

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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TUESDAY,  
JUNE 8, 2004

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*This transcript has not  
been edited and FDA  
makes no representation  
regarding its accuracy*

The above entitled Meeting was conducted at  
8:00 a.m., at the Hilton Washington D.C.  
North/Gaithersburg, Salons A, B, and C, 620 Perry  
Parkway, Gaithersburg, Maryland, Dr. Warren Laskey,  
Chairperson, presiding.

PANEL MEMBERS PRESENT:

WARREN K. LASKEY, M.D., Chairperson, Uniformed  
Services University of the Health Sciences,  
Bethesda, MD

SALIM AZIZ, M.D., Voting Member, Capitol  
Cardiovascular & Thoracic Surgery Association,  
Takoma Park, MD

MITCHELL KRUCOFF, M.D., Voting Member, Duke  
University Medical Center, Durham, NC

CYNTHIA TRACY, M.D., Voting Member, George  
Washington University, Washington, DC

KENT R. BAILEY, Ph.D., Consultant, Mayo Clinic,  
Rochester, MN

THOMAS B. FERGUSON, M.D., Consultant, Washington  
University School of Medicine, St. Louis, MO

JOHN W. HIRSHFELD, M.D., Consultant, University of  
Pennsylvania Medical Center, Philadelphia, PA

JOHN C. SOMBERG, M.D., Consultant, Professor of  
Medicine and Pharmacology, rush University,  
Lake Forest, IL

NORMAN S. KATO, M.D., Consultant, Cardiac Care  
Medical Group, Encino, CA

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JOANNE LINDENFELD, M.D., Consultant, University of Colorado Health Sciences Center, Denver, CO  
 JUDAH Z. WEINBERGER, M.D., Ph.D., Consultant, Columbia University, New York, NY  
 CLYDE YANCY, M.D., Consultant, University of Texas Southwestern Medical Center, Dallas, TX  
 MICHAEL MORTON, Industry Representative, Carbomedics, Inc., Austin, TX  
 CHRISTINE MOORE, Consumer Representative, Baltimore, MD  
 GERETTA WOOD, Executive Secretary, Food and Drug Administration, Rockville, MD  
 BRAN ZUCKERMAN, M.D., Food and Drug Administration, Rockville, MD

SPONSOR PRESENTERS:

RODERICK M. BRYDEN, President and CEO, World Heart Incorporated  
 JAL S. JASSAWALLA, MSME, MBA, Executive Vice President & Chief Technical Officer, World Heart Incorporated  
 JAMES B. YOUNG, M.D., Chairman, Division of Medicine, The Cleveland Clinic Foundation Lerner College of Case Western Reserve University; Medical Director, Kaufman Center for Heart Failure

FDA PRESENTERS:

MICHAEL BERMAN, Ph.D., FDA/CDRH/ODE/DCD  
 CHUL H. AHN, Ph.D., Biostatistician, CDRH/FDA  
 ILEANA PINA, M.D., Professor of Medicine, Case Western Reserve University, Consultant to FDA

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## A-G-E-N-D-A

<b>Call to Order</b> . . . . .	4
<b>Open Public Session</b> . . . . .	9
<b><u>Sponsor Presentation</u></b> . . . . .	11
Roderick Bryden	
Jal Jassawalla	
Dr. James Young	
Dr. Phil Oyer	
Dr. Brooks Edwards	
Dr. Peer Portner	
<b>FDA Presentation</b> . . . . .	67
Dr. Michael Berman	
Dr. Chul Ahn	
Dr. Ileana Pina	
<b>Reviews</b>	
Dr. Mitchell Krucoff . . . . .	113
Response by FDA . . . . .	149
Dr. John Somberg . . . . .	160
<b>Open Committee Discussion</b> . . . . .	168
<b>FDA's Comments</b>	
Dr. Ileana Pina . . . . .	234
<b>Additional Material Provided by Sponsor</b> . . . . .	236
<b>Review of Questions</b> . . . . .	240
<b>Public Session</b> . . . . .	255
<b>FDA Comments</b>	
Dr. Zuckerman . . . . .	256
<b>Sponsor Comments</b>	
Mr. Bryden . . . . .	257
<b>Consumer Comments</b>	
Ms. Christine Moore . . . . .	259
<b>Industry Comments</b>	
Michael Morton . . . . .	261
<b>Recommendations and Vote</b> . . . . .	264

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## P-R-O-C-E-E-D-I-N-G-S

8:07 a.m.

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CHAIRPERSON LASKEY: Well, good morning.

I'd like to call this morning's session to order.

This morning's session is the Circulatory System Device Panel addressing the topic of a premarket application for World Heart Novacor N100PC and N100PC(q) left ventricular assist system.

If I may have Ms. Wood read the 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 effect their or their employer's financial interests. However, the agency has determined that participation of certain

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1 members and consultants, the need for whose services  
2 outweighs the potential conflict of interests  
3 involved, is in the best interest of the government.  
4 Therefore, a waiver has been granted for Dr. Kent  
5 Bailey for his interest in a firm that could  
6 potentially be effected by the panel's  
7 recommendations. Dr. Bailey's waiver involves a  
8 contract to his institution for the sponsor's study  
9 in which he has no knowledge of the funding and has  
10 no involvement in data generation or analysis. The  
11 waiver allows this individual to participate fully  
12 in today's deliberations.

13                   Copies of this waiver may be obtained  
14 from the agency's Freedom of Information Office,  
15 Room 12A-15 of the Parklawn Building.

16                   We would like to note for the record  
17 that the agency took into consideration certain  
18 matters regarding Dr. Clyde Yancy. He reported a  
19 current involvement with a firm at issue for which  
20 he is uncompensated. Because his involvement is not  
21 directly related to today's agenda, the agency has  
22 determined therefore that he may participate fully

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1 in the panel's deliberations.

2 In the event that the discussions  
3 involve any other products or firms not already on  
4 the agenda for which an FDA participant has a  
5 financial interests, the participant should exclude  
6 him or herself from such involvement and the  
7 exclusion will be noted for the record.

8 With respect to all participants we ask  
9 in the interest of fairness that all persons making  
10 statements or presentations disclose any current or  
11 previous financial involvement with any firm whose  
12 products they may wish to comment upon.

13 CHAIRPERSON LASKEY: If I may have the  
14 members of the panel introduce themselves before we  
15 begin, starting at my left.

16 DR. ZUCKERMAN: Bran Zuckerman,  
17 Director, FDA Division of Cardiovascular Devices.

18 DR. AZIZ: Salim Aziz, Adult Thoracic  
19 surgeon, clinical professor of surgery at GW.

20 DR. KRUCOFF: Mitch Krucoff,  
21 intraventional cardiologist, Duke University and the  
22 Director of Intraventional Clinical Device Trials.

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1 DR. SOMBERG: John Somberg, Professor of  
2 Medicine and Pharmacology, Rush University.

3 DR. HIRSHFELD: I'm John Hirshfeld,  
4 Professor of Medicine at the University of  
5 Pennsylvania, intraventional cardiologist.

6 DR. WEINBERGER: Judah Weinberger, I'm  
7 Director of Intraventional Cardiology at Columbia,  
8 New York.

9 DR. LINDENFELD: Joanne Lindenfeld. I'm  
10 the Director of the Heart Transplant program at the  
11 University of Colorado.

12 CHAIRPERSON LASKEY: Warren Laskey,  
13 intraventional cardiologist from Uniformed Services  
14 University here in Bethesda.

15 MS. WOOD: Geretta Wood, Executive  
16 Secretary.

17 DR. BAILEY: Kent Bailey. I'm a  
18 biostatistician at Mayo Clinic.

19 DR. TRACY: Cynthia Tracy. I'm an  
20 electra-physiologist at George Washington  
21 University.

22 DR. FERGUSON: Thomas Ferguson, cardia

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1 thoracic surgeon, Washington University, St. Louis.

2 DR. YANCY: Clyde Yancy, Professor of  
3 Medicine, Director of Heart Transplantation, UT  
4 Southwestern in Dallas.

5 DR. KATO: Norman Kato, cardiovascular  
6 surgeon, Encino, California.

7 MR. MORTON: Michael Morton, and I'm  
8 employed by Carbomedics. I'm the industry  
9 representative.

10 CHAIRPERSON LASKEY: Thank you.

11 Geretta, if you could read the voting  
12 status statement, please.

13 MS. WOOD: Pursuant to the authority  
14 granted under the Medical Devices Advisory Committee  
15 charter, dated October 27, 1990 and as amended  
16 August 18, 1999 I appoint the following individuals  
17 as voting members of the Circulatory System Devices  
18 Panel for this meeting on June the 8, 2004:

19 Kent R. Bailey, Ph.D; John W. Hirshfeld,  
20 M.D.; Thomas Be. Ferguson, M.D; Norman S. Kato,  
21 M.D.; Clyde Yancy, M.D.; Judah Z. Weinberger, M.D.,  
22 Ph.D.; Joanne Lindenfeld, M.D.; John C. Somberg,

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1 M.D.

2 For the record, these individuals are  
3 special government employees and are consults to  
4 this panel under the Medical Devices Advisory  
5 Committee. They have undergone the customary  
6 conflict of interest review and have reviewed the  
7 material to be considered at this meeting. This is  
8 signed by Linda Cohn for Daniel G. Schultz, M.D.,  
9 Acting Director, Center for Devices and Radiological  
10 Health, and dated June the 3rd.

11 CHAIRPERSON LASKEY: Thank you.

12 Before we begin the open public hearing  
13 portion, I just want to read the following  
14 statement.

15 "Both the Food and Drug Administration  
16 and the public believe in a transparent process for  
17 information gathering and decision making. To ensure  
18 such transparency at the open public hearing  
19 sessions of the Advisory Committee meeting, FDA  
20 believes that it is important to understand the  
21 context of an individual's presentation. For this  
22 reason, FDA encourages you, the open public hearing

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1 speaker at the beginning of your written or oral  
2 statement to advise the Committee of any financial  
3 relationship that you may have with the sponsor, its  
4 product and if known as direct competitors.

5 For example, this financial information  
6 may include the sponsor's payment of your travel,  
7 lodging or other expenses in connection with your  
8 attendance at this meeting. Likewise, FDA  
9 encourages you at the beginning of your statement to  
10 advise the Committee if you do not have any such  
11 financial relationships.

12 If you choose not to address this issue  
13 of financial relationships at the beginning of your  
14 statement, it will not preclude you from speaking."

15 I'd like to now ask the audience if  
16 there's anyone who wishes to address the panel on  
17 today's topic? If not, I'll close the open public  
18 hearing portion and invite the sponsor to make his  
19 presentation.

20 MS. WOOD: I would like to remind the  
21 speakers for the sponsor to introduce themselves and  
22 to state their conflict of interest before speaking.

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1                   Your presentation is scheduled for an  
2 hour, and I would ask you to limit the presentation  
3 to data that has been reviewed in the PMA by FDA.

4                   MR. BRYDEN: Good morning.

5                   My name is Roderick Bryden, I'm the  
6 President and the Chief Executive Officer of World  
7 Heart Corporation. I am a full time employee of the  
8 corporation, and of course it pays my income and  
9 expenses for this panel.

10                  With me today presenting is Jal  
11 Jassawalla, whose the Executive Vice President and  
12 Chief Technical Officer of the corporation.

13                  Dr. James Young, whose the Chairman of  
14 the Division of Medicine of the Cleveland Clinic  
15 Foundation Lerner College of Medicine of Case  
16 Western Reserve University and the Medical Director  
17 of Kaufman Center for Heart Failure.

18                  Also with us and available to respond to  
19 questions, Dr. Phil Oyer, a Professor of  
20 Cardiovascular Surgery at Stanford University School  
21 of Medicine.

