

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL
OPEN SESSION

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P R O C E E D I N G S

Call to Order

1
2
3 DR. LASKEY: I would like to call this
4 panel meeting session to order. This morning's
5 topic will be a discussion of the supplement to a
6 Premarket Application for Thoratec Corporation's
7 HeartMate VE Left Ventricular System.

8 I would like to now have the Executive
9 Secretary read the Conflict of Interest Statement.

10 **Conflict of Interest Statement**

11 DR. EWING: Good morning. I would like to
12 welcome everyone to the meeting this morning and
13 especially I would like to thank the panel members
14 for their time in reviewing this application.

15 The following announcement addresses
16 conflict of interest issues associated with this
17 meeting and is made part of the record to preclude
18 even the appearance of an impropriety.

19 To determine if any conflict existed, the
20 Agency reviewed the submitted agenda for this
21 meeting and all financial interests reported by the
22 committee participants. The conflict of interest
23 statutes prohibit special government employees from
24 participating in matters that could affect their or
25 their employer's financial interests.

1 The Agency has determined, however, that
2 the participation of certain members and
3 consultants, the need for whose services outweighs
4 the potential conflict of interest involved is in
5 the best interests of the Government.

6 We would like to note for the record that
7 the Agency took into consideration matters
8 regarding Drs. Salim Aziz, Francis Klocke, and
9 Marvin Konstam. Each of these panelists reported
10 interests in firms at issue, but in matters that
11 are not related to today's agenda. Drs. James
12 DeWeese and Anthony Comerota reported that their
13 institution has an involvement with the firm at
14 issue.

15 The Agency has determined that all of
16 these individuals may participate fully in the
17 discussions.

18 In the event that the discussions involve
19 any other products or firms not already on the
20 agenda, for which an FDA participant has a
21 financial interest, the participant should excuse
22 him or herself from such involvement, and the
23 exclusion will be noted for the record.

24 With respect to all other participants, we
25 ask in the interest of fairness that all persons

1 making statements or presentations disclose any
2 current or previous financial involvement with any
3 firm whose products they may wish to comment on.

4 DR. LASKEY: Thank you, Lesley.

5 I would like to now have the panel members
6 introduce themselves starting on my right.

7 DR. ZUCKERMAN: Bram Zuckerman, Acting
8 Director, Division of Cardiovascular and
9 Respiratory Devices, FDA.

10 DR. WITTES: Janet Wittes, panel member.
11 I am a statistician at Statistics Collaborative in
12 D.C.

13 DR. KONSTAM: Marv Konstam from Tufts
14 University, New England Medical Center.

15 DR. COMEROTA: Anthony Comerota, vascular
16 surgeon from Temple University in Philadelphia.

17 DR. NISSEN: I am Steve Nissen. I am a
18 cardiologist from The Cleveland Clinic.

19 DR. AZIZ: Salim Aziz, Associate Professor
20 at the University of Colorado Clinic.

21 DR. EWING: Lesley Ewing, Executive
22 Secretary.

23 DR. LASKEY: Warren Laskey, interventional
24 cardiologist from the University of Maryland.

25 DR. PINA: Ileana Pina, Cardiology, Case

1 Western Reserve University, Cleveland.

2 DR. OSSORIO: Pilar Ossorio, University of
3 Wisconsin at Madison, bioethicist and lawyer.

4 DR. DeWEESE: Jim DeWeese, cardiac and
5 vascular surgeon, University of Rochester, New
6 York.

7 DR. KLOCKE: Francis Klocke. I am a
8 cardiologist from Northwestern University Medical
9 School.

10 MR. DACEY: Robert Dacey, Consumer
11 Representative, Boulder, Colorado.

12 MR. MORTON: Michael Morton. I am
13 employed by Alcon Laboratories, and I am the
14 Industry Representative.

15 DR. KNAPKA: Joe Knapka, Patient
16 Representative, from Olney, Maryland.

17 DR. LASKEY: Thank you, members.

18 Dr. Ewing, would you now read the voting
19 status statement, please.

20 DR. EWING: This is the Appointment to
21 Temporary Voting Status. Pursuant to the authority
22 granted under the Medical Devices Advisory
23 Committee Charter, dated October 27, 1990, and as
24 amended August 18, 1999, I appoint the following
25 individuals as voting members of the Circulatory

1 System Devices Panel for this meeting on March 4,
2 2002: Pilar Ossorio, Michael Domanski, who will be
3 coming soon, James DeWeese, Francis Klocke, Anthony
4 Comerota.

5 For the record, these people are special
6 government employees and are consultants to this
7 panel under the Medical Devices Advisory Committee.
8 They have undergone the customary conflict of
9 interest review and have reviewed the material to
10 be considered for this meeting.

11 In addition, I appoint Dr. Warren Laskey
12 to serve as Panel Chair for the duration of this
13 meeting.

14 I also have another Appointment to
15 Temporary Voting Status to read into the record.

16 Pursuant to the authority granted under
17 the Medical Devices Advisory Committee Charter of
18 the Center for Devices and Radiological Health,
19 dated October 27, 1990, and as amended August 18,
20 1999, I appoint the following individuals as voting
21 members of the Circulatory System Devices Panel for
22 the meeting on March 4 and 5, 2002: Steven E.
23 Nissen, Ileana Pina, and Marvin A. Konstam.

24 For the record, Dr. Nissen is a voting
25 member, and Drs. Pina and Konstam are consultants

1 to the Cardiovascular and Renal Drugs Advisory
2 Committee of the Center for Drug Evaluation and
3 Research. They are special government employees
4 who have undergone the customary conflict of
5 interest review and have reviewed the material to
6 be considered at this meeting.

7 **Open Public Hearing**

8 DR. LASKEY: I would like to now open this
9 morning's session for the open public hearing.

10 Are there any individuals requesting floor
11 time?

12 [No response.]

13 DR. LASKEY: If not, then, I would like to
14 close the public hearing and move on to the
15 sponsor's presentation.

16 DR. EWING: While the computers are being
17 set up, I would like to remind all the speakers,
18 especially the speakers for the sponsor, to
19 identify themselves and to state their conflict of
20 interest.

21 Each time you speak, because we are
22 labeled up here on the panel, but the people that
23 are not so labeled, if you could state your name,
24 so the transcriptionist can write who is speaking.

25 **Sponsor Presentation**

1 **Thoratec Corporation**

2 **P910014/S016, HeartMate VE LVAS**

3 **Introduction**

4 **Donald A. Middlebrook**

5 MR. MIDDLEBROOK: Thank you, Dr. Laskey,
6 and good morning to all.

7 My name is Don Middlebrook. I am Vice
8 President of Regulatory Affairs and Quality
9 Assurance for Thoratec Corporation. I am also
10 currently a shareholder.

11 I would like to begin this morning with a
12 word of thanks to the FDA, especially to our FDA
13 reviewers, all of the FDA invited panel members,
14 and our clinical investigators and experts that are
15 here on our behalf.

16 All of you, and certainly to all my
17 Thoratec associates, all of you have worked hard to
18 prepare for today's discussions, and those efforts
19 are very much appreciated.

20 [Slide.]

21 This is a brief outline of our
22 presentation that we will be making this morning.
23 We will be discussing the very important results
24 from the REMATCH trial, a first of its kind
25 clinical trial to compare a medical device to a

1 drug therapy for the treatment of end stage
2 congestive heart failure in patients ineligible for
3 cardiac transplantation.

4 [Slide.]

5 Our speakers this morning are: Victor
6 Poirier, who will provide a brief overview of the
7 HeartMate VE LVAS; Dr. Eric Rose from Columbia
8 Medical Center, who will discuss the safety and
9 effectiveness results documents in the REMATCH
10 trial; and Dr. Lynne Warner Stevenson from Brigham
11 & Women's Hospital in Boston, who will provide
12 information on the patient population study, and
13 also discuss medical management in the control
14 treatment group.

15 [Slide.]

16 We have also invited a number of
17 independent REMATCH experts who may be called upon
18 to speak on our behalf, who were involved in some
19 way in the study, either in the study design, the
20 study management, or in the analysis of the
21 results.

22 [Slide.]

23 Just a brief word about our company
24 Thoratec Corporation. The company was founded in
25 1976 in Berkeley, California. We merged with

1 Thermo Cardiosystems in February 2001, to be known
2 thereafter as Thoratec Corporation.

3 Our product focus is circulatory support,
4 vascular grafts, and diagnostic blood testing.

5 Our corporate offices are located in
6 Pleasanton, California. We have 800 employees
7 worldwide, and we are a world leader in cardiac
8 assist device technology.

9 [Slide.]

10 We will be presenting a summary of the
11 contents of the PMA that contain the results from
12 the REMATCH trial. This is a landmark multicenter,
13 prospective, randomized, controlled trial that
14 looked at the HeartMate VE LVAS versus optimal
15 medical management.

16 This study was initiated under a
17 cooperative agreement between Thoratec, the NIH,
18 and Columbia University.

19 The PMA we have submitted is seeking
20 approval to expand the current HeartMate VE LVAS
21 indications for use to include patients with
22 end-stage left ventricular failure who are
23 ineligible for cardiac transplantation.

24 Before I conclude my opening remarks, I
25 would like to state that the REMATCH study has been

1 the subject of a number of important scientific
2 publications. I would like to just mention a few
3 of those.

4 In January 2001, the ACC published a
5 consensus report entitled, "Mechanical Circulatory
6 Support 2000, Current Applications and Future Trial
7 Designs." This was the proceedings from a
8 conference sponsored by leading cardiology and
9 heart failure professional societies and included
10 participants from the FDA and the NIH.

11 In this report, the REMATCH study was
12 cited several times as a benchmark study for
13 evaluating mechanical circulatory support device
14 treatment outcomes in patients with end-stage
15 congestive heart failure.

16 Also, in November 2001, the REMATCH study
17 results were published in The New England Journal
18 of Medicine and were presented at the American
19 Heart Association annual meeting that same month in
20 Anaheim, California.

21 In December of 2001, the American Heart
22 Association named the REMATCH study the number 2 in
23 the top ten research advances for 2001.

24 With that said, I would like to ask Victor
25 Poirier to come to the podium, who will provide

1 some information on the device overview.

2 **Device Overview**

3 **Victor Poirier**

4 MR. POIRIER: Thank you. I am Victor
5 Poirier. I am an employee of Thoratec and a
6 shareholder of Thoratec.

7 [Slide.]

8 To begin with, the device that was used in
9 this clinical study is the HeartMate Left
10 Ventricular Assist Device. The device is implanted
11 either in the peritoneal cavity or in a
12 surgically-created pocket in the abdominal wall.

13 The inlet of the device is inserted into
14 the left ventricular cavity while the outlet is
15 anastomosed to the ascending aorta. With this
16 arrangement, blood simply drains from the natural
17 heart into the device, and we provide the energy to
18 propel blood through the body.

19 The device has a volume of 83 ml and can
20 produce in excess of 10 liters per minute above
21 flow. Power is delivered to the device through a
22 percutaneous lead. This is a coaxial lead. The
23 center of the lead is an electrical conductor, and
24 surrounding that is a cavity to propel air in and
25 out of the system.

1 This lead is attached to an external
2 controller that controls the function of the
3 device, allows the patient to operate in an
4 automatic mode or a fixed rate mode, has all of the
5 alarms that are required, and that controller is
6 then attached to the power.

7 The power is obtained either from
8 batteries worn by the patient, there is one on each
9 side of the patient, or it can be attached to a
10 bedside console.

11 [Slide.]

12 When we started the trial, we started with
13 the HeartMate VE system, and in that configuration,
14 there are screw rings that are used to attach the
15 components. To lock those screw rings in, we
16 utilized locking sutures, which were either applied
17 by the physician during implant or at the factory.

18 In reality, we learned that these were not
19 100 percent safe. In addition to that, from pump
20 migration or patient movement, we also uncovered
21 that in some patients, a kink would develop at the
22 outflow. This would be a complication which we
23 would have to increase the pump chamber pressure to
24 overcome this resistance to propel the blood out
25 through the outflow.

1 In addition to that, rubbing of the
2 adjacent areas of the graft could cause abrasion,
3 which could cause a hole to develop. So, we made
4 modifications to correct that, and we configured
5 the SNAP device.

6 What we did is we changed the screw rings
7 to use locking screw rings, which essentially
8 replaced the suture with a metal lever to lock the
9 rings in place. In addition to that, we added a
10 bend relief.

11 So, the differences between the VE system
12 and a SNAP system are only those two things. There
13 is nothing else that has changed. The internal
14 components are identical. So, any information that
15 we gain from the endurance testing or the
16 evaluations that we did in the past are still
17 valid. The only changes are the rings and the bend
18 relief, and these were not evaluated in the
19 in-vitro life test.

20 [Slide.]

21 Four and a half years ago, we started a
22 reliability test. We took 15 systems and we put
23 them on test. What we learned from that test was
24 that there is an 88 percent chance that the LVAD
25 will be free of critical failures at one year, and

1 a 76 percent chance that LVAD will be free of
2 critical failures at two years, and this is at a 90
3 percent confidence interval. The mean time to
4 failure is 3.1 years.

5 If you look at these results and compare
6 them to what we experience clinically, you will see
7 that there is a difference. These results are
8 better. So, what happened clinically? There are
9 three factors clinically that affect reliability.

10 One, it's the device itself, is there a
11 design flaw in a device, or, the second factor that
12 you need to consider is patient comorbidity, do the
13 patients have infection which can affect the
14 long-term durability of the tissue valves, or
15 patient management, which is the third factor that
16 you have to consider, the patient's arterial
17 pressure being maintained at low levels, so that
18 the pump does not have to produce high pump chamber
19 pressure.

20 So, those three factors affect in-vivo
21 reliability. In the in-vitro test, we only
22 evaluated the device, and if you only consider the
23 device, this is what I think you can expect in
24 terms of reliability.

25 [Slide.]

1 We are obviously continuously improving
2 the device. When you develop a new technology,
3 improvements are necessary, and if I just give, for
4 an example, the pacemakers, the original pacemakers
5 were external and the patients had to carry
6 batteries on a cart.

7 We all know how that technology has
8 developed through continuous improvements, and the
9 same with the implantable defibrillators. Well,
10 the same is true here. We started off with a system
11 that incorporated a double lead. There was one
12 lead coming out of the system for the wire and one
13 lead for the pneumatic operation.

14 After we gained some experience, we
15 concluded that one penetration would be better than
16 two, so we developed a coaxial exit line, and we
17 exited through the lower left quadrant of the
18 patient.

19 With more experience we gained knowledge
20 that this was not the most optimum site in terms of
21 exit sites, so we changed the exit site and we
22 reverted to an exiting at the right upper quadrant
23 of the patient. This helped in reducing exit site
24 infections.

25 As I spoke before about the SNAP VE, we

1 changed the outflow bend relief, we changed the
2 locking screw ring, and we improved the system
3 controller battery module. These are the result of
4 experience that was gained in the field, and we
5 haven't stopped there.

6 We have looked at all of the malfunctions
7 that we have experienced in the clinical program,
8 the REMATCH with the program in the bridge to
9 transplant in the commercial application of these.

10 We have addressed all of the malfunctions
11 that we experienced, and we made modifications to
12 either eliminate those malfunctions or to greatly
13 reduce the possibility of those occurring.

14 This is in the XVE configuration, which is
15 now being used in the bridge to transplant field.
16 We have extended the leads, we have made them
17 smaller, more supple, so that the exit site would
18 heal better.

19 We modified the way that we hold the
20 diaphragm in place to eliminate the stresses that
21 had caused us fractures in the clinical use. We
22 have changed the leads on how we attach them to the
23 controller.

24 We changed the materials at a wire to
25 prevent the wire breakage, we use stronger, more

1 durable materials throughout the system, so we are
2 continuously improving the technology to try to
3 make it better and to have these systems go longer
4 and longer.

5 I think if you look at the evolution of
6 this technology and where we have come from and
7 where we are going, I think it is quite impressive.

8 [Slide.]

9 Our first trial that we were involved with
10 was in 1975, even before FDA had any involvement
11 with devices. Our average duration in that trial
12 was four days. Our longest patient support was 41
13 days.

14 The second trial we did, the HeartMate
15 pneumatic device, our average duration was 69 days.
16 Our longest duration was 344. The first trial on
17 our electric system, 113 days.

18 What we tried to do is develop technology
19 that we could improve and get longer and longer
20 durations. If you look at what our experience is
21 in terms of longevity, we went from four days to 69
22 days, to 113 days, to 276 days, and on the REMATCH
23 program, our average duration, 344 days, and a
24 maximum duration of support now past 3.1 years, and
25 that patient is still ongoing.

1 We have made significant progress. This
2 represents 3,100 patients, 3,100 implants
3 worldwide, a vast amount of experience and a
4 consistent improvement in performance and in
5 reliability.

6 [Slide.]

7 So, in conclusion, clearly, the VE LVAS is
8 clinically proven technology for bridge to
9 transplant. Worldwide, the VE LVAS experience
10 provides strong platform for expanded indication,
11 and Thoratec is dedicated to circulatory support
12 and heart failure patients, and they are committed
13 to continuous improvements of this device.

14 If you look at the technology today, you
15 might say yes, we have had malfunctions, yes, there
16 have been adverse events, yes, there have been
17 complications, but even considering all of those
18 things, if you look at how has the patient done
19 with the device compared to a control group, the
20 patient with the device has done significantly
21 better even with all those complications.

22 Can we make it better? Of course, we can
23 make it better. We know how to design these, we
24 know how to improve them, and we will do that. We
25 can make these devices better. We can learn better

1 on how to manage patients, we can learn how to pick
2 patients more appropriately for this patient
3 category.

4 So, for going forward, I think there is a
5 lot of up-side potential with this technology.

6 With that, I would like to turn the podium
7 over to Dr. Eric Rose.

8 **REMATCH Trial Clinical Results**

9 **Eric Rose, M.D.**

10 DR. ROSE: I am Eric Rose. I am the
11 Milstein Professor and Chairman of the Department
12 of Surgery at Columbia University, and the
13 principal investigator for the REMATCH trial. I
14 have no financial interest in Thoratec, and my
15 presence here today is supported financially by the
16 company for being here.

17 [Slide.]

18 To get to the punch line first, the
19 REMATCH trial makes the following critical clinical
20 findings. There is a clear survival benefit, which
21 we strongly believe, as well, is clinically
22 meaningful and quality of life in device patients
23 is at least equal to, if not better, than medically
24 managed patients in the control group.

25 With regard to safety, the incidence of

1 adverse events in context of the mortality
2 reduction and the quality of life improvement
3 trends provides very reasonable assurance of the
4 safety of the device.

5 In conclusion, we believe that the VE LVAS
6 is a scientifically validated alternative, in fact,
7 now the only scientifically validated alternative
8 therapy for end-stage heart failure patients who
9 are not candidates for cardiac transplantation.

10 [Slide.]

11 What I would like to walk through in my
12 talk today is the history of the trial itself, the
13 trial's design and how it was administered.

14 Lynne Warner Stevenson, a trial
15 investigator and leader of the medical management
16 group of the trial will summarize the description
17 of the patient population and the nature of medical
18 management, which is a critical limb in this trial.

19 I will then come back and review the
20 effectiveness results, the safety results, and
21 summarize our views.

22 [Slide.]

23 Anyone who works in the field of
24 management to patients with end-stage heart
25 disease, and certainly the patients themselves,

1 recognize the enormous gap in our treatments
2 available for those with end-stage disease.

3 Heart transplantation has shown enormous
4 promise, but it is only benefitting approximately
5 2,000 patients per year compared to the many more
6 who could potentially benefit.

7 We have had enormous experiences Vic just
8 described with more than 3,000 patients worldwide
9 using the device that we tested in REMATCH for
10 bridging to transplantation.

11 Based on that experience, we did a pilot
12 trial we called PREMATCH in 1996 to 1998, in which
13 we randomized 10 patients to a control group and 11
14 patients to LVAD, and found that randomization was
15 feasible.

16 We found that doubling in one-year
17 survival from 20 to 40 percent in the device
18 patients, which was not statistically significant,
19 yet, these observations generated the necessary
20 clinical equipoise to support a full-blown
21 randomized REMATCH trial, and REMATCH trial
22 enrollment began in May of 1998.

23 [Slide.]

24 The trial itself is the product of a
25 cooperative agreement between Thoratec, Columbia

1 University, and the National Heart Lung, and Blood
2 Institute. The trial was coordinated by an
3 independent coordinating center, the International
4 Center for Health Outcomes and Innovation Research
5 at Columbia led by Annetine Gelijns and Alan
6 Moskowitz.

7 It was a multicenter, randomized,
8 controlled trial. Patients and physicians were not
9 blinded to treatment in this obvious major surgical
10 intervention. There was a prospective plan for
11 interim analyses to be done by an independent Data
12 Safety Monitoring Board.

13 The analysis was done by an
14 intent-to-treat, and the primary statistical
15 analysis employed the Kaplan-Meier actuarial
16 survival method and using a log-rank test to assess
17 differences between the entire area under the
18 Kaplan- Meier curve. Paul Meier himself was one of
19 our statistical advisers.

20 [Slide.]

21 In order to control bias, first and
22 foremost, this was a randomized trial. Again, we
23 used an independent coordinating center independent
24 of the sponsor. The sponsor Thoratec was blinded
25 to control data.

1 Investigators and the InCHOIR staff except
2 for the statisticians were blinded to the overall
3 data until the trial ended. We used credentialed
4 investigators, both cardiologists and surgeons, at
5 the trial sites. An independent gatekeeper
6 reviewed each patient's eligibility prior to entry
7 into the trial to ensure that patients did indeed
8 meet the stringent entry criteria.

9 We used an independent Data Safety
10 Monitoring Board appointed by the NHLBI, as well as
11 an independent Morbidity and Mortality Committee to
12 adjudicate the etiology of adverse events and
13 causes of death, and there were Medical and
14 Surgical Management Committees that actively met
15 during the course of the trial to ensure that
16 patients got optimal care in both limbs.

17 [Slide.]

18 The key study objectives were to evaluate
19 the efficacy of the HeartMate on survival of
20 patients with end-stage heart disease who were
21 ineligible for cardiac transplantation, and with
22 regard to safety, to document and analyze adverse
23 events and the incidence of device malfunction and
24 failure, of course, in the context of the disease
25 population we studied.

1 [Slide.]

2 The secondary endpoints of the trial
3 included quality of life, the patient's functional
4 status, the patient days in and out of the
5 hospital, cardiovascular mortality, and cost. We
6 will not address cost in this discussion today.

7 [Slide.]

8 The key assumptions guiding this trial was
9 that patients and clinicians would not adopt use of
10 a device like this unless all-cause mortality over
11 a two-year observation period was reduced by a
12 third or more.

13 Conversely, I think there was generally
14 strong feeling that demonstration of this kind of
15 benefit would indeed lead to adoption when
16 indicated for this type of technology.

17 We also assumed that quality of life with
18 the VAD should equal or exceed the OMM group in
19 order to essentially allay the concern that a
20 device like this could literally prolong death
21 instead of prolonging and enhancing life.

22 [Slide.]

23 The trial was powered to survival and not
24 to secondary endpoints. We also hypothesized that
25 survival over time would decay roughly

1 exponentially and that the hazard ratio between the
2 two groups of LVAS to OMM would be approximately
3 0.56.

4 Using these assumptions, the endpoint is
5 the number of deaths in this trial, not the number
6 of patients enrolled, and we calculated that we
7 needed to see 92 deaths in order to have an 80
8 percent power in a log-rank test to find the
9 hypothesized benefit.

10 We estimated that we would need up to 140
11 patients in order to prove that benefit, but again
12 the 92 deaths was the decided prespecified endpoint
13 to this trial. I want to emphasize this trial was
14 not stopped early. This trial was stopped when we
15 reached the predefined endpoint for the study.

16 [Slide.]

17 The patients were randomized between the
18 two limbs in a 1 to 1 ratio. The randomization was
19 stratified by center, and this was put in place by
20 blocking on a center-specific basis, and the block
21 sizes were also randomly selected so that
22 investigators could not gain the assignment to
23 patients.

24 [Slide.]

25 REMATCH study sites included 20 highly

1 experienced centers in cardiac transplantation and
2 medical management to patients with end-stage heart
3 disease.

4 I am going to turn the podium at this
5 point over to Lynne Stevenson, who ran our Medical
6 Management Committee in order to describe the
7 patient population and medical management.

8 **REMATCH Patient Population**

9 **Lynne Warner Stevenson, M.D.**

10 DR. STEVENSON: Thank you very much. I
11 have no financial interests in Thoratec. They are
12 reimbursing me for the cost of travel to this
13 meeting.

14 [Slide.]

15 To see where the REMATCH population fits
16 in, let's look at the big picture of heart failure.
17 It is estimated that there are 4 to 5 million
18 patients in the United States with heart failure.
19 Of those, about two-thirds have heart failure with
20 low ejection fraction or systolic dysfunction. The
21 other third have heart failure with a preserved
22 ejection fraction which dominates in the elderly.

23 Some patients over 80 also have heart
24 failure with low ejection fraction. In general,
25 they have such comorbidities that they would be

1 considered appropriate candidates for cardiac
2 replacement therapy, so we will focus on this group
3 here in the turquoise of patients under 80 with
4 ejection fractions that are reduced.

5 It is estimated that approximately
6 one-quarter of those patients have Class III to IV
7 heart failure with symptoms that limit their daily
8 lives. Multiple models have demonstrated that
9 approximately 50 to 100,000 of these patients might
10 be considered as candidates for cardiac replacement
11 therapy, but probably a smaller number of these are
12 truly appropriate recipients.

13 [Slide.]

14 The REMATCH trial aimed to identify a
15 population of those patients for whom primary
16 cardiac replacement could be considered. The
17 initial eligibility criteria were New York Heart
18 Association Class IV symptoms for 90 days on
19 standard therapy, left ventricular ejection
20 fraction less than or equal to 25 percent, peak VO₂
21 less than 12 ml or inotrope dependent. These
22 criteria were relaxed in late 1999, but, in fact,
23 123 patients enrolled met the original criteria
24 rather than the revised one shown in blue.

25 The mortality estimates at the time this

1 trial was designed were that there would be a
2 two-year mortality of approximately 75 percent.
3 This was based primarily on data that we had for
4 potential cardiac transplant candidates, but since
5 we additionally required that these patients be
6 ineligible for cardiac transplantation, that, in
7 fact, was an additional contributor to their
8 mortality.

9 [Slide.]

10 The reasons that patients were not
11 transplant candidates are shown here. It was
12 predominantly for age and for diabetes.

13 [Slide.]

14 Let's now look at where these patients
15 fall on the spectrum of escalating therapies for
16 heart failure. Standard therapies for heart
17 failure are angiotensin converting enzyme
18 inhibitors, beta blockers is tolerated, digoxin,
19 diuretics for fluid retention, and spironolactone
20 when renal function is acceptable.

21 We had anticipated that patients enrolled
22 in REMATCH would fall somewhere in here, such that
23 multiple additional interventions could be made in
24 expert hands. In fact, the patients referred and
25 ultimately randomized in REMATCH more often fell

1 approximately here.

2 In many of these patients, beta blockers
3 would not even be considered due to hemodynamic
4 decompensation. Fluctuating renal function
5 frequently made spironolactone not possible, and
6 many of these patients had even become intolerant
7 to ACE inhibitor therapy.

8 Inotropic therapy was frequently employed
9 in these patients with the hope that a brief
10 infusion might turn things around. Often that does
11 not happen, and one is left with the difficult
12 problem of trying to wean therapy to allow hospital
13 discharge, which in some cases was not possible.

14 [Slide.]

15 If we look now at the REMATCH therapy at
16 baseline in the OMM arm, off of medical management,
17 75 percent of patients were on IV inotropes at the
18 time of randomization, 53 percent were on ACE
19 inhibitors, and another 18 percent were on A2
20 receptor antagonists.

21 [Slide.]

22 If we look at ACE intolerance in advancing
23 heart failure, this again defines where we are with
24 this population. This is now looking at a number
25 of trials of patients unable to take ACE inhibitor

1 therapy. You can see in the two trial here, this
2 is the ESCAPE trial and the OPTIME trial in which
3 patients are hospitalized with heart failure at the
4 time of treatment, that rates approximately 20 to
5 25 percent of being unable to tolerate ACE
6 inhibitors. In this trial, in fact, it's 29 percent
7 when you consider the patients who were able to
8 tolerate A2 receptor blockers.

9 [Slide.]

10 Let's look now at other REMATCH patient
11 baseline characteristics. You can see the age is
12 67, which is a higher average age than most heart
13 failure populations studied. The cardiac index is
14 2 liters per minute per meter squared, and you need
15 to remember that 75 percent of patients were on
16 inotropes at the time that this very low cardiac
17 index was measured.

18 The Minnesota Living with Heart Failure
19 score of quality of life shows a higher degree of
20 disability than in any trial previously reported.

21 [Slide.]

22 If we look now at renal dysfunction, we
23 are just coming now to realize how important a
24 predictor this is for outcome in heart failure.
25 Every tenth of a milligram predicts a higher

1 mortality in heart failure. REMATCH, with an
2 average baseline creatinine of 1.8 is higher than
3 any trial previously reported in heart failure.

4 [Slide.]

5 Let's now line up the profile of REMATCH
6 patients and compare it to other trials of heart
7 failure that is considered to be severe. The
8 closest population we can come up with is in the
9 first trial. This is a trial in which IV
10 prostaglandin therapy was administered chronically
11 through an in-dwelling catheter.

12 If we look at other trials, CONSENSUS from
13 1987 is shown here. This is the initial trial of
14 ACE inhibitors in Class IV heart failure. If we
15 look at the ejection fraction, it wasn't routinely
16 measured at that time, but if we move across in
17 trials of what are considered to be severe heart
18 failure, you can see that REMATCH has the lowest
19 ejection fraction of any of these trials.

20 Serum sodium remains a very robust
21 predictor of outcome in heart failure, and you can
22 see that the serum sodium is lower in REMATCH than
23 in any other patient population studied.

24 Perhaps most telling is the systolic blood
25 pressure, which was 103 in the REMATCH population,

1 much lower than any other trials. I would point
2 out in COPERNICUS, a trial of beta blockers in
3 severe heart failure, the average baseline blood
4 pressure was instead 123, which is 22 mm higher.

5 [Slide.]

6 In terms of the medical management of the
7 OMM population, this was the result of very
8 intensive review and approval by the Cardiology
9 Committee of all the investigators with additional
10 input from Dr. Gary Francis outside the trial.

11 The primary goal was survival without
12 suffering. Specific goals were to maintain
13 perfusion for organ function, to relieve
14 congestion, to treat exacerbating factors, and then
15 to maintain stability with a regimen of
16 neurohormonal antagonists which would be considered
17 standard therapy.

18 In fact, however, most of these patients
19 were beyond what we considered to be standard
20 medical therapy. Inotrope infusion, the net use
21 decreased by the first month, but had increased
22 again by the last follow up.

23 In terms of the ACE inhibitor use, the use
24 increased, but, in fact, by the last follow up was
25 lower than at the time of initiation because the

1 patients continued to deteriorate.

2 [Slide.]

3 We specifically thought long and hard
4 about what we should say about the use of IV
5 inotropic agents. It was recognized that we should
6 make every attempt to try to discontinue these
7 agents and use any other regimen if possible.

8 It was agreed this therapy would not be
9 used unless everything else had been tried. In
10 fact, there was considerable effort to try to
11 modulate the inotrope use. During the initial
12 hospitalization, 20 percent of patients who started
13 out on inotropic infusions came off of the
14 infusions, another 10 percent had the number of
15 drugs infused decreased, so they were on fewer
16 inotropic agents, however, 40 percent of the
17 patients who were not on inotropic agents at the
18 randomization were found to need inotropic agents.

19 It was well recognized by all the
20 investigators that inotropic therapy is only
21 palliative in this population, that it does not
22 improve survival, and, in fact, might even worsen
23 mortality. The problem was that current medical
24 therapy had reached an end, and there just were
25 not other options.

1 [Slide.]

2 Understanding the profile of the REMATCH
3 population now allows us to look at where the
4 mortality of this group fits in. With every factor
5 being worse than in the previous trials, it is not
6 at all surprising that there was a very high
7 one-year mortality of 76 percent in the REMATCH
8 population. They had moved beyond what could be
9 offered by the medical therapy.

10 [Slide.]

11 So, in summary, REMATCH patients define a
12 new profile of severe heart failure, different than
13 what had been considered severe in previous trials.
14 By the time of randomization, REMATCH patients had
15 already received optimal management in the most
16 cases and had moved beyond current medical therapy.

17 [Slide.]

18 How are we to determine what would be a
19 meaningful benefit in this population? In trying
20 to decide, this committee accepts a major
21 challenge. We don't really have previous
22 precedence that should guide us in how to decide
23 this.

24 Let's review what we do know of therapies
25 that are accepted as beneficial in heart failure.

1 If we take ACE inhibitors, the cornerstone of our
2 therapy of heart failure at the SOLVD trial is
3 considered to be the landmark trial for this, if we
4 look at the one-year mortality, it was decreased
5 from 14 to 11 percent.

6 It has become very common in drug trials
7 to look at percent, of a percent improvement, which
8 in fact magnifies a benefit that is relatively
9 modest. This impacts 3 patients per 100 treated in
10 the first year.

11 A similar relative benefit was observed in
12 the CONSENSUS trial, an ACE inhibitor in Class IV
13 failure, but because the one-year control mortality
14 was higher, there is an absolute benefit that is
15 greater in terms of the number of patients treated,
16 which here is 17.

17 Dosing of ACE inhibitors has been felt to
18 be important in optimal management of heart
19 failure. That is based primarily on the ATLAS
20 trial, shown here, with the one-year mortality, a
21 relative small difference between a high and very
22 dose ACE inhibitor, which in fact led to a survival
23 benefit of less than 1 patient per 100 in the year
24 treated.

25 The COPERNICUS trial, demonstrating

1 unequivocally the benefit of beta blockers in
2 severe heart failure, had a mortality in the
3 control arm that was less than 20 percent, and the
4 RALES trial, showing a similar benefit with a
5 slightly higher baseline mortality.

6 Accepting these benefits for therapy, how
7 should we now evaluate a population in which the
8 one-year mortality on controlled therapy is 76
9 percent, do we look at relative benefit, do we look
10 at absolute benefit, what will our patients look
11 at? We are stepping into a new horizon.

12 I would like to turn it back to Eric Rose,
13 who will further discuss the results of the trial.

14 **REMATCH Trial Clinical Results**

15 **Eric Rose, M.D.**

16 [Slide.]

17 DR. ROSE: Almost 1,000 patients were
18 screened for REMATCH, of whom 128 were randomized,
19 67 to the device limb and 61 to medical management.

20 [Slide.]

21 The baseline characteristics here in
22 sample for critical ones, age, ejection fraction,
23 cardiac index, serum creatinine, IV inotropes,
24 Minnesota Living with Heart Failure score, across
25 virtually all baseline characteristics. There were

1 no differences between the two groups, illustrating
2 the success of the randomization.

3 [Slide.]

4 This is a Kaplan-Meier plot illustrating
5 survival of the VAD group compared to the OMM group
6 at the time that the study was stopped in June of
7 2001. The difference, the area under the curve,
8 under the LVAD curve, between the two curves, shows
9 a 46 percent reduction in mortality hazard over the
10 two-year observation period, again, the primary
11 endpoint of the trial, the p-value being 0.003.

12 In addition, at this time of analysis,
13 there was a 52 percent, one-year survival in the
14 device group compared to 26 in the control group,
15 and 23 percent at two years compared to 8 percent
16 in the control group. The one-year difference was
17 statistically significant, the p-value at two years
18 was 0.09.

19 [Slide.]

20 In terms of causes of death, the
21 overwhelmingly most common cause of death in the
22 OMM group was heart failure. In contrast, in the
23 device group, the most common cause of death was
24 sepsis related typically to the device, following
25 by a range of mortality related to either failure

1 or cessation of function of portions of the device.

2 Two devices failed completely to support
3 the circulation, while three had partial failures
4 of the device not meeting the formal definition,
5 but did require device replacement ultimately
6 leading to death.

7 In addition, fortunately, there was only
8 one death due to bleeding. The next most common
9 cause of death was cerebrovascular disease.

10 [Slide.]

11 To summarize these effectiveness results,
12 the one-year survival doubled. There was an
13 absolute reduction of mortality of 27 percent at
14 one year meaning that for each 100 patients
15 treated, we would estimate that 27 deaths would be
16 averted during that first year.

17 The two-year survival was tripled, and the
18 median survival time increased to 408 days for LVAS
19 patients compared to 150 days for OMM patients.

20 [Slide.]

21 As we said, the all-cause mortality was
22 reduced by 46 percent exceeding the primary
23 objective of a 33 percent reduction.

24 [Slide.]

25 Now, with regard to safety, looