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CIRCULATORY SYSTEM DEVICES PANEL

Wednesday, March 17, 2004

9:00 a.m.

Hilton Gaithersburg Washington D.C., North
Salons A, B and C
620 Perry Parkway
Gaithersburg, Maryland

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Cynthia Tracy, M.D., Acting Chair
Geretta Wood, Executive Secretary

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Salim Aziz, M.D.
Mitchell Krucoff, M.D.
William Maisel, M.D., MPH
Christopher J. White, M.D.

CONSULTANTS

Clyde Yancy, M.D.
Judah Z. Weinberger, M.D., Ph.D.
John W. Hirshfeld, M.D.
Thomas B. Ferguson, M.D.
Norman S. Kato, M.D.
Brent Blumenstein, Ph.D.
Charles Bridges, M.D.

Industry Representative

Michael Morton

Consumer Representative

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Bram Zuckerman, M.D.

C O N T E N T S

Call to Order: Cynthia Tracy, M.D.	4
Conflict of Interest Statement: Geretta Wood	4
Introductions	6
Open Public Hearing: Leo Corbet	9
Sponsor Presentation: SynCardia Systems, Inc. P030011: Syncardia Systems CardioWest Total Artificial Heart	
Introduction: Marvin J. Slepian, M.D.	15
CardioWest TAH Overview: Richard G. Smith, MSEE, CCE	18
IDE Clinical Trial: Jack G. Copeland, M.D.	26
Clinical Perspective: Walter E. Pae, M.D.	54
Conclusion: Marvin J. Slepian, M.D.	64
Questions and Answers	67
FDA Presentation	
Summary: Eric Chen, M.S.	83
Statistical Summary: Lilly Yue, Ph.D.	88
Clinical Review: Julie Swain, M.D.	98
Questions and Answers	108
Open Committee Discussion	130
Open Public Session: Robert Jarvik, M.D. Aly El Banayosy, M.D.	290 292
Recommendation and Vote	297

P R O C E E D I N G S

Call to Order

DR. TRACY: Good morning everybody. Happy St. Patrick's Day. I would like to call to order this meeting of the Circulatory System Devices Panel.

The topic today will be a discussion of a premarket application for the Syncardia Systems CardioWest Total Artificial Heart P030011.

Conflict of Interest Statement

MS. WOOD: The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers financial interests, however, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest

1 involved, is in the best interests of the
2 government. Therefore, a waiver has been granted
3 for Dr. Clyde Yancy, and a waiver was previously
4 granted for Dr. Judah Weinberger, for their
5 interests in firms that could potentially be
6 affected by the panel's recommendations.

7 Dr. Yancy's waiver involves consulting
8 services with a firm that has a financial interest
9 in the product at issue for which he receives an
10 annual fee of less than \$10,000. His services are
11 not related to the subject matter before the panel.

12 Dr. Weinberger's waiver involves a
13 stockholding in a firm that has a financial
14 interest in the product at issue. The value is
15 between \$25,001 and \$50,000. The waivers allow
16 these individuals to participate fully in today's
17 deliberations.

18 Copies of these waivers may be obtained
19 from the Agency's Freedom of Information Office,
20 Room 12A-15 of the Parklawn Building.

21 We would like to note for the record that
22 the agency took into consideration other matters
23 regarding Drs. Thomas Ferguson, Mitchell Krucoff,
24 Cynthia Tracy, Judah Weinberger, and Clyde Yancy.
25 These panelists reported past or current interests

1 DR. YANCY: Clyde Yancy, UT Southwestern
2 in Dallas, cardiologist.

3 DR. WHITE: Chris White, Ochsner Clinic
4 Foundation in New Orleans. I am an interventional
5 cardiologist.

6 DR. KATO: Norman Kato, cardiovascular
7 surgeon, private practice, Encino, California.

8 MS. WOOD: Geretta Wood, Executive
9 Secretary.

10 DR. TRACY: I am Cindy Tracy. I am from
11 George Washington University, electrophysiologist.

12 DR. FERGUSON: Tom Ferguson,
13 cardiovascular surgeon, Washington University, St.
14 Louis.

15 DR. KRUCOFF: Mitch Krucoff. I am an
16 interventional cardiologist at Duke Medical Center,
17 and Chair of Clinical Trials for devices at the
18 Duke Clinical Research Institute.

19 DR. MAISEL: William Maisel. I am an
20 electrophysiologist at Brigham and Women's Hospital
21 in Boston.

22 DR. BLUMENSTEIN: I am Brent Blumenstein,
23 biostatistician in private practice.

24 DR. BRIDGES: Charles Bridges,
25 cardiothoracic surgeon, University of Pennsylvania.

1 DR. AZIZ: Salim Aziz, adult cardiac
2 surgeon, clinical associate professor, George
3 Washington University.

4 MS. WELLS: Chris Wells. I am the
5 consumer representative on this panel.

6 DR. ZUCKERMAN: I am Bram Zuckerman,
7 Director, FDA Division of Cardiovascular Devices.

8 MS. WOOD: Pursuant to the authority
9 granted under the Medical Devices Advisory
10 Committee charter dated October 27th, 1990, and as
11 amended August 18th, 1999, I appoint the following
12 individuals as voting members of the Circulatory
13 System Devices Panel for this meeting on March the
14 17th, 2004: Clyde Yancy, M.D., Judah Z.
15 Weinberger, M.D., Ph.D., John W. Hirshfeld, M.D.,
16 Thomas B. Ferguson, M.D., Norman S. Kato, M.D.,
17 Brent Blumenstein, Ph.D., Charles Bridges, M.D.

18 For the record, these individuals are
19 special government employees and are consultants to
20 this panel under the Medical Devices Advisory
21 Committee. They have undergone the customary
22 conflict of interest review and have reviewed the
23 material to be considered at this meeting.

24 In addition, I appoint Cynthia Tracy, M.D.
25 to act as temporary chairperson for the duration of

1 this meeting.

2 Signed by David W. Feigal, Jr., M.D.,
3 M.P.H., Director, Center for Devices and
4 Radiological Health, and dated March the 11th,
5 2004.

6 **Open Public Hearing**

7 DR. TRACY: Thank you.

8 Now we will have the open public hearing.
9 I have a statement to read before we invite our
10 guests up.

11 Both the Food and Drug Administration and
12 the public believe in a transparent process for
13 information gathering and decisionmaking. To
14 ensure such transparency at the open public hearing
15 session of the advisory committee meeting, FDA
16 believes that it is important to understand the
17 context of an individual's presentation.

18 For this reason, FDA encourages you, the
19 open public hearing speaker, at the beginning of
20 your written or oral statement, to advise the
21 committee of any financial relationship that you
22 may have with the sponsor, its product, and, if
23 known, its direct competitors.

24 For example, this financial information
25 may include the sponsor's payment of your travel,

1 lodging, or other expenses in connection with your
2 attendance at the meeting. Likewise, FDA
3 encourages you at the beginning of your statement
4 to advise the committee if you do not have any such
5 financial relationships.

6 If you choose not to address this issue of
7 financial relationships at the beginning of your
8 statement, it will not preclude you from speaking.

9 Mr. Leo Corbet of Phoenix, Arizona, has
10 requested time to address the panel, I believe.

11 MR. CORBET: Good morning, ladies and
12 gentlemen.

13 I normally don't get very nervous at this,
14 but you can imagine, as a transplant patient, how
15 nervous people with your credentials make me. I
16 had a heart transplant in 2001 and prior to that, I
17 was on the machine that is under consideration this
18 morning.

19 I am a lawyer by education, I was a
20 politician by accident, and I ended up in business
21 for the last 20 years and was president of an
22 ethanol company in Nebraska for the time until I
23 got so sick that in 1998, I was told that I had to
24 have a transplant or I would die.

25 Being St. Patrick's Day and I am an

1 Irishman with an Italian heart, I will try not to
2 speak with my hands too much.

3 When I went to the hospital in 2001, I had
4 never been in the hospital at all until 1998, and
5 then I had the misfortune of all at once, I came in
6 contact with a lot of medicine, a lot of medical
7 opinions, and finally, they told me I had to get on
8 the heart transplant list, and I went to Arizona,
9 the University of Arizona.

10 I was lucky enough to be put on that list
11 where I was for two years, and I went to the
12 hospital in March, oddly enough, March 10th of
13 2001, where I just thought I would have to go down
14 there and get a checkup and a cleanup, and then I
15 would be leaving, but I didn't leave the hospital
16 for another four months.

17 I got so sick and all my parts were going
18 down the drain, I guess, so it was determined that
19 I would be put on this CardioWest machine, which I
20 came to know fondly as Big Blue.

21 Big Blue and I were partners for 3 1/2
22 months in the hospital. It's a 300-pounder
23 machine. I had some picture, but my wife told me
24 that it wouldn't be within the rules if I started
25 walking around to the jury and started handing them

1 out to you, so I left them with her in the
2 audience.

3 I was on that machine for 3 1/2 months
4 until we could find the human or they could find
5 the human heart to give me, and after that, I was
6 in the hospital another two weeks.

7 Since that time, I have retired as an
8 attorney, I have cashed out of my business in
9 Nebraska, and now I am on the board of directors of
10 the Arizona Coalition for transplantation, the New
11 Heart Society. My wife and I work jointly with the
12 donor network.

13 This machine is so vitally important to
14 people like myself. If I could have brought these
15 pictures up here, you would see six of us on this
16 same machine, all of us who just would not have
17 made it without this bridge to a time when you can
18 get a heart.

19 According to the donor network, 50 percent
20 of all of the donors that actually are considered
21 aren't qualified. This is for organs in general or
22 whatever.

23 So, we have a big job there trying to get
24 people to know about transplants. So, what do you
25 do? You have to have machines similar to this or

1 some other way to keep these people alive, and that
2 is what this particular instrument does, and it
3 does it well.

4 The only negative some people say it has
5 is the sound, the whirring sound that it makes
6 while you are there, and for 24 hours a day I knew
7 I was alive as long as that sound was being made,
8 and most of the guys that were involved did. I say
9 "guys," not because I am sexist, but because it's
10 the people with large chest cavities were the ones
11 that were prime candidates for this particular
12 machine.

13 When I got out of there, I felt it was
14 incumbent upon me, because of a number of factors,
15 my ability to dump everything else I was doing and
16 get involved in this thing.

17 My wife and I do own shares of stock in
18 this company. That is not very much of my net
19 worth at all, but I am told I had to disclose that
20 to you today.

21 We believe that this staff that sits
22 behind me, and this machine, are a vital part of
23 the technology that has paved the way to success
24 stories like mine and others, where we could be
25 here today to stand and tell you what we have been

1 through.

2 I didn't want to talk very long, so I
3 won't, I will just stop. If you have any
4 questions, I was there, I can tell you the thing
5 ran 24 hours a day for probably, I think it was
6 about 110 days, and then I was on it, and when it
7 was time to get off, it was kind enough to let me
8 have this human heart, which is working very well.

9 I appreciate the opportunity to be here
10 today. Well, actually, I appreciate the opportunity
11 to be anywhere, and if there any questions, I will
12 be happy to answer them. I know you have a long
13 day, so I am going to cut this and wait if you have
14 any questions.

15 DR. TRACY: Thank you, Mr. Corbet. That
16 was a very powerful presentation. I think if you
17 will be around a little while later, the panel may
18 have some questions for you at a later point.

19 MR. CORBET: Yes, ma'am. I have made it
20 67 years, I am not going to stop now. I will be
21 here.

22 DR. TRACY: Thank you, sir.

23 Are there any other members of the
24 audience who wish to address the panel today
25 regarding this topic or any other topic?

1 [No response.]

2 DR. TRACY: If not, then, we will close
3 the open public hearing at this point.

4 MS. WOOD: I would remind the speakers
5 that are about to present to introduce themselves
6 and to state their conflict of interest.

