. PAGE: Dr. Borer.

DR. BORER: Yeah, I mean, if I had my wish list. First of all, I absolutely agree with Dr. Somberg. One of the things that's missing from what we've been looking at here as a characteristic of this population is a

biomarker integrator, some way of interrogating the biology of the disease, whether it be BNP or some other biomarker. I would say serum sodium would be another.

But then there's something else. We're treating these people who have end-stage -- I mean so end stage that we were told that their mortality risk, in the absence of something, was 50% per year, which it is. And we don't know the adequacy of the drug therapy that was being used. It wasn't recorded for us.

You know, when we do drug trials in people with heart failure, that's number one, we look at the adequacy of drug therapy. There are targets published in guidelines. I'm not a big fan of guidelines, but there are targets published in guidelines of how much ACE inhibitor, each ACE inhibitor, should be given optimally, how much beta blocker should be given. And we measure the adequacy of new therapy on the basis of what it adds to these targets, and we weren't told about that here.

So I would say that would be something that would be good for us to know. It may not be part of the INTERMACS registry. You know, it may not be. Maybe it should be. But I think that certainly these measures of the biology of the disease might help us to understand the severity of the disease in comparator groups, particularly if we're using propensity scoring, and it would help us to see what this new device adds.

DR. PAGE: Thank you.

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Dr. Cigarroa, did you have a comment?

DR. CIGARROA: Two comments. One, the pulmonary circuit and the state of disease or lack of disease certainly is predictive. So I think it would be reasonable to consider pulmonary vascular resistance to use as a discriminating tool for consideration of whether somebody's transplant eligible or not and can be discriminated. So consider that, potentially, for propensity score analysis.

And, second, I forget who made the comment, but adherence to protocol in terms of extraction of the important data so we have complete datasets.

DR. PAGE: Thank you. And we are going to be discussing the protocol adherence.

Dr. Zuckerman, have you received an adequate response from the Committee? If I may summarize, among the data that may be valuable, first of all, getting the data that's in the model, in the first place, but BNP, CVP, right atrial pressure, obviously, and possibly albumen and sodium, the adequate dosing of drugs, lung disease, all as potential features.

And I hope I can speak for the Committee that, ideally, prospectively it would be negotiated among the Sponsor, INTERMACS, and FDA for future trials, to negotiate not just efficacy but safety data from the INTERMACS.

DR. ZUCKERMAN: Yes, that's very helpful.

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DR. PAGE: Great. We have the questions still to do. Before we go on with that, I would like to make note of Ms. McCall, our Patient Representative; Mr. Barrett, our Industry Representative; and Mr. Dubbs, our Consumer Representative. I'll be calling on you during the question period, but before we go into questions, do any of you have any specific comments at this time?

Ms. McCall.

MS. McCALL: This actually came up earlier by Mr. Dubbs, the low numbers of females that you have in studies, and I've seen this off and on.

I'm a member of three A-fib online groups, and I moderate a fourth. Over and over and over again this comes up among patients. Why is it always males? It's always men. A large number of the females are active online. Why aren't we included? And from my own experience of what has been and what I've seen online, again, women frequently don't seem to be offered to be part of clinical studies.

I've sat in EP offices and cardiology offices prior to my own surgery, and I've listened to who was offered, "we've got this study going." More frequently it was males that were offered. I don't know the criteria of why they were offered.

Another reason I believe why women don't come forward and volunteer to be in studies -- and this happened to myself, and it's over and

over again in forums -- is that when we come to a physician, a cardiologist, or a primary care with, you know, I'm just having this heart issue, and oh my goodness, whether they come with hard data or they just come with I don't feel right, the decision comes back with, well, it's anxiety. It's menopause.

There's probably not as much trust between the female and the physician, and so I think that's why you're not getting as many females in your studies, because we're already reticent of being boxed, being put in a corner or being discounted.

DR. PAGE: Your points are very well made.

Mr. Dubbs.

MR. DUBBS: Well, I'd like to thank Scott for his very clear remarks on the gender, the male/the female issue. He didn't address the black/white issue, but maybe you could add something to what you've already said. They were very, very good remarks.

But in terms of the female participation in the studies and the answer by the Sponsor that they don't with the INTERMACS data, as it was pick from it and the overrepresentation of males versus females in it, I don't buy it. To me, if you want to get a representative sample, you make an extraordinary effort to get a representative sample.

And although we were very fortunate to hear from these two very fortunate ladies who gave us their history and they made excellent presentations, I still don't feel that we have enough data as to females, and

I'm bothered by that.

DR. PAGE: Fair enough. I'll ask Dr. Evans to comment in just a moment, but in the meantime, Mr. Barrett, do you have any other comments before we move on?

MR. BARRETT: I guess just the one thing I'll mention is, for the rest of industry who may be paying attention today, the Agency has just issued a draft guidance on this topic last December, and I think it's very helpful for everybody in industry who's conducting studies or planning on conducting studies to take a look at that.

DR. PAGE: Thank you.

Dr. Evans, do you have any further comments on the gender issue? And perhaps to clarify whether, from your perspective, you see the signal in women as being mildly concerning, very concerning. Obviously it's a subgroup analysis, and it's a smaller subgroup, as has been pointed out by our other representatives.

DR. EVANS: Yeah, I'll have to go back and look at the race data in a bit more detail.

Again, in terms of the gender, I think the bottom line is you need more data. But what concerned me was that there's some evidence of an interaction. The interaction means that the effect for males is different than the effect for females. That may be fine, particularly if the effects are going in the same direction, if they're both positive. But in this particular

case they were in different directions, and that becomes a little bit more of a complicated issue and would suggest to me that we need more data, because if you did do subgroup analyses on females, you'd have more concern.

DR. PAGE: Okay, Dr. Borer.

DR. BORER: I'd like to make one unrelated comment. It came up in a different way earlier, but before we get into the questions, and that's with regard to the quality of life measures.

This device kept people going, by and large, through the endpoint of the study, and the projected survival for those people would have been far less, and that's very impressive. But these were very sick people who were living very limited lives. And we heard from some of the public speakers about the benefits they achieved, in terms of their quality of life, from having the device in place, and I think that we need to consider that carefully as we move forward in these formal deliberations.

The Kansas City Cardiomyopathy Questionnaire here was used quite appropriately. I mean, it is validated in this population. It wasn't in the valve population we heard about a few months ago, but it is here, and the change was awesome. Most people here are familiar with it, too, I think.

But to state it formally, the average change from before to after device was so large that I have to say that my intuition is that I don't care that the study was single-arm, unblinded. This was a dramatic change in quality of life, and I think that's a benefit, and I think that we have to be

aware of it.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I just want to say, when I saw the quality of life, yes, it looks very dramatic, but there is such a large amount of missing data. It really places it in question. People who do well tend to fill out questionnaires. People who do poorly, especially if they're more comatose, et cetera, don't fill out questionnaires. So I don't know what to make of that type of data.

DR. PAGE: Okay, it's time to take a break. I have 27 minutes after the hour. We will reconvene at 3:40. I'm sorry. Yes, 3:40. And then we'll start going through the questions.

Thank you.

(Off the record at 3:27 p.m.)

(On the record at 3:40 p.m.)

DR. PAGE: Okay, why don't we reconvene.

At this time, let's focus 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 the 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 the expertise around the table. With this said, I would like each Panel member to identify him- or herself each time he or she speaks, to facilitate transcription.

And let's put up the first question, please.

And let me remind the audience that:

This is the first ventricular assist device trial for which data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is being used as a contemporaneous control. The IDE study was designed to evaluate non-inferiority of the proportion of study patients alive, transplanted, or explanted for recovery at 180 days to the same proportion obtained from the INTERMACS registry cohort. The study's statistical plan allowed for a traditional performance goal (PG)-based primary endpoint analysis if it was determined that the patients in the two study arms were not similar enough in baseline characteristics to justify a treatment-control comparison.

Number 1: Adverse Events.

1a. Stroke rate.

FDA considers the trial's 180 observed ischemic stroke rate (ICVA) to be 8% (11 patients), and the observed hemorrhagic stroke (HCVA) rate to be 3% (4 patients). Since adverse event line data from the INTERMACS registry could not be obtained in order for FDA to conduct a detailed comparison of treatment to control, a comparison of neurological event rates for the HeartWare VAS to those reported in published literature is shown below.

And I draw your attention to Table 2, percent of subjects

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affected with neurologic events per trial.

Data from patient outcomes after stroke reveal that 27% of ischemic stroke patients either died or were deemed transplant ineligible because of their neurological event, and 100% of the hemorrhagic stroke patients died or lost their transplantation eligibility.

Clinical data (including IDE and CAP cohorts) obtained through February 28, 2011 show that the peri-operative ICVA stroke rate was not decreased, despite updates to physician training and the anticoagulation protocol.

Question 1a: Please comment on the neurological event rates and the subsequent patient outcomes and discuss these events in the context of the overall safety profile for this patient population.

And I'll open this up to comments from the Panel. If I say your name and I'd like to be able to call on you, you don't need to state your name for the record again. Who would like to comment first?

Dr. Slotwiner.

DR. SLOTWINER: Thanks, I'll start.

I think, you know, we just have to look at the alternative for these patients and the small number of patients. I think, ideally INTERMACS -- well, INTERMACS is unprecedented for what it's offering here, but it just doesn't yet have the depth and breadth that we need to have the ability to distinguish this level of detail for comparison. But I don't think that the event

rate, the stroke rate, given the alternative these patients are facing, which is certain or imminent death, I think it's an acceptable rate.

DR. PAGE: Thank you.

Dr. Borer. I'm sorry. Dr. Somberg.

DR. SOMBERG: Well, I take exception to what you said. I don't think we have to. I think sometimes you just say no. So my impression is, when you have no alternative therapy and you have the first device, you have to compare it to no therapy, and if it brings benefit but the device has side effects, that's something you put in the label.

The next device that comes down the pike has to have -- you put it in context. As was properly discussed, it needs a comparator; it needs something to calibrate it.

I do not agree with the registry's refusal to provide the adversities, but I can't force them to do that, so it's unfortunate. So I say, without that data, I don't know how to put a value judgment on this. No, it's not a lot of strokes. Yes, people do better. But we really don't have any comparator.

So I would say there's a lot in the works. There are control trials with destination therapy, and I would say, be cautious. Don't jump to saying that this is acceptable because it sets a precedent that we don't need comparative data, and I think that's a precedent that we should not set and that should be -- you know, over the years, should have been clearly

expressed that this was not something panels would go along with.

So I think this is a worrisome number. It's not unprecedented. I don't know how to compare it to what's in the literature, and I would have liked to have at least had a contemporaneous comparison with the registry database. But lacking their cooperation, it's quite unfortunate, and I don't think you can make a judgment on safety with this particular device.

DR. PAGE: Thank you, Dr. Somberg.

Dr. Borer.

DR. BORER: First, of course, I think that Dr. Somberg is right. It would be much more satisfying if we had a contemporaneous control that was matched to the data. We don't. But we do have the literature, and we do have to use our best judgment, and the way I look at the data, number one, the event number is small, therefore the precision of the point estimate has wide confidence, but it doesn't look substantially different from what we've seen in the literature. And it is in a patient population that is very sick, just as David Slotwiner said, where there really is -- where the alternative is terrible, assuming that another LVAD isn't put in, which probably has about the same stroke rate.

I think we need some refinement of guidelines for modifying the stroke rate. And when I say guidelines, I mean starting points for doctors to think about what to do. I don't mean rigid rules that they have to follow. I think we do need that for prophylaxis, as we discussed.

But I think that we really -- given the terrible alternatives, that this is a reasonably acceptable stroke rate compared to the benefits that were achieved. So I agree with David.

DR. PAGE: And let me remind -- thank you, Dr. Borer. Let me remind the Panel that, at this stage, what I'll try to do is get a sense for the Panel and then pass that on to Dr. Zuckerman. If you feel like your perspective has already been reflected, don't feel obligated to speak up. On the other hand, if you do have an alternative or a complementary perspective to add, I want to hear that.