22                  Dr. Brooks Edwards will join us. He had

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1 to remain at his clinic last evening, so he will be  
2 in sometime during the course of the morning. He's  
3 Professor of Medicine and Cardiology at the Mayo  
4 College of Medicine and Medical Director for Cardiac  
5 Transplant Team.

6 Dr. Peer Portner is consulting professor  
7 of Cardiothoracic surgery at Stanford University  
8 School of Medicine.

9 Dr. William Anderson consulting  
10 biostatistician.

11 I will make a brief overview of our  
12 presentation and the bulk of the presentation will  
13 be presented by Dr. Young and Mr. Jassawalla.

14 We are proposing an expansion in our  
15 existing bridge to transplantation indication. That  
16 expansion is highlighted on this slide that you see  
17 on the screen and in the slides before the panel.

18 The purpose of the expansion us to  
19 remain as a part of the bridge to transplantation  
20 indication and to ensure that patients with relevant  
21 contraindications to transplant who are expected to  
22 become transplant candidates have access to this

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1 therapy. The judgment as to whether the patient  
2 suffers from a relative contraindication and whether  
3 that patient may be expected to become a candidate  
4 is supported by a mechanical circulatory device is a  
5 judgment that would be made by the transplant  
6 center.

7 That patient must also, as with the  
8 current indication, be at risk of imminent death.  
9 That judgment would be made by the transplant  
10 center. That is in distinction to a destination  
11 therapy indication, which this is not. The  
12 destination therapy indication also requires the  
13 transplant center to apply judgment, the first  
14 judgment being that the patient is not eligible for  
15 cardiac transplantation and the second judgment  
16 being that the life expectancy is less than two  
17 years.

18 The same centers that will make the  
19 judgment with respect to becoming eligible for  
20 destination therapy would make the judgment as to  
21 whether the patient would be eligible under the  
22 expanded bridge transplant indication.

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1 World Heart is pursuing a randomized  
2 pivotal trial now with the acronym RELIANT for the  
3 purpose of making a submission to the FDA when that  
4 data is complete for a PMA for destination therapy.  
5 And this indication is not intended to in anyway  
6 become a part of that therapy.

7 There is a clinical need. The class of  
8 patients with relative contraindication to  
9 transplant but an expectation of listing for  
10 transplant do not now currently have an established  
11 consistent access to the mechanical therapy which  
12 for patients at risk of imminent death is often the  
13 only therapy available. Approval of this proposed  
14 expansion in our label would provide more of these  
15 patients with a routine method of accessing this  
16 therapy.

17 Our presentation will deal with two key  
18 questions. First, are the data from the Novacor  
19 bridge to transplant study sufficient to support  
20 approval of the expanded indication? And secondly,  
21 if it is, would these patients be eligible today to  
22 receive the Novacor LVAS under the existing labeling

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1 and therefore there's no need for the expanded  
2 indication? There have been specific questions  
3 raised by the FDA in its reference to the panel, and  
4 we have responded to these both during the course of  
5 the presentation by Dr. Young and Mr. Jassawalla,  
6 but also at the end of that summary presentation  
7 each question is dealt with and a brief summary of  
8 our response for your record.

9 To deal first with the adequacy of data.  
10 There is a clear subgroup of patients within the  
11 Novacor bridge to transplant study which experienced  
12 one or more relative contraindications at the time  
13 of enrollment. In fact, 39 percent of the 225 cases  
14 experienced such relative contraindications, 61  
15 percent did not. One might ask then how did they  
16 become a part of the trial if they had a  
17 contraindication? The answer is in two areas.

18 One is, as you know, the criteria for  
19 eligibility for transplant are not legislated or  
20 regulated on a national basis. The process is for  
21 each center to define its standards within a broad  
22 set of reasonable norms and then to consistently

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1 apply those standards to the patients on whom it has  
2 to make judgments. The center practices, therefore,  
3 very from center-to-center. They did during the  
4 course of enrollment, they continue to vary from  
5 center-to-center.

6 Secondly, the enrollment in this trial  
7 was completed in September of 1998 and during the  
8 intervening period, indeed during the period of the  
9 enrollment itself, the evolution and experience has  
10 resulted in adjustments in the criteria from time-  
11 to-time. So there is both the eventuality of the  
12 patient having presented at a center, which in some  
13 cases enrolled patients with this contraindication  
14 and the fact that over time the effects of certain  
15 contraindications have varied as experience with  
16 this therapy has been gained.

17 This data arises from a prospective  
18 controlled pivotal trial, and that trial was found  
19 sufficient to result in the FDA's approval of the  
20 indication label for bridge to transplantation which  
21 exists for Novacor. All aspects of that trial were  
22 established and reviewed and the approval for the

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1 indication given by the FDA in light of it,  
2 including the nature of controls which was a thorny  
3 issue at the time in light of ethical and other  
4 issues and were carefully managed and negotiated  
5 with the FDA at that time. There have been no  
6 changes made in that database, either controls the  
7 recipient group.

8 Today there are twice as many patient  
9 years of data available from that trial as were  
10 available from the trial in September when the  
11 original label was issued. The trial was only  
12 completed in January of 2002, and the final patient  
13 was translated after more than three years of  
14 support on the Novacor.

15 The data supports this indication first  
16 by comparison with the control group, which is the  
17 control that was the basis for the entire trial, in  
18 the reduction of mortality and in the improvement in  
19 the survival to transplant. But secondly, within  
20 this group while 39 percent experienced relative  
21 contraindications, 61 percent did not. If one were  
22 to attempt to structure today a prospective trial,

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1 it is probably impossible, certainly hard to  
2 imagine, that that trial could be done with the  
3 control group receiving optimal medical therapy when  
4 they are facing imminent death and optimal medical  
5 therapy demonstratively does not succeed and with  
6 the evidence that devices are successful in that  
7 regard. So a prospective trial today would have to  
8 be in some fashion done with a control group which  
9 has different indications but also receives the same  
10 therapy. That is precisely what we have. We have  
11 here 61 percent of a group who were implanted within  
12 a controlled prospective trial who did not have  
13 contraindications and 39 percent who did. And the  
14 evidence is clear that the results for those who  
15 suffered from contraindications, both with respects  
16 to their transplant rate and with their post-  
17 transplant survival was substantially the same as  
18 the results of those who were implanted with the  
19 same device and who did not relative  
20 contraindications.

21 The evidence also indicates that the  
22 patients with these contraindications would not

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1 today have a routine access to the device within the  
2 current indication. Dr. Young will review both the  
3 literature and a survey of ten centers in which the  
4 details of all the data points collected for these  
5 patients, which I believe are some 59, were provided  
6 to these centers to determine whether or not today  
7 these would be listed for transplant. Both within  
8 the literature and with results of that survey,  
9 almost all of the patients with relative  
10 contraindications would not be listed at some of the  
11 centers, and a majority of those with the relative  
12 contraindications would not have been listed at any  
13 of the centers.

14 While the criteria vary and there is no  
15 absolute standard, there are a few standards which  
16 are generally and relatively consistently applied,  
17 one of those being that the patient should meet the  
18 accepted criteria for transplantation and be ready  
19 to undergo the transplant procedure on the day of  
20 listing. Not listed in advance in anticipation of  
21 some future event with which they would be eligible,  
22 but eligible on the day that they list. These with

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1 these relative contraindications for the majority of  
2 centers and the majority of patients would not meet  
3 that test. It is not appropriate in our view to  
4 suggest that we should rely on clinics bending the  
5 rules and not living by their own criteria as the  
6 method of giving access to these devices.

7 Finally, we have suggested that the  
8 indication include the terms "short" or "long term"  
9 in the labeling. We have since the completion of  
10 the trial and since the granting of the PMA in  
11 September, completed the trial with a total of twice  
12 the number of patient years of experience and up to  
13 3.4 years of support.

14 Secondly, the waiting times for  
15 transplant organs is highly variable.

16 And thirdly, the relative  
17 contraindications are somewhat unpredictable as to  
18 the time that will be required.

19 The intention was simply to draw  
20 attention in the label to the fact that longer term  
21 support in the context of a bridge does have  
22 demonstratively increased rates of adverse events.

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1 It is not our intention to have any other meaning  
2 than the one that is intended, and we would be quite  
3 happy to adjust that language in the event that  
4 other words would be more precise.

5 I would now like to proceed with a  
6 review by Mr. Jassawalla of the overview of the  
7 trial data and also of the Novacor reliability data,  
8 and then proceed directly without my return to the  
9 podium to Dr. Young who will present clinical  
10 evidence with respect to these issues that we  
11 believe clearly support the approval of this  
12 requested expansion.

13 Thank you very much.

14 Mr. Jassawalla?

15 MR. JASSAWALLA: Good morning. I am an  
16 officer of the company, and an employee and as such  
17 I do have a financial interest in the company.

18 This slide shows system configuration  
19 and anatomic placement. The pump drive unit is  
20 implanted in the upper left quadrant of the abdomen.  
21 The inflow conduit canulates the apex of the left  
22 ventricle, the outflow graft is connected to the

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1 ascending aorta. There is a single percutaneous  
2 lead that carries the power and signal wires out to  
3 the external control. The controller is designed to  
4 have two power sources connected to it at all times.

5 The system is totally self regulating  
6 and responsive to flow from the left ventricle and  
7 as such, there are no user controls. The recipient  
8 simply needs to manage his or her power sources.

9 There is extensive history with this  
10 device starting with the first clinical use in 1984  
11 at Stanford University. There have been over 1500  
12 implants worldwide to date. We've accumulated over  
13 500 patient years of experience.

14 The current configuration, which is the  
15 N100PC was CE marked in 1993 in Europe for all  
16 indications. FDA granted bridge to transplant  
17 approval in 1998. And there have 1,077 implants  
18 through April of last year, which is the cut off for  
19 the submission.

20 MS. WOOD: Excuse me, sir. It's come to  
21 my attention that this was not part of the original  
22 PMA, and I would like to inform the panel this will

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1 not be part of the discussion today.

2 MR. JASSAWALLA: That data was in the  
3 submission, but I won't debate. We're just trying  
4 to give you the reliability in the context of this  
5 indication.

6 DR. ZUCKERMAN: Right. Let me clarify  
7 the comment.

8 MR. JASSAWALLA: Yes.

9 DR. ZUCKERMAN: I believe that in the  
10 subsequent discussion there is reference made to a  
11 1,077 implants and some of the data that pertains to  
12 those 1,077 implants. That data and the review of  
13 that data are not in the PMA and cannot be utilized  
14 for this important discussion today. It's just a  
15 heads up that Ms. Wood was giving you.

16 MR. JASSAWALLA: May I ask in which PMA  
17 you were referring to? The original 1998?

18 DR. ZUCKERMAN: I'm sorry. For the PMA  
19 supplement that is under discussion today, June 8,  
20 2004.

21 MR. JASSAWALLA: Yes.

22 In support of the original 1998 approval

1 for bridge to transplant there was an in vitro life  
2 test that was conducted. These are the results of  
3 that life test. We had a dozen systems that were  
4 placed on tests under simulated clinical conditions.  
5 The goal of this test was to run the systems to  
6 failure. The mean duration was 4.2 years with a  
7 range from a little over 3 years to 5.6 years.

8 The demonstrated reliability using the  
9 Wible model with a 80 percent low confidence limit  
10 gives you the results that are listed in the slide.  
11 For the first year it gives us 99.9 percent  
12 reliability. For the second year 98.5. And for the  
13 third year 87.4. There were no random failures  
14 uncovered.

15 And in addition to the demonstrated high  
16 reliability and multi-year durability there was a  
17 single progressive non-catastrophic wear-out mode  
18 that could be monitored invasively. The clinical  
19 experience has been consistent with the in vitro  
20 life test results and there be no deaths attributed  
21 to device failure.

22 Long term patient experience with this

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1 system shown here within the 1,077 implants, there  
2 have been 285 that have gone over six months, 121  
3 that have been supported for over a year and 27 and  
4 10 for more than two and three years respectively.

5 The likelihood of reoperation to replace  
6 or repair the LVAS from all causes is shown in the  
7 next table. The likelihood in the first six months  
8 is 1.6 percent. The subsequent six month period of  
9 2.1. Eleven percent in the second year and 16  
10 percent in the third year.

11 There was --

12 MS. WOOD: Excuse me again, sir, but  
13 it's also been brought to my attention that this was  
14 not a part of the PMA supplement and therefore, this  
15 data will not be discussed today.

16 MR. JASSAWALLA: The next slide.

17 The overview results of the BTT study  
18 where the study was conducted in a NYHA class four  
19 end stage heart failure patient population at risk  
20 of imminent death were 225 patients, 190 LVAS  
21 recipients, 35 controls. FDA approved the system  
22 for bridge to transplant in September of 1998 and

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1 at study close there were 67 total patient years of  
2 support, approximately twice the total at approval,  
3 the longest duration of support being 3.4 years.

4 Overall results of mortality and adverse  
5 event risk decreased substantially after the post-  
6 opt period. Sixty-eight percent of LVAS recipients  
7 were transplanted. The median survival on LVAS of  
8 about 11 months. Thirty-seven percent of the  
9 controls were transplanted with a median survival of  
10 less than half a month. The LVAS support provided a  
11 seven fold reduction in mortality of risk with a  
12 very significant p-value of .0001.

13 I'll now turn over to Dr. Young to talk  
14 about the specific study results and transplant  
15 listing practices.

16 DR. YOUNG: Thank you, Jal.

17 Mr. Chairman, ladies and gentlemen of  
18 the FDA and the panel, my name is Jim Young. And  
19 for those of you that don't know me, I am at the  
20 Cleveland Clinic Foundation. Today I am acting as a  
21 consultant to World Heart. I do not own any stock or  
22 equity in that corporation. They are paying me for

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1 my activities of advice given for clinical trial  
2 design and also data analysis.

3 And what I am going to be talking about  
4 specifically is the data analysis in the Novacor  
5 bridge to transplant study. And by way of  
6 introduction I would like to, again those of you  
7 that don't know me, point out that I am a heart  
8 failure/heart transplant cardiologist and have been  
9 involved in this arena, unfortunately to say, for  
10 over two decades now. And one of the fascinating  
11 things is the increase in our knowledge base with  
12 regard to how we can treat patients with advanced  
13 end stage heart failure. And, in fact, the roles of  
14 heart transplantation ventricular assist device  
15 therapy and mechanical support in general. And much  
16 of the issues driving why this retrospective  
17 analysis of a prospectively controlled trial was  
18 done lies in those efforts, efforts to clarify how  
19 we should be selecting patients for transplantation,  
20 selecting patients for ventricular assist device  
21 therapies and tail in well with the ongoing  
22 discussions, I won't say debate but ongoing

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1 discussions regarding which patients should be  
2 listed for heart transplant and when.

3           The bridge to transplant study, as has  
4 been alluded to, actually has patients in them which  
5 consensus would agree have no relative  
6 contraindications to cardiac transplantation. As we  
7 have gained knowledge over time and reviewed a  
8 variety of other databases, however, we note now  
9 that many relative contraindications to patients  
10 receiving heart transplant at a time when a  
11 ventricular assist device is placed actually do  
12 exist. And this has created contention and debate  
13 in some circles, much discussion in other circles.

14           We in this database had the ability to  
15 come down on listed here seven specific relative  
16 contradictions which robust information was  
17 available in and which, as I will show you, fit the  
18 type of relative contraindications that have emerged  
19 from other databases and the focus of discussion  
20 when we select patients for listing for cardiac  
21 transplantation at review board meetings or, indeed  
22 as we do it in the state of Ohio, at a panel review

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1 by the Ohio Solid Organ Transplant Consortium.

2 Status II now makes up patients with one  
3 or more of these relative contradictions at  
4 enrollment into the Novacor BTT study. And these  
5 specific contradictions were creatinine greater than  
6  $2\frac{1}{2}$ , pulmonary systolic pressures over 60 mmHg,  
7 pulmonary vascular resistance higher than 6 Wood  
8 units, total bilirubin greater than 5 milligrams,  
9 obesity or body mass index that would suggest  
10 excessive ponderosity at 32 cubic grams per meter  
11 squared or cachexia at 19 kilograms per meter  
12 squared. And then age, which still is a terribly  
13 contentious issue at 66 years.

14 Could I have the next slide?

15 Now, those were picked based on several  
16 different things. One, literature review including  
17 rather extensive analysis of data in the cardiac  
18 transplant research database group, which now has  
19 very compulsive information on over 7,000 patients  
20 followed for ten years as well as the advice of  
21 experience clinicians, heart failure and transplant  
22 clinicians, both cardiologists and cardiac surgeons.

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1                   And these were the most clinically  
2 relevant of the 59 variables that were in the  
3 database which could be analyzed. Now, this doesn't  
4 include all of the variables that may create  
5 relative contraindications to cardiac  
6 transplantation. And three of the most vexing ones  
7 that we have to deal with on a day-to-day basis are  
8 presence of allosensitization in a patient with end  
9 stage failure who may or may not be a transplant  
10 candidate but who is coming to the decision about  
11 needing mechanical circulatory support.

12                   Presence of a malignancy, for example.  
13 This creates a very vexing problem if you've had a  
14 patient who is only out two years from a successful  
15 resection of a breast malignancy and there's  
16 questions about those patients.

17                   As well as other examples, and in Ohio  
18 perhaps one of the more frequent ones we see is with  
19 the state review whether or not a patient might have  
20 psychosocial issues that create relative  
21 contraindications; cigarette smoking, past history  
22 of drug abuse or whatnot. And a requirement has

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1       been raised about putting the patient through  
2       psychosocial counseling for a period of time.

3               Those are just examples of some of  
4       additional variables that would not be in the BTT  
5       study that could be looked at.

6               Next slide.

7               Now, these thresholds that we choose are  
8       consistent with many current consensus guidelines  
9       for transplant listing and the literature. And,  
10       indeed, if you look at a few examples here's one  
11       from Blue Cross/Blue Shield which excludes patients  
12       with pulmonary systolic pressures greater than 60,  
13       TPGs greater than 4 Woods units, obesity as they  
14       define 150 percent of ideal body weight, which would  
15       translate somewhere into the range of a BMI of about  
16       32. And this is on vas therapies, as well. So we  
17       believe that these relative contradictions that have  
18       been listed are consistent with clinical practice  
19       and data.

20               Next slide.

21               And, in fact, if you look at the  
22       references that have focused on these relative

1 contradictions going back to the conference led by  
2 Les Miller back in 1998 when we first really began  
3 looking at how we pick patients and list them for  
4 cardiac transplantation and focus on this question  
5 of if you list a patient, ipso facto an organ  
6 becomes available, you should accept that organ for  
7 the individual patient. And then vetting the  
8 contentious issues of those relative contradictions  
9 has been expanded into several other efforts,  
10 including the one I just alluded to the most recent  
11 publication by Jim Kirklin of over 7,000 patients in  
12 the CTRD database.

13 And so there's robust information in the  
14 literature about this relative contradictions and  
15 how they contribute to excessive risk post-  
16 transplantation and then begins to introduce the  
17 concept of an individual that has one or more of  
18 these relative contraindications the rationale of  
19 implanting a ventricular assist system to support  
20 hemodynamics with the expectation that these  
21 complications will in fact resolve and make the  
22 patient a better heart transplant patient.

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1 Next slide, please.

2 And so group two was this group of  
3 individuals that came out of the BTT study. And  
4 overall in the BTT study now, 225 patients were in  
5 that study. And if you looked at group one, those  
6 are the individuals that were receiving LVAS therapy  
7 for hemodynamic indications that didn't have these  
8 tangible relative contraindications that were  
9 listed. In the control group, the historical control  
10 group for the BTT study, there were also individuals  
11 in whom we applied the same criteria, and you can  
12 see 23 of those original 35 control patients had no  
13 contraindications with 12 having one or more of the  
14 contraindications similar to the individuals that  
15 eventually received a VAD but had contraindications  
16 present at that time.

17 Next slide.

18 Now, if you look at the control group,  
19 this is an important element but to me perhaps not  
20 the real issue, as I'll get into in a minute. But  
21 the control group was the basis for the BTT approval  
22 and as was alluded to after a lot of discussion.

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1 And we did use the same criteria for picking in the  
2 control group as in the test group, the LVAS group,  
3 the relative contraindications.

4 And interestingly enough if you looked  
5 at multivaried analysis correction for the multiple  
6 covariates that are involved in the control group  
7 and the treatment group, there remained a highly  
8 significant difference as those of us clinicians  
9 might have expected.

10 Next slide.

11 Now, interesting to me was the number of  
12 relative contraindications that appears and what  
13 they were. And here you see the contraindications  
14 listed. For me the two particularly vexing  
15 difficulties when you're at the bedside looking at  
16 these patients and trying to make a decision about  
17 going forward with listing for transplant is: (1  
18 renal insufficiency as marked by a serum creatinine  
19 of 2½ or greater and; (2) pulmonary hypertension  
20 particularly after a lot of therapies have been  
21 given to try to optimize it and so pulmonary  
22 pressures at their best that are greater than 60

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1 millimeters of mercury. And so two of the top three  
2 relative contraindications were in fact related to  
3 that.

4 We also have a troublesome time with  
5 many ponderous patients that come in to see us, and  
6 that represented the top number in the LVAS group.  
7 And this is the group that I think is most  
8 important. Interestingly enough, congestive  
9 hepatopathy from heart failure and even age wasn't  
10 as much of an issue in this data set.

11 Next slide.

12 Now, the important observation to me  
13 really is here on this slide, and it's the fact that  
14 even though by many different other analysis,  
15 database analysis, the relative contraindications  
16 lead to worse outcome after transplantation, when  
17 you look at those individuals who received a  
18 ventricular assist device in group one versus group  
19 two individuals that did not have in group one and  
20 individuals that did have one or more relative  
21 contraindication, you can see here that there was no  
22 statistically significant difference when those two

1 groups were compared censoring the patients at  
2 transplantation, obviously sense that was the goal.

3 So it suggests that you can use left  
4 ventricular assist device therapy even in patients  
5 with these relative contraindications to support  
6 them to transplantation. And even we have data  
7 demonstrating that during the period of support,  
8 many of these relative contraindications abate or at  
9 least improve.

10 Also important is when you do compare it  
11 to the control groups in group and group two, again  
12 there was a highly statistically significant  
13 advantage in both group one and group two of  
14 receiving the left ventricular assist device. And,  
15 again, I think this is consistent with many other  
16 analyses, anecdotal experience and also longer term  
17 destination therapy controlled clinical trials with  
18 these patients that are being evaluated and being  
19 looked at with transplantation as an end point, as  
20 BTT looked at, are in fact quite ill.

21 Next slide.

22 Now to me also important is the rate of

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1 transplantation that occurs in this group. Because  
2 this an end point that gets to whether or not  
3 hemodynamically we are being able to resuscitate  
4 these group two patients to get them to a level,  
5 particularly with pulmonary hypertension and renal  
6 insufficiency, to get them to a level where the  
7 clinician is comfortable accepting a heart when it's  
8 offered.

9           What happens in reality right now is  
10 many patients who resemble individuals in group two  
11 would be listed for a heart transplant, yet when the  
12 VAD was put in would be immediately made status 7.

13           Now, for those of you that may not know  
14 the UNOS allocation schemes, there are really three  
15 active schemes. Status 1, status 2 and status 7. A  
16 status 2 patient is an outpatient, sort of the  
17 walking wounded not requiring a lot of intensive  
18 therapies that is on the waiting list and now  
19 represents only about a third of the transplants  
20 done in the United States. A status 1 patient is an  
21 individual either in the hospital on intravenous  
22 medications with invasive lines present on

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1 hemodynamic support with mechanical circulatory  
2 sustenance.

3 And the practice in these types of  
4 patients would either be to make a patient status 7  
5 or, if you left them status 1 or status 2, turn down  
6 parts listing the turn down reason being the patient  
7 "too ill" generally that's the category that would  
8 be tipped.

9 So what this observation demonstrates  
10 here is if you compare the patients with and without  
11 these relative contraindications, the rate of  
12 transplantation was similar statistically in these  
13 two groups, and actually pretty good from a  
14 clinicians assessment in those patients. And, of  
15 course, compared to the controlled group the rate of  
16 plantation was much, much higher again suggesting  
17 the hemodynamic support is pulling these patients  
18 back from the brink much more readily.

19 Next slide, please.

20 And then another issue which a lot of us  
21 have been interested in is what are these relative  
22 contraindications either with or without left

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1 ventricular assist device therapy mean to the post-  
2 transplant survival group. Again, as I alluded to,  
3 having renal insufficiency, having pulmonary  
4 hypertension is independent risk factors by  
5 themselves for higher adverse event rates, post-  
6 transplantation. What you can see here, again  
7 comparing the patients with relative  
8 contraindications to the patients with no  
9 contraindications is no significant difference in  
10 survival rates once transplant has occurred. And, in  
11 fact, numerically over the follow-up period survival  
12 was actually better in this group of patients.

13 Next slide.

14 So we believe that this is a unique  
15 dataset and, in some sense, this may be a fortuitous  
16 at the time not know perspective comparison of the  
17 group that creates problems for us today and the  
18 group that we were challenged to try to help. And I  
19 believe that we have demonstrated improved survival  
20 while awaiting transplantation even when relative  
21 contraindications exist and compared to control  
22 patients on a ventricular assist device therapy, I

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1 believe the dataset, again, clearly shows as it did  
2 before an improved rate of transplantation. And  
3 very important is that survival is similar in the  
4 patients with relative contraindications, those  
5 group two patients, to those without those group one  
6 patients.

7                   And the link, I think, is this fact:  
8 There is resolution of specific conditions present  
9 and we can present data specifically regarding what  
10 happens with those seven parameters which created  
11 the relative contraindication. And I alluded to the  
12 fact that pulmonary artery pressure does fall,  
13 creatinines do improve, renal function does get  
14 better as two specific examples.

15                   Next slide.

16                   MS. WOOD: Excuse me, Dr. Young. But  
17 it's been brought to my attention that the  
18 information in the previous slide was not submitted  
19 to the FDA for review as part of this PMA  
20 supplement, and we will not be discussing that  
21 information today.

22                   DR. YOUNG: Thank you.

1  
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22

Now, if you look at the analysis specific to these risk factors and relative contraindications and try to determine what the impact of ventricular assist device therapy is, the reduction in mortality risk is virtually unchanged when considering any of the differences in individual patient covariates. And importantly, the analysis suggests that there's a six fold reduction in mortality risk in these patients with relative contraindications. And to a clinician what this means is that we can make decisions in a patient that today if we listed him, would not clearly be a heart transplant candidate, we can make decisions to place a ventricular assist device with the expectation that those contraindications will in fact be treated and resolved. And that is the purpose of the request on the labeling.

Next slide.

Now, another interesting thing to me is that these patients in group two here in the yellow are, in fact, more ill going into these operations and during the observation period one might expect

1 complications which are nemeses in taking care of  
2 ventricular assist device patients were seen more  
3 frequently during the post-VAD implantation follow-  
4 up period. And this data is set up so that group  
5 one patients are normalized here at 100 percent and  
6 then the relative increase in complications observed  
7 here in the group two patients are noted. And you  
8 can see that though numerically more frequent, these  
9 are 95 percent confidence intervals. There's  
10 extremely wide confidence intervals. And in the end  
11 there were no statistically significant differences  
12 between the two groups, though numerically some of  
13 the problems were more significant in the group two  
14 patients. Again, my interpretation suggesting that  
15 you can get these patients through, you can improve  
16 them and that ultimately they can be transplanted.

17 Next slide.

18 Now one of the things we also did was  
19 went back and looked at now ten, this was nine  
20 centers. We do have data now from Columbia which is  
21 not going to be in this presentation as it came it  
22 late. But these nine centers were picked because

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1 they were participants in the BTT trial and they  
2 representative of the wide spectrum of centers that  
3 were in the study. We had both very large centers,  
4 the Cleveland Clinic doing 75 to 80 transplants a  
5 year --

6 MS. WOOD: Excuse me, Dr. Young.

7 It's also been brought to my attention  
8 that this data as not part of the PMA supplement  
9 submitted for review and will not be part of the  
10 discussion today as well as the next slide.

11 DR. YOUNG: Okay.

12 The query here, however, that will be  
13 discussed demonstrated agreement, basically -- can I  
14 have the next slide -- with the relative  
15 contraindications that we had identified. And so  
16 though it won't be discussed, 83 of the 87 patients  
17 by the panel -- and this was done in a blinded  
18 fashion, agreed that there was one or more  
19 contraindications for transplanting on the day of  
20 listing.

21 Next slide.

22 So really what this boils down to is the

1 challenge as clinicians that we have with respect to  
2 the end stage heart failure patient population which  
3 fortuitously was represented quite nicely in the BTT  
4 study here. You have those patients that clearly  
5 are not a transplant candidate nor will they ever  
6 be, and we can give many examples of those patients.  
7 Perhaps an older patient with a malignancy that's  
8 been resected and allosensitization identified pre-  
9 transplantation, they're just not going to be a  
10 transplant candidate. Perhaps they would be a  
11 candidate for destination therapy. Those are not  
12 the types of patients that were in the BTT trial,  
13 nor were they the types of patients that in our  
14 retrospective analysis made up those individuals  
15 with the relative contraindications. We're really  
16 focusing on this part here, which are individuals  
17 who fall outside the limits of transplant criteria  
18 but who may be expected to become transplant  
19 patients who then are in this status 7 or this  
20 repetitive turndown mode.

21 Next slide.

22 And also we know that transplant listing

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1 practice varies. And, indeed, this was seen in the  
2 BTT study. This is a commonly discussed issue  
3 amongst programs, and there may be some centers who  
4 are willing to list a patient who have relative  
5 contraindications particularly if a ventricular  
6 assist device is going to be placed, to move them  
7 into a category where if an organ became available,  
8 it would be utilized. And, of course, driving this  
9 has been primarily changes in practice over our time  
10 and our understanding of transplantation and  
11 ventricular assist device therapies and a lot of  
12 that has been done with the retrospective analysis  
13 of existing database. Transplantation and  
14 ventricular assist device utilization is a boutique  
15 science and unfortunately we don't have the ability  
16 to be able to do very large scale randomized  
17 clinical trials. So we know this from the UNOS  
18 databases, the CTRD databases which are readily  
19 available.

20 Next slide.

21 And so the issue of the clinical need  
22 for an indication of this sort I believe is present.

1 And I believe when you look at the BTT study you can  
2 see patients that early on were placed into this  
3 study and went through and did demonstrate that you  
4 could rehabilitate them and get them to  
5 transplantation.

6 Next slide.

7 And so if you look at the BTT group,  
8 which was a perspective and it was a controlled  
9 clinical trial and subjected to the retrospective  
10 analysis addressing the questions that have risen  
11 more contemporaneously, we believe that the data is  
12 there to support the request. There is a six-fold  
13 reduction in mortality in this particular targeted  
14 population. This would be a population that would be  
15 problematic to randomized, given all of the  
16 information about high mortality rates and, indeed,  
17 as characterized by the control group in this  
18 particular trial although there were some problems  
19 with that.

20 I think that a prospective study where  
21 you randomized these sort of patients would be  
22 impractical. I would be very loathe to enter into

1 that, particularly because of the ethical issue.  
2 And I don't think that other tactics can be used to  
3 clarify the issue. I believe that the analysis of  
4 this particular database has done that. And,  
5 obviously, databases are continuing, post-marketing  
6 surveillance is continuing. There's large  
7 registries that are being developed, responses to  
8 the NIH RFA has been made.

9 Next slide.

10 And so to summarize, I believe that a  
11 population does exist with patients with relative  
12 contraindications to transplant. And in those  
13 individuals there's no assured access to ventricular  
14 assist device and transplant therapy even if the  
15 clinician suspects that many of these parameters  
16 could resolve with ventricular assist device  
17 support. And, indeed, if you do that retrospective  
18 look at the bridge to transplant study, there were a  
19 significant number of patients in that trial that  
20 met this contemporaneous characterization. And I  
21 believe that we have demonstrated that there is  
22 effectiveness as a bridge to transplant with the

1 LVAD survival being greater than control and perhaps  
2 even more important to me, the survival in group two  
3 patients, those with relative contraindications  
4 supported by the ventricular assist device being  
5 similar to group one patients, those without.

6 Next slide.

7 And so if you look at the benefits  
8 versus the risks, approving an expanded indication  
9 would provide more uniform access to that therapy in  
10 these patients with the demonstrated survival  
11 benefit. And those bad recipients who survive  
12 transplant do have the opportunity to benefit from  
13 really the gold standard therapy for really the  
14 terminally ill bad hemodynamic patient. And that in  
15 this analysis those patients with relative risk did  
16 have a six-fold reduction in mortality. And I  
17 personally believe that what this would lead to is  
18 more consensus regarding listing and ultimately  
19 utilization of scarce donor organs.

20 I think that was my final slide. Next  
21 slide. Oh, this is the final slide.

22 In response to the questions that have

1       come out, I do think that we have addressed and  
2       answered them. Many of the other slide summaries are  
3       in the handout, but I do believe that the core data  
4       analysis that is here from the BTT study does in  
5       fact justify the expanded indication and the  
6       labeling rewording that has been requested.

7                     Thank you.

8                     MR. BRYDEN: Thank you very much. That  
9       concludes the presentation from the sponsor. And we  
10      would be pleased to take any questions now, and also  
11      of course there is the time following the FDA's  
12      presentation when we look forward to responding to  
13      question from the panel.

14                    Thank you.

15                    CHAIRPERSON LASKEY: So, panel members,  
16      are there any questions for an of the three  
17      presenters this morning?

18                    DR. FERGUSON: Warren, I have a  
19      question. I'm sorry, I'm sure it's in the material,  
20      but I couldn't find it.

21                    When you talk about the group two  
22      patients, they could have relative contraindication

1 or seven, each individual. Do you have any data  
2 breakdown of that because the lumping seems to me to  
3 be a bit unfair, perhaps, unless you do that?

4 DR. YOUNG: Well, it turns out that the  
5 majority had one relative contraindication; 17 of 87  
6 subjects had two of them and 2 of 87 had three.

7 DR. FERGUSON: Right. Exactly.

8 DR. YOUNG: So the numbers in those that  
9 had multiple contraindications were 17 with two and  
10 two with three.

11 DR. BAILEY: I wonder if you could just  
12 summarize the recruitment into the original BTT  
13 study; that is how were patients recruited into that  
14 prospective study, in particular the control  
15 patients versus the LVAS patients? I guess I'm  
16 interested in the timing, sort of the time flow of  
17 that.

18 MR. JASSAWALLA: Yes. The actual  
19 enrollment, the bridge to transplant study, the one  
20 that resulted in the approval, the LVAS patients  
21 were recruited between March of 1996 and September  
22 of 1998. Prior to that we had another study that was

1 ongoing with the FDA. And because of the problem  
2 and ethical considerations in enrolling patients,  
3 the FDA permitted us to use the controls because the  
4 inclusion and exclusion criteria were essentially  
5 the same from the previous study when we finalized  
6 on the study that started enrollment in March of  
7 1996.

8 DR. BAILEY: Okay. Then the control  
9 patients were not actually concurrently recruited?

10 MR. JASSAWALLA: Some of them were, but  
11 several of them were from an era slightly ahead of  
12 when the pumps were implanted.

13 DR. BAILEY: And what were the selection  
14 criteria for choosing controls retrospectively then?

15 MR. JASSAWALLA: Many of them came from  
16 centers that were in training for the LVAS, and we  
17 had a rule where we skipped no controls. That once  
18 a center was going to provide controls, they went  
19 back to their database and looked at the study  
20 exclusion criteria and then uniformly included them  
21 as controls.

22 DR. BAILEY: But what is the starting

1 date? When they're first listed, is that the  
2 starting date for follow-up, when they're first  
3 listed on the transplant list?

4 MR. JASSAWALLA: Yes. Yes.

5 DR. BAILEY: Okay. But then the  
6 controls would be defined by ones who are listed and  
7 who didn't receive a device?

8 MR. JASSAWALLA: Correct. They would  
9 have met inclusion criteria at that point.

10 DR. BAILEY: And would the fact that  
11 they were not going to receive the device be known  
12 at the time they were listed, that is they had  
13 already refused or were already at a center that  
14 didn't have a device available?

15 MR. JASSAWALLA: For the prospective  
16 controls, they would have refused a device or a  
17 device may not have been available. A surgeon may  
18 have been out of town. For the retrospective ones,  
19 there were those that would have met inclusion but  
20 the study hadn't started in terms of a trained group  
21 of people.

22 DR. BAILEY: Okay. Their status as far

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1 as not being able to receive the device would be  
2 known at the time of listing? You'd know  
3 prospectively?

4 MR. JASSAWALLA: Yes. Yes.

5 DR. BAILEY: In other words, if they had  
6 been in a perspective study --

7 MR. JASSAWALLA: Yes.

8 DR. BAILEY: -- they would have known at  
9 that time that they weren't going to get the device?

10 MR. JASSAWALLA: Right.

11 DR. LINDENFELD: The median survival of  
12 your controls in group two is 7 days? I guess when  
13 we're comparing the control group here to the device  
14 group, I mean the median survival of the medical  
15 group in REMATCH was 105 days. Seven days seems  
16 awfully short, and you have to wonder that is a  
17 pretty short median survival. These patients, this  
18 control group doesn't seem to me like the average  
19 control group listed for transplantation. I mean,  
20 the median survival 7 days after listing, it's hard  
21 for me to compare to the LVAS group because it  
22 doesn't seem like a reasonable comparison.

1 DR. YOUNG: Yes. First of all, I think  
2 we need to be careful when we look at the control of  
3 REMATCH. I hesitatingly mention it because they are  
4 different patients. They are not transplant  
5 candidates, number one. And number two I think  
6 their median survival is higher because those  
7 patients at risk of imminent death wouldn't get into  
8 REMATCH. At least I know for a fact they did not  
9 get into PREMATCH, which I was involved in.

10 Now, I agree completely. These are  
11 patients that are very ill and that when you list  
12 them, the median survival of a week after that  
13 characterizes them as a group that if you had a VAD  
14 available and were capable of putting it in,  
15 probably would have ended up getting a ventricular  
16 assist device. So I think the fact that they only  
17 have this short survival reflects the fact that  
18 these are very ill patients and yet matched well  
19 with the patients in the BTT that ended up getting a  
20 ventricular assist device.

21 DR. LINDENFELD: And how many of the  
22 control group and the device group were on

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1 amyotrophic therapy at the time at the initial time  
2 of either device placement or listing for  
3 transplant? It looks to me like in the briefing  
4 book it's around 12 percent?

5 DR. YOUNG: There's a backup slide that  
6 I think has got the -- 100 percent; that's the  
7 answer to that. And there's a backup --

8 DR. LINDENFELD: In both groups were on  
9 amyotrophic therapy, the control and the device  
10 group?

11 DR. YOUNG: Yes. Yes. Yes. And again  
12 because of the era that BTT was done, these were I  
13 think very ill individuals and the options,  
14 obviously, were not great.

15 DR. LINDENFELD: And then do we have  
16 data about the reversibility of the pulmonary  
17 hypertension? I think in most places there's some  
18 evaluation of the reversibility. Do we have any  
19 data for that?

20 DR. YOUNG: Yes. There is data both in  
21 the original PMA submission for the entire group  
22 about what happens to pulmonary hypertension and we

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1 also have data in individuals who have pulmonary  
2 hypertension is the reason for their relative  
3 contraindication. And both of them show reduction  
4 in systolic pulmonary pressures and also  
5 transplumony gradients.

6 If you look up there --

7 CHAIRPERSON LASKEY: Dr. Young, is that  
8 pre-transplant or post-transplant?

9 DR. YOUNG: Pre-transplant on the  
10 ventricular assist device.

11 CHAIRPERSON LASKEY: So they're  
12 empirical studies?

13 DR. YOUNG: Yes. Yes.

14 DR. LINDENFELD: No, I'm sorry. I'm  
15 talking about reversibility at the time of listing  
16 or device placement.

17 DR. YOUNG: The reversibility would have  
18 been demonstrated after device placement. These are  
19 patients that would have been already on drugs and  
20 drips.

21 DR. LINDENFELD: I'm sorry I'm not being  
22 clear. What I wanted to know is if PA pressure is

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1 greater 60, most of the time the way that's  
2 evaluated is to see if patients respond to therapy  
3 and if those drop, and do we know what happened to  
4 those pulmonary pressures and the pulmonary  
5 resistance prior to either LVAD placement or  
6 listing? In other words, were they reversible prior  
7 to that?

8 DR. YOUNG: I can't tell you  
9 specifically what was done, but I can tell you that  
10 the PA pressures were listed as greater than 60 on  
11 optimal therapy. So I can only assume that the  
12 cardiologist and the surgeons have been trying to  
13 lower them with the best means that were available.  
14 And again, anecdotally from my experience, this is a  
15 problematic issue, probably more so in Denver at  
16 6,000 feet. But I can't tell you specifically what  
17 was done.

18 What I can show you here is what  
19 happened over the period of time where hemodynamic  
20 assessments were available in the individuals who  
21 received LVAD therapy whether or not they were  
22 transplanted or not. And you can see that those

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1 patients with pressures above 60, LVAD therapy  
2 invariably dropped those systolic pressures. So one  
3 assumes that as the individuals were treated,  
4 pressures remained at 60. It was the addition of the  
5 ventricular assist device that effected that  
6 decrease in pulmonary hypertension.

7 CHAIRPERSON LASKEY: Yes, Dr. Hirshfeld?

8 DR. HIRSHFELD: I'd like to ask, do you  
9 have a slide comparable to the one you just showed  
10 for pulmonary vascular resistance? I didn't see  
11 that data in the briefing book.

12 DR. YOUNG: I believe that we do. We  
13 don't have it for pulmonary vascular resistance. No  
14 late wedge pressure measurements in the database.

15 DR. HIRSHFELD: So you don't know --

16 DR. YOUNG: I can tell you why that is.

17 DR. HIRSHFELD: Okay.

18 DR. YOUNG: In the ICUs with the  
19 Swangantz in place, most of our surgical colleagues  
20 don't like us blowing the balloon up.

21 DR. HIRSHFELD: Because I think  
22 interpreting a drop in pulmonary pressure by itself

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1 may just reflect dropping left ventricular pressures  
2 and not reflect reversal of pulmonary arterial or  
3 constriction.

4 DR. YOUNG: Sure. And that's the one  
5 major challenge that we have at the bedside trying  
6 to figure out the patient. But I can tell you that  
7 if the blood pressure goes up, flows go up and the  
8 pulmonary artery systolics drop, we're at least much  
9 more comfortable that the patient will do okay.

10 CHAIRPERSON LASKEY: Mitch?

11 DR. KRUCOFF: In the white paper section  
12 5A of our panel pack and 5B, you all have several  
13 multi-variable models considering some of these  
14 features. Is anybody actually going to discuss  
15 those models?

16 MR. BRYDEN: We would be happy to  
17 discuss those. We could do it now or in the  
18 afternoon when there may be a bit more time. Which  
19 would be your preference?

20 CHAIRPERSON LASKEY: Well, we're  
21 actually doing well time wise. It may be somewhat  
22 more involved. If you want to save it for either

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1 your turn this afternoon --

2 DR. KRUCOFF: I actually just wondered  
3 if anybody was going to talk about them.

4 CHAIRPERSON LASKEY: Yes.

5 DR. YOUNG: We will, I'm sure, that  
6 given the opportunity we will present that fully  
7 this afternoon.

8 CHAIRPERSON LASKEY: Great. Thank you.

9 Dr. Aziz?

10 DR. AZIZ: What percent of your VAD  
11 implant patients have had prior heart surgery?

12 DR. YOUNG: Oh, it's a good question and  
13 I can't give you that off the top of my head.

14 DR. BAILEY: Do you have any analyses  
15 that don't don't -- just looking at overall survival  
16 including a post-transplant, just as all one  
17 endpoint?

18 DR. YOUNG: Not that I've personally  
19 looked at.

20 DR. BAILEY: I guess the concern is just  
21 that, you know, I guess if one group gets earlier  
22 transplants, than you're sort of looking at a

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1 different point on the curve than starting from time  
2 zero when they're listed. So, you could imagine if  
3 one group got a differential rate of getting  
4 transplants, and I guess to do that you'd have to  
5 look at the transplant endpoint, censoring it and  
6 see if practice patterns are the same in the two  
7 groups. But, you know, it sort of influences the  
8 interpretation of survival post-transplant.

9 MR. BRYDEN: Yes. For your efficiency,  
10 we will pull it out so it's efficiently delivered.  
11 But that data is available.

12 CHAIRPERSON LASKEY: Dr. Yancy, you had  
13 a question?

14 DR. YANCY: Thanks, Warren.

15 I'd like to go back to an issue that Dr.  
16 Lindenfeld raised because I think that the strength  
17 or weakness of the presentation really hinges on the  
18 aberrant outcomes in the control group. And I'd like  
19 to know beyond the inotrope question what other  
20 clinical characteristics you can share with us  
21 regarding that control group. Because I think a  
22 critical issue is whether or not the same mortality

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1 expectation would exist under a contemporary  
2 practice model, so I think it's important to know a  
3 little bit more about that comparison group.

4 DR. YOUNG: Well, what I can tell you is  
5 this was the characteristics of the overall group.  
6 And I can also tell you that the parameters were not  
7 significantly different between the two groups. I  
8 don't know that I actually have the control group  
9 listed out. But I think perhaps the most telling  
10 tale, again, is the low index, low systemic  
11 pressure. And to me the most important  
12 characteristics were that over 70 percent were  
13 supported with either intra-aortic balloon pump or  
14 some other mechanical circulatory support, whatever,  
15 and that 13 pumps had had cardiac arrest or  
16 cardiopulmonary resuscitation within 48 hours before  
17 enrollment. So the whole BTT group was in fact  
18 extraordinarily ill.

19 DR. LINDENFELD: Is it possible to see  
20 the groups with IABP and post-cardiac arrest? I  
21 mean, what percentage of each of those two groups  
22 were post-cardiac arrest and had ballooning?

1 DR. YOUNG: Yes, we can get that for  
2 you.

3 MR. BRYDEN: The datapoints, of course,  
4 were collected on both control and the implant  
5 group. And with those specific questions we can  
6 query the database and probably by this afternoon  
7 have pretty accurate answers on those questions.

8 CHAIRPERSON LASKEY: All right. Well,  
9 before we proceed with the FDA's presentation, I  
10 just one I guess overall philosophic question. Your  
11 BTT study looked at survival post-transplant as the  
12 primary endpoint and survival on LVAS as your  
13 secondary endpoint. Now you're looking at survival  
14 on LVAS as a primary endpoint in the same study,  
15 just switching your primary and secondary endpoints.  
16 Can you just tell us what sort of concerns were  
17 addressed up front when you do this kind of relook?

18 DR. YOUNG: It's a very fair point, and  
19 I did I hope openly and fairly point out this is a  
20 retrospective analyses with all of the inherent  
21 problems and weakness of that sort of database. That  
22 being said, that's one of the ways in

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1 transplantation and ventricular assist device  
2 therapy that has guided us down the road.

3           The questions shifted over time, and the  
4 questions initially were could you get a patient to  
5 transplant and then would in fact the post-  
6 transplant outcomes be reasonable. So post-  
7 plantation became the focus of attention. So that's  
8 why I think in the original perspective study that  
9 was the relevant issue. Because again, as a  
10 clinical it's more important to get the device out,  
11 the transplant done and have good outcomes.

12           Now the question has really shifting  
13 driven by the timing of listing a patient for  
14 transplant vis-à-vis these relative  
15 contraindications and what are our tools available  
16 to try to repair things like pulmonary hypertension  
17 and renal insufficiency and some of these other  
18 relative contraindications listed. So the attention  
19 has shifted to what the device can do before  
20 transplantation. And I think that's the best  
21 explanation that I can give for the reason that  
22 we're looking at a different outcome.

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1                   You guys want to --

2                   MR. BRYDEN: I'd like to just comment  
3                   briefly. The summary data that was reviewed and  
4                   then the more detailed data that is available was  
5                   reviewed first from the standpoint of survival post-  
6                   transplant, which was the endpoint in the primary  
7                   study. And, in fact, the survival post-transplant in  
8                   the group two, those suffering contraindications was  
9                   not statistically significantly better, but slightly  
10                  better than the survival post-transplant by those  
11                  who did not have the relative contraindications.  
12                  And the survival to transplant, again, was not  
13                  statistically significantly different but slightly  
14                  less favorable for those who had relative  
15                  contraindications than for those who did not.

16                  So while the presentation may have been  
17                  in a different order, the precision of the data  
18                  collected and the judgments made, it was not  
19                  intended to be adjusted.

20                  CHAIRPERSON LASKEY: Well, I'll leave  
21                  that to the statistical folks to hash out. I  
22                  understand the clinical science of it, but when you

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1 do a study and you assign primary and secondary  
2 endpoints on the one hand, you assign different  
3 levels of confidence in your results. And then when  
4 you switch a secondary endpoint and make it a  
5 primary endpoint and raise the level of confidence  
6 required for those results, it just raises some  
7 questions particularly with respect to the nature of  
8 the control group.

9 All right. Well, we're doing very well  
10 for time, so let's proceed if we may -- do we need a  
11 break? It's so early. Okay. Well, I've been told  
12 we'll have a 10 minutes. I have 20 after 9:00.  
13 Let's regroup at 9:30. We have a real shot at  
14 getting done early today, so 9:30 it will be. Thank  
15 you.

16 (Whereupon, at 9:20 a.m. a recess until  
17 9:37 a.m.)

18 CHAIRPERSON LASKEY: Okay. Before we  
19 begin, Ms. Wood wanted to read one statement?

20 MS. WOOD: Yes. I would like to correct  
21 one of my previous comments. The reliability of  
22 1,077 patients on slide 18 of the sponsor's

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1 presentation was in fact submitted in the PMA  
2 supplement on August of 2003, however it was not  
3 included in the panel packs to the members of this  
4 panel.

5 CHAIRPERSON LASKEY: Thank you.

6 And I'd like to invite the presenters  
7 from the FDA to do their thing.

8 DR. BERMAN: Good morning.

9 For the record, the matter before the  
10 panel today is a proposal or a request by World  
11 Heart Corporation for an expanded indication for use  
12 for their model N100PC and N100PC(q) left  
13 ventricular assist system, and the information was  
14 provided in supplement -- in amended 7 to supplement  
15 4 of P980012.

16 I will present the FDA review summary  
17 for this file.

18 My name is Mike Berman. I am the lead  
19 reviewer for this file.

20 The FDA review team consisted of Dr.  
21 Ahn, who is a FDA statistician, myself as the lead  
22 reviewer, Dr. Ileana Pina who is a heart failure

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1 cardiologist. She is a consultant to the FDA. And  
2 Dr. Julie Swain, she is a cardiac surgeon and is a  
3 consultant tot he FDA.

4           So that we can focus, this the part of  
5 the sponsor's request, this is the proposed language  
6 for their expanded indication for use. The language  
7 in yellow is the language they currently had. "The  
8 LVAS is intended for use as a bridge to  
9 transplantation in cardiac transplant candidates at  
10 risk of imminent death from nonreversible left  
11 ventricular failure. The LVAS is indicated for use  
12 both inside and outside of the hospital." That's  
13 approved currently.

14           The sponsor wants to add language so  
15 that the indication for use will now read: "The  
16 LVAS is intended for use as a short or long term  
17 bridge to transplantation in cardiac transplant  
18 candidates and in patients with relative  
19 contraindications to transplantation who are  
20 expected to become transplant candidates with  
21 mechanical circulatory support at risk of imminent  
22 death" etcetera.

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1           The term "indication for use" has a  
2           specific regulatory meaning, and this is what it is.  
3           This is a quote from the regulations within which  
4           the FDA must operate. "An indication for use has to  
5           include a general description of the disease or the  
6           condition that the device will diagnose or treat and  
7           it must include a description of the patient  
8           population for which the device is intended."

9           So, did the sponsor's request include a  
10          description of the disease? Yes, it did; it's end  
11          stage heart failure, nonreversible LV failure, risk  
12          of imminent death.

13          Did they include a description of the  
14          patient population? Well, they still have  
15          candidates for cardiac transplant, but now they want  
16          to add those with relative contraindications to  
17          transplant who are expected to become transplant  
18          candidates with mechanical circulatory support.  
19          That matter will be addressed further by Dr. Pina in  
20          her review.

21          So as part of our review process and our  
22          decision process we must determine whether there is

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1 a reasonable assurance of safety and effectiveness  
2 for this device used for this purpose and safety and  
3 effectiveness are determined under our law. We have  
4 to determine it with respect to the patients for  
5 whose use the device is intended. In this case it  
6 would be patients with relative contraindication who  
7 are expected to become, and that will be addressed  
8 further by Dr. Pina.

9 As well we have to take into account the  
10 conditions of use which are prescribed, recommended  
11 or suggested in the label, and we have to assess  
12 probable benefit versus probable injury.

13 As a reminder, this is a description of  
14 the device. The implanted components consist of an  
15 encapsulated blood pump which is placed sub-  
16 diaphragmically. There are two valved conduits and  
17 part of the percutaneous tube which connects the  
18 pump to the outside world is implanted. There are  
19 external components. There is a controller. There  
20 are battery packs, there are other power sources and  
21 there are various accessories. This is from the  
22 operator's manual.

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1                   Again, you can see the blood pump, the  
2                   inflow to the pump comes from the apex of the left  
3                   ventricle. It is conveyed to the pump by a conduit  
4                   or a valved conduit. The blood is pumped out of the  
5                   pump, again, through a valve conduit into the  
6                   ascending aorta. A percutaneous tube connects the  
7                   pump to the outside, to the controller. There's also  
8                   a capability, a vent capability which allows the  
9                   venting of the interior space of the pump to the  
10                  outside. And there are battery packs shown in this  
11                  view and it doesn't show the other components.

12                  If this device system were being  
13                  presented de novo for any purpose, that is if we had  
14                  not seen it before, we would assess multiple  
15                  characteristics of the device system determined from  
16                  bench testing. For example, we would examine  
17                  manufacturing processes for the device system. We  
18                  would be concerned about the sterilization process,  
19                  how the system would be packaged and shipped,  
20                  whether the materials out of which the device was  
21                  manufactured were biocompatible. We would examine  
22                  device software, mechanical safety, electrical

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1 safety, electromagnetic compatibility and so on.

2 None of these matters are at issue in  
3 today's discussion. There are no aspects of the  
4 items listed here which are in question. They have  
5 all been examined in detail previously, mostly as  
6 part of the bridge to transplant indication, and the  
7 FDA has judged them to be adequate for bridge to  
8 cardiac transplantation and we see no concerns with  
9 any of these items for the expanded indication  
10 that's being proposed.

11 However, the FDA does have remaining  
12 concerns regarding the expanded indication for use,  
13 and they can be divided into clinical concerns and  
14 statistical concerns.

15 We're concerned that the patients  
16 evaluated are not the same as those patients for  
17 whom the device will be indicated.

18 We have some concerns about the term  
19 "long" or "short term" about the meaning of relative  
20 contraindication and about this idea that these  
21 patients are expected to become transplant  
22 candidates.

1           As far as the statistical analyses, we  
2           are concerned that subgroup analyses as presented  
3           can be extended to the intended patient population  
4           and whether or not the selected treatment and  
5           control groups are, in fact, comparable.

6           As far as the clinical concerns, we note  
7           that the patients in the analyses data subset which  
8           was drawn from the bridge to transplant trial were  
9           transplant eligible and patients for the expanded  
10          indication for use may not be.

11          As far as "short" or "long term" goes,  
12          out of 160 of the 190 LVAS patients in the BTT trial  
13          were on device six months or less, and that's from  
14          tab 5A figure 4-1. Of the 30 LVAS patients who were  
15          six months or more on device, 15 of them were at a  
16          year or more and only four went out for two years or  
17          more. So we're concerned about that in terms of use  
18          of the term "long term."

19          Relative contraindication, it's not  
20          clear to us from the data provided why those  
21          specific seven parameters were chosen and why the  
22          specific thresholds were chosen.

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1           And the term "expected to become" is  
2           problematic because the patients who were analyzed  
3           in the subset analyses were all transplant patients.

4           And we do not see in this submission  
5           objective evidence of reversal or normalization of  
6           the relative contraindications or of an improvement  
7           of the opportunity for transplant, nor do we see any  
8           objective evidence that one can determine a priori  
9           whether a particular patient with relevant  
10          contraindication is likely to become a transplant  
11          candidate on device.

12          The statistical concerns we think, and  
13          Dr. Ahn will address this in more detail, that the  
14          subgroup analyses may not be extendable to the  
15          intended patient population. And there is concern  
16          about the comparability of the selected patient  
17          subgroups because covariates are not matched.

18          The FDA presentation will now continue.  
19          Dr. Ahn will discuss the statistical aspects of the  
20          submission.

21                   DR. AHN: Good morning. I'm Chul Ahn,  
22          the FDA statistician for this file.

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1           The BTT study was submitted in World  
2           Heart original PMA application for use of the LVAS  
3           device system for bridge to cardiac transplantation.  
4           This PMA was approved in 1998.

5           BTT trial was a two arm nonrandomized  
6           study based on 225 patients. Either the patient  
7           received the Novacor LVAS or was treated with  
8           medical management.

9           Among the 225 patients, 190 patients  
10          were in the treatment group and 35 patients in the  
11          control group.

12          The primary endpoint of this study was  
13          survival to 30 days post-transplant. The PMA  
14          supplement under consideration today use as a subset  
15          of data drawn from the sponsor's original PMA  
16          application. The sponsor proposes to expand the  
17          current indication for use to include patients with  
18          so called relative contraindication. The sponsor use  
19          seven criteria to choose a patient with relative  
20          contraindication.

21          They retrospectively identify 87 such  
22          patients out of 225. Among 87 patients there were

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1 75 LVAS patents and 12 control patients. The sponsor  
2 argues that information derived from these selected  
3 87 patients supports their proposal for an expanded  
4 indication for use.

5 The sponsors proposed expanded  
6 indication for use implies that patients with  
7 relative contraindication who are not eligible for  
8 transplant will become transplant eligible with LVAS  
9 support.

10 So the device's intended patient  
11 population is those with relative contraindication  
12 who are expected to become transplant candidates.  
13 Notice that this intended patient population is  
14 different from BTT population.

15 Panel members, I want to look at screen  
16 since there will be an animation.

17 This red circle shows the 225 patients  
18 from the BTT study. They were a sample from BTT  
19 population. The cloud shows the intended expanded  
20 patient population. It is different from BTT  
21 population. There is no overlapping between two  
22 populations.

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1           The sponsor found the subgroup with  
2           relative contraindication from BTT sample. There  
3           were 87 patients; 75 from the treatment and 12 from  
4           the control.

5           Did the patient with relative  
6           contraindication improve their opportunity for  
7           transplantation with LVAS support? We know that  
8           these 87 patients were transplant eligible when they  
9           were entered into the BTT study. However, even if  
10          we accept that these 87 patients were not transplant  
11          eligible, there is no evidence to demonstrate that  
12          these 75 LVAS patients became transplant eligible  
13          while on support. The sponsor provided baseline  
14          patient characteristics but they did not provide the  
15          outcome data for the seven relative contraindication  
16          criteria that could potentially result.

17          Therefore, the data does not directly  
18          address intended patient population. We don't know  
19          how effective the device will be for the intended  
20          patient population. Let's revisit the previous  
21          graph once more.

22          The cloud population is intended patient

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1 population for the proposed expanded indication for  
2 use. They are the patients with relative  
3 contraindications who are expected to become  
4 transplant candidates with mechanical circulatory  
5 support. But the data we have is for those 87  
6 patients from the red circle with relative  
7 contraindications who were transplant candidates  
8 when they received the LVAS and we don't know  
9 whether they result or not. Therefore, it is  
10 problematic whether the result from these 87  
11 patients can be extended to the intended patient  
12 population.

13 After the sponsor identify 87 patients  
14 as those with relative contraindication, they  
15 compared the survivor curves between 75 LVAS and 12  
16 controls. However, the question is whether these  
17 two treatment groups are comparable. We will look  
18 at three items to examine this.

19 They are the year implants, an example  
20 of especially covariate and baseline covariate in  
21 general and propensity scores. This graph shows the  
22 distribution of patients over the years when the

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1 device was implanted. For the control group the  
2 year of implant refers to the year when they were  
3 enrolled into the study.

4 In the graph blue is for the treatment  
5 group and red for the control group. Note that most  
6 of the control patients, nine out of 12, were  
7 enrolled in the first half of the 1990s while all of  
8 the LVAS patients were involved in the last half of  
9 the 1990s. There has been a drastic change in  
10 medical management during the last ten years,  
11 therefore the year of implant is a very important  
12 covariate. However, as you can see from this graph  
13 there is very little overlap in the time of  
14 enrollment between the two treatment groups.

15 Now I would like to show you that there  
16 are large differences in several other baseline  
17 covariates between the two treatment groups.

18 This is the list covariates which shows  
19 statistically significantly difference between the  
20 two treatment groups with p-value less than 10  
21 percent. They are sorted by the magnitude of p-  
22 value. They are Milrinone, pre and

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1 antihypertension, age, history of transient TIA,  
2 dosages of Dobutamine, creatinine level and  
3 bleeding.

4 So far we have seen that these two  
5 treatment groups are not comparable due to imbalance  
6 of the year of implants and imbalance in multiple  
7 baseline covariates. And any direct treatment  
8 comparisons on effectiveness endpoint are  
9 problematic. Also, all p-values from direct  
10 treatment comparisons are not interpretable.

11 What about treatment comparisons  
12 adjusting for imbalanced covariates? We may  
13 consider two analyses methods. They are traditional  
14 covariate analysis and propensity score analysis.

15 For the traditional covariate analysis  
16 let's consider an example of adjustment for one  
17 covariate; health condition. We say that health  
18 condition is an important covariate when the event  
19 rate depends on health condition. Suppose the event  
20 rate is higher in the control group where there are  
21 sicker patients. Then the low event rate in the  
22 treatment group may not be due to the treatment, but

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1 simply because there are healthier patients in the  
2 treatment group. In this case we need to compare  
3 patients with similar health condition, and we want  
4 to see some overlap in the health condition between  
5 the two treatment groups. Otherwise, the two  
6 treatment groups won't comparable.

7                   What about if there are many covariates?  
8 One solution is to replace the collection of  
9 covariates with one single number called propensity  
10 scores. Propensity score is a condition of  
11 probability of receiving the LVAS given a patient's  
12 observed baseline covariate values, such as age,  
13 gender, prior cardiac surgery and so on. Like  
14 health condition in the previous slide we compare  
15 patients with similar propensity scores. When the  
16 propensity scores are balanced across the treatment  
17 and control groups, the distribution of all the  
18 covariates are balanced in expectation across the  
19 two treatment groups. So we can use the propensity  
20 scores as a diagnostic tool to measure treatment  
21 group comparability.

22                   And the two treatment groups will be

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1 comparable if there is enough overlap between them,  
2 however, the two treatment groups in this study did  
3 not overlap enough to allow a sensible treatment  
4 comparison. We performed propensity score analysis.  
5 We adjusted for all imbalance and clinical important  
6 baseline covariates.

7 This is a box plot graph. A box plot  
8 provides an excellent visual summary of many  
9 important aspects of a distribution. The left box  
10 plot shows a distribution of propensity scores for  
11 the control group. The box stretches from the lower  
12 hinge defined as the 25th percentile to the upper  
13 hinge, the 75th percentile and therefore contains  
14 the middle half of the scores in the distribution.

15 The median is shown as a line across the  
16 box. The right, 57 observations corresponding to 76  
17 percent of the data are above the lower hinge.  
18 Those 76 percent of the data from the treatment  
19 group do not overlap with any observations from the  
20 control group. As we can see, there isn't enough  
21 overlap to compare to treatment groups.

22 This is another way of expressing two

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1 distributions of propensity scores. Here the  
2 propensity scores are categorized into five groups  
3 so that the number of patient in each group are  
4 evenly distributed. In the first bin there are  
5 eight controls and ten treatment. In the second bin  
6 there are four controls and 13 treatment. And the  
7 rest of the bins are all LVAS patients. We can see  
8 clearly the two distributions did not overlap enough  
9 to allow a sense of comparison between LVAS patients  
10 and control patients.

11 The propensity score analysis,  
12 therefore, tells us that any treatment comparison  
13 adjusting for imbalanced covariates are problematic.

14 The sponsor performed the survivor  
15 analysis, and these are the survivor curves from the  
16 original BTT study. The red line indicates the  
17 survivor curve for 190 patients in the treatment  
18 group and the black line is for the 35 patients in  
19 the control group. As you can see, there is a large  
20 difference between the two treatment groups. Now,  
21 the sponsor picked 75 patients from the treatment  
22 group and 12 patients from the control group. The

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1 sponsor was interested in whether there will be any  
2 significant difference between the two treatment  
3 groups.

4 Let's find out, and this is what they  
5 got. And as you can see, there is a significant  
6 difference between the two treatment groups.  
7 However, there are some concerns with sponsor  
8 survivor curves. It was mentioned before that the  
9 two treatment groups may not be comparable and there  
10 is also another concern for the censoring, because  
11 event is not independent at censoring in this case.

12 It implies that any difference in  
13 survivor curves between the two treatment groups may  
14 be problematic. Even if we assume that two  
15 treatment groups were comparable, we may also find  
16 other subgroups with significant difference in  
17 survivor curves between the two treatment groups.

18 We choose a subgroup of patients with  
19 certain characteristics. We found that 76 patients  
20 with such characteristics from BTT sample, there are  
21 64 patients from the treatment group and 12 patients  
22 from the control group. As we can see in this

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1 graph, there is a significant difference between  
2 these two treatment groups. You might be interested  
3 in what the characteristic was. They are the  
4 patients with age evenly divisible by three.

5 In the BTT sample the sponsor found 87  
6 patients with relative contraindications and it show  
7 that there is a significant difference between the  
8 two treatment groups. And we also found a subgroup  
9 X of 76 patients with age divisible by three where  
10 there is a significant difference between the two  
11 treatment groups. Our findings from these two  
12 subgroups had been expected because there was  
13 already a large difference between the two treatment  
14 groups from which they were picked.

15 We may also find such subgroup Y. In  
16 fact, any sample from the BTT study will likely show  
17 a significant difference between the two treatment  
18 groups.

19 Now let me make a conclusion. The  
20 result from subgroup with relative contraindications  
21 may not be extended to the intended patient  
22 population. The two treatment groups are not

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1 comparable so that any direct or covariate adjusted  
2 treatment comparison is problematic.

3 Thank you.

4 Let me turn the podium to Dr. Pina.

5 DR. PINA: Thank you, Dr. Ahn.

6 Panel members, ladies and gentlemen, I  
7 cannot resist but to take a dig at my friend Jim  
8 Young. I've also been doing this maybe for three  
9 years less than you, since you're a little bit older  
10 than I am, but I've known you for all those 17  
11 years. And I am also part of the Ohio Transplant  
12 Consortium. Did not have the opportunity to see the  
13 sponsor's slides except for a few minutes prior to  
14 the panel. And I agree with Dr. Young that there  
15 are patients that still continue to make us scratch  
16 our head and wonder what we're going to do next.

17 You've seen this slide before, the  
18 intended population. So you've seen this before.  
19 Dr. Berman shown this in white, the current  
20 indications and in blue the intended indication for  
21 expanded use for patients who have a relative  
22 contraindication to transplantation but are expected

1 to become transplant candidates.

2 Just to review one more time, the  
3 dataset that has been presented as part of the  
4 dataset for this PMA includes 190 LVAS patients with  
5 35 controls divided up into two groups. And I'll  
6 show you a graphic of that. Group one patients with  
7 no relative contraindications. Group two the  
8 subgroup retrospectively drawn from the original  
9 dataset that have the relative contraindications  
10 chosen by the sponsor which constitutes 75 patients  
11 with LVAS and 12 controls.

12 This is sort of my diagram of what you  
13 have seen now several times just to remind everyone  
14 that all these patients were considered transplant  
15 eligible by their individual institutions and, in  
16 fact, had been listed for transplantation.

17 Here we see the 75 patients chosen with  
18 these relative contraindications of the LVAS group  
19 and 12 of the control from the 35 original controls.  
20 It should also be noted that out of these 75, 65  
21 percent of these patients were ultimately  
22 successfully transplanted.

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1                   Here is the list of relative  
2                   contraindications that now you have seen several  
3                   times, and it's also included in your panel pack.

4                   I just want to address briefly the short  
5                   or long term. We really have no accepted current  
6                   definition for short or long term in the context of  
7                   using left sides mechanical circulatory support. In  
8                   fact, of this dataset, 160 of the patients were on  
9                   the device for less than six months; of 30 patients  
10                  who had been on the device for more than six months,  
11                  15 patients had had device for greater than one year  
12                  and four had had it for greater than two years.

13                  I want to address the relative  
14                  contraindications. I think through the years those  
15                  of us who have been doing this for a long time have  
16                  seen the traditional contraindications have become  
17                  relative contraindications. And I think the best  
18                  example of that is when I started doing this we were  
19                  really not transplanting diabetes. That was  
20                  something that was sort of voodoo and we stayed away  
21                  from it. And as the years have gone through and we  
22                  know to manage each patient better, we have better

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1 immun suppressive agents, we have better  
2 antibiotics, we are now transplanting diabetes.

3 One paper that's included in your pack  
4 there from Cimato and Mariell Jessup, who has  
5 extensive experience in this area, in fact talk  
6 about the old traditional contraindications now  
7 becoming relative contraindications. And I've  
8 highlighted here in blue those that have been chosen  
9 by the sponsor, but you can see that there are a lot  
10 of others that every center considers individually.

11 I should also note that during these  
12 years, and one of the reasons that we have become  
13 more into the relative contraindication field as  
14 opposed to traditional, is our medical therapy has  
15 changed. In 1987 consensus was published, so we  
16 were introduced ACE inhibitors. In 1992 SALT  
17 published and we were introduced to ACE inhibitors  
18 in a group of patients. Jim Young always reminds me  
19 that coronary surgery has gotten better and better  
20 and that we're doing more procedures that are  
21 bringing patients, perhaps, to us later but that are  
22 keeping patients alive for a longer period of time.

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1                   β-blocker use didn't really come into  
2 its forefront until the 1998/99. And now we have  
3 nitric oxide available to us for dilating the  
4 pulmonary vascular tree.

5                   Milrinone IV was not available also  
6 until the early '90s and didn't get really increased  
7 in use until like 1994/95. So we have really seen  
8 some dramatic changes in this area.

9                   So of these relative contraindications  
10 it's unclear why those seven were chosen and not  
11 others. For example, high plasma reactive  
12 antibodies, which we know do exist and can exist in  
13 patients with devices and make it very difficult to  
14 transplant, and we always try to reverse these.  
15 History of cancer, psychosocial issues and, as I  
16 said before, diabetes.

17                   And it's also unclear how the relative  
18 thresholds were chosen for contraindications. If I  
19 remember correctly, back in the SALT trial our  
20 creatinine level maximum was three, the patients  
21 were allowed into the trial and very often the  
22 creatinine does in fact get better.

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1                   Let me touch on just a few of these  
2 parameters that have been listed as relative  
3 contraindications. We realize that renal  
4 dysfunction can be a marker of poor outcome, that  
5 keeps coming out in every single study having to do  
6 with heart failure patients. We also recognize that  
7 renal function can improve with profusion, but if  
8 the renal function is abnormal due to intrinsic  
9 renal disease, it may not improve with profusion.  
10 However, I have a tough time telling ahead of time,  
11 and many of my colleagues do, who is going to  
12 reverse and who isn't. And that definition of renal  
13 dysfunction really varies quite a bit throughout the  
14 literature.

15                   And this is taken from the Cleveland  
16 Clinic and Dr. McCarthy, a very prominent surgeon at  
17 the Cleveland Clinic. These are 25 LVAD recipients  
18 who were actually listed for transplant, critically  
19 ill patients. Six of them died of progressive organ  
20 failure. And this paper is included in the panel  
21 pack for you to review.

22                   The LVAD survivors did tend to have

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1 lower serum creatinine and BUN. But Dr. McCarthy in  
2 this paper states that there was no predictor of  
3 failure to improve renal function. In fact, three of  
4 the survivors have the highest BUNs of greater than  
5 50.

6 Another example from another transplant  
7 center, a group of 11 patients all listed for  
8 transplant. And the authors here state that no  
9 patients were excluded from listing due to renal  
10 dysfunction. Here you can see that the BUN dropped,  
11 as did the serum creatinine.

12 The authors go on and make a statement  
13 that they really don't see a renal function that  
14 they will not transplant, and they can address  
15 things like dialysis and many patients then get  
16 renal transplant after they get their hearts. And  
17 some centers actually do both at the same time. I  
18 know we do.

19 Let me address the pulmonary  
20 hemodynamics. This can be the vain of the existence  
21 of many of us who take care of these patients.

22 An elevated pulmonary vascular

1 resistance that does not reverse is a risk factor  
2 for RV failure and poor outcome. However, if you  
3 get a group of us together we will tell you there is  
4 no consensus on how to do this. There is nothing in  
5 the guidelines that tell you how to do this. And  
6 these are all the agents that we use. We use nasal  
7 cannula oxygen, we use intravenous nitrates. We  
8 like nitric oxide. We use ACE inhibitors. The A2  
9 receptor blocker is now on the forefront. Direct  
10 acting basodilators like hydralazine and IV  
11 Milrinone, which has shown very nicely to lower PA  
12 pressures. And then we know that LVADS also do  
13 this. However, you cannot predict with the current  
14 published literature which patient will reverse and  
15 if they do reverse, to what degree will they  
16 reverse.

17 So here are some examples from the Texas  
18 Heart Institute of patients pre and post LVAD  
19 insertion in the sort of tan bars here and then the  
20 purple bars are PA mean pre and PA mean post LVAD  
21 insertion.

22 This is from St. Louis, another very

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1 large transplant center showing significant  
2 decreases in PA mean pressure.

3 And this is a collection from the  
4 Cleveland Clinic and from Stanford published by Dr.  
5 McCarthy showing a very nice decrease in the PA  
6 diastolic pre and post implantation of an LVAD. So  
7 we know that this can happen.

8 Again, from McCarthy's paper in '95,  
9 cardiac index improvement, a drop in pulmonary  
10 vascular resistance, which is kind of a drop that I  
11 like to see, and all these parameters dropping in  
12 that group of patients. However, he makes a very  
13 important point in that paper. It says they could  
14 not identify a priori who would need an LVAD  
15 support. Now why is that important? Because if the  
16 PA pressures don't come down, the right ventricle  
17 can fail and you may need to put in a right  
18 ventricular assist device to support the right  
19 ventricle even when you have a left ventricular  
20 assist device. This is not something that we enjoy  
21 or like doing, but they could not identify a priori  
22 who need one and who would not.

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1                   Finally, let me just touch on hepatic  
2                   dysfunction from the same paper by Burnett that's  
3                   also in your pack. Eleven patients that were listed  
4                   for transplant, I showed you previously their renal  
5                   function, total bilirubin at listing was 4.4 and at  
6                   transplant 1.6. One of the patients did not recover  
7                   and in fact had cirrhoses.

8                   There's also a statement in there  
9                   stating that sometimes when the LVAD is initially  
10                  put in, that the right ventricle may suddenly feel  
11                  it and hepatic function actually worsens  
12                  temporarily. And I think we've all seen this, and  
13                  this slowly resolves.

14                  So once again the proposed expanded  
15                  indication are for patients with relative  
16                  contraindications who are expected to become  
17                  transplant candidates with mechanical circulatory  
18                  support. So in my summary we have no standard  
19                  definition for long or short term LVAS use. The  
20                  number of patients with more than one year is  
21                  limited so that the conclusion re long term cannot  
22                  be made. That relative contraindications in fact

1 are relative.

2 And including these seven relative  
3 contraindications and excluding others is not  
4 justified in the dataset. The thresholds and  
5 definitions of relative contraindications chosen by  
6 sponsor do vary in the literature quite a bit. And  
7 that the patients that are selected for the dataset  
8 were, in fact, listed for transplant and most of  
9 them, as I have shown you, were transplanted. And  
10 that even those patients with relative  
11 contraindications are currently being listed for  
12 transplantation.

13 From the dataset presented, panel, there  
14 is no way to predict which patients with the  
15 relative contraindications as identified by the  
16 sponsor will in fact become transplant candidates if  
17 they are not prior to device placement. Therefore,  
18 writing an FDA approved label would be difficult.

19 And I thank you.

20 CHAIRPERSON LASKEY: Thank you, FDA  
21 personnel.

22 Any questions from the panel here for

1 the presenters?

2 DR. WEINBERGER: Yes, Warren. I'd like  
3 to ask Dr. Berman, in the original PMA when this  
4 device was approved under the BTT PMA was there an  
5 intent to send patients home with the device or is  
6 that a new request for the current PMA supplement?  
7 And I'm asking vis-à-vis the bioengineering  
8 examinations.

9 DR. BERMAN: Both devices, the N100PC  
10 and the N100PC(q) are currently approved for  
11 hospital discharge for patients who are bridged to  
12 transplant.

13 DR. WEINBERGER: So that the original  
14 examination of bioengineering parameters included  
15 the possibility that a patient would use the device  
16 at home?

17 DR. BERMAN: Yes. For example,  
18 electrical safety, EMC alarms, all of that was  
19 examined and we have no questions regarding those  
20 issues.

21 DR. TRACY: Did the propensity score  
22 that you did include the seven relative

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1       contraindications that the sponsor included in their  
2       list?

3                   DR. AHN: Not all of them. I showed six  
4       baseline covariates with p-value less than 10  
5       percent. I included those six.

6                   DR. BAILEY: A couple of those were drug  
7       utilization I guess at baseline. Those were amazing  
8       differences, and I'm wondering what accounts for  
9       that difference in the two groups?

10                   DR. AHN: It is more of a medical  
11       question, so --

12                   DR. PINA: Yes. I can answer that. I  
13       think I said in my presentation that Milrinone  
14       intravenously we had an early trial called -- I  
15       think it was called a PROMISE trial with oral  
16       Milrinone. And IV Milrinone did not really start to  
17       get used extensively until later than 1991/'92. I  
18       remember in my practice really '93/'94. So  
19       dobutamine was the main drug being used at the time  
20       and then I think we've slowly turned around.

21                   DR. BAILEY: So in a sense then the  
22       propensity score is largely a proxy for time, which

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1 as you showed very nicely, there was very little  
2 overlap in the time?

3 DR. AHN: Yes. And notice that when I  
4 did a propensity score analysis I did not include  
5 the year of implant.

6 DR. BAILEY: But I suspect if you had,  
7 you would have gotten similar results?

8 DR. AHN: Maybe more. More drastic.

9 DR. BAILEY: I don't know if this is the  
10 right forum, but you made a very nice argument about  
11 noncomparability. The same argument would have  
12 applied to the overall comparison that was the  
13 original submission. I'm wondering what was  
14 different then versus now? I mean, why was it  
15 deemed acceptable before?

16 DR. BERMAN: Dr. Bailey, I'm afraid you  
17 were right that this isn't the forum for that. It's  
18 not up for discussion right now.

19 CHAIRPERSON LASKEY: The rules of the  
20 game have changed. I'll say it.

21 DR. YANCY: Two questions, please.

22 First ask Dr. Berman has to do with

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1 whether or not in the original application the issue  
2 of durability was evaluated and if so, what was your  
3 assessment of the durability of the device,  
4 particularly since there's a question of long term  
5 application here?

6 DR. BERMAN: The sponsor submitted  
7 information from bench testing, which is in your  
8 panel pack, and which was submitted in support of  
9 the original bridge application to demonstrate a  
10 multi-year expectation of life with this device.

11 DR. YANCY: I saw those data. But in my  
12 judgment there are none physiological because it  
13 basically was a water bath.

14 In the clinical data submitted --

15 DR. BERMAN: The clinical datasets --

16 DR. YANCY: -- there were two patients  
17 that --

18 DR. BERMAN: The clinical dataset that  
19 I'm aware of is very consistent with the bench data,  
20 that is device longevity is about what the bench  
21 says it will be. And that is based on an admittedly  
22 limited dataset because there are not many patients

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