7 DR. TRACY: Can we ask the sponsor to come
8 forward at this point to discuss the SynCardia
9 Systems, Inc., CardioWest Total Artificial Heart.

10 **Sponsor Presentation: SynCardia Systems, Inc.**

11 **P030011: SynCardia Systems CardioWest**

12 **Total Artificial Heart**

13 **Introduction**

14 DR. SLEPIAN: Madam Chairman,
15 representatives of the FDA, members of the
16 Circulatory Device Panel, good morning. I am Dr.
17 Marvin Slepian. I am the CEO of SynCardia, and I
18 have an equity interest in this company.

19 [Slide]

20 Our purpose here today is to seek panel
21 recommendation for the SynCardia CardioWest Total
22 Artificial Heart.

23 [Slide.]

24 Assembled with me here today are the
25 following presenters and representatives. In

1 addition to myself, to my right is Richard Smith,
2 who is the Chief Operating Officer of SynCardia, an
3 engineer, Director of the Artificial Heart Program
4 at the University of Arizona.

5 To his right is Dr. Jack Copeland,
6 Professor of Surgery and Chief of the
7 Cardiothoracic Surgical Section, and Principal
8 Investigator in the trial that we will present here
9 today, also from the University of Arizona.

10 With us is Dr. Walter Pae, behind me,
11 Professor of Surgery in the Section of
12 Cardiothoracic Surgery at Penn State in Hershey.

13 Also, is Mary Dancer, who has been our
14 clinical consultant with Data Management; Dr. Mark
15 Knowles, our statistician; and Sharon Rockwell, our
16 regulatory consultant.

17 [Slide.]

18 We have several additional responders with
19 us: Dr. Jim Long, who is Associate Professor in
20 Cardiothoracic Surgery, as well as a Professor in
21 Biomedical Engineering, and Director of the
22 Artificial Heart Program at the University of Utah.

23 In the audience is Dr. Walter Dembitsky,
24 Cardiothoracic Surgery, in practice at Sharp
25 Memorial Hospital in San Diego.

1 From outside the United States is Dr. Aly
2 El-Banayosy, who is Director of the Artificial
3 Heart Program at the Rhur University Heart Center
4 in Bad Oeyenhausen, Germany, and we have just heard
5 from Leo Corbet.

6 [Slide.]

7 Our presentation will be delivered as
8 follows. I will provide a very brief introduction.
9 Richard Smith will then discuss the technical
10 aspects of the CardioWest heart. Dr. Copeland will
11 present the IDE clinical trial. Walter Pae will
12 provide a clinical perspective, and I will make a
13 brief concluding remark.

14 [Slide.]

15 The indication for use that we are seeking
16 is as an in-hospital bridge to transplantation in
17 cardiac transplant candidates at imminent risk of
18 death due to irreversible biventricular heart
19 failure.

20 [Slide.]

21 To provide a brief history, this
22 technology evolved originally from work at Utah
23 with Dr. Jarvik. There has been significant early
24 experience with the early technological construct
25 of this heart.

1 This technology was then transferred to
2 the University of Arizona at the University Medical
3 Center in the early nineties, and it was developed
4 subsequently under the CardioWest aegis.

5 From 1993 to 2002, we have been conducting
6 the IDE trial. In 1998, we received European CE
7 approval for this, and subsequently have gained
8 experience with this device outside the United
9 States.

10 In 2001, SynCardia was formed as an entity
11 acquiring all this technology under one umbrella
12 with the primary purpose of completing these
13 clinical studies and of submitting this technology
14 for approval to bring it out for clinical use for
15 cardiovascular medicine.

16 I would now like to call on Richard Smith
17 to provide a technical overview of this heart.

18 **CardioWest TAH Overview**

19 MR. SMITH: Thank you, Marvin.

20 [Slide.]

21 My name is Richard Smith. I am the Chief
22 Operating Officer of SynCardia. I have an equity
23 interest in this company. I also am the Director
24 of the Artificial Heart Program in Tucson, Arizona,
25 at the University Medical Center. I have been in

1 that position since 1985, and I have been involved
2 with this project since 1991.

3 [Slide.]

4 The system we are discussing here is the
5 CardioWest TAH System. There are three main
6 pieces. The implantable piece is implanted in the
7 chest and exits the chest wall. There is an
8 external console and there are 7 feet of a
9 driveline that hooks the two together. I will
10 discuss each one of these.

11 [Slide.]

12 The implantable system--and I have put on
13 the tables two artificial devices, the actual
14 implantable systems themselves--but there are 6
15 components that make up the implantable system.

16 The two inflow connectors are attached to
17 the remanent atria after the natural ventricles and
18 valves are removed. Those are sown on. The
19 outflow connectors are sown onto the pulmonary
20 artery and the aorta, and then the actual
21 ventricles are snapped into those four connectors.

22 Once that is accomplished, it actually
23 occupies the space where the diseased heart was
24 removed. The displacement volume is 400 ml. The
25 actual weight is 160 grams, which is less than the

1 actual heart that was removed in most cases.

2 In that position, the blood flow path is
3 very similar to what the natural heart is. There
4 is a very short inflow cannula or connector 2
5 centimeters or less, and the actual path of blood
6 between the natural atria to the great vessels is
7 less than 20 cm.

8 The system is designed to be tailored to
9 the individual, so there is an adjustment that can
10 be made after the ventricles are in place, so that
11 we can achieve the best fit, or if there is not the
12 best fit, that we can actually adjust it to make it
13 a better fit.

14 The other unique thing about this system
15 as compared to other systems is there is no
16 surgical pocket, so the only space that is used is
17 the actual chest cavity.

18 [Slide.]

19 Inside the actual ventricles themselves,
20 here is an x-ray to demonstrate that the mechanical
21 valves, Medtronic Hall mechanical valves, the
22 inflows are larger than the outflows, 27 mm versus
23 25.

24 It is hard to see, but there are 4
25 diaphragms that actually separate where the air

1 comes in and where the blood comes in, in between
2 there. There is also a wire-reinforced driveline
3 that actually connects to the outside driveline.
4 So, these three components are part of the
5 reliability aspect of this particular device.

6 [Slide.]

7 The external console is shown here, and
8 incorporates many redundancies in terms of to
9 provide a good reliability. For example, the
10 primary controller is all that is actually used to
11 operate the device, and there is an actual total
12 backup controller inside the console.

13 In this console is also backup air and
14 power sources, and you can see an alarm panel here.
15 The computer on the top provides information to the
16 user related to ongoing rate of the device when it
17 is set, the actual stroke volume that is caught and
18 calculated, and then from the combination of those
19 two, an ongoing reading of cardiac output.

20 [Slide.]

21 The system is a fairly simple system to
22 use and tries to mimic the Starling Principle of
23 the natural heart. The drive pressures are set in
24 order to achieve what we call "full eject" in both
25 ventricles, so you are overcoming the pressure in

1 the pulmonary system and the systemic system on
2 each beat. Then, the rate is set in order to
3 achieve what we call "partial fill," so we do not
4 want the whole ventricle to fill.

5 It can fill to 70 ml, so we try to set it
6 up and the computer tells us about 55. In that
7 mode, we don't have to make many adjustments after
8 that, and as the patient then requires more cardiac
9 output as he returns more blood to the heart, more
10 gets filled, and since at each beat, it is ejected,
11 the cardiac output goes up automatically and
12 adjusts both up and down without any adjustments
13 from the user.

14 In achieving this in the chest, and with a
15 short pass, we can accomplish 9 1/2 liters of
16 cardiac output. Typically, we are running at 7 to 8
17 1/2 in most of these patients.

18 [Slide.]

19 This is a schematic of the system
20 simplified for your review. If you can pay
21 attention to the far right, these are 3 air sources
22 we plug into the wall, and there are 2 internal air
23 sources.

24 All 3 of these are hooked up at any one
25 time, and as the patient is moved around to

1 exercise or to walk, the wall is detached and then
2 these other systems take over. I will go through a
3 couple of cycles.

4 This is what the controller operates.
5 There is valves in there that basically turn from
6 this high compressed air during a systolic cycle
7 and pumps air and pushes the diaphragm up. So,
8 that is half the cycle.

9 On the second side of the cycle--and it is
10 all timed--the valve turns to room air and the air
11 is then exhausted to the outside.

12 It is a very simple system and these
13 sensors that are inside the console monitor this
14 non-invasively, so on the systole, the pressure
15 sensors provide this wave form.

16 This wave form tells that we have
17 accomplished the pressure gradients against the
18 pulmonary and systemic system, and this little
19 notch here says that we are fully ejecting, so the
20 user has a feedback that basically, you have
21 accomplished rule number 1, which is full eject.

22 On the diastole side, we generate this,
23 and this actually calculates the air coming back,
24 and from that we get a stroke volume measurement
25 estimate, so by multiplying the rate that we set on

1 the console and the stroke volume we get indirectly
2 at the cardiac output fed back at all times.

3 There are a series of alarms that are
4 constantly monitoring this system also.

5 [Slide.]

6 Now, to differentiate this from other
7 devices, in the very simplistic of viewpoints, you
8 are taking out the natural ventricles and valves.

9 The VADs are hooked when they are hooked
10 to the natural heart, so issues, such as
11 arrhythmias, for example, if you put an LVAD in,
12 then arrhythmias can actually affect the filling of
13 that LVAD, are alleviated obviously because you
14 don't have the ventricles in place.

15 Any type of right ventricular dysfunction
16 by any cause is alleviated because you have an
17 artificial right ventricle in place.

18 Aortic valve issues, whether it is a
19 prosthetic aortic valve or maybe the aortic valve
20 has insufficiency, affect how VADs are filled in
21 that type of setting and again are not an issue
22 when you put a TAH in.

23 Things like thrombus in the left
24 ventricle, septal defects, all these things are
25 technical issues that if you have a VAD in place,

1 they affect the performance of those VADs and are
2 not issues when the TAH is implanted.

3 [Slide.]

4 Here is again a simplistic viewpoint of
5 the circulatory system. Here I have shown that the
6 right ventricle, artificial ventricle is in place,
7 and the left artificial ventricle is in place.

8 When this occurs, immediately we see in
9 the OR that the central venous pressure is reduced
10 because you now have a good pump in place that
11 basically pushes blood across the lungs, and
12 therefore guarantees in most cases 6 or 7 liters of
13 flow to the left side, which then basically is
14 delivered to the organs.

15 So, there are two effects here that
16 accomplishes. You get an increase in your blood
17 pressure because of your increase in cardiac output
18 on this side, and you get a decrease in the central
19 venous pressure on this side, so the actual
20 differential of pressure across these organs is
21 maximized.

22 So, you get an increase on this side,
23 decrease on this side, and that allows us to have
24 the best situation for potential organ recovery in
25 a lot of these patients that begin with organ

1 dysfunction.

2 [Slide.]

3 During the trial, we have worked with the
4 FDA in terms of in-vitro testing. The original
5 setup was to run 8 systems, 4 of them to 6 months,
6 and the other 4 to failure. That has occurred.

7 In addition, we have taken 3 systems that
8 were actually placed on the shelf, a sterilization
9 period, for 3 years, and then we put those on the
10 mock circulations also, and those have been run to
11 failure. To date, we have not had any failures,
12 and these systems have run for over 3 1/2 years.

13 [Slide.]

14 So, in conclusion, the CardioWest TAH
15 provides biventricular cardiac flow up to 9.5
16 liters/minute. The component and design features
17 provide very good safety and facilitate the implant
18 procedure.

19 There are no reliance or limitations
20 related to any native heart dysfunction, and the
21 CardioWest TAH function is simple and reliable.

22 Thank you.

23 At this time, I would like to invite Dr.
24 Copeland to talk about this study.

25 **IDE Clinical Trial**

1 DR. COPELAND: Thank you, Rich.

2 My name is Jack Copeland. I am the
3 principal investigator in this study. I am Chief
4 of the Section of Cardiovascular Surgery at the
5 University of Arizona and Professor of
6 Cardiothoracic Surgery.

7 I do have an equity interest in SynCardia.

8 We are going to present the results of
9 this SynCardia CardioWest Total Artificial Heart
10 IDE Study.

11 [Slide.]

12 First of all, I would like to mention the
13 clinical need for the total artificial heart. This
14 is simply in patients who have biventricular
15 failure, who have either impending or ongoing
16 end-organ failure and decompensation, a very sick
17 patient group who can be transplanted if a heart is
18 available.

19 As we all know, hearts aren't so readily
20 available as they should be or we would like them
21 to be, and most often these patients die unless
22 there is some intervention, the intervention being
23 the total artificial heart which provides
24 hemodynamic stabilization, organ recovery, and
25 allows bridge to transplantation. So, this is used

1 when medical therapy fails.

2 [Slide.]

3 If we look at the most recent data from
4 the UNOS waiting list, we see that in 2002, 14.4
5 deaths per patient year occurred on the waiting
6 list, so there is a real need that has been
7 documented by the United Network for Organ Sharing,
8 our national donor group.

9 [Slide.]

10 The aims of the study are to look at the
11 efficacy and safety of cardiac replacement with the
12 CardioWest Total Artificial Heart in bridge to
13 transplantation.

14 [Slide.]

15 Our hypothesis is this - that patients
16 with irreversible biventricular failure could be
17 saved utilizing the CardioWest Total Artificial
18 Heart as a bridge to transplantation.

19 [Slide.]

20 The study design is a prospective,
21 non-randomized, multi-center study of critically
22 ill patients with irreversible end-stage congestive
23 heart failure, all of whom are in a New York Heart
24 Association Class IV, who are also
25 transplant-eligible.

1 Historical controls are patients who were
2 put into the study who met identical entry criteria
3 to the study patients.

4 [Slide.]

5 The study endpoint variables are shown on
6 this slide. First, there is a multifactorial
7 endpoint that is called "primary efficacy endpoint"
8 or a treatment success.

9 Treatment success means that at 30 days
10 post-transplant the patient is alive, New York
11 Heart Association Class I or II, is ambulatory, is
12 not on a ventilator, nor is he on dialysis.

13 So, the idea is that the patient is up and
14 around and reasonably healthy hopefully.

15 The secondary efficacy endpoints are:
16 survival, hemodynamic recovery, end-organ recovery,
17 and ambulation.

18 Finally, we looked at safety parameters as
19 reflected by adverse event analysis.

20 [Slide.]

21 The key issues for us in the design of the
22 study were as follows: To define a patient
23 population that needs biventricular bridge to
24 transplantation, and to define the natural history
25 of untreated patients using historical controls.

1 [Slide.]

2 In this study, there were 5 centers and 12
3 surgeons including the University Medical Center in
4 Tucson, myself and Francisco Arabia; Loyola
5 University Medical Center, Chicago, Drs. Foy,
6 Sullivan, and Montoya; LDS Hospital in Salt Lake,
7 Dr. Long and Doty--we are hoping that Dr. Long will
8 arrive soon, he is scheduled to be in--St. Luke's
9 Medical Center, Milwaukee, Drs. Tector, Schmahl,
10 and Kress; and University of Pittsburgh Medical
11 Center, Drs. Griffith and Kormos.

12 [Slide.]

13 The study patients in this study are
14 divided up as you see on this slide. There were
15 130 patients, 35 controls, 95 patients received
16 implants, 81 of these were core patients or
17 patients who met all of the entry criteria, and
18 there were 14 out-of-protocol patients who did not
19 meet entry criteria.

20 [Slide.]

21 The study inclusion criteria are shown on
22 this slide. First of all, the patient had to be
23 eligible for cardiac transplantation. He had to
24 meet the criteria for transplant at the local
25 center.

1 He had to be New York Heart Association
2 Class IV. He had to be large enough to have a
3 reasonable chance of fit or an excellent chance of
4 fit of the total artificial heart. By this, in the
5 inclusion criteria, it means a body surface area of
6 1.7 square meters or an AP diameter from the
7 posterior sternum to the anterior spine of 10 cm at
8 T10 on CT scan. The patients had to have
9 hemodynamic insufficiency.

10 [Slide.]

11 By "hemodynamic insufficiency," we mean
12 either one of two things, either Criteria A or
13 Criteria B. These criteria are multifaceted. In
14 Criteria A, it is a cardiac index of less than or
15 equal to 2 L/min/M² with one of the following: low
16 arterial pressure or high central venous pressure
17 greater than or equal to 18 mm of mercury.

18 Criteria B, it was two of the following
19 list: Basically, high dose inotropic support
20 including such drugs as dopamine, dobutamine,
21 amrinone, and others at maximal or near maximal
22 levels. Also, intra-aortic balloon pumping and
23 being on cardiopulmonary bypass, so two of those on
24 that list.

25 [Slide.]

1 The exclusion criteria for this study are
2 shown on this slide. Use of any ventricular assist
3 device, pulmonary vascular resistance of greater
4 than or equal to 8 Wood units, dialysis in the
5 previous 7 days, serum creatinine of greater than
6 or equal to 5 mg/dl, total bilirubin or greater
7 than or equal to 5 mg/dl, and cytotoxic antibody
8 levels of greater than or equal to 10 percent.

9 [Slide.]

10 Now, how did we decide to choose a total
11 artificial heart rather than an LVAD in this study?
12 This slide shows perhaps better than any other part
13 of this presentation the criteria for using a total
14 heart as opposed to an LVAD.

15 We start with 81 core patients, 15 of
16 those patients were on heart/lung machines, CPS
17 pumps or ECMO at the time they were implanted with
18 a total artificial heart, and had global cardiac
19 dysfunction.

20 Fifty-one of the patients had evidence of
21 right ventricular failure as evidenced by a high
22 central venous pressure greater than 18 mm of
23 mercury.

24 Eleven of the patients had right
25 ventricular ejection fractions of less than 20

1 percent.

2 This leaves 4 miscellaneous patients who
3 all were intra-aortic balloon pump support, maximal
4 inotropes, and had failing hemodynamics, and, in
5 addition, 2 had incessant ventricular tachycardia,
6 1 had a mechanical aortic valve, which is a
7 contraindication to LVAD implant, and 1 had a right
8 ventricular injury at sternotomy and was therefore
9 in the embarrassing situation of having a divided
10 right ventricle.

11 [Slide.]

12 This shows a representative heart for the
13 type of heart that is removed from these patients
14 when a total artificial heart is implanted, quite
15 similar to what we see when we remove the heart
16 when we do the transplant.

17 It is very thinned out both on the left
18 and the right sides and has this baggy shape, it
19 has no form, it doesn't stand up and look like a
20 normal heart, and you see, interestingly enough,
21 some left ventricular thrombus that was neither
22 detected by transthoracic nor transesophageal
23 echocardiography.

24 [Slide.]

25 Now, a few words and a few slides about

1 the control group. First of all, the
2 identification of the control group. There were
3 some historical controls that were found from the
4 period of 1991 through 1993, 22 patients.

5 There were some prospective controls that
6 were added during the study, and there were some
7 controls that were found by looking back in 2002
8 through the UNOS Class I patients from all 5
9 centers, and we found 10 additional patients there,
10 so there are 35 patients in the control group. All
11 of these controls had to meet the study inclusion
12 and exclusion criteria, and that is how they were
13 selected by retrospective analysis.

14 [Slide.]

15 Now, a few words about the comparison of
16 the controls with the core patients.

17 First of all, there were lots of things
18 that were similar statistically, demographics,
19 things like age, ethnic group, and gender, and risk
20 factors, such as diabetes, hypertension, cardiac
21 arrest, acute myocardial infarction, previous PTCA,
22 the presence of an automatic implanted
23 defibrillator, pacemaker, being on the ventilator,
24 and being obtunded and drowsy. All of these were
25 essentially the same between the two groups.

1 [Slide.]

2 On the other hand, there were some
3 non-comparable baseline characteristics of the
4 controls versus the core patients. It turned out
5 that the control group had more ischemic patients,
6 a higher incidence of smoking history.

7 More of the patients were anticoagulated,
8 but then as we looked at the laboratory data, there
9 was no difference in the coagulation tests between
10 the two groups. In other words, the core group had
11 elevated PT and INR presumably from a liver
12 synthetic dysfunction because they weren't on
13 anticoagulation as much as the control group.

14 Prior cardiac surgery, there was more
15 history of that in the control group, as you might
16 expect in an ischemic population, and a higher
17 incidence of use of intra- aortic balloon pump.

18 On the other hand, 18.5 percent of the
19 core group were on cardiopulmonary bypass when they
20 were implanted with the total artificial heart, and
21 none of the controls were.

22 [Slide.]

23 On the other hand, there were some
24 non-comparable baseline characteristics, a lot of
25 hemodynamic factors that were identical. The ones

1 that weren't are shown here.

2 The mean arterial pressure was not
3 significantly different, but the systolic arterial
4 pressure was slightly lower, and this might reflect
5 the use of intra-aortic balloon pumping.

6 The pulmonary arterial pressure was higher
7 in the core patients or the implant patients than
8 it was in the controls, and the central venous
9 pressure was also higher in the core or implant
10 patients than it was in the controls.

11 [Slide.]

12 If we look at the hierarchy of support at
13 baseline, the characteristics that relate to amount
14 of drug use, intra-aortic balloon use, and use of
15 cardiopulmonary bypass, and you look at the white
16 line, above the white line is greater than or equal
17 to 3 drug support.

18 Sixty-six percent of the core patients
19 fell into that category, the green patients, as
20 opposed to 80 percent of the control patients were
21 below the line. They were on less than 3 drugs
22 support.

23 [Slide.]

24 We looked at a whole variety of laboratory
25 values and nearly all the chemistry, hematology,

1 and blood gases were comparable. One interesting
2 value that wasn't, was a total bilirubin, which in
3 the core patients was 2, and in the controls was
4 1.3.

5 [Slide.]

6 So, what is the usefulness of the control
7 group? We are in complete agreement that the
8 control group is not for formal statistical
9 comparison. What we found in looking at all the
10 different characteristics that we looked at, at
11 baseline, comparing control and core patients, was
12 that 53 of 65 characteristics matched, and 12 did
13 not match.

14 There was more ischemic disease, more
15 previous coronary bypass, and more characteristics
16 of an ischemic population in the controls than in
17 the core patients.

18 [Slide.]

19 So, it is our hope that in this study, the
20 controls will give an approximation of the natural
21 history of patients meeting entry criteria who do
22 not have mechanical support. That is what we
23 believe to be the value of the controls in this
24 study.

25 We also want to point out that in a way,

1 each one of the patients that is implanted in this
2 study serves as his own control, because he starts
3 very, very sick, and then has an implant and has a
4 history following that of hemodynamic and general
5 recovery.

6 Finally, there are comparisons from the
7 published VAD studies that provide a perspective on
8 our core patient results, and I think these are
9 very important. They will be mentioned in detail
10 by Dr. Pae's presentation, but we may refer to them
11 from time to time in this presentation, as well.

12 [Slide.]

13 So, let's go on then to the study results
14 with respect to efficacy.

15 [Slide.]

16 The primary endpoint in this study was
17 called treatment success. As you remember, it is a
18 multifactorial endpoint - patient alive, functional
19 Class I or II, ambulatory, not on ventilator, not
20 on dialysis. Sixty-nine percent of patients in the
21 core group met that endpoint, 37 percent in the
22 controls.

23 [Slide.]

24 Looking at survival endpoints, perhaps the
25 most important is survival to transplant. After

1 all, that is the point of putting in a bridge to
2 transplant device. Seventy-nine percent of the
3 total artificial heart patients survived to
4 transplant. The 95 percent confidence intervals
5 are shown here. The lower limit of our confidence
6 interval was 68.5.

7 Survival to 30 days post-transplant was
8 71.6 percent. Survival at 1 year from the study,
9 looking at all patients, was 70.4 percent.
10 Survival of the transplanted patients after
11 transplantation at 1 year was 85.9 percent. This
12 does compare favorably with published survival data
13 for bridge to transplantation.

14 [Slide.]

15 Now, what happened to these patients that
16 were implanted? This shows the core patients. The
17 mean time on the device was 79.1 days or the time
18 to transplant. The median was 47, and the longest
19 patient on device was 414 days. This compares to
20 the controls who had a mean time to transplant of
21 8.5 days and a median of 6.

22 There were 6,411 study days for the core
23 patients and 299 for the controls.

24 [Slide.]

25 These two Kaplan-Meier curves show

1 survival to transplant or death, and this really
2 gives the history of what happened to these two
3 groups of patients. The core
4 patients for the most part survived and got
5 transplanted. The control patients either got
6 transplanted or were dead within 6 weeks. The
7 control patients, on the other hand, have a history
8 that goes out 50 weeks.

9 [Slide.]

10 Now, the overall duration of survival,
11 this looks at from the beginning to as far as we
12 have followed these patients, and it goes out, for
13 the control group, to 12 years since some of the
14 controls were enlisted from a time prior to the
15 start of the study, and it goes out to about 9
16 years for the study group, and you can see the big
17 falloff in survival early on, and then parallel
18 curves after transplantation, indicating a
19 uniformity of the result in transplantation, but a
20 high mortality rate early on without the device.

21 [Slide.]

22 These curves show survival from
23 transplantation of both the control and core
24 groups, and we have added the red dots, and the red
25 dots give you an idea of survival that has been

1 reported from the UNOS registry for the entire
2 population of patients in UNOS for over a period of
3 years.

4 You can see the core group is right on
5 after transplantation with the UNOS group, and
6 these very sick control patients who were crashing
7 and in trouble did not have as good an early result
8 after the transplant, but then have a parallel
9 result sometime later, starting at about 1 year.

10 [Slide.]

11 Now, if we look a little more closely at
12 the UNOS versus core patients, so these are the
13 implanted patients, 64 implanted patients were
14 transplanted, and we are comparing with 4,481 UNOS
15 patients. Survival at 1 year, 85.9 for the core
16 patients, 84.7 for the UNOS, or the United Network
17 for Organ Sharing, and at 5 years it was 63.8 for
18 the core patients and 69.8 for UNOS, quite
19 comparable.

20 [Slide.]

21 Now, getting on past the survival results
22 to secondary efficacy endpoints, I want to first
23 discuss hemodynamic recovery, and this slide
24 summarizes the key components of that.

25 First of all, immediately after

1 implantation, as Mr. Smith mentioned, the cardiac
2 output goes up with this device. It went from 1.9
3 to 2.9 L/min/M², and this was a significant and a
4 sustained change.

5 Systolic arterial pressure rose from 92.8
6 to 121. Central venous pressure fell immediately
7 from 19.7 to 13.6, and organ perfusion pressure, or
8 the difference between mean arterial pressure and
9 the central venous pressure, or that force that
10 perfuses the end organs, went from 48.6 to 67.5.

11 [Slide.]

12 Here, you see a curve for the cardiac
13 index over 70 days. You see the immediate rise and
14 sustained level at about 3 L/min/M².

15 [Slide.]

16 This gives you an idea of what that kind
17 of perfusion and drop in central venous pressure,
18 increased organ perfusion pressure does to
19 end-organ function. Here is the creatinine
20 starting at about 1.7, an elevated level rising to
21 2.5 and then falling to normal within about 3 to 4
22 weeks.

23 [Slide.]

24 The hepatic function. There is the total
25 bilirubin starting at 2 mg/dl, rising to about 3.7

1 to 4, and then falling to normal within 3 weeks.

2 [Slide.]

3 This slide shows ambulation, which was one
4 of the endpoints, functional recovery. On the left
5 you see the percent of patients that were able to
6 get out of bed. You see by 14 days, 80 percent of
7 patients were essentially ambulatory or out of bed.

8 On the right, you see the percent of
9 patients who are able to walk greater than 100
10 feet. At 14 days, it was around 60 percent of this
11 core total artificial heart population.

12 [Slide.]

13 We will go on now from efficacy to safety
14 and review adverse events.

15 The first slide is one that we are not
16 going to go into in detail. It covers the 81 core
17 patients prior to transplant. This data is in your
18 packet in case you want to refer to it in more
19 detail, but I show it just to show you the number
20 of adverse events that were looked for.

21 All of this was part of our study from the
22 very beginning. We did not find anything that fell
23 outside of these categories of adverse events, nor
24 did we find anything that was outside of what would
25 have been expected with LVADs or BiVADs.

1 [Slide.]

2 Let me explain. First, let's look at
3 infection, the adverse event of infection in the 81
4 core patients during the implant period, the time
5 that the device was implanted.

6 There were a total of 125 events, 48
7 respiratory, 29 genitourinary, some
8 gastrointestinal, some driveline infections, and
9 these were superficial skin type infections. There
10 were 8 blood infections.

11 There were 6 mediastinal infections, all
12 but 1 of these were found incidentally at the time
13 of transplantation, to they were not clinical
14 mediastinitis, the 5, 1 was, and I will explain
15 that in a moment, and there were 6 line infections
16 or intravenous line, central line, that type of
17 thing, infections.

18 [Slide.]

19 Looking more carefully, then, at the
20 clinically adverse event infection, and separating
21 out what were the clinically significant
22 infections, we see that 5 of these infections
23 delayed transplantation.

24 There were no instances of ascending
25 driveline infections. The types of infections are

1 shown here, driveline, blood, respiratory, and
2 mediastinal.

3 There were 7 infections that contributed
4 to death, 5 respiratory or pneumonia, 1 line
5 infection or sepsis, and 1 mediastinal infection.
6 There was 1 infection that caused death, pneumonia.
7 Neither the ones that contributed to death or
8 caused death were related to the device.

9 [Slide.]

10 Let's go on to the adverse event of
11 bleeding. This is for 81 core patients during the
12 implant period. We had various definitions of
13 bleeding, so we looked very broadly at bleeding,
14 trying to pick up every event that would reflect
15 abnormal bleeding, abnormal loss of blood, or
16 abnormal replacement of blood.

17 First of all, they are the takebacks.
18 Takeback means take back to the operating room for
19 bleeding or cardiac tamponade, early after the
20 implant, usually. All but one of those takebacks
21 were at less than 21 days after implantation.

22 There was post-implant bleeding. This is
23 greater than 48 hours after transplant and the
24 patient needed 3 units of blood within a 24-hour
25 period. There were 18 such events. Surgical

1 bleeding meant that the patient bled greater than 8
2 units or had greater than 8 units replaced while he
3 was in the operating room having the implant.

4 The abdominal bleeding refers to 1 case of
5 abdominal bleeding that required a takeback
6 operation.

7 There were 2 deaths from bleeding in our
8 experience.

9 [Slide.]

10 We go on then to neurologic adverse events
11 in 81 core patients during the implant period.
12 There were 10 stroke, 4 TIAs, 5 episodes of
13 encephalopathy, 1 transient loss of consciousness,
14 1 metabolic encephalopathy, and 5 seizures.

15 A stroke in this study was defined as
16 neurologic dysfunction of greater than or equal to
17 24 hours duration. There were 25 total neurologic
18 events in this study of the 81 core patients during
19 implant.

20 [Slide.]

21 Now, let's expand our patient population
22 to the 95 patients that were implanted, so that we
23 include every stroke that occurred in this study.
24 This is the core group plus the out-of-protocol
25 group.

1 For this total group of patients during
2 the implant period, there were 11 strokes in 10
3 patients or a 10.5 percent incidence.

4 In 6 of the strokes, there was no--that
5 should be "no," I am sorry, it says "mo"--but there
6 was no residual after 48 hours, and there was no
7 delay of transplant, so these were what you might
8 call very minor neurologic abnormalities.

9 There were 4 that had residual, but did
10 not delay transplant. There was 1 dense hemiplegia
11 only. The other strokes were of much less
12 magnitude. This did delay transplant, but later
13 the patient did get transplanted and met treatment
14 success criteria.

15 The events per patient month or the
16 strokes per patient month in this study were 0.05
17 linearized rate.

18 [Slide.]

19 I want to go on and mention device
20 malfunctions because device malfunctions I think
21 give us, looking at this gives us confidence of the
22 reliability of this device. This is in all 95
23 patients. This is a greater than 19-year
24 experience on the device, 19 patient years.

25 There were 11 driveline kinks. That

1 means the alarm went off on the device, indicating
2 a driveline kink. These were very transitory,
3 lasting seconds or less. Occasionally, they were
4 associated with a loss of consciousness, but not
5 often, and they caused no effect on the outcome.

6 There were 3 patients that had 5 driveline
7 leaks. This was due to the method of coupling the
8 lines that come out of the patient with the
9 external plastic lines that connect to the device.

10 This was redesigned and following the
11 redesign and the retraining of all centers, there
12 were no more events in 33 patients. We discovered
13 this when we were about 50 some-odd patients into
14 the experience, and it only occurred in 3 patients.

15 There were a couple of miscellaneous
16 events. Once, there was loss of consciousness for
17 just a second while an air tank was being changed.
18 There was no effect on the outcome. There was 1
19 controller that kept showing a low alarm. There
20 was never a low output in this patient, the
21 controller was changed, and the patient was fine,
22 there was no effect.

23 Then, there was the 1 major event that
24 occurred of device malfunction that caused major
25 difficulty, and this was a tear in one of the

1 diaphragms. The diaphragm is a 4-layered structure
2 of polyurethane with a little bit of graphite
3 between each of the layers.

4 On day 90, this patient started showing
5 signs of low output and eventually we diagnosed
6 that he did have a tear in this diaphragm. The
7 reason for this is unknown.

8 We checked the entire history of this type
9 of device, which includes well over 500 implants
10 and probably 50 patient years of experience. It is
11 the only time this ever happened in this device, it
12 was not catastrophic.

13 The patient finally died on day 124, the
14 event happened on day 90. He refused implantation
15 of a second total artificial heart and support was
16 eventually withdrawn in his case.

17 [Slide.]

18 I want to go on now to fit complications
19 since patient size is a requirement for entry into
20 the study and fitting a device into the chest is an
21 important concept that has to be appreciated by
22 every surgeon that implants and every cardiologist
23 that refers patients for implantation of this
24 device.

25 We looked at this in 95 implanted

1 patients, in other words, all the implanted
2 patients, and there were 5 events. Two of these
3 occurred in the operating room and were detected
4 immediately when the chest was closed. It was
5 reopened and the device was repositioned. There
6 was no effect on outcome.

7 One was detected after the patient was
8 returned to the intensive care unit. He was
9 returned and the device was repositioned, there was
10 no effect on outcome.

11 A fourth event was compression of the
12 pulmonary veins that was corrected by repositioning
13 the device, but the patient continued to be in
14 pulmonary edema and eventually died of other
15 complications, but the pulmonary edema contributed.

16 Finally, there was a patient who came to
17 the operation in severe pulmonary edema with stiff
18 lungs. The device never really fit well. He was
19 left with an open sternum and closed with a PTFE
20 graft, and this was a contributing cause of death.

21 [Slide.]

22 Going on then to causes of death. All of
23 the causes of death in the 81 core patients are
24 listed here. There were 17 deaths, for a percentage
25 of 21 percent.

1 Seven patients died of multiple organ
2 failure, 4 patients died of procedural/technical
3 causes, and those causes are listed on the bottom
4 of the slide.

5 Two died of hypercoagulable states after
6 transplantation. They were being given aprotinin
7 and, in addition, they received an activated factor
8 VII complex called FEIBA, and they had
9 intravascular coagulation.

10 Two of the patients in this group died
11 from wedging of a central line in the tricuspid
12 valve of the total artificial heart.

13 Two contraindications for the use of this
14 device are the use of FEIBA and aprotinin at the
15 time of transplantation should not be done, and
16 central lines should not be placed in the right
17 atrium.

18 Once we experienced this, we, of course,
19 made it known to all of the implanting centers, and
20 there are strict criteria with respect to where
21 central line tips should be, and they are located
22 radiographically, and this is confirmed in patients
23 at this time and from the time of this experience
24 forward.

25 To carry on with the causes of death,

1 bleeding in 2 patients, sepsis in 2,
2 pre-implantation cardiac arrest in 1, and pulmonary
3 edema in 1.

4 [Slide.]

5 In summary, we had immediate hemodynamic
6 recovery with using this device. We had end-organ
7 recovery, and patients got out of bed and were
8 walking usually within a week, most of them within
9 2 weeks.

10 [Slide.]

11 We had a treatment success of 69.1
12 percent. This compares favorably with the bar that
13 has been set in the FDA presentation of 65 to 70
14 percent for survival to transplant, and it includes
15 a number of other criteria.

16 [Slide.]

17 Seventy-nine percent of the patients
18 survived to transplant, and the lower limit of our
19 confidence interval again exceeds that bar set in
20 the FDA report.

21 Survival at 30 days post-transplant was
22 71, and 1 year survival from entry into study was
23 70.4. Survival from the time of transplant to 1
24 year was almost 86 percent.

25 [Slide.]

1 These results were generalizable or were
2 found across the 3 major centers in the study. You
3 can see survival to transplant at the LDS hospital
4 was 75 percent, Loyola 84, and University Medical
5 Center 79 percent.

6 Treatment success was found in 63 percent
7 of LDS, 76.9 of Loyola patients, and 69 percent of
8 UMC patients.

9 [Slide.]

10 In conclusion, we feel that this is a
11 reliable device. There was 1 serious device
12 malfunction in 19 patient years of support.

13 The performance was excellent, giving a
14 high cardiac output, a low venous pressure, and
15 good organ perfusion. There were significant
16 adverse events including bleeding, stroke,
17 infection, and other events, but we feel these are
18 acceptable in the face of the efficacy of the
19 device.

20 The efficacy basically is that 79 percent
21 of patients were maintained to transplantation. We
22 therefore feel that the CardioWest Total Artificial
23 Heart offers significant benefit at reasonable
24 risk.

25 [Slide.]

1 I would like to conclude by showing you a
2 slide of another one of our patients. This one is
3 in the middle. He had a transplant two years prior
4 to November of 2003 when he rode in a bicycle race
5 for 70 kilometers. He had the CardioWest Total
6 Artificial Heart for 4 months prior to his
7 transplant.

8 Thank you very much. I would like to go
9 on now to the presentation of Dr. Walter Pae.

10 **Clinical Perspective]**

11 DR. PAE: Good morning. My name is Walter
12 Pae.

13 [Slide.]

14 I am a Professor of Cardiothoracic Surgery
15 at the Pennsylvania State University. I have been
16 involved with circulatory support and the
17 development, as well as the clinical application of
18 devices, throughout most of my adult life which
19 started nearly 30 years ago now.

20 [Slide.]

21 What I would like to do is to give a
22 little bit of a clinical perspective on the need
23 for circulatory support in bridge to transplant.

24 DR. TRACY: Sir, could you please state
25 your financial interest.

1 DR. PAE: I don't have any financial
2 interests. Thank you. I have no conflicts.

3 To go on a little bit about the need for
4 total artificial hearts. There is no doubt that
5 there is a donor shortage, and this continues to
6 exist and will continue to exist into the future.
7 For example, in the year 2002, there were about
8 3,800 transplants performed, that are listed, and
9 only about 2111 patients transplanted in the United
10 States.

11 Now, a donor shortage is not only the
12 absolute number of donors, but also timing.
13 Patients get sick and hearts aren't available.

14 The mortality rate is substantial among
15 patients that are awaiting cardiac transplantation,
16 and certainly those individuals with severe Class V
17 heart failure have an exceedingly high risk of
18 death.

19 I think it is important to note that these
20 patients are the individuals that are now way past
21 beta blockers and ACE inhibitors, and biventricular
22 pacers. They are individuals who have failed all
23 of these modalities and need heart replacement
24 therapy.

25 I think that a very good argument has been

1 made that there is a need for practical device
2 therapy for not only the prevention of death, but
3 medical stabilization. Many times one can argue
4 that many of these patients that are moribund are
5 better off with a device prior to transplantation
6 than they are going on to immediate transplant if a
7 heart was available.

8 [Slide.]

9 This has been alluded to in the past and I
10 think we can skip over it in the interests of time.

11 [Slide.]

12 There is a few caveats about right
13 ventricular failure. The incidence of right
14 ventricular failure in individuals who are on left
15 ventricular assist device depends on the
16 definition.

17 It has been reported in the literature,
18 peer-reviewed literature, in anywhere from 11 to 26
19 or perhaps as high as 30 percent of the patients on
20 ventricular assist devices.

21 About one-third to one-half of those
22 patients have required with right ventricular
23 failure fail inotropic support and go on to an
24 additional right ventricular assist device or
25 sequential device therapy, ending up with

1 biventricular support.

2 I think that in the clinical arena of
3 those individuals who do a lot of this and report
4 it in the peer-reviewed literature, it is much more
5 likely to occur in the individual who is sicker, in
6 the individual who undergoes an emergent therapy
7 versus what we call elective urgent implantation.

8 Certainly, this affects outcomes. Right
9 ventricular failure, if you look at the outcomes,
10 it has about one-half of the successful bridge rate
11 as compared to those individuals who do not exhibit
12 right ventricular failure.

13 I think the last thing is that our
14 prospective ability to predict this is inaccurate
15 in many situations, but I think there are certain
16 clinical scenarios that exist that make clinical
17 decisionmaking more often right than wrong in this
18 particular instance.

19 [Slide.]

20 So, we are definitely left with a need for
21 biventricular support. How do we provide this at
22 the present time?

23 Well, we can use hybrid systems where we
24 use a left ventricular assist device of one
25 manufacturer's or another rigged with a second

1 device from another manufacturer, and if you are to
2 go back and look through the literature a little
3 bit, one of my fellows, is now a partner of mine,
4 published or was a co-author on a paper of mine,
5 that indicated throughout the registry experience,
6 when it existed through the ISHLT and the AIO, that
7 only about one-third of those patients who got
8 "hybrid" systems went on to actually get orthotopic
9 cardiac transplantation.

10 Now, your paracorporeal systems that are
11 utilized for biventricular support are flow
12 limited, and they are flow limited by design. They
13 have inlet and outlet cannulae that are long and it
14 takes a certain amount of time to fill and empty
15 these devices.

16 They also require a competent aortic
17 valve, and they are clearly limited by the
18 liability of native heart pathology in certain
19 instances.

20 The total artificial heart, on the other
21 hand, provides immediate high flow. It is not
22 limited at all by the native heart pathology since
23 the native heart is extirpated just like it will be
24 in orthotopic cardiac transplantation after
25 successful bridging.

1 [Slide.]

2 So, I think there is a clinical need for
3 the total artificial heart both in biventricular
4 failure, but in a number of instances where the
5 native heart presents a liability, where there are
6 large ventricular thrombi, and in our own personal
7 published experience in individuals with large
8 anterior wall myocardial infarctions and
9 cardiogenic shock, the incidence of stroke in those
10 individuals bridged with univentricular support was
11 about 85 percent.

12 Individual with ventricular septal
13 defects, post-myocardial infarction, massive
14 ventricular ruptures post-myocardial infarction,
15 refractory arrhythmias, prosthetic aortic valves
16 and incompetent aortic valves, particularly the
17 failed cardiac transplant.

18 There are a number of instances of adult
19 congenital heart disease which makes standard
20 ventricular assist devices very difficult.

21 We have also actually dealt with patients
22 with cardiac malignancies where this is a useful
23 technique, and I believe Dr. Copeland actually
24 alluded to complex reoperative situations, and some
25 of these are just simply unavoidable tactical

1 misadventures or acts of the devil.

2 [Slide.]

3 There is a very large body of
4 peer-reviewed literature, which is labeled here for
5 reference, and was selected for review. Each one
6 of these is labeled with a number, so that you can
7 go through and follow these as I speak about this.

8 [Slide.]

9 Now, survival to transplant. In these
10 peer-reviewed studies, basically, ranges between 51
11 and 71 percent. This compares clinically very
12 favorably with what has been presented with the
13 SynCardia device.

14 [Slide.]

15 Interestingly, out of the registry paper,
16 published in 1995, if you look at the numbers,
17 quite comparable despite the fact that this was
18 obviously a voluntary registry and there are
19 problems with that.

20 [Slide.]

21 When you begin to look at the literature
22 review in terms of adverse events, there are
23 clearly a number of very important issues, things
24 to keep in mind. The definitions are very, very
25 varied. There is no set definition to define

1 adverse events. They are broad definitions with
2 subcategories.

3 Much of this is device-related data
4 reporting. The rates of these events, the numbers
5 of patients with each event is not always provided,
6 and I think that everyone needs to understand from
7 a statistical standpoint that these are not always
8 constant hazard functions, and even when the event
9 rates are linearized, it doesn't necessarily tell
10 the entire story.

11 The time frames that devices are utilized,
12 for example, a device being used for 10 days may
13 not have any events during that 10 days, and if it
14 carries out to 100 or 200 or 300, we begin to see
15 the pile-up of adverse events, so it is many times
16 very difficult to compare.

17 Obviously, all of the registry data
18 previously was voluntary and that makes statistics
19 difficult at best.

20 [Slide.]

21 At any rate, recognizing the limitations
22 of the peer-reviewed literature, if you begin to
23 look at adverse events, infection, for example,
24 tends to range between 2 and 55 percent, and I
25 think that tells us that there is a very broad

1 range of infectious problems that occur that may be
2 device related or it may have to do with
3 definitions.

4 If one looks at bleeding, again, a very
5 wide range of 31 to 51 percent. Strokes, TIAs,
6 neurologic events, again zero to 59 percent.

7 If you eyeball these sorts of things, I
8 think that you will see that the total artificial
9 heart question today falls well within those
10 ranges.

11 [Slide.]

12 The same thing for death during implant.
13 If one looks at multi-organ failure, for example,
14 amongst the various devices, biventricular devices
15 or univentricular devices, it tends to range
16 somewhere between 8 and 29 percent, comparing
17 favorably with 9 percent.

18 Please keep in mind that many, many of the
19 patients that die with multi-organ failure from
20 univentricular support are really dying of right
21 ventricular failure, and that is a manifestation as
22 such.

23 Cerebral events, 8 to 21 percent, again
24 compares favorably. Sepsis, zero to 14 percent,
25 again comparing favorably. Bleeding, again, a

1 very, very wide range, but again comparing
2 favorably. The same as right ventricular failure
3 and air embolism.

4 [Slide.]

5 When we go down to the miscellaneous
6 events, and I am sure there is hundreds of those,
7 once again compares favorably.

8 [Slide.]

9 Lastly, when we begin to look at device
10 malfunction, again from the published literature,
11 device failure, meaning exactly what it means in
12 terms of the device not working, we have ranges
13 between 1 and 20 percent.

14 These are usually referred to as critical
15 device failures versus device malfunctions, which
16 can be things that are very, very simple like
17 driveline kinks, or even things as external
18 controller failures that are easily replaced, but
19 they go anywhere between 4 and 100 percent.

20 When you look at these again clinically,
21 the device in question falls well within those
22 ranges.

23 [Slide.]

24 So, I think from a clinician's
25 perspective, this particular device of CardioWest

1 Total Artificial Heart has successfully salvaged
2 patients that have severe biventricular failure.

3 The survival to transplant with this total
4 artificial heart is clinically comparable to the
5 left ventricular assist devices and the
6 biventricular assist devices without limitations of
7 the diseased native heart.

8 The safety of the devices appears
9 clinically similar to the available devices, and
10 the clinical benefit of this seems to outweigh the
11 associated risk. I think there is definitely a
12 clinical need for the total artificial heart. It
13 is a useful device that fills a therapeutic gap
14 that will clearly extend our ability to treat
15 cardiovascular disease.

16 Thank you.

17 **Conclusion**

18 [Slide.]

19 DR. SLEPIAN: Therefore, in conclusion, a
20 need exists for safe and effective therapies which
21 can save lives for these debilitated patients and
22 stabilize them in imminent danger of dying from
23 biventricular failure.

24 The total artificial heart provides
25 hemodynamic normalization which then leads to

1 end-organ recovery.

2 The Total Artificial Heart System was
3 demonstrated to be safe and reliable, bridging
4 patients to transplantation.

5 The study was a success with demonstrated
6 efficacy in all endpoints.

7 The CardioWest TAH is the first total
8 artificial heart to demonstrate life-saving
9 results, with benefits outweighing risks, in such a
10 sick group of patients.

11 [Slide.]

12 The indication for use therefore is as an
13 in-hospital bridge to transplantation in
14 transplant-eligible candidates at imminent risk of
15 death due to irreversible biventricular failure.

16 [Slide.]

17 TAH candidates would include those that
18 are transplant-eligible, New York Heart Class IV or
19 the new AHA/ACC Class D heart failure, with
20 hemodynamic insufficiency that is refractory to
21 medical therapy and would be best served with this
22 type of device with situations including RV
23 failure, the presence of a clot in the LV,
24 refractory arrhythmias, prosthetic valve, holes in
25 the heart, stone heart, or a rejected transplant or

1 a failed transplant, or unresuscitatable patients
2 following cardiac arrest, failure to wean from
3 bypass with biventricular injury, or due to
4 surgical technical issues with LV situations with
5 massive MI.

6 [Slide.]

7 The contraindications for this system are
8 those patients that are ineligible or not cardiac
9 transplant candidates that are small with body
10 surface areas less than 1.7.

11 [Slide.]

12 Our proposed training will be as follows.
13 It will include a didactic hands-on animal
14 implantation and on-site proctoring component.
15 Didactic training will be provided by experienced
16 surgeons and others on the technical side that have
17 been involved in this study.

18 There will be direct instruction. A
19 training manual has been developed, study of which
20 will be required. Complete literature review and
21 being familiar with the published literature will
22 be emphasized, and a video of implantation is also
23 part of the training.

24 Surgeons then move on to hands-on
25 experience, as well as technical people with the

1 TAH, as well as with the console and drivelines.
2 Then, from there, animal implantation will be
3 required with a minimal implant of two separate
4 acute studies in a pig model.

5 Finally, on-site proctoring will be
6 provided by experienced surgeons and other
7 technical personnel that are familiar with the
8 device.

9 [Slide.]

10 In addition, in discussion with the FDA,
11 we have proposed post-market surveillance which
12 will involve follow-up on enrolled study patients.
13 Fifty additional U.S. patients will be in this to
14 demonstrate generalizability. Less than 10 percent
15 will be from any one center.

16 Adverse events will be captured during the
17 implant period, as well as survival to transplant
18 followed, and one year follow-up.

19 [Slide.]

20 This study provides reasonable assurance
21 of the safety and effectiveness of the CardioWest
22 TAH for the proposed indication for use.

23 Thank you very much.

24 **Questions and Answers**

25 DR. TRACY: Thank you.

1 At this time I would like to ask the panel
2 members if they have any brief clarifying questions
3 for the sponsor.

4 Dr. Aziz.

5 DR. AZIZ: This is probably for Dr.
6 Copeland. The out-of-use of the device, the 14
7 patients that you had who couldn't come off
8 cardiopulmonary bypass, were they mainly in one
9 center or were they in different centers?

10 DR. COPELAND: That was not restricted to
11 one center. There were several episodes in each of
12 the three major centers in the study.

13 DR. AZIZ: These are patients who the
14 operator felt that even in a period of protracted
15 rest like that, peripheral bypass for 24 hours
16 wouldn't allow recovery of the donor heart?

17 DR. COPELAND: I can only speak for my own
18 experience with respect to the exact situations,
19 and these were situations where there was
20 irrevocable evidence that the heart was permanently
21 and irreversibly damaged either by the patient's
22 disease or the patient's disease with a
23 combination, with the operative intervention that
24 was being done.

25 MR. SMITH: Could I comment further on

1 that? That group was also people that were put on
2 portable ECMO machines and then transferred to the
3 operating room, so they weren't just patients that
4 were actually in cardiac surgery at the time.

5 DR. BRIDGES: This question is for Dr.
6 Copeland primarily, but the others could respond,
7 as well.

8 One question is in your presentation, it
9 seemed that you indicated that two of the patients
10 with coagulopathies, that is, those that had
11 received aprotinin and the other factor 7 agent--

12 DR. COPELAND: FEIBA.

13 DR. BRIDGES: --had received that during
14 the transplantation? That is what I was a little
15 confused about, why would they not be included in
16 the transplant group if they, in fact, got to
17 transplantation.

18 DR. COPELAND: The reason they were
19 included is because that is the way the study was
20 designed. In other words, the patient is in the
21 implant to transplant period until he leaves the
22 operating room after being transplanted, so all of
23 the adverse events from the transplant operation,
24 the removal of the total artificial heart and the
25 transplanted heart are captured in that period of

1 time.

2 Then, the post-transplant to 30-day
3 complications are captured after the patient is
4 post-operatively, so that is why we see that.

5 DR. BRIDGES: Another question was where
6 were the takebacks bleeding from, was there a
7 pattern to where 25 percent of the patients were
8 taken back for bleeding within the first 48 hours?

9 DR. COPELAND: Generally, this is, first
10 of all, I would like to point out that the
11 prothrombin time and the INR in these patients on
12 the average was in the anticoagulated range, so
13 these are patients who were very sick, who have, in
14 general, a high incidence of liver synthesis
15 problems, and therefore have coagulopathies.

16 Also, about 30 percent of the patients
17 were reoperative patients, so most of the bleeding
18 was not from anything related to the device, but
19 just simply patient-related soft tissue, diffuse
20 oozing sternal wires, the usual kind of things that
21 we see in routine cardiac surgery.

22 DR. BRIDGES: One last question. All of
23 the controls met the inclusion/exclusion criteria,
24 but were all of the patients that met the
25 inclusion/exclusion criteria included in the

1 control group?

2 DR. COPELAND: All of the charts that were
3 reviewed and found patients that fulfilled these
4 criteria were used. There were something like 635
5 charts reviewed. These were all about UNOS Class I
6 patients. Over half of these were not used because
7 they weren't sick enough to meet the inclusion
8 criteria.

9 About a fourth of them were excluded
10 because they received a VAD, and another sizable
11 number were excluded because they had some medical
12 contraindication to transplantation. So, that is
13 the way we found the control patients.

14 DR. BRIDGES: It just seemed that there
15 weren't as many controls enrolled after 1993 as I
16 would have expected if all of the patients who met
17 the inclusion/exclusion criteria were included in
18 the control group.

19 DR. COPELAND: Well, when we looked back
20 in 2002 at each of the five centers, at all of
21 their patients who had been listed UNOS Class I,
22 that is all we could find, so our assumption was
23 that in that interval, there was an increased use
24 of other devices that would make them ineligible
25 for this study as control patients.

1 DR. BRIDGES: Thank you.

2 DR. TRACY: Dr. Yancy.

3 DR. YANCY: Several points of
4 clarification, and I appreciate the caution that
5 was raised and the answer regarding those 14
6 out-of-protocol patients, because I, too, had some
7 questions about that.

8 One question regarding outcomes. There
9 were 51 patients in Dr. Copeland's presentation who
10 had a CVP greater than 18 mm of mercury,
11 purportedly the main indication for bypass support
12 in this setting of RV dysfunction.

13 I am curious as to the outcomes in that
14 specific group that had a clear hemodynamic
15 construct for RV dysfunction.

16 DR. COPELAND: I think it is dangerous to
17 look at one number and assume that that was the
18 reason, the sole reason for putting in a total
19 artificial heart.

20 I mean these are patients who are
21 critically ill, who are declining rapidly, who are
22 on lots of inotropes, who have end organ
23 dysfunction, and in putting together that
24 particular slide for this presentation, we were
25 looking for, within the group of patients, things

1 that stood out as indicators of right ventricular
2 failure, and that is how we came upon that.

3 So, all of these patients were severe
4 Class IV, they were all on inotropes. You know,
5 they might have been on intra-aortic balloon pumps,
6 and so forth, and so on, as well, and they had
7 severe abnormalities in their baseline
8 hemodynamics.

9 Then, you say okay, are we going to put in
10 an LVAD or a BiVAD or a total artificial heart, and
11 basically, the way we decided was looking at these
12 criteria plus those things that you saw recorded on
13 that slide including a high CVP, generally in face
14 of a normal pulmonary artery pressure, which is in
15 an indicator of severe right ventricular
16 dysfunction.

17 DR. YANCY: You haven't qualified it as
18 such, and I assume that that group did as well as
19 the overall trial result?

20 DR. COPELAND: Yes.

21 DR. YANCY: A second question is about
22 adverse events. There is a slide that Dr. Pae
23 referred to that suggested numbers that were not
24 consistent with data that Dr. Copeland presented
25 and this may just need a point of clarification.

1 The slide in reference is Slide 81, and it
2 shows an infection rate for the SynCardia of 28.3
3 percent, which is in variance to the Slide 56, that
4 shows an infection rate of 71.6. I am assuming
5 that this is a question of definition.

6 I would just like to know the variance.
7 The same can be said for bleeding, 42 percent
8 versus 37 percent, and for stroke/TIA 24.7 for
9 neurologic versus 12.6 for stroke/TIA, but by
10 calculating it, it would still be 17 percent for
11 the events that occurred in the trial.

12 So, are these points of definition, what
13 are the differences here in those two slides?

14 DR. COPELAND: Yes, what was done--can we
15 have the slide up, please, P81--what was done in
16 this to try to make these adverse event numbers
17 comparable was to redefine infection according to
18 the way it was defined by the majority of articles
19 in the literature. Bleeding and stroke were
20 treated in the same way.

21 So, the numbers that you see for our core
22 patients or for our combined core and
23 out-of-protocol patients are not going to be the
24 same as what you see here.

25 DR. YANCY: The third question, if I may,

1 had to do with the fact that there is a statement
2 in our packet that says the device has been
3 approved for use in several outside of U.S.
4 countries.

5 I am wondering if there can be a
6 statement, too, about the general experience of the
7 device, I think it's France, Canada, and Germany,
8 is there any statement that can be made about the
9 experience with the device in the out-of-U.S.
10 countries.

11 DR. COPELAND: First of all, I can
12 summarize by saying the survival to transplant in
13 the out-of-U.S. experience has been about 60
14 percent, that the involvement of the centers
15 utilizing this device in Western Europe primarily
16 have been people who were not constrained by a
17 protocol, namely, a protocol that is this type and
18 that limits the use to transplant candidates, for
19 instance, which is a pretty strict criterion, and
20 also that limits it to use in people who have not
21 had a VAD in place.

22 There have been many uses of this device,
23 for instance, in patients who have failed either
24 BiVAD or univentricular support and then gone on to
25 total artificial heart.

1 Now, if it's permissible, I could have Dr.
2 Aly Banayosy from Bad Oeyenhausen comment on that
3 question, as well.

4 DR. TRACY: Actually, there is going to be
5 a lot more time for discussion after lunch. Maybe
6 we can hold off and just any other brief clarifying
7 questions.

8 Dr. Krucoff.

9 DR. KRUCOFF: Dr. Copeland, I just want to
10 make sure that I heard what you said about the
11 identification of the control population, because
12 at least what I heard you say was not in our pack.

13 The charts that were reviewed, is the
14 implication they were triggered by UNOS I
15 categories? How did you identify the 600-some
16 charts that you reviewed?

17 DR. COPELAND: The 600-some refers to sort
18 of the total review that was done, and the
19 definition of UNOS Class I, as you may know,
20 changed over the course of time, but, in general,
21 that is a true statement that the patients did meet
22 UNOS Class I, which means on inotropic support
23 either out of hospital or in hospital, perhaps on
24 hemodynamic monitoring in hospital.

25 That would cover both what we call UNOS

1 Class IB, which is the out of hospital, and UNOS
2 Class IA, which is the in hospital with hemodynamic
3 monitoring and inotropes.

4 DR. KRUCOFF: So, the 600 were identified
5 presumably out of thousands of charts in the
6 medical center using what?

7 DR. COPELAND: That is correct.

8 DR. KRUCOFF: How did you identify those
9 600?

10 DR. COPELAND: By going directly to the
11 UNOS Class I patients.

12 DR. KRUCOFF: So, that is what triggered
13 that list.

14 DR. COPELAND: Right, exactly.

15 DR. KRUCOFF: Within that, if I heard you
16 correctly, of the patients who would have fit the
17 criteria, for a control patient, about half of
18 those patients had had VADs, so you excluded them,
19 is that what you said?

20 DR. COPELAND: About 130 some-odd had had
21 VADs, about nearly 300 were not sick enough by the
22 hemodynamic insufficiency criterion.

23 DR. KRUCOFF: But of the ones who were
24 sick enough, about half of them had VADs?

25 DR. COPELAND: That is correct.

1 DR. KRUCOFF: Have you looked at those
2 data?

3 DR. COPELAND: We actually have, and I am
4 not--do you remember that data? We can--

5 DR. KRUCOFF: If you have it this
6 afternoon when we have time, I think that would be
7 very relevant.

8 DR. COPELAND: We can get that for you,
9 yes. I recollect that--let's wait until this
10 afternoon, we can get you the right numbers, but
11 the experience just to the best of my memory was
12 about a 40 to 50 percent survival at transplant in
13 that group.

14 DR. TRACY: Dr. Hirshfeld.

15 DR. HIRSHFELD: Dr. Copeland, I would like
16 to try to get a better handle on what the
17 thromboembolic potential of this device is. You
18 reported a total of 11 strokes. That sounds as
19 though they were likely to be thromboembolic
20 events.

21 There is also a report of 9 peripheral
22 thromboembolic events, which weren't really
23 discussed this morning, and I wonder--I assume,
24 first of all, those are different events than the
25 strokes, it's not just another rubric for the

1 strokes.

2 DR. COPELAND: No, it's not.

3 DR. HIRSHFELD: I wonder if you could tell
4 us what the nature of these peripheral
5 thromboembolic events were, what the consequences
6 were, and whether you think it is appropriate to
7 combine the frank strokes and the peripheral
8 thromboembolic events as a measure of the overall
9 thromboembolic potential for the device.

10 DR. COPELAND: Most of those events were
11 Amaurosis fugax. They were transient retinal
12 problems that lasted seconds to minutes and
13 disappeared. There were a few that were emboli to
14 either the spleen or the kidneys, and we have that
15 data, and we have reviewed that data, and to the
16 best of my memory, that is a summary of the
17 findings with the peripheral embolization.

18 DR. HIRSHFELD: The second question is it
19 seems to me that there was a high frequency of
20 perioperative bleeding at the time of the
21 transplantation, as well as at the time of the
22 initial implant of the device, and it seems to me
23 plausible that this is due to the fact that these
24 patients were on full warfarin anticoagulation and
25 fairly aggressive antiplatelet therapy at the time

1 that they underwent transplantation.

2 I wondered whether your experience is that
3 this is a real phenomenon that doing the transplant
4 is technically more challenging because of the
5 anticoagulation status of the patient.

6 DR. COPELAND: Yes, my impression, and,
7 you know, I am coming out of an experience of over
8 200 pulsatile pump bridge to transplant, so over
9 two-thirds of our experiences with LVADs and
10 BiVADs, and I will have to say that my experience
11 is that they all bleed at the time of transplant
12 and usually very badly.

13 I don't really see that the total
14 artificial heart is any different in any major way
15 from those devices.

16 DR. HIRSHFELD: One last point of
17 clarification, if I might.

18 DR. TRACY: I would like to remind the
19 panel, though, that there is plenty of time for
20 discussion all afternoon, so unless these are
21 really to clarify something that you need to
22 discuss things further this afternoon, I would like
23 to hold off, so if anybody has just a brief
24 question.

25 Dr. Maisel.

1 DR. MAISEL: Perhaps you could clarify a
2 little bit about who the patients were who were
3 being enrolled in the study. I certainly recognize
4 that they are critically ill and have horrible
5 heart failure, but, for example, about 50 percent
6 of the patients were ischemic patients.

7 Were they chronic ischemic patients, how
8 long from their initial heart failure diagnosis to
9 the time that they ended up getting their device,
10 were they presenting with acute myocardial
11 infarction, were they post-CABG and didn't do well,
12 who were the patients that were enrolled in this
13 study?

14 DR. COPELAND: You are asking with respect
15 to the ischemic patients?

16 DR. MAISEL: With respect to everyone, but
17 particularly with respect to the ischemics who
18 seemed to have a worse outcome.

19 DR. COPELAND: I am just pausing for a
20 moment. I am trying to get you as quantitative an
21 answer as I can.

22 Let's go to B3D, please.

23 [Slide.]

24 This is a slide on the etiology of disease
25 of these study patients. First of all, with

1 respect to acute myocardial infarction, I can tell
2 you that 5 of the core patients had just
3 experienced acute myocardial infarctions. None of
4 the control patients had just experienced an acute
5 myocardial infarction, and that distant myocardial
6 infarction incidence was about the same in both
7 groups. It was around 25 to 30 percent for both.

8 Unfortunately, the printing on this slide
9 doesn't show up as well as we would like, but it is
10 idiopathic, ischemic, viral, acute myocardial
11 infarction, acute rejection, failure to wean from
12 bypass, and other are the major categories, and we
13 can provide you with this slide if you would like
14 to examine it in more detail, but in terms of is
15 your question directed towards--

16 DR. MAISEL: That answers my question,
17 thank you.

18 DR. COPELAND: Okay, thanks.

19 DR. TRACY: I think in the interest of
20 time here, we will pause at this point for a brief
21 break. Let's try to reconvene at 11 o'clock,
22 please.

23 [Break.]

24 DR. TRACY: At this point, we are going to
25 move on and I will ask the FDA to begin their

1 presentation.

2 **FDA Presentation**

3 **Summary**

4 MR. CHEN: Good morning, Madam Panel
5 Chair, panel members. I would like to welcome you
6 to the Circulatory Support Devices Panel today.

7 [Slide.]

8 The PMA application to be discussed today
9 is PMA No. 030011 for the SynCardia Systems
10 CardioWest Total Artificial Heart.

11 [Slide.]

12 My name is Eric Chen and I was the lead
13 reviewer for this application.

14 [Slide.]

15 I would like to present a brief overview
16 of the presentation today. I will be presenting a
17 history of the clinical study along with the
18 preclinical evaluation of the device. The
19 statistical evaluation will be presented by Dr.
20 Lilly Yue, and Dr. Julie Swain will be addressing
21 the clinical evaluation.

22 At the end of the FDA presentation today
23 will be the Questions to the Panel, which we will
24 discuss in the afternoon session.

25 [Slide.]

1 Due to the complexity of the device, a
2 wide variety of specialists were called upon to
3 review this application. The FDA Review Team
4 consisted of engineers, statisticians, and
5 clinicians, and their names have been listed here
6 for their recognition.

7 [Slide.]

8 The following is a picture of the
9 CardioWest Total Artificial Heart System. I will
10 not go into too much detail with the device's
11 function since the sponsor has already presented a
12 full explanation of the device, however, the
13 device, as you can see, consists of two implantable
14 artificial ventricles, two pneumatic drivelines
15 that exit the chest and attach to an external
16 console.

17 The external console contains a computer
18 that monitors the device's function. The external
19 console also contains a controller and a backup
20 controller along with an alarm panel. As well, the
21 external console has backup compressors and a
22 backup power supply in the event of an emergency.

23 [Slide.]

24 Shown in this cartoon is the anatomical
25 fit of the device inside a patient. As you can see

1 from the picture, the native ventricles of the
2 patient have been resected in order to implant the
3 device.

4 Once again, you can see the pictures of
5 the left and the right ventricles along with the
6 pneumatic drivelines and driveline exit sites.

7 [Slide.]

8 The proposed indication for use for the
9 device is as a bridge to transplant in cardiac
10 transplant-eligible candidates at risk of imminent
11 death from non-reversible biventricular failure.
12 The device is solely intended to be used inside the
13 hospital.

14 [Slide.]

15 Presented in this slide is a history of
16 the clinical study. The clinical study was
17 approved in October of 1992 as a two-arm
18 prospective and retrospective, non-randomized,
19 multi-center clinical trial.

20 The initial enrollment of the trial began
21 in September of 1993 with a sample size of 64
22 patients with an equal amount of device patients
23 and control patients. This was based on a 90
24 percent power to detect a difference in the
25 clinical outcome between control patients and

1 device patients surviving to 30 days
2 post-transplant.

3 The assumption was that 20 percent of the
4 control patients would survive to 30 days
5 post-transplant, while 60 percent of the device
6 patients would survive to 30 days post-transplant.

7 The control arm of the clinical study
8 consisted of 3 different groups. It should be
9 noted that all patients within these groups met the
10 inclusion and exclusion criterias of the study.
11 Thirty-two of the 35 control patients were
12 identified through a retrospective examination of
13 medical records.

14 Twenty-two of the 32 control patients were
15 identified from 1991 to 1993, before the first
16 implant of the device in the trial had actually
17 occurred. Ten of the 32 patients, however, were
18 identified from 3 of the primary implant centers
19 from 1994 to 2002. Three of the control patients
20 were found concurrently through the trial and had
21 refused treatment with the device.

22 [Slide.]

23 According to our regulations, a device
24 that is intended to support or sustain human life
25 is subject to premarket approval. In order to

1 demonstrate premarket approval, a sponsor must
2 provide data that adequately demonstrates a
3 reasonable assurance of safety and efficacy of the
4 device.

5 In order to demonstrate a reasonable
6 assurance of safety and efficacy, the following
7 relevant factors must be considered. The patient
8 population for which the device is intended, the
9 conditions for use as suggested in the labeling,
10 the probable benefit of the device versus the
11 probable injury it may cause, as well as the
12 reliability of the device.

13 [Slide.]

14 In regard to the preclinical or
15 engineering topics that were involved in this
16 application, these were some of the issues that
17 were considered. These topics were deemed adequate
18 in determining reasonable assurance of safety of
19 the device.

20 [Slide.]

21 These engineering topics, however, are
22 still under review and we are actively working with
23 the sponsor to resolve them in a matter of time.
24 We do not believe that any of these issues will
25 hinder the progress of our review.

1 [Slide.]

2 In conclusion, the results of the
3 preclinical testing in conjunction with the outcome
4 of the reliability results from the clinical trial
5 demonstrate a reasonable assurance of the device's
6 safety. Dr. Julie Swain, however, will be
7 presenting the efficacy of this device.

8 I now turn over the rest of the
9 presentation to Dr. Lilly Yue, who will be
10 presenting the statistical analysis.

11 **Statistical Summary**

12 DR. YUE: Good morning. My name is Lilly
13 Yue, statistician in the Division of Biostatistics,
14 CDRH, FDA.

15 [Slide.]

16 In this presentation, I will briefly speak
17 on study design and concentrate on statistical
18 evaluation of effectiveness, and then give a
19 statistical summary.

20 [Slide.]

21 This is a two-arm, non-randomized clinical
22 trial conducted at five centers in the United
23 States between January 1991 and September 2002. Of
24 the 35 control patients, 32 were identified by
25 retrospective review, and the remaining 3 were

1 found by prospective measurement during the study.

2 Ninety-five patients received the total
3 artificial heart. Of these, 81 patients were
4 defined out of the implant group for evaluation of
5 effectiveness.

6 The primary effectiveness endpoint was
7 treatment success at 30 days post-transplant
8 according to prespecified clinical criteria.

9 Secondary effectiveness endpoints included
10 survival to transplant and survival to 30 days
11 post-transplant.

12 Adverse events were evaluated for the
13 determination of the safety of the device.

14 I will focus on the statistical evaluation
15 of effectiveness.

16 [Slide.]

17 On this slide, x axis denotes the year of
18 implant, and the y axis represents the number of
19 patients. Red is for control and blue is for
20 implanted group.

21 The majority of control patients were
22 collected in the early nineties, and the implant
23 time is imbalanced between the two treatment
24 groups.

25 [Slide.]

1 Also, there are multiple imbalances of
2 baseline covariates, such as risk factors and
3 previous intervention. In terms of some baseline
4 covariates, implant patients were sicker than
5 control patients, and with respect to some others,
6 control patients were sicker. For example, 60
7 percent control patients had a prior cardiac
8 surgery and 38 percent implant patients did.

9 [Slide.]

10 Given these imbalances, we can see that
11 the two treatment groups are not comparable before
12 the implant, so any direct treatment comparisons in
13 the effectiveness endpoints are inappropriate, and
14 all p-values from direct treatment comparisons are
15 not interpretable.

16 [Slide.]

17 An immediate question to ask is, "Can we
18 do treatment comparisons adjusting for these
19 imbalanced covariates?"

20 The sponsor performed traditional
21 covariate analysis, such as logistic regression,
22 and propensity score analysis on the proportion of
23 patients with treatment success, survival to
24 transplant, and survival to 30 days
25 post-transplant, respectively.

1 For the propensity score analysis, I would
2 like to give you a little introduction. Let's
3 assume we have just one covariate to adjust for,
4 for example, age.

5 [Slide.]

6 We can do this in two ways. Number 1,
7 matching patients with respect to age. We randomly
8 select one implant patient, then match him or her
9 with a control patient with the closest age.

10 We have a matched pair. Now, we continue
11 the process. Finally, we can compare the two
12 treatment groups based on the matched pairs.

13 Number 2. We can divide all patients into
14 several age subclasses. Within each subclass,
15 patients age is relatively similar, and the
16 distribution of age is relatively balanced between
17 the two treatment groups, so that treatment groups
18 are comparable with respect to age.

19 Within each age subclass, we compare two
20 treatments and obtain subclass-specific treatment
21 difference, then estimate overall treatment
22 difference by a weighted average.

23 However, if patients from one treatment
24 group are much older than those from the other
25 group, that means the two treatment groups do not

1 overlap with respect to age, then age factor could
2 be confounded with the treatment, and no
3 statistical methodology can be used appropriately
4 to adjust for age in this extreme case.

5 [Slide.]

6 However, usually we have many covariates
7 that should be adjusted simultaneously. One way to
8 do this is to perform propensity score analysis.

9 The basic idea of propensity score is to
10 replace the collection of covariates with one
11 single number, which is called the propensity
12 score.

13 For example, giving a patient's age,
14 duration of disease, and the status whether the
15 patient had prior cardiac surgery, and so on, we
16 can estimate a propensity score for the patient
17 through a statistical model.

18 Each patient just had one propensity
19 score, just as the patient has just one age value.

20 [Slide.]

21 In definition, propensity score here is
22 the conditional probability of receiving the total
23 artificial heart, given a patient's observed
24 baseline covariate values.

25 [Slide.]

1 When we use a propensity score to
2 simultaneously balance many covariates and reduce
3 the bias in treatment comparison, we have to point
4 out its limitations for use.

5 Propensity score methods can only adjust
6 for observed covariates and not for unobserved
7 covariates. It is always a limitation of
8 non-randomized studies compared with randomized
9 studies, when the randomization tends to balance
10 the distribution of all covariates, observed and
11 unobserved.

12 Propensity score works better when there
13 are many measured covariates, and it is seriously
14 degraded when important variables affecting
15 treatment selection have not been collected.

16 [Slide.]

17 In expectation, when the propensity scores
18 are balanced across the treatment and control
19 groups, the distribution of all regional covariates
20 are balanced across the treatment groups, so the
21 propensity score is also called a balancing score.

22 We can use the propensity scores as a
23 diagnostic tool to measure treatment group
24 comparability.

25 If the two treatment groups overlap well

1 enough in terms of propensity scores, we compare
2 the two treatment groups adjusting for the
3 propensity score, just as adjusting for age.

4 [Slide.]

5 In this study, we performed multiple
6 imputations for 19 percent patients with missing
7 baseline covariate values. Otherwise, these
8 patients would be excluded in propensity score
9 modeling.

10 We adjusted for all imbalanced and/or
11 clinically important baseline covariates as well as
12 the year of the implant, since over last 10 years,
13 the medical management of heart failure has changed
14 significantly.

15 We found that the propensity score model
16 accurately predicted the treatment group
17 membership. However, the two treatment groups did
18 not overlap enough with respect to propensity
19 scores to allow sensible treatment comparison.

20 [Slide.]

21 Here are boxplots demonstrating the
22 distributions of the propensity scores for the two
23 treatment groups, respectively. Let's look at the
24 boxplot for the control group.

25 The blue box here covers the middle 50

1 percent of patients. The lower and upper edges are
2 respectively, the first quartile and the third
3 quartile. The median is the line here with red
4 dot. The width of the box is arbitrary and has no
5 real meaning.

6 "Whiskers" here, actually, we should have
7 one here and a line here in the bottom, extend
8 vertical lines from the center edge to extreme
9 values. All points that are more extreme than the
10 "whiskers," if any are here, are potential
11 outliers. Now, here, the control group does not
12 have outliers, but TAH group has a lot outliers.

13 More than 75 implant patients do not have
14 any overlap with the control patients. Only 14
15 outliers, about 17 percent implant patients, have
16 some degree of overlap with control group.

17 [Slide.]

18 Let's check the treatment comparability in
19 another way. If we divide all patients into 5
20 quintiles, in the fourth and fifth quintiles, 56
21 percent implant patients do not have any control
22 patients to compare with.

23 At the same time, in the first quintile,
24 66 percent of control patients do not have any
25 implant patients to compare with. In the third

1 quintile, we have 23 implant patients, but only 1
2 control patient.

3 Only in the second quintile, the treatment
4 comparison is meaningful with 15 percent implant
5 patients and 31 percent control patients.

6 So, what can we do with the 56 percent
7 implant patients in the first and the fifth
8 quintiles? Throw them away? No, we would have
9 serious concerns with that no matter what study
10 results you could get from the remaining patients.

11 So, we have to conclude that the two
12 treatment groups are not comparable at all, and
13 then, any treatment comparisons adjusting for
14 imbalanced covariates are problematic.

15 [Slide.]

16 How to proceed? Now, we have to say any
17 judgment of the performance of the device has to be
18 based on the results from the total artificial
19 heart group alone.

20 [Slide.]

21 In this group with 81 patients, the
22 treatment success at just 30 days post-transplant
23 has a point estimate of 69 percent and 95 percent
24 confidence interval from 58 to 79 percent.

25 Please note that it is inappropriate to

1 consider the point estimate alone and ignore the
2 variability associated with the point estimate
3 since 7 survivors out of 10 patients will give you
4 a different degree of evidence from 70 survivors
5 out of 100 patients.

6 The difference is reflected in the lower
7 limit here, so we need to pay attention to lower
8 limit of a confidence interval.

9 [Slide.]

10 Here are some results for 6-month survival
11 from implant, 1-year survival from implant, and
12 1-year conditional survival from transplant based
13 on proportion.

14 [Slide.]

15 The mean time to transplant or death
16 before transplant is 79 days and median is 47 days.

17 The sponsor also performed Kaplan-Meier
18 survival estimates prior to transplant.

19 Here, death is an event and transplant is
20 treated as censoring. However, it is not clear to
21 us if sicker patients received transplant sooner in
22 this study. If that is the case, the assumption
23 underlying Kaplan-Meier estimates of independence
24 of censoring and event is invalid.

25 So, the Kaplan-Meier probability estimates

1 are biased, and the survival probability estimates
2 based on proportion demonstrated before are more
3 appropriate.

4 [Slide.]

5 In summary, without appropriate control,
6 it is difficult to perform statistical evaluation
7 of the effectiveness of the device.

8 For survival prior to transplant,
9 Kaplan-Meier survival estimates are potentially
10 seriously biased.

11 Thank you .

12 **Clinical Review**

13 DR. SWAIN: Thank you.

14 [Slide.]

15 I am going to present the clinical review
16 of the CardioWest TAH, and this review was done by
17 both Eleana Pina, heart transplant cardiologist,
18 and me as a cardiac surgeon.

19 [Slide.]

20 It is first important to note, as Dr. Yue
21 just said, that we really don't find that it is
22 statistically or scientifically valid to consider
23 the control group, probably not clinically valid
24 either, so we essentially have a single-arm study,
25 and what are we to do to evaluate the study.

1 It is first important to note that there
2 are really no randomized control studies for
3 bridge-to-transplant devices, and in devices that
4 have been approved, when you look at the
5 literature, there is really no comparable control
6 groups in previous BTT studies that would withstand
7 the rigorous analysis that the FDA does at this
8 time on control groups.

9 Also, in general, there is slow enrollment
10 because of the relatively small number of patients
11 requiring ventricular assist devices for a bridge
12 to transplant, so the 10-year duration of this
13 study is really not out of line with previous
14 devices.

15 What we decided to do, not relating to
16 this device, but two years ago the agency decided
17 to see if performance goals for left ventricular
18 assist devices could be developed using both inside
19 and outside consultants, it was looked at to see if
20 the literature could help us develop performance
21 goals.

22 It is probably important for the panel and
23 especially the audience to understand that this
24 does not imply that in the future, the agency will
25 accept proposals for single-arm

1 bridge-to-transplant trials, and also it really
2 doesn't imply that for bridge to recovery or
3 destination therapy devices for ventricular assist
4 devices, that the agency will accept performance
5 goals in single-arm trials.

6 [Slide.]

7 So, what we did was look at the
8 literature, and as a surgeon, I can say that with a
9 decade of experience with these devices, it is a
10 little disappointing to find a paucity of rigorous
11 scientific studies in this area, but these are some
12 of the inclusion criteria that we used, as well as
13 the exclusion criteria for papers. Again, this is
14 left ventricular assist devices.

15 [Slide.]

16 Well, what did we come up with? We came
17 up with a performance goal, not an OPC, but a
18 performance goal based on the literature for
19 survival to transplant.

20 That appeared to be the one area that we
21 could find some number of papers with somewhat
22 comparable results, and we came up with a goal of
23 65 to 70 percent. Again, this was started about
24 two years ago and finished about a year ago, well
25 before we saw any of the results of the CardioWest