But right now perhaps, Bram, I can summarize from what I'm hearing from the Panel, and generally what I'm hearing is concern, but that this is not necessarily out of proportion to what has been seen elsewhere. We have somewhere between very little or a modest amount of comparison data from the literature, where this seems to compare satisfactorily, although we wish we had more data in terms of safety. Specifically, there is the desire that we wish we had better INTERMACS safety data, but obviously those are not available.

Is that adequate, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, although I would like to know if there are any other Panel members who would like to add any refinements to Dr. Page's good comments because this is a critical question as far as the FDA is concerned. So speak now.

DR. PAGE: Dr. Amato.

DR. AMATO: Yeah, speaking as a surgeon and looking at the evidence and lack of data, or data, and having done LVADs and transplants, you're looking at a beautifully designed little pump that is gorgeous, and I think that lack of data really means nothing to a patient who is dying and you're looking at him and saying I have this alternative and I think this pump is a good alternative.

DR. PAGE: Great, thank you.

Dr. Dehmer.

DR. DEHMER: Yes, thank you.

And moving forward, just as an idea for the future, with all the controversy about the carotid artery stenting, you know, there is an NIH Stroke Scale, and what is required in some of those studies is to actually have an independent analysis of the presence or absence of a stroke. We've already heard from the Sponsor and from the FDA that there were a few cases, not very many, where they couldn't really decide was there a stroke or was there not a stroke, and who is making that decision?

So moving forward in thinking about the future, if stroke is such a critical issue, it may be appropriate to mandate that there be an independent, third-party evaluation of the presence or absence of a stroke.

DR. PAGE: Great, thank you.

And the other thing that I left out of my summary was the

desire that I would share, to have more clear guidance in terms of anticoagulation guidelines, not mandated protocols, but better guidance and adherence to protocol.

I'll move on to Question 1b. Pump failure and exchange rates.

Seven HVAD pumps were exchanged in seven patients within 180 days of the initial implantation. Based on FDA's review of the patient narratives, all cases of device exchange were associated with signs and/or symptoms of intraventricular/pump thrombosis. Device exchange therefore accounted for 54% of the treatment arm's 13 failures. FDA notes that one patient who underwent exchange to bi-VAD support had intraventricular/pump thrombosis, but was not considered a thrombosis-associated pump failure by the Sponsor.

The study's most recent annual report indicates that 15 of 250 combined IDE and CAP HVAD pump implantations have experienced pump failure necessitating exchange. Of these 15 failures, 11 were due to thrombus. The PMA and annual report (including IDE and CAP cohorts) further identify at least 5 of the 250 patients with pump failures from thrombosis that were salvaged with intraventricular tPA. Therefore, FDA believes that cumulatively, 16 of 250 HVAD pump implantations (6.4% of the combined CAP and IDE cohorts) experienced thrombosis-associated pump failure.

Please discuss whether the device exchange and thrombosis

rates seen for the HeartWare device are clinically acceptable.

And that's Question 1b. I'll open that up to the Panel.

Dr. Allen.

DR. ALLEN: You know, I do think there's a concerning signal for pump thrombosis. Having said that, though, from a clinical perspective, you know, I want to weigh the risk of that pump thrombosis and the consequences, which didn't result in a high death rate; the pump thrombosis rate could be managed pretty effectively and didn't often result in the death of the patient.

So you want to weigh the potential benefits of a device like this that may be easier to put in and have some advantages in certain body habitus patients. And going along the lines of being able to put it in less invasively -- none of those questions of which were answered by this study, of course -- you know, although there are concerning signals, I think the risk of pump thrombosis is outweighed by the potential benefits of this device, in my opinion.

DR. PAGE: Thank you.

Other comments? Dr. Borer.

DR. BORER: Yeah, I just want to add one thing, though. We don't have the data, and the FDA hasn't had a chance to look at the data, but we heard about the effect of sintering, and I'm impressed by that. I mean, I'd like to see the data, and I think the FDA needs to see the data, and the FDA

will see the data before it makes any final judgment here.

But it sounds to me as if possibly a countermeasure has been developed that could possibly reduce the frequency of this problem, and the Sponsor will have data about that by the time the FDA gets to see the data. And if that's true, I absolutely agree with Dr. Allen.

DR. PAGE: Thank you, Dr. Borer.

Any other comments regarding this issue? Is it the Panel's impression that things have not gotten better, or are they optimistic that things are improving in terms of thrombosis? I've heard somewhat alternate perspectives on the data.

Dr. Somberg.

DR. SOMBERG: I'll just say that there's a minority opinion here, and that is that without a comparator, you really can't put this in context. And that's the problem. So is 6.4% a lot? Well, if everything else gives you 1.2%, yes. If everything else gives you 24%, no, it's a reduction.

So, you know, this is certainly a consideration here, and how can we possibly hypothesize to what sintering does when we don't even have a comparator for the un-sintered pump? So I ask that question.

DR. PAGE: Thank you, Dr. Somberg.

Any other complementary or contrasting perspectives?

(No response.)

DR. PAGE: So for Question 1b, Dr. Zuckerman, what I'm hearing

from the Panel is that this is concerning. It's hard to know how this compares to a control group because we really don't feel like we have a control group. The issue of sintering may be cause for optimism, but that has yet to be well proven.

Is this adequate from your standpoint?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Thank you.

Going on to 1c. Adverse event comparison to the literature.

FDA was not able to access patient line data in INTERMACS to make direct adverse event comparisons between the treatment and control groups. Although FDA acknowledges that this would be a post hoc analysis, the Agency considers the totality of the data to make a safety and effectiveness determination.

Question 1c: Please comment on whether comparisons to published literature are sufficient to address questions concerning adverse event rates with the device, or whether direct comparisons to the INTERMACS control arm adverse event line data are appropriate for drawing inferences regarding the device's safety profile.

Dr. Cigarroa.

DR. CIGARROA: So to me, the answer to this is based on the study design. By design, the study was looking at the primary endpoint. And so I think that, for me, the answer to that is yes. Now, the question is, as a

precedent, should we in the future not have a comparison group? But as this study was designed, it was looking at efficacy, and the single arm as it relates to safety.

DR. PAGE: And if I may ask further, Dr. Cigarroa, are you satisfied, given that we do not have INTERMACS comparison? And I'll just say, this states it as if we had a choice. We don't have line item event data. But absent that, are you satisfied with comparisons to published literature, in terms of adverse event rates of the device?

DR. CIGARROA: I don't know, as it relates to devices, that we've ever had this precedent set where there isn't a comparison when there is an approved device. So I'm not satisfied with the design and what we are studying. I am satisfied with the event rates that have been reported and understanding the context historically.

DR. PAGE: Thank you.

Other comments? Dr. Brindis.

DR. BRINDIS: So with the data, what we have is what we have. And, you know, based on that I feel as comfortable as we possibly can in making inferences related to issues surrounding safety.

I do want to comment that we shouldn't beat up too much what I consider a terrific new paradigm, that is, the concept of utilizing registry data in being able to analyze new devices in comparison.

In fact, I want to congratulate the Sponsor and the FDA and

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INTERMACS for taking on what I consider a fairly heroic effort. When FDA and the Sponsor came up with trying to deal with the design of a randomized clinical trial, my understanding is it wasn't really possible because there was nothing out there to do such with.

The alternative of retrospective data, I want to congratulate, I guess, my Panel peers past, where I'm sitting on the shoulders of those giants who suggested the concept of using contemporary data that one could obtain from a registry such as INTERMACS.

And so now we really have the opportunity to first see how that data can actually help us and the FDA in trying to make comparators and inferences related to safety and efficacy. I think that we -- at least I personally can feel very comfortable related to the primary endpoint, but the challenges that we are appreciating is the issues of how you evaluate safety, looking at registry data versus what we have related to the Sponsor's program.

And I think that's going to be our challenge going forward, how we can work with registries, how we can support their infrastructure, how we can -- again, this is outside the purview of the FDA, but you know, thinking about registries so we can make them more, if you will, close to mandatory as opposed to voluntary, so we don't have to deal with that bias that was talked about and figure out -- I think Greg said it. Maybe if we do not only adjudication related to stroke outcomes, related to the device under therapy,

but even do such in a registry fashion so we can have that adequate comparator, which we would like from a clinician's point of view and the FDA point of view in a postmarket environment.

So, again, the data is what we have. We've learned a lot on how it can help us, and we've also learned how -- what we need to do working with registries going forward to be able to better appreciate and evaluate safety.

DR. PAGE: Thank you.

Dr. Yuh.

DR. YUH: I think that there was a general impression that the answers to the question, the two parts of the question, were no and no. But I think it raises -- in my mind the question is would it really have killed us to look at the INTERMACS data? The line data. I mean, understanding the limitations, and I understand the reasons for not trying to make a direct comparison head to head with the INTERMACS data, but it still would've been useful, I think, and it would have actually added value to INTERMACS, I think, and also guided us in how to go forward with refining the INTERMACS construct in helping further design.

So I mean, that's kind of an 800-pound gorilla sitting in the room. What's the downside of just looking at that data, understanding the constraints? We have no idea what INTERMACS shows. None.

DR. PAGE: And we will not have any idea for our deliberations

today.

DR. YUH: Correct, correct.

(Laughter.)

DR. ZUCKERMAN: Actually, Dr. Page, could I interrupt?

Because, Dr. Yuh, thank you for asking a really important question that the Agency would like some feedback on.

As you know, Dr. Page, one decision that the members of this Panel can make today is the data are the data, and Panel members may believe that there is enough data to make a positive benefit/risk decision.

Another is to think about other options to solidify what the data are before making a final decision. And hence I do think, even though we have the letter that was included in your FDA Executive Summary, that there are members of INTERMACS here today, they've heard the Advisory Panel talk about some of the limitations of the adverse event data comparison.

So if we can flesh out Dr. Yuh's comments. Specifically, I'd like to hear whether other Advisory Panel members might be of the same persuasion as Dr. Yuh. Should we make one final attempt to get these data?

DR. PAGE: Dr. Zuckerman, thank you.

Just for clarification, my past experience has been that the panelists had to deal with the data that we have at hand in order to make a recommendation. Are you suggesting that we make a recommendation

contingent on data that we have not yet obtained or make a recommendation but emphasize the importance of obtaining the data, if possible, prior to final FDA decision and for future studies?

DR. ZUCKERMAN: You know, I think you have it correct. And, again, we're in still the question section, and we'd just like to flesh out what is an optimal way to look at the data. Now, there may be some Panel members -- and I don't want to put words in anyone's mouth -- who think that even if one were to go back and look at the INTERMACS data in comparison, that due to some of the problems that Dr. Naftel and Dr. Allen noted with the current INTERMACS construct, that that might not have that much value added, and these Panel members might just want to go forward and make a decision, the decision being a yes. Others might say, hey, let's stop the train. Let's be a little bit more careful and take one final look so that we can be a bit secure, and that's fine also.

What the FDA is asking for is expert clinical advice. We have a dataset right now. I think we all agree that, in an ideal world, it's not the most optimal dataset. But should the Agency and Sponsor consider the option that Dr. Yuh put forward?

DR. PAGE: Very well stated. Thank you.

Dr. Somberg.

DR. SOMBERG: It seems common sense to me that if you're basing the efficacy determination on the INTERMACS database, you should be

able to then say you can base the safety part of it, and then you can balance the two off. But what we're saying is we only have the efficacy, and we don't have the safety. We have downsides to that, to all registries, and no one is going to say that these are comparable and you can analyze the data on and on. But what you can do is at least have an inclination of which way it's going.

It'll be much more reassuring that if that data plus the literature data shows that this adversity for stroke and for thrombus inflammation, et cetera, is about the same, then you have consistency of the data and it supports it. But without that, it's a tremendous gaping hole, and it's asking, I believe, the Panel to make a leap of faith on data that's just not there.

So I don't think you have to approve or disapprove something on the basis of expecting data. I think one could also hold off on a decision until one had that database. And that's what I think should've been done.

Thank you.

DR. PAGE: Thank you, Dr. Somberg.

Another other comments? Dr. Allen.

DR. ALLEN: I think I've already made my point on the fact that I think I would turn this around and ask the Panel, if we had a line-by-line analysis of INTERMACS, we're still left with data going in that's not -- hasn't been adjudicated, not validated, and self-reported in a registry. If the FDA

feels so uncomfortable, I actually wouldn't want to make a decision based on INTERMACS. Why not wait until the DT trial when you actually had to have data, which is what everybody is kind of jockeying around. We don't have any of that.

So I wouldn't feel comfortable if you gave me line-by-line data because I think you could make an argument that line-by-line data might not be accurate, whether it was favorable for the device or unfavorable for the device.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: To echo what Dr. Brindis said, I think we just have to be incredibly appreciative of what INTERMACS has given us so far and recognize that this is a potential model for not just this but many other areas for registries. And this is the first time we're really using that data in the approval process, and I think we're seeing some of the weaknesses and things we'd like to have. From what INTERMACS is telling us, I don't know that that data would be valuable, and so I would not push at this point, but I would hope that this would move forward that registry to get further information.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, I certainly agree with David and with Ralph. I mean, I think this is a precedent-setting effort, and if it didn't turn out

perfect the first time, we still have to appreciate what it is. I'm concerned. I think it would be very important for the FDA to attempt to get more data, understanding, as Dr. Allen said, they may not be as useful as we think they might be.

But I am concerned also by what Dr. Naftel said about losing the integrity of the INTERMACS dataset by interrogating it at a time when it wasn't intended to be interrogated. That's a problem, and I think that that's a problem, again, that we're not going to solve here today. But it has to be taken into consideration. If this dataset is going to be of value in the future, it must maintain its integrity. So that has to be considered.

Having said all of that, there's something that we haven't said. We're talking about a single-arm trial and, you know, no comparator and whatever. Everybody at this table has been comparing the data we've heard to something, and what is it? It's the experience that we've had and the literature we've read.

Virtually everybody sitting here, among the physicians, anyway, have been involved in treating patients with heart failure, in serving on study sections, evaluating heart failure trials, in serving on executive committees, running heart failure trials, being on CECs, DSMBs, et cetera, and there are data against which we're comparing what we're hearing. That's not optimal. It's not what the FDA should have at its best. But we're not comparing to nothing. We're comparing to a cumulative experience and the general sense

is that this sort of sounds pretty good.

So I think we have to consider that in providing an opinion here. Yes, we don't have a randomized controlled trial. Yes, we don't have all the data we would like to have from whatever contemporaneous registry exists. But we don't have nothing.

DR. PAGE: Dr. Borer, thank you.

And I'm going to cut off discussion for a moment here. I'm going to try to summarize it for you, Bram.

I see Dr. Cigarroa has his hand raised. If my summary doesn't reflect your perspective, then we'll go back to you, Dr. Cigarroa.

But I'm hearing some variety in the panelists as to the answers to Question 1c. And the reason I'm moving forward is we have 40 minutes to do the next six questions.

Question 1c asks whether the comparison data from the literature are sufficient and whether it would be better to have line item data from INTERMACS, and I'm hearing that they are -- I don't think anybody is thrilled with what we have with comparison. But whether it's satisfactory to make an informed vote, I'm hearing some tending that way and others voicing concern. I'm also hearing that line item data from INTERMACS would be nice. Maybe we can still go after that. But if we did, maybe we wouldn't trust it anyway.

So there's clear division among the panelists right now. This

will come up, I think, in the further questions as well. But does that help you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it does. And I do appreciate the Panel's very thoughtful comments on this key issue.

Thank you.

DR. PAGE: Dr. Cigarroa, did I include your perspective in that summary?

DR. CIGARROA: What you stated accurately reflects it. I just want to make one additional comment.

DR. PAGE: Thank you. Please go ahead.

DR. CIGARROA: I totally agree with Dr. Brindis about the critical ability and the resource that registries are. If, however, we're going to begin using them as a comparator, then best practices, by respect of societies and the FDA, must be implemented.

If one takes a look at a NCDR as an example and one looks at the variability of how things are coded, if you simply go to the NCDR meeting and you take a look at that, the variability can approach 35% to 40% in terms of how something is coded.

So best practices must be implemented if we're going to be utilizing these as comparators.

DR. PAGE: A point well made. And I think I can speak for the entire Panel, that we want to have data -- if we're going to be comparing to

INTERMACS, we want data that we can count on, and we'd like to have line item data.

I'll move on to Question 2. Is that all right, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Treatment and Control Group Comparability.

The comparability between the treatment and control groups was evaluated using a propensity score analysis (PSA) based on eight pre-specified covariates: age, gender, BUN, right atrial pressure, creatinine, body surface area, prior cardiac surgery, and INTERMACS patient profile (scale 1-7). Based on the propensity score analysis, the groups were somewhat comparable. Therefore, the primary endpoint used to evaluate the study success was survival at 180 days, which is defined as alive on the originally implanted device or transplanted or explanted for recovery. Assuming the validity of the propensity score analysis, the HeartWare VAS met the primary endpoint of non-inferiority (which was set prospectively at a 15% margin), with a success rate of 90.7%.

Question 2a. Missing baseline covariate data.

Among the eight pre-specified baseline covariates, three covariates had missing data. In particular, 80% of patients in the HeartWare VAS group and 44.5% of patients in the INTERMACS group had missing data on the RAP parameter.

For subjects with missing baseline covariates, the missing data

were imputed by replacing the missing value with the median value for their respective treatment group. Thus, all missing RAP data for HeartWare were replaced with a value of 9.5 mmHg, and all missing RAP data for INTERMACS were replaced with a value of 11 mmHg.

Question 2a: Please comment on the impact the missing covariate data imputation may have had on the interpretability of the propensity score analysis.

I open this up to the Panel.

Dr. Somberg.

DR. SOMBERG: I think this is less important than some of the other issues we've asked before about the comparator group. But with that said, just quickly, this is one way of doing it, and it's a fair way to do it, but I would appreciate hearing from our statistical person because I've heard otherwise that maybe you should take a worst-case scenario. By putting in the means, you're more likely to decrease the worst case. Maybe you should take the high end of the range and put that in to look at a worst-case scenario for looking at comparability of the groups.

DR. PAGE: Thank you.

Dr. Evans, did you have a comment?

DR. EVANS: Well, the prevalence of the missing data is concerning because -- and the effect of any, almost any imputation could go in either direction. So you don't know, and because there's so much of it, it

could go in any direction.

So what you need to do is sensitivity analyses to see how robust the result is, depending on what assumptions you make. And so a very natural assumption would be to assume something very bad, and if even under a bad scenario you still make out well, then you feel pretty good. But, unfortunately, in the recent cases I've seen, when the prevalence of the missing data is that high and you make an assumption of something bad, you sort of overwhelm the analysis with this assumption. And so that's worth looking into.

Now, there's going to be a lot of discussion about if you make sort of a pessimistic assumption about what you're missing, then is that really realistic? Well, who knows. We don't have the data, and that's the problem. But I think we could do the sensitivity analyses to try to figure out, if we assume something pessimistic, do we still make the grade? And it might happen because there was -- obviously, in the non-inferiority analyses, there was a bit of slack. We had some play there. We made it by a substantial amount. But the magnitude of that missing data can overwhelm that as well. And so it may be worth looking into.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: Although the magnitude of missing data is substantial, by design, the absence of right-sided heart failure, which is

persistent in the presence of approximately 66% of patients being classified as INTERMACS 3 through 7, I think, makes it less an issue.

DR. PAGE: Thank you.

Other comments?

(No response.)

DR. PAGE: So I guess what I'm hearing from the Panel is that we wish we didn't have missing data and there are concerns about management of this trial that I think we're going to be discussing further. At the same time, using a worst-case scenario might also throw out -- if it still reached a positive endpoint, we'd all feel very good about that, but we might miss out on an effective device by being so pessimistic, as Dr. Evans mentioned. So I'm not hearing from the Panel that this is a fatal flaw, but there is concern and we wish we had the data. But we have the data that we have.

DR. ZUCKERMAN: Thank you, Dr. Page.

DR. PAGE: Thank you.

Question 2b. Difference in INTERMACS profile (i.e., patient baseline clinical status).

INTERMACS profiles, though not validated, are intended to help to better define the VAD population's overall clinical condition as it relates to heart failure. Profile levels 1 and 2 represent the most critically ill heart failure patients who are being considered for mechanical support.

Table 1 shows the distribution of the patients in each profile for the trial. And I'll refer your attention to Table 1 that demonstrates INTERMACS profiles for HeartWare as well as INTERMACS.

There was a statistically significant difference between the two arms of the trial for this covariate at baseline (p-value of 0.0015 by a t-test) before the propensity score adjustment. Proportionately, nearly twice as many patients in the INTERMACS control arm were in profile 1 or 2 (60%) as compared to the treatment device arm (33%).

Question 2b: Please comment on the clinical significance of the difference in INTERMACS patient profile (particularly profiles 1 and 2) between the treatment and control groups. Please also comment on the potential impact of this difference on the interpretation of trial results.

Comments from the Panel.

Dr. Slotwiner. Thank you.

DR. SLOTWINER: I think this is a critical and fascinating piece of data and critical for INTERMACS to understand and try to flesh out. I'm not a heart failure expert or a transplant expert, so I don't want to try to indicate what I think might be the differences. But I think people who do this can figure it out, and I think that that will be critical in understanding whether the INTERMACS criteria are off, and how to use the INTERMACS for future comparisons as a registry. But I think, at the end of the day, we're left with a device in a situation where there are few alternatives.

DR. PAGE: Let me press you a little bit further. There were various ways of looking at these data, trying to rebalance. Did you find that compelling? Was it helpful to you?

DR. SLOTWINER: Well, I did find it helpful, but I can think of many other criteria to throw in there, such as arrhythmias. But I think I would defer to people with more expertise in this field, what might be more accurate. Dr. Brindis.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: Well, my comment, again, I'm not a heart failure expert and I'll have to -- I'm not sure about the accuracy in terms of how these patients were put in the different categories. But I was impressed with the Sponsor's response in terms of looking at the primary endpoint and how they were more or less equivalent in each group, and when they did rebalancing analysis in trying to make assumptions if there was evidence of more equal distribution, that the overall results would not change, and I was comfortable with their explanation.

DR. PAGE: Thank you, Dr. Brindis.

Other comments complementing those already made or in contrast?

(No response.)

DR. PAGE: So, Dr. Zuckerman, what I'm hearing from the Panel

is that this is a difference that's concerning, and whether this played a role in the overall endpoint, I think, is unknown. But when the grouping was rebalanced, you still saw a substantially favorable result in terms of the endpoint for this trial. So I'm not hearing this as being of great concern but being of some concern and this is -- how this might be rebalanced in the future, I don't know.

DR. ZUCKERMAN: Thank you, that's very helpful, and it brings up why, then, FDA is asking Question 3, which is the performance goal assessment as an adjunctive strategy for comparison.

DR. PAGE: Perfect. Thank you for setting me up for Question 3, the Primary Endpoint Assessment Using the Performance Goal Method.

FDA is interested in comparing device performance against the pre-specified performance goal, or PG, due to issues surrounding critical adverse event rates and adjudication despite the propensity score analysis.

Patient success under the PG assessment required either ongoing support at day 180 while maintaining UNOS listing status of 1A or 1B, transplantation by the date of data lock, or explant for recovery. Testing for non-inferiority to the INTERMACS control group did not include consideration of maintaining transplantation eligibility. FDA reasons that the presence of disabling strokes or similarly important serious adverse events would be partially reflected in the difference in endpoint success rates between the

non-inferiority and PG methods.

Under the performance goal method, a total of 109 out of 140 (77.9%) patients reached the endpoint success. The lower bound of the one-sided 95% confidence interval is 72.09%, which is higher than the performance goal of 65% ($p\text{-value} < 0.01$), therefore demonstrating study success. However, by comparison, published data from INTERMACS for BTT LVAD therapy between 2006 and 2009 demonstrate a survival rate of approximately 88%, although this INTERMACS survival rate does not explicitly consider transplantation eligibility and does not distinguish between patients who received a device exchange.

Question 3: Please provide your interpretation of the success of the device using the performance goal method in the context of both non-inferiority analysis and the recently published aggregate INTERMACS results for BTT LVAD therapy.

DR. PAGE: I open this up to the Panel.

Dr. Lange.

DR. LANGE: Well, I agree the performance goals can be a useful method of analysis. In this particular case, it was more confusing than helpful, that is, when someone goes to UNOS Level 7 and we don't know whether it's because they're doing so much better or the LV function has suddenly gotten better or whether or not they had a stroke and now they're no longer eligible, so it really wasn't very helpful to me.

So what I would say is if we're going to use performance goals, we need to define, a little bit more rigorously, whether it's an adverse event that's defining why they're taken off of the transplant status or whether it's something that's actually favorable.

DR. PAGE: So, Dr. Lange, in your opinion, would that mitigate toward making the device look better or worse?

DR. LANGE: It makes the device look worse in this particular case and that is, if your only performance goal is you either have had a transplant or you remain on the list, we took you off the list for good reasons, it unfairly penalizes the device.

DR. PAGE: So if anything, this is a pessimistic view of these data?

DR. LANGE: Correct.

DR. PAGE: Thank you. Other comments.

Dr. Allen.

DR. ALLEN: Well, I would hope that, over a period of time, as surgeons, we do get better. And I think performance goal is admirable, and it is a moving target. I don't know how the FDA gets around that moving target, because when you agree on something in 2004 and that target changes a little bit, it becomes a paradigm shift to hold somebody to, then, a different level, and that's a hard thing for the FDA and a company to balance. But there are a lot of things that go into this increased goal, and I think Richard

pointed that out very nicely.

The other issue that I think makes this device oftentimes -- or it makes it look worse in using the performance goal is that if we're very honest about how transplantation and VAD therapy is initiated because of how VADs were paid for, BTT versus bridge-to-decision versus destination therapy, I think there are times when VADs get placed, when they're being placed really for destination therapy but they're labeled as BTT, and I think that does occur, and those would be misapplied in this group.

DR. ZUCKERMAN: Okay, so let's take a timeout a moment because this is a really important discussion. We want to decide if the performance goal and the comparison against the performance goal helps us in any way to determine if the device is working in a robust fashion.

And I think that Dr. Sapirstein wants to make a few comments about clarification of our performance goal? Or --

(Laughter.)

DR. ZUCKERMAN: Dr. Patel, why don't we volunteer you?

DR. PAGE: Dr. Sapirstein, while you're gathering your thoughts, let me just look at the Panel and ask whether anybody -- whether the Panel believes the -- and primary endpoint was reached with regard to the performance goal.

I'm looking not for comments, but for hands raised. Does anybody not believe the performance goal, primary endpoint was reached,

even though this was not -- this was complementary because propensity score was allowed.

So that's helpful for me, and I hope it's helpful for you, Dr. Zuckerman, that to cite the concerns, the feeling is that that endpoint was met.

Now, you've had a couple of minutes to gather your thoughts.

DR. SAPIRSTEIN: Well, there are probably not too many clarifying comments I can add.

We acknowledge what the Panel was saying, and I understand what Dr. Lange was saying about patients not being 1A/1B for a beneficial reason as opposed to an unbeneficial or lack of beneficial reason. But we were just interested in the Panel's assessment of an updated performance goal as opposed to what was developed and used at the time of IDE. But it was, as Dr. Allen mentioned, already discussed. It's a difficult conundrum that we can get into.

DR. PAGE: Thank you very much.

Dr. Somberg.

DR. SOMBERG: I think it's important to have the performance goal set at the clinically appropriate time and -- well, it's traditional, and I've seen that for years, using the six months. I don't think that correlates with what the device is going to have to be used for. The reality is, it's more like a year. So I think it's, one, important to say that you have to set the

performance goal at the appropriate time.

And the second, aren't performance goals a way to try and get appropriate data when it is not feasible or it's excessively overly burdensome to do a clinical trial? And I think one has to be cautious about exploring that because I hear, in destination therapy and with other types of devices, we can do a clinical trial. So I think this should be a fallback position, but not a first choice, to do a performance goal because it's a little easier. It gives us a lot less information.

DR. ZUCKERMAN: Okay. I think we've had a lot of good comments, but Dr. Somberg, again, we're not looking at an indication for destination therapy where the Agency agrees a randomized trial is possible. We're looking at a niche population, bridge-to-transplant, a very difficult and desperate patient population with a relatively fixed sample size.

As Dr. Page has indicated, our prior approvals have rested on the performance goal concept, even with all the limitations. He's pointed out that, as a result of these limitations, we've tried to move a step in a different direction. But what is of most use to the FDA today is whether just using this as an important secondary analysis with all the known limitations of a performance goal helps to clarify whether these data are more robust. And I think that Dr. Page has previously summarized the general gist of the Panel.

DR. PAGE: All right, thank you.

And I think the other question that you may be asking is, would

a future performance goal, if it were primarily more likely a secondary backup endpoint, if you will, would we expect a more robust, a higher bar, if you would? And my own perspective is that would need to be considered based on the data we have now as compared with when the performance goal was set.

But my own perspective is that you can't move the target in terms of performance goal unless -- and the performance goal was met, and I don't think it -- my personal perspective is it's not irresponsible, in my sense, from the committee, it's not irresponsible to consider this as the secondary or primary endpoint, if you will, but we might set the bar higher for future studies.

DR. ZUCKERMAN: Thank you. That's very helpful.

DR. PAGE: The Panel -- did I capture the sentiment satisfactorily?

(No response.)

DR. PAGE: Okay, great.

We're on to Number 4. And this is regarding Trial Conduct.

4a. Patient enrollment.

Screening and subsequent enrollment practices were not homogenous for the HeartWare VAS group. The top four enrolling centers, accounting for 34% of intent-to-treat implantations, had a screening failure rate of 30%, and the top two enrolling centers, accounting for 17% of

implantations, had no screening failures. Conversely, nearly 60% of all screening failures occurred at four low enrolling sites that enrolled only 10% of intention-to-treat patients. In addition, 17 of the consented patients (who were not implanted with the device) were "enrolled in error" (having not met all of the inclusion/exclusion criteria) and thus were not appropriate for the pre-specified intention-to-treat analysis cohort. Three of these "screen failures" were on the basis of either physician decision or patient preference to receive the approved HeartMate II LVAD, and could alternatively have been considered as protocol violations. In addition, three other patients likewise did not fulfill the inclusion/exclusion criteria, but did undergo the HeartWare VAS placement on an "emergency use" basis.

Question 4a: Please comment on whether the variations in screening and enrollment practices may have reflected biases that could affect data interpretability.

Dr. Borer.

DR. BORER: Number 1, yes, I think it could affect data interpretability. But let's step back for a minute and think about why there was such a discrepancy, 0% and 30%. And I will suggest a reason, and that is that there was a tremendous amount of prescreening that went on. That's not stated in the protocol.

But in one particular heart failure trial using a device in which I'm involved right now, I suggested, at our first meeting, at our organizational

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meeting, that since this was double-blinded and randomized, that we could expect 1 out of every 20 people who was approached to accept inclusion in the protocol. And my colleagues from Europe, primarily, laughed at me. They said oh no, we'll get everybody. And they were right, I was wrong. They're getting one in five or one in three.

Well, how are they doing it? They're prescreening. They're looking at the patients and deciding who they think they get into the trial and they're very successful at it. Does that potentially alter the population and alter the conclusions you could draw? Of course it does. Of course, we don't know how. But it does.

Nonetheless, what we have here is a population. The population is defined by a variety of objective descriptors; an intervention was performed; and we see what happened with the intervention. I think the data remained valuable. Are the data or the interpretation of data somewhat different than if we truly had the same screening procedures used everywhere? Sure, of course. But I don't think that's a fatal flaw. I think that's just a fact of life. I think the lesson to be learned is that the screening procedure should be specified precisely in the research protocol.

DR. PAGE: Thank you. Other comments?

(No response.)

DR. PAGE: So what I'm assuming is that people are in agreement, this may have had an effect. It's hard to know exactly why was

there prescreening going on, and probably better bookkeeping of those considered screened and enrolled would be helpful and might, according to Dr. Borer, actually smooth out what seems to be a real discrepancy between infrequent enrollment and 100% enrollment of those screened.

Does that help you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it does.

DR. PAGE: Dr. Lange.

DR. LANGE: And per the Sponsor's comments, having two different forms. One is a screening form that is done first, and the second is a consent form that's done second, rather than having both be the same form.

DR. PAGE: Thank you, good point.

4b. Study monitoring.

The Sponsor states that study monitoring between enrollment and April 2010 was inadequate. In particular, the Sponsor acknowledges that during this period, "monitoring visit frequency was insufficient to maintain pace with enrollment, training on the protocol required procedures, and follow-up on site deficiencies was ineffectively executed."

Please comment on the potential impact that the suboptimal study monitoring may have had on the overall study data collection and ability to interpret the results.

Dr. Somberg.

DR. SOMBERG: Study monitoring is very important. There are

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two aspects of this. One is yes, if the Sponsor doesn't get kept up to date on what's happening, a lot of problems can develop. But the missing data is another aspect of it, and if the monitoring doesn't pick up data or picks it up incorrectly and there's not proper quality assurance, that can be problems. And I wasn't sure if these were inflated in this discussion.

Are we talking about having problems with data accuracy, reproducibility, quality assurance, or are we talking more about slow to react on trend, like maybe device exchange or replacement, you weren't getting the proper information? So those things are kind of important. I suggest one remedy.

Unfortunately, when we all do studies, there's about 4,000 different items to pull together, and whenever you have so many items, you tend to have things that go by the wayside. So it's probably a priority to identify those things that are most salient, to have telephone information and to get those in, you know, patients alive or dead; patients needing an exchange; patients had an embolus, a stroke. Those things should have almost real-time input, and other things like the BUN, the CBC, things like that, can be obtained at a later date and not with the same urgency.

DR. PAGE: Dr. Somberg, I'm going to ask you to expand on that. You and I have sat on panels together for probably a decade now.

Relative to other studies that you've seen come through, how would you say study monitoring in this trial compares?

DR. SOMBERG: This is very highly scientific.

(Laughter.)

DR. PAGE: There's a method to my madness, and I'll answer my own question, if you like, but I think it's important to answer it to get --

DR. SOMBERG: Well, I'll start you off. I've seen far better, and I've seen far worse.

Is this right in the middle? No. It's a little bit towards the negative.

DR. PAGE: Thank you.

Dr. Lange, did you have a comment?

DR. LANGE: Right. For the primary endpoint, I'll acquiesce that the Sponsors and the reviewer was able to count who was alive at the end and who had an LVAD still in and who had a new heart.

But for all the secondary endpoints, quite frankly, all the data is garbage. There's not a single secondary endpoint that I can look at and say oh yeah, I trust this. And that's either because we're missing data or we had to second-guess the CEC and go back and try to get them to re-adjudicate things. Or the CEC didn't do their job or the CRO got fired. So all in all, that part, the secondary endpoints, was disappointing.

Fortunately, the trial primary endpoint was met. But the secondary endpoints are really unbelievable, and that part is very disappointing, even from getting a New York Heart Association class, just fell

off the form and nobody recognized it. So the whole thing was just disappointing.

So my encouragement is, for the next part, is to beef that up a bit because there's a lot of important information there.

DR. PAGE: Thank you, Dr. Lange.

Dr. Allen.

DR. ALLEN: I think this actually is more of a question to Dr. Zuckerman because I am disappointed in how the trial was conducted and monitored, and I think it's a reflection on how the company, if we were to approve this device, might execute this device into the market. And if they have difficulty in keeping up with a clinical trial and this explodes onto the market and is used by a lot of centers that don't get appropriately trained or so forth, how does that impact the results?

And so I would ask, maybe Dr. Zuckerman and the FDA, how they plan or how they would suggest monitoring in the post-approval period that would take into account that effect.

DR. ZUCKERMAN: Okay, I'm going to answer that in a moment, but the point of these panel discussions is that these really should be independent advisory panel discussions. We have a remarkable group of clinicians and clinical trialists here, and I'd like to hear their viewpoint, and then I will make some comments because this is a critical issue that you pointed out, Dr. Allen.

DR. PAGE: Thank you, Dr. Zuckerman.

I think it is worthwhile further discussing. We've talked about quartiles and quintiles. I'll put it out there.

Does anybody see this as being above the bottom quartile in terms of data management?

(No response.)

DR. PAGE: So the question as it's put forward is: Please comment on the potential impact that the suboptimal study monitoring may have had on the overall study data collection and ability to interpret the results.

This is a problem. And the concern would be it could have a significant impact on whether the Panel trusts the data enough to give a positive result. So going forward, if there is further study from this sponsor and certainly for other sponsors, that you can't throw the CRO under the bus. The sponsor is responsible for the CRO. And the fact that we got behind on the CEC, which we're going to talk about next, shouldn't happen. So I'm afraid it jeopardizes the submission, and it certainly appears to have slowed down the arrival to panel. But I might hear other comments from the FDA later about that.

Dr. Cigarroa.

DR. CIGARROA: I agree with that statement as it relates to the secondary endpoints, not the primary.

DR. PAGE: Thank you.

Okay, did that adequately summarize concerns or comments regarding Question 4b, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. PAGE: Great.

Let's move on to 4c. Adverse event adjudication.

The CEC's adjudication process required review of events by two voting members; in the event of disagreement of adjudication between the two members, final adjudication was decided by the CEC chairman. After initially empanelling a CEC in 2008, the Sponsor made three subsequent modifications to the committee's membership during the course of the IDE. In one instance, the number of members of the CEC was increased from three to eight.

Please comment on the potential impact that the changes in CEC operations may have had on the reproducibility of serious adverse event adjudications and on the ability to interpret the results.

Comments from the Panel. Dr. Borer.

DR. BORER: Well, the primary problem here -- and let me start out by saying, again, this is a problem, I think an important problem, but not a fatal flaw.

The problem here is one of consistency. The changes that were made in the CEC when the Sponsor presented them didn't sound as bad as I

thought they were. But they really do minimize the capacity of the CEC to provide consistent adjudications. and that's a problem, particularly when there are so few events.

I'll go one step further. I think that it's inappropriate for the CEC to make the determination as to whether an event was -- the causation of an event. I don't think that's right. I don't think that should be the CEC's job. The CEC is blinded and that's good, so --

DR. PAGE: But I don't know that this is blinded because the CEC was only looking at events from the hardware, correct?

DR. ZUCKERMAN: That's correct.

DR. PAGE: So there was no blind here.

DR. BORER: You are quite right, I'm sorry. Then it's even worse than I thought it was.

When I sit on a DSMB and I look at the investigator's determination of the causality of an event in a trial, I just throw it out. You know, all I'm interested in is the body count. So I don't think it was a good idea to have a CEC providing an opinion about causality. I think that really should have been handled in another way, if it could be handled at all, in an unblinded study.

I think really what we care about are the events, and I'm concerned that the consistency of the CEC's decisions was suboptimal because of all the changes that were made in the post hoc assessments.

Having said that, does that negate the results? I don't think so because -- you know, Dr. Lange said it best, really, and Dr. Cigarroa echoed it. At the end of the day, what we have here are some pretty hard events, life and death, which really is hard to mis-adjudicate. Causality of the death could be mis-adjudicated, but the fact that it occurred is hard to miss.

So I think that this is not a fatal flaw, but I think it's a problem, and in going forward and doing additional studies, this kind of design shouldn't be used. If there are going to be a lot of events and you're afraid the CEC will fall behind and the reporting time lines won't be met, then appoint a larger CEC to begin with, have them meet, have them set up a charter so that they're all reviewing events in a virtually identical way, and don't give them the responsibility of defining causality.

DR. PAGE: Thank you, Dr. Borer.

And I will just mention, we're almost to Question 5. We still need to finish Question 4c. On Question 5, when we do discuss safety and effectiveness, I'm going to go down the line and ask everybody to comment.

Dr. Lange.

DR. LANGE: In addition to what Dr. Borer mentioned about consistency, I think I'd just mention that it's important that they be independent. And so you need to isolate yourself from that and the data safety monitoring board.

DR. PAGE: Dr. Yuh.

DR. YUH: I just find it somewhat humorous and ironic that in reviewing Dr. Naftel's letter from INTERMACS about how the line item, that it would not be provided, it says that our concern is that adverse effects are not subject to the same adjudication as the adverse effects in the clinical trial. So when you have both ends of it, I don't think you can have it both ways, in many respects.

I did question the use of just three members, essentially, with the initial construct. It seems very thin and subject to potential bias as opposed to a larger group of CEC members. I don't know if anybody has more experience with that in terms of accounting. It just seems like it's a very small number to adjudicate a complication or a major adverse event.

DR. PAGE: Thank you.

Dr. Somberg, do you want to enlighten us on your perspective of event committees?

DR. SOMBERG: Well, I just want to say, just quickly, yes, it's a small number, but on the other hand, the larger the number, the harder it is to get people together, the slower the response and the more variable the evaluation. So it cuts both ways.

You know, I saw some of the explanations, that people had different workloads, et cetera. I mean, it's a comedy of errors, if you will. Maybe not a comedy, but a series of them. I wouldn't just put it all on the Sponsor. These things sometimes have problems.

But I'm more concerned about what the comparator is than whether it was a potential stroke or not a stroke or some brain syndrome or something like that. So I mean, we have to put this in context. This is a concern, but to me, it's a lesser concern than the overall design of the study.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: So I would say I'm reflecting what Dr. Borer mentioned, the fact that it is unblinded and there isn't a comparator. I think these issues are issues when the CEC has changed over time and when they're assigning causalities that relates the device or not in a small number of patients.

DR. PAGE: Okay, so the only other comment I would make is, having sat on a number of event committees over the years, this is a very small event committee; having just two and then the chair adjudicate is an awfully small group.

The only other thing I'd comment, as opposed to being reassured by the fact that they agreed with the investigator -- I think it was 97% of the time, is that right? That's way higher than I've ever seen, and it makes me wonder what they were doing, because my experience is to have the event committee agree with the investigator 97% of the time is beyond what I've ever seen.

But shall I summarize for you, Dr. Zuckerman, or do you feel like you've gotten the flavor from the Panel?

DR. ZUCKERMAN: Well, I think what I've heard is that this was not a well executed trial, and I'd ask the Panel members, when they go to Question 5, to take that into consideration when they weigh benefits versus risks because certainly a lack of good execution can change a p-value and bias results, and I think that's obvious.

For the more general question and concern raised by Dr. Allen, I think there are two comments.

One is, as Dr. Page mentioned, the FDA has an important mission for promoting innovative medical devices in this country, but it's significantly hampered when trial sloppiness becomes a part of the routine here. And I think Dr. Page alluded to the long time lines that we're seeing for a device, regardless of a panel vote, that people are interested in, (a).

(b) is, given this situation, Dr. Allen, the Agency would feel obliged to monitor this device or any similar device extremely carefully in a post-approval setting, and if we have concerns about conduct of a post-approval study, these days we have a very, very low threshold for taking our concerns to an advisory panel, and we'll be sure to invite you, if you're available.

DR. PAGE: Thank you.

Dr. Amato, did you have another comment?

DR. AMATO: Yes. I'm just listening to all of this, and sometimes I want someone to get into a hospital situation where you're

dealing with a trial like this and try to keep people together for two, three years, four years, and getting people on your committee from three to eight, getting decisions made while they're doing other things, it just seems this is real life, this is impossible. And I think we're dealing with a life and death situation, and we have to, as a committee, look at what's the difference? If you disapprove the item or the pump, I think you're losing life and it's a very --

DR. PAGE: We will get to that --

DR. AMATO: Thank you.

DR. PAGE: -- in just a moment. Thank you.

So your comment is we're maybe being too hard on them?

DR. AMATO: Yes.

DR. PAGE: Thank you.

Let's move on to Number 5: Safety And Effectiveness.

Question 5: Please comment on whether you believe the totality of the data presented and discussed demonstrates a reasonable assurance of safety and effectiveness for the HeartWare VAS in the intended patient population.

Ms. Waterhouse is going to describe the definitions of safety and effectiveness before the actual vote. I would encourage the Panel to remember that we are commenting on safety as it relates to the patient population we're dealing with.

Obviously, it's not -- if this weren't a life threatening problem, any time you're getting an open chest procedure, that's unsafe in some ways, but what we're commenting on is when we look at the effectiveness and the safety, based on the data we have at hand, do we feel that this is satisfactorily safe and effective?

And this is not really a straw vote, but this is just letting the group know what you are thinking in advance of the true vote, which, as you know, is going to be electronic and one time.

So if I may, Dr. Slotwiner, do you mind if I start with you?

DR. SLOTWINER: No, absolutely.

DR. PAGE: And the other thing I'll comment is, it's 5:00. It's actually time to sum up from the Sponsor and the FDA. We're obviously going longer than that, but I think this discussion is tremendously important. And after we get through this, Number 5, we still have Number 6 and 7 before we get to the summaries from the Sponsor and FDA.

Dr. Slotwiner.

DR. SLOTWINER: I'll be brief.

I think we have reasonable data that it's effective. I think safety is relative. And we've, I think, discussed a lot of the concerns quite thoroughly. But these patients don't have much alternative in that setting. I think it's reasonable.

DR. PAGE: Thank you.

Dr. Evans.

DR. EVANS: So as I've mentioned before, I'm not sure how I interpret the safety data without, sort of, context in reference to a control. So I can't say I'm reasonably assured of safety, and actually, the discussion about issues with monitoring, maybe more concerned because there's a possibility that safety events could go under-reported with poor monitoring.

The effectiveness, I think it's probably effective if effective is defined as within 15% of the control. Whether that's reasonable assurance, I'm still questioning because of the missing data issue. This is an epidemiological study. You do not have the integrity of a randomized trial, and that's the design of this. So you have to take that in consideration when you're comparing these.

And I would like to maybe make a follow-up comment to some of the earlier discussion about the use of registry data, particularly for control groups.

By all means, I'd like to support further development and enhancing of registries. They are invaluable to have these types of data. But I say that with a bold footnote, is be very careful about trying to use registry data, particularly in pivotal trials, as control groups unless you have -- you have to do it very responsibly.

If you don't have a thorough understanding of the confounding factors -- and make sure that the data in the registry has similar populations,

similar ways in which the intervention and the environment in which the intervention is applied, you have -- the burden of proof is on you to rule out effects of any other factors on outcome so that you can isolate the effect of an intervention. And if you can't do that, don't be using a registry as a control.

Now, I'm not saying that this is necessarily the case in this trial; I think there are some issues. But I do want to make sure that the message is not conveyed that registry data is going to replace randomized trials.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: So I agree that efficacy has been met, I think for all the reasons that we've spent a substantial amount of time this afternoon discussing. Assessing safety is challenging.

DR. PAGE: Thank you.

Dr. Amato.

DR. AMATO: Looking at this and dealing with three items, the effectiveness of the data, the non-effectiveness of the data, and life, and we've seen four people that are alive because of this device, and I can't say anything else, but I congratulate them.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: I think that the data are sufficient to convince me

that the device is effective, that the efficacy is met. There are obvious problems with the data about safety; we've discussed them ad nauseam. When I weigh them, I think that I can accept them -- with some hesitation, but I can accept it.

DR. PAGE: Thank you.

Dr. Dehmer.

DR. DEHMER: I think everybody has learned a lot by just examining this whole process and what went right and what went wrong.

In terms of effectiveness, I believe that the Sponsor has met what was set up for them, that this device is effective for the purpose that it is intended.

In terms of safety, these data had more holes in it than Swiss cheese. So it is very, very difficult to say that it is completely a safe device, realizing the patient population is a very unsafe population.

I feel a little bit like Dr. Borer, to my right, that within the construct of the data, it is reasonable to assume that there is some measure of safety here, but I say that with not a terribly high level of confidence.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: Thank you.

I think, as everyone said so far, that the performance criteria for effectiveness has been met. The safety issue is the concern; the

methodology is poor. I like the comparison with Swiss cheese, but maybe more like a strainer. And this is where, I think, one has to give consideration.

If this was a situation where yes, it was the only thing offering as a bridge to save lives, one would put all this quibbling aside. But if it's not the only potential alternative, if there are other means to define the safety better, then I think it's prudent to withhold judgment and to obtain further information.

So I do not think, at this time, I would be inclined to say that the balance is in favor of safety and effectiveness being proved and therefore recommending approval. I think that we're still -- should be undecided in this affair.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: I concur.

DR. PAGE: Dr. Brindis.

DR. BRINDIS: The device is effective, and in terms of the patient population, the conditions of use, its probable benefit versus probable injury with the understanding of the challenge of the secondary endpoints of safety, I will still say it's safe for its use.

DR. PAGE: Thank you.

Dr. Allen.

DR. ALLEN: Based on the a priori-ly defined limbo bar, the

Sponsor has limboed under that bar with regard to effectiveness.

I think, from a safety standpoint, for the indication that they're going for, which is BTT, the totality of the data, in my opinion, would suggest that it is safe for BTT.

DR. PAGE: Thank you.

Dr. Yuh.

DR. YUH: I would echo those. I think that the Sponsor has clearly demonstrated effectiveness with the constraints and the definitions of the study.

In terms of the totality of the data, I think it does contribute to reasonable assurance, in my mind, in terms of safety, in the context of its application.

DR. PAGE: Thank you.

Now, the other three non-voting members, I will be asking for your comments just after the summary.

Dr. Zuckerman, am I allowed to comment at this point? I know I don't vote.

DR. ZUCKERMAN: Sure, but you can comment.

DR. PAGE: Yeah, thanks.

I think this has met the efficacy bar, and it actually represents a real advance in technology.

In terms of safety, I'm actually inclined that the safety signal is

okay, but the trial conduct has jeopardized passing in this Panel. But as I try to sift through this, I'm going to be inclined to say that it wins out in terms of safety as best I can sort through, really, what is a mess in terms of trial data.

Let's move on to Number 6, the Post-Approval Study.

FDA believes that if the HeartWare VAS is approved, post-approval studies should be required as a condition of approval for this device and that INTERMACS line data be available to draw appropriate comparisons regarding outcomes and adverse events. FDA recommends that, in addition to continued follow-up of the premarket cohort, a Newly Enrolled PAS should be conducted. The Newly Enrolled post-approval study would examine multiple secondary endpoints, including re-hospitalizations, quality of life, neurocognitive status, and functionality in addition to monitoring the occurrence of mortality, neurological events, device malfunctions and exchange and other adverse events.

Additionally, the following issues are noted:

HeartWare intends to pursue a labeling claim for patients with a BSA < 1.5m². However, only one patient with a BSA < 1.5m² was enrolled in the pivotal pre-market trial.

In the premarket, four of the seven pumps exchanged due to thrombus malfunctioned due to high power alarms, and two transplants occurred as a result of these device malfunctions.

Question 6a: Please comment on whether a Newly Enrolled

PAS is needed to assess the following:

- body surface subgroup performance;
- the association between adverse events (namely thrombus necessitating transplant) and device malfunctions, and if the order in which these events occur should be monitored.

And so let me put that out to the Panel.

Dr. Somberg.

DR. SOMBERG: I think those are important things to evaluate.

I also think the duration of the trial is an important aspect. And I saw discussion from the Sponsor doing 180 days versus a year or further. I think at least follow up for a year, and I know the FDA, in an outline I saw, was talking about a five-year study. I don't think going out five years is appropriate, but as a bridge-to-transplant, a year, a year and a half are the times we are now seeing. So I think that's kind of important.

And looking both at efficacy and safety, those -- and not to try -- I mean, if it comes to postmarketing, not to get information for an approval because it's postmarketing, but I think it would give a lot of people assurance that this device is safe and effective in terms of long-term activity if they were able to get information from a comparator group.

DR. PAGE: Other comments?

Dr. Cigarroa.

DR. CIGARROA: It's difficult to obtain a specific labeling claim for a BSA < 1.5m² when only one patient was enrolled. So I think that, to me, is a challenge set forth.

I would like, certainly, in the adverse events and newly enrolled PAS, the issue of gender addressed given the potential interaction that we saw in the small number of women that were enrolled.

DR. PAGE: Thank you.

Other comments?

Dr. Lange.

DR. LANGE: I'm less interested in the subgroup analysis of BSA. I'm more interested in people that have a BSA < 1.5. That's really the group for that indication.

And I'm not sure one can tell the difference between which occurs first in an outpatient, whether it's the device malfunction or the thrombus. But what I would like to see in here is some mention of anticoagulation; how it affects thrombosis rates and device malfunction, I think, would be very helpful.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: I just want to emphasize one point in the question, not the actual questions, but that in a PAS study, INTERMACS line data be available to draw appropriate comparisons.

DR. PAGE: We're not there yet.

DR. SLOTWINER: It's in the question.

DR. PAGE: No, I know. We're still on a.

DR. SLOTWINER: Oh.

DR. PAGE: I stopped at a.

DR. SLOTWINER: Oh, that's for b. I'm sorry.

DR. PAGE: No problem. We'll get there soon.

So, Dr. Zuckerman, I'm hearing that perhaps a longer -- first of all, these two would be of some value. The body surface area and specifically, looking at the adverse events, including thrombosis perhaps extending beyond a year.

And the issue of what to do with $< 1.5\text{m}^2$ is a tough one. What we've seen is it's being -- would it be used off label anyway? I know we can't comment or approve of that, but in terms of it makes some sense that if this is an approved device, a surgeon may choose it for a patient who is small.

So one way or another, I imagine it's going to be used and -- if approved and as such, we would want to follow those data and gather really what would be the only data on patients that size.

Is that helpful to you?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Now, Dr. Slotwiner, we will go on to Question 6b.

Please discuss if, within the PAS, INTERMACS line data would be

an appropriate comparator and what covariates would be appropriate to consider in a possible propensity score analysis?

And we've heard of a number of potential additions.

What would you like to add, Dr. Slotwiner?

DR. SLOTWINER: Well, I think that there are people who are more knowledgeable in this than I, so I am reluctant to suggest individual items, although certainly arrhythmia seems like an appropriate addition. But I would hope that this first INTERMACS is just the beginning and that we can move forward and use it in more robust comparisons to understand not just mortality comparisons.

DR. PAGE: Thank you.

Are there any other comments regarding 6b?

Yes, Dr. Brindis.

DR. BRINDIS: Well, you know, I think this requires a lot of incredible thought and work with the INTERMACS group and how they would want to go forward and do such. We appreciate the challenge already discussed of un-adjudicated volunteer data being utilized in this format of a PAS.

So one mechanism might be -- again, I'm thinking a little out of the box here, is working with some of the enrolling centers and trying to get patient consent who are in the INTERMACS to actually do -- have a higher quality subset data with which to utilize in a PAS study with the potentially

approved device.

So I think, again, this is interesting work going forward trying to push the envelope and utilizing registries, and it would be an interesting discussion, trying to work with David and INTERMACS and how we could do this in a manner that we would feel comfortable in looking at the data.

DR. PAGE: Thank you.

Other comments?

(No response.)

DR. PAGE: Do you need a summary of that, Dr. Zuckerman?

DR. ZUCKERMAN: No. I would just like to ask Dr. Brindis a question because I think he's hit the thumb on the -- put the thumb on the nail.

The Panel has struggled with key safety events in adjudication this afternoon, specifically bleeding, infection, and stroke. And so I think you're heard from Dr. Naftel that it's not possible, with the INTERMACS construction, which includes every hospital in the U.S., to have consecutive patients and adjudication of events.

But for the Agency and Sponsor's purposes, I could see a scenario where maybe 10 to 15 sites could agree to that type of rigor with respect to those specific safety events, which is really what we've been lacking here.

And I see you shaking your head yes.

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I was wondering if other people would think that that's the direction in which the Agency, Sponsor, and NHLBI should move?

DR. PAGE: I'm seeing people affirming that.

Dr. Somberg.

DR. SOMBERG: Can I just -- I think that's optimum. But there is an intermediate where, at least, having some comparator and having some information.

So if you can't get 15 centers to do consecutive, sequential, and maybe even adjudicated data, at least having, when you're using a registry as a comparison for efficacy, you also can use it as a comparison for safety, even though -- because the other data or the efficacy data is not adjudicated. It's not consistent; it's not consecutive, either.

DR. ZUCKERMAN: And I agree. And certainly I think we want to have those general comparisons. But to really move the field forward for LVADs, we're going to need better safety data to see what's going on.

And do you have any other suggestions, or do any other people have suggestions?

DR. PAGE: Dr. Allen.

DR. ALLEN: You know, I think, unfortunately, as much as we'd like to get out of doing randomized trials, the Agency is stuck between a rock and a hard spot in that VAD therapy has been around for a long time, but here it is, 2012, and we're only looking at our second device to be approved.

Or third device.

And I think, as we move forward, more devices will become available, and I think you're going to be stuck with putting the bar on a device that's currently used and approved, that we have good data on, and then moving forward with randomized trials, to figure out what is going to be the best device because all of these devices are a little bit different.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, just one thought.

Today we're talking about this device, we have these data, and we have to make a decision. And what Bram was asking is, in Phase IV, can we get some better data that will help to refine a label if this is approved. And I think the answer is yes, and I think the subset that Ralph has suggested is the way to go.

DR. PAGE: Thank you.

Okay to move on to 6c?

Please discuss if, within the PAS, there are other:

- effectiveness endpoints that should be included as secondary endpoints; and
- safety endpoints that should be included.

Dr. Borer.

DR. BORER: Yeah. You know, we talked about other measures

that could be made, but I don't think that's the issue. I think there were many endpoints that were quite reasonable in the study. The question is to measure them. I think the problem is they weren't measured. There were many missing data.

So I don't think we should be focusing on additional endpoints. I think we should be focusing on trial management so that the endpoints are done.

DR. PAGE: Thank you.

So making use of the endpoints that we have. Anybody have any burning additions to what's already been out?

Dr. Lange.

DR. LANGE: I'd just try to make the learning curve a little more quantitative, rather than saying we're going to see how centers do. That's the only thing that wasn't part of the secondary endpoints now but should be when they roll it out.

DR. PAGE: Great.

Dr. Slotwiner.

DR. SLOTWINER: I would just try to collect some information on patients with defibrillators to help us understand better how to manage them.

DR. PAGE: Very good.

DR. ZUCKERMAN: Okay, that's very helpful.

I do have a specific question for Dr. Cigarroa, since he mentioned it.

I think the one endpoint, perhaps, that you might want included is the TTR, so that good anticoagulation guidelines could be developed and we could monitor how it's being used, or am I putting words in your mouth, Dr. Cigarroa?

DR. CIGARROA: No, I would agree because I don't know. Maybe the target INR of 1.8 is where we should be. And so I think that understanding and having that data is critical, and I would have that.

DR. PAGE: Thank you.

Let's go on to Question 6d: Please comment on the clinical acceptability of a 10% margin for non-inferiority for the Newly Enrolled PAS.

And I think we've already discussed this, and it's a bit more rigorous than 15%, but is it appropriate? I think that needs to be developed between the FDA and the Sponsor and with input according to more recent data.

Anything else any of the panelists want to add to that?

Dr. Somberg.

DR. SOMBERG: Doesn't it also matter what's the performance standard? You're talking about comparing to performance, so I mean if we're raising the bar to 94%, then maybe 15% is okay. But if we're staying at 65%, maybe it should be 5%.

DR. PAGE: Thank you for clarifying that. I was anticipating that we both reestablish what the bar is and then, according to the trial design, determine, with the likes of Dr. Evans, determine how close the standard should be, whether it's 10%, 5%, 15%.

Dr. Borer.

DR. BORER: Well, we must not forget that the number that's selected has to be realistic, which means that it's necessary to be able to recruit the number of patients that would be needed to have the power to see the difference, if it's really there. But as was said before, that's something that really should be discussed between the FDA and the Sponsor.

DR. PAGE: For sure.

Dr. Cigarroa.

DR. CIGARROA: And the power to detect that may lessen as individuals in this arena, both heart failure specialists, from a cardiology perspective and surgical perspective, are better at selecting the patients. So patient selection, in addition to device, in addition to surgical and postoperative care, may lessen the ability to see that 10% difference.

DR. PAGE: Point well made.

I'm going to move on to Number 7: Labeling.

Draft labeling was provided by the Sponsor. We're specifically asked to comment on the appropriateness of the study data included in the labeling, and discuss whether there are any analyses or data not provided in

the labeling that would be important to provide to the user in the labeling.

And I might just mention that some analysis has already been requested of the Sponsor, and that might be appropriate. But beyond that, any other comments or concerns about the data included in the labeling before we move on to summary and vote?

(No response.)

DR. PAGE: I'm not seeing -- Dr. Lange.

DR. LANGE: Again, I just have trouble -- if any of the secondary data is in there in the labeling, and I can't recall whether it's -- I want to put it out there as representative of good data, and so the primary analysis is fine, but I have trouble with the secondary analysis in the data labeling.

DR. PAGE: Would you put no data in there, in terms of safety, or would you put in the data that we have available with the caveat that there are concerns?

DR. LANGE: All the quality of life, six-minute walk, all that stuff, incomplete data. The other stuff, in terms of adverse events, is fine.

DR. PAGE: Okay.

Dr. Cigarroa.

DR. CIGARROA: I was just looking for the labeling. I just wanted to review it.

DR. ZUCKERMAN: Dr. Cigarroa, I would go to Appendix M and --

DR. PAGE: I'm going to submit that if we haven't reviewed it already, we can't review it right now. We can address that offline.

Is that okay, Dr. Zuckerman?

DR. ZUCKERMAN: Okay. So I don't quite understand Dr. Lange's point because the quality of life data is currently in the label, so you would take it out, given the inadequacy of -- okay.

DR. PAGE: Dr. Somberg, do you want to comment on that?

DR. SOMBERG: I don't think he's suggesting that you take it out. I think he was saying that incomplete is the word you use. What I would say, that you should say that there was missing data, that there is not a comparator, this is what's in the literature as the rates of problems, the major thing, and that each time you say, like, for a six-minute walk, there may be 46% of the data was not available for the analysis, so a clinician can make the judgment of how reliable each point is in his mind. His or her mind.

DR. LANGE: Let me speak for myself. I would take the data out.

DR. PAGE: Thank you, Dr. Lange.

Others?

I personally wouldn't and would put the data that we have. I think we've heard a compelling argument that when patients are at death's door, they don't fill out quality of life surveys. But if we have some that filled it out before and after, and some before and more after, I think the fact that

more people filled them out is at least interesting to me. So I'd put the data in with the caveat, as Dr. Lange mentioned, that there are concerns about absent data.

DR. BRINDIS: I agree.

DR. PAGE: That's just an alternate opinion.

DR. BRINDIS: I don't know if you want to raise hands or something, but I would agree with what you just said.

DR. PAGE: Okay. And I'm seeing others saying -- so the consensus isn't necessarily to throw the data out of the label.

DR. ZUCKERMAN: Okay, thank you. But the limitations of the data need to be appropriately underlined.

DR. PAGE: I'd say we all agree on that.

Thank you.

We've gone through all of the questions now, and now it's time for FDA and Sponsor summations.

At this time, the Panel will hear summations, comments, or clarifications from the FDA. You have 10 minutes. If you don't want to take all 10 minutes, we will forgive you.

DR. ZUCKERMAN: The FDA wants to decline.

DR. PAGE: We forgive you. Thank you.

At this point, I welcome comments, summary, and clarifications from the Sponsor. You have 10 minutes.

DR. AARONSON: Keith Aaronson.

I guess I'd like to start by thanking the Panel for letting us present this data.

I think one thing that's come through clear, I hope, success with this device was, in fact, excellent. The success was, in fact, the best ever in the clinical trial of a ventricular assist device for the bridge-to-transplant indication. The principal outcome was met, it was met by a wide margin, and it was met no matter how you do the analysis. We went through a number of different scenarios, and each way, it was quite strong.

The improvements in quality of life were huge. I think it's important to recognize that there were 140 patients who started this study; there were 88 patients available at six months. That's not because of loss to follow-up; that's mostly because of success. Patients got transplanted; that's what was supposed to happen in this trial.

If you look at the number of patients who were available for quality of life measures or six-minute walk measures, it was largely in 74, I believe, paired patients that were available. That's not that far off from the 88. If you applied KCCQ scores of zero to the 14 patients who were not available for paired analysis, and if you imputed zeros, the difference wouldn't have been 30; it would have been about 24.

When the validation studies for the KCCQ done by Spertus and colleagues, who created the measure, they determined what would be small,

medium, and large improvements in quality of life in the KCCQ. And 22 is large. So these were huge improvements in quality of life.

We've had a very thorough discussion of the trial, warts and all, and I certainly acknowledge the warts. I think the discussion has been appropriate and enlightening. And I think it's clear that study of bridge-to-transplant population is tough. These are sick patients. There's always going to be a limited number of them.

There are 2300 heart transplants done a year in the United States. Not all of those patients require a VAD to get to a transplant. Not all patients who require VADs get to transplant consent to be in a clinical trial. So I think it's important that the Panel keep that in mind when they discuss randomized clinical trials in this context as opposed to the DT context.

VADs, all VADs, including the HVAD, are associated with serious adverse events. The incidence of AEs in this study were quite similar to the incidents of AEs that have been observed with the HeartMate II. If one examines the magnitude of the point differences that we're seeing compared to the literature, if the comparator arm in this study was a randomized comparator arm, there would not be even remotely enough power to identify differences in these rates.

The HeartMate II is the VAD that's being used in the vast majority of implants for durable bridge-to-transplant in the United States. It's a very, very good VAD. We've placed over 250 of them at the University of

Michigan. I believe we have the longest living patient on a single one of them in the world, over seven years, so no means want to demean it. But we need another option. Each device is going to have its relative strengths, and our patients deserve to have these options available to them.

And then, finally, as a cardiologist treating patients with advanced heart failure, advanced stage heart failure, I feel strongly that we need to have competition in this field. The competition is good in most things. We need to reduce the incidence of adverse events, and that's going to happen when there are more players in this arena, when there are more companies, when there's more investment, when there are more clinical trials, clinical studies. The HVAD, I think, has clearly shown very positive results. It's a good step in the direction of having more competition, and I believe that we've given you evidence to support its approval.

Thank you.

DR. PAGE: Thank you very much.

Before we proceed with the vote, I'd like to ask Robert Dubbs, our Consumer Representative; Burke Barrett, our Industry Representative; and Deb McCall, our Patient Representative, if they have any additional comments.

Mr. Dubbs.

MR. DUBBS: I don't know whether it's possible to provide approval in part and rejection in part, but I don't feel that it's been shown to

be safe in the population of women and minorities. So I would encourage and am encouraged by the effectiveness, regardless of all the discussions that we've had. I do think it's effective. But I don't think it's safe in those two subgroups in terms of the data that we've seen so far. And I'd encourage that we bifurcate our decision and request much more information before we just give blanket approval.

DR. PAGE: Thank you.

Mr. Barrett, do you have comments?

MR. BARRETT: Yeah. I'll be very brief; it's been a long day.

I think this one point that I want to make that's been touched upon throughout the day, but maybe it's worth reemphasizing, is first to compliment the Sponsor and the Agency for taking a field where studies were conducted using -- I call them OPCs, Objective Performance Criteria; here we call them PGs, Performance Goals -- to the next step in what is clearly going to be an evolution.

And I hear and understand the diversity of opinion of the quality of data that would be ideal. But we have to remember, as is often the case when we're here reviewing these studies, that it's about five years when the design was solidified to where we're here today looking at the results. The regulatory predictability is an important thing to the sponsors of these studies, to industry, and I think on that point, the Sponsor clearly met the pre-specified endpoints.

I want to reiterate something I think Dr. Lange said the best, about the reasons why certain elements of INTERMACS were used as a comparator and others weren't. It didn't seem to me that this wasn't carefully considered. My impression was it was carefully considered and that because some data elements captured in a registry are ideally more concrete than others, the endpoint primary efficacy comparator was chosen to be used from INTERMACS and safety wasn't. So I think the way Dr. Lange said it was very clear. Alive on the originally implanted device, transplanted, or explanted for recovery, it's pretty crisp that you could capture that from a registry as compared to some of the side effects. So to me, at the time, I think that a careful decision was made.

I do want to say something to my colleagues in industry. We all strive, those of us who run these studies, to run high-quality studies, and certainly there are lessons to be learned from the review today that I hope everybody will pay attention to.

And, again, I just want to encourage the Panel, as you close your deliberations and enter the voting phase of this meeting, that you keep in mind that the pre-specified endpoints of the study were met.

Thank you.

DR. PAGE: Thank you very much.

Ms. McCall, do you have any comments?

MS. McCALL: Yes, thank you.

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As a Patient Representative, my ultimate goal is to weigh risk versus benefit. We have plenty of experts here who have decades of clinical experience behind them. My job is to basically look at it and say would I recommend this?

When I read the data, as I listened to the discussions today -- and I really appreciate the patients that came and talked about their experiences with it -- I'm conflicted.

If this were a family member, a friend, someone I cared about and they were male, absolutely. I would recommend this and say go for it.

Based on the number of females that had so many problems in this study, I would have to recommend it with reservations, think about it before they do it.

DR. PAGE: Thank you.

Before we take the vote, we need to take care of a technical issue which will take five minutes, so we're going to take a five-minute break. There isn't enough time to go to the restroom, it's just enough time for us to take care of this technical issue before the electronic vote, so I ask you to stay in the hall, and we'll start as soon as we're ready to move forward.

(Off the record.)

(On the record.)

DR. PAGE: We are ready to go. And I do not have an electronic voting machine because I don't get to vote unless there's a tie.

We're 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 --

DR. ZUCKERMAN: Excuse me, I think we lost two Panel members.

DR. PAGE: Thank you, Dr. Zuckerman.

(Pause.)

DR. PAGE: Dr. Zuckerman will be joining us in just one minute.

Before we do take the vote, I would like to thank both the Sponsor and the FDA for their hard work at putting together very clear presentations for the Panel. We do appreciate that.

We appreciate the audience. And this has been a long day. We're coming to the finish line.

Now, we're ready to vote. 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 - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories

conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is a 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: Thank you.

The HeartWare VAS, an implantable, electrically powered, centrifugal-flow rotary blood pump with external driver and power sources, is the first ventricular assist device that does not require the creation of an abdominal pump pocket. The HVAS is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage left ventricular heart failure. The HeartWare VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed-wing aircraft or helicopter.

We will now proceed with the vote.

Ms. Waterhouse, will you go through the voting procedure for us?

MS. WATERHOUSE: Please locate the handheld remote. For the next three questions, please press 1 to vote yes, 2 to vote no, and 3 to abstain. Please be certain of your response before you select your answer.

Once the selection is made, there will be no opportunity to change your vote. Before we begin, we will take a test vote to verify that the voting devices are working properly.

Press 1 for yes, 2 for no, and 3 to abstain. As you vote, your name will disappear from the screen. Please lock in your vote.

(Panel vote.)

MS. WATERHOUSE: Okay, the poll is closed. All the devices appear to be working properly, so proceed to the voting questions.

Voting Question 1: Is there reasonable assurance that the HeartWare VAS is safe for use in patients who meet the criteria specified in the proposed indication?

Press 1 for yes, 2 for no, and 3 to abstain.

(Panel vote.)

MS. WATERHOUSE: The poll is closed. We will proceed to Question 2.

Question 2: Is there reasonable assurance that the HeartWare VAS is effective for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WATERHOUSE: The poll is closed.

Final question: Do the benefits of the HeartWare VAS for use in patients who meet the criteria specified in the proposed indication outweigh

the risks for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

UNIDENTIFIED SPEAKER: I pressed it twice.

DR. PAGE: We seem to have a technical difficulty.

UNIDENTIFIED SPEAKER: I pressed it three times, and I held it this time.

MS. WATERHOUSE: The votes have been captured. I will now read each Panelist's vote into the record.

For Question 1: Dr. Cigarroa voted 1 for yes; Dr. Borer voted 1 for yes; Dr. Slotwiner voted 1 for yes; Dr. Lange voted 2 for no; Dr. Yuh voted 1 for yes; Dr. Brindis voted 1 for yes; Dr. Dehmer voted 1 for yes; Dr. Somberg voted 1 for yes; Dr. Allen voted yes; and Dr. Amato voted yes. Dr. Evans also voted yes.

For Question 2: Dr. Cigarroa voted yes; Dr. Borer voted yes; Dr. Slotwiner voted yes; Dr. Lange voted yes; Dr. Brindis voted yes.

Oh, sorry. Dr. Yuh voted yes.

Dr. Brindis --

DR. BRINDIS: I pressed the wrong button. I apologize

MS. WATERHOUSE: -- voted 2 on the remote and meant to vote yes.

Dr. Dehmer voted 1 for yes; Dr. Somberg voted 1 for yes;

Dr. Allen voted 1 for yes; Dr. Amato voted 1 for yes; Dr. Evans voted 2 for no.

Question 3: Dr. Cigarroa voted yes; Dr. Borer voted yes;
Dr. Slotwiner voted yes; Dr. Lange voted yes; Dr. Yuh voted yes; Dr. Brindis
voted yes; Dr. Dehmer voted yes; Dr. Somberg voted no; Dr. Allen voted yes;
Dr. Amato voted yes; Dr. Evans voted no.

DR. PAGE: So to summarize, please.

MS. WATERHOUSE: Can we just take that off the screen? And
please give us a moment while we tally the official votes.

DR. PAGE: And just to give the panelists a heads-up. I will ask
the voting members to each comment on their vote, especially if you voted
no, but we'll go through each individual. I'll start with you, Dr. Yuh, in just
one moment.

(Pause.)

MS. WATERHOUSE: On Question 1, the Panel voted 10 to 1
that the data shows that the HeartWare VAS is safe for use in patients who
meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 10 to 1 that there is reasonable
assurance that the HeartWare VAS is effective for use in patients who meet
the criteria specified in the proposed indication.

Just as a note, we had one mis-vote on our record, which was
Dr. Brindis, who voted 2 for no and meant to vote 1 for yes.

On Question 3, the Panel voted 9 to 2 that the benefits of the

HeartWare VAS do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Please pass the voting devices to the end of the table for collection.

DR. PAGE: I'll now ask for the panelists to briefly discuss their votes.

Dr. Yuh.

DR. YUH: Yes. I think this device represents a clear advance in assist device technology, and I think that the Sponsor met the pre-defined criteria for efficacy fairly convincingly.

I think that the concerns that we've all talked about with respect to the safety are mitigated by the advantages of this device in terms of its technical features. And so I think with the totality of the data, I was very much convinced that this device should move forward in the process, and I didn't see any stark red flags with the data provided that would make me decide otherwise.

DR. PAGE: Thank you.

We seem to have one problem with the voting, and Dr. Somberg tells me that -- we noticed that we had trouble getting his vote up. He actually voted no on safety, and that's consistent with his vote no.

I think we had two noes. Dr. Evans and Dr. Somberg both voted no on safety, is that correct? Is that correct? Yes.

DR. SOMBERG: I voted no on safety, I wasn't sure if -- so there are three votes no, and it says that one vote was no.

DR. PAGE: I need to understand exactly.

DR. ZUCKERMAN: Okay, so let's --

DR. PAGE: Let's go through --

DR. ZUCKERMAN: -- take a step back and --

DR. PAGE: Can we go through individually --

DR. ZUCKERMAN: Yeah.

DR. PAGE: -- and ask people exactly how they voted?

Dr. Yuh -- and just --

DR. YUH: Yes on all three.

DR. PAGE: Yes on all three.

Dr. Allen.

DR. ALLEN: Yes on all three.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: So I voted yes on 1 and 3. I meant to vote yes on 2 and pressed the wrong button.

DR. PAGE: So your vote is yes on all three?

DR. BRINDIS: Correct.

DR. PAGE: Dr. Lange.

DR. LANGE: That's an adjudication problem, by the way.

(Laughter.)

DR. LANGE: I voted no, yes, yes.

DR. PAGE: No, yes, yes.

Dr. Somberg.

DR. SOMBERG: I voted no, yes, no.

DR. PAGE: Thank you.

Dr. Dehmer.

DR. DEHMER: Yes on all three.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yes on all three.

DR. PAGE: Thank you.

Dr. Amato.

DR. AMATO: Yes on all three.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: Yes on all three.

DR. PAGE: Thank you.

Dr. Evans.

DR. EVANS: Yes, no, no.

DR. PAGE: Yes on safety? It was safety, efficacy, and overall.

DR. EVANS: I don't know. It's been too long a day.

(Laughter.)

DR. EVANS: The only thing I know is the Bruins are going to win.

DR. PAGE: Can you just clarify? Safety was yes or no?

DR. EVANS: Safety was no.

DR. PAGE: No. Efficacy was yes?

DR. EVANS: Efficacy was yes.

DR. PAGE: And overall no?

DR. EVANS: Correct.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yes on all three.

DR. PAGE: Yes on all three.

So as I see it, we had three noes on safety and two noes overall, and all affirmative on effectiveness.

So moving on with Dr. Allen.

DR. ALLEN: I think, in totality, the bar that was set for efficacy was clearly passed by the company, even with the issues of trial conduct, considering the extremely ill population that this device was used in.

I think safety, based on my own clinical experience treating these patients, is favorable.

I think one of the key drivers for me in this is that this field

needs competition in order to drive innovation, and I think that approval of this device will speed along the development of future devices.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: I think this device is of incredible benefit to patients who are very ill. It saves lives, it includes quality of life based on the data that we have.

And I'm looking forward to the new paradigm of utilizing registry format for a post-approval study so that we can better understand efficacy issues and how to better apply adjunctive therapy in patient selection in utilizing this device going forward.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: I'd like to thank the Sponsors for excellent presentations and for being responsive to our questions and queries.

I voted no on safety for two issues. One is because we didn't have comparator data. It's not your fault. But the second is I had a little bit of trouble with your data.

And so what I say is I'm not looking for a perfect device, but I'm looking for reliable data, so I'd encourage you, going forward.

To the FDA for a very thoughtful and very thorough analysis and also for the use of the INTERMACS registry, which is groundbreaking and

working with the Sponsor to do that.

And I would encourage Dr. Naftel, if he's still in the audience, to help us in the future to refine this technique.

DR. PAGE: Thank you, Dr. Lange.

Dr. Somberg.

DR. SOMBERG: I think this device has great potential. I'm concerned with what has been said repeatedly about the safety problem, but if you don't have the safety information, you can't make a risk/benefit assessment, and I think we're setting a very bad precedent.

DR. PAGE: Thank you, Dr. Somberg.

Dr. Dehmer.

DR. DEHMER: Like others, I feel this device has great promise. It does represent a lot of technical advances over existing technology. I believe that the Sponsor has met the basic question of showing that the data or that the device is effective.

The safety data is a little questionable, but I think in the totality of all data, I am reasonably assured that it's safe to move forward.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: I think the effectiveness data were convincing and I would point out -- and you'll correct me if I'm wrong. We've talked a lot about randomized trial versus controlled with a registry, et cetera. When this

study was designed, there was no approved comparator. So there was no capacity to do a randomized trial with a comparator that was then available. So I think that the design was the best that could be established at the time, and the company did it, and I'm convinced by the data.

The safety data, we've discussed the problems with the trial management, which makes them less compelling than I wish they were, but the overarching conclusion I draw is that the benefit-to-risk relationship strongly favors the device and that the device has technical characteristics which differentiate it from the existing device, which is a potentially important advantage.

DR. PAGE: Thank you.

Dr. Amato.

DR. AMATO: Using my artistic cap, I looked at the device, and I think it's one of the most beautiful devices that I've seen in the years of my practice, handling other devices which are crude compared to this.

Using my surgical cap, however -- and I'm going to reiterate my points on the safety of going back in on a non-covered pericardium, having seen by either myself or my colleagues rip through conduits and internal memories, et cetera. I would like to see the placement of a GORE-TEX membrane of some sort.

Now, I'm not paid by the company, nor do I have stock in the company, but I think you must, I think, utilize the safety device, and I'd like to

see that pericardium covered.

Thank you very much.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: I voted yes on all three primarily because I think as it relates to efficacy, it certainly met its endpoint robustly.

With regards to Question Number 1, safety, I was conflicted and I remain conflicted. And I voted yes on that only because of the term reasonable. I don't think it's anywhere beyond reasonable and is right in that range.

And I would certainly hope that, moving forward, the data is complete and that we, again, develop best practices with voluntary registries hospital to hospital. Who is abstracting and inputting the data and their level of training is quite variable. And the degrees of auditing are quite variable.

DR. PAGE: Thank you.

Dr. Evans.

DR. EVANS: I voted that I thought it was effective, though somewhat reluctantly. The reluctance came from the fact that there's a key variable from this trial that is half missing and that's quite substantial. So that's where my reluctance came from. And I think we probably should have spent more time thinking about that issue.

But I do think that probably the imbalance with respect to that

factor would have to be extremely significant in order to actually sway the result, given that there was quite a bit of buffer zone in the non-inferiority -- the confidence interval that demonstrated non-inferiority.

I voted no on safety. I don't know how to interpret what was there. We're asking the question is it safe, and yet there's no definition of what safe means. Usually, statistically, I take that to mean that a certain significant event rate is less than something -- is small enough to be acceptable or not important. But there's no discussion of what that is or no rationale for what it should be. And so I have no idea how to interpret that. And without knowing that, I couldn't say that I know that the benefits outweigh the risk, so that's where I came down.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yeah, I voted yes on all three, and I want to compliment the Sponsor, the Agency, and INTERMACS for performing such a thorough study in such a difficult population. And I'm really excited by the model of the INTERMACS registry, and I look forward to getting more precise and further data in the future.

There were some holes in the safety, but I think overall this is a novel device for a desperate population, and I really hope that it's available soon.

Thank you.

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DR. PAGE: Thank you, Dr. Slotwiner.

Before I close this session, I will comment on my own perspective, but before we do that, Ms. Waterhouse needs to read into the record the results of the vote.

MS. WATERHOUSE: I just wanted to clarify, for the record.

Dr. Evans, we had you in our system voting as yes for safety, no for efficacy, and no for the risk/benefit. You said afterwards that you voted no for safety, yes for efficacy, and no for the risk/benefit. Is that correct?

DR. EVANS: Yes, the latter is correct.

MS. WATERHOUSE: Okay.

Then we have, on Question 1, the Panel voted 8 to 3 that the data shows that the HeartWare VAS is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 11 to 0 that there is reasonable assurance that the HeartWare VAS is effective for use in patients who meet the criteria specified in the proposed indication.

And Question 3 remains the same; the Panel voted 9 to 2 that the benefits of the HeartWare VAS do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

DR. PAGE: Thank you very much.

I would like to also thank the Sponsor for putting together an excellent presentation; to the FDA, as well.

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I'd like to thank the Panel for sitting through a long meeting.

I will comment that my own perspective is that this is a masterpiece in engineering and the elegance of it is really compelling, and I believe it has reached an efficacy signal that's important, robust, and I think this will make the difference for many patients, some of whom we saw today.

It almost was, I think, fatally harmed by the issues of safety, and as much as anything, I believe it has shown adequate safety in this population. Unfortunately, the conduct of the trial fell short of what I would expect, and I would encourage the Sponsor in the future, for the post-approval study and future sponsors, to work closely with the FDA so we don't have this conflict in terms of data. And frankly, I believe this might have come to panel sooner if a little bit more time and effort had been invested in managing this study from the outset and throughout.

That being said, for what I could tell from the safety, in the setting of the efficacy, I would vote in favor of this device being approved.

And with that, I'll ask Dr. Zuckerman if he has any other comments.

DR. ZUCKERMAN: I would just like to thank Dr. Page and all the Panel members for an extremely fruitful panel day today. This was a tremendous discussion, and the FDA has learned a lot and got in the necessary advice that we sought to.

DR. PAGE: Great.

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As such, the April 25th, 2012 meeting of the Circulatory System
Devices Panel is now adjourned. Everyone have safe travels. Good night.

(Whereupon, at 6:10 p.m., the meeting was adjourned.)

C E R T I F I C A T E

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

CIRCULATORY SYSTEM DEVICES PANEL

April 25, 2012

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.

CATHY BELKA

Official Reporter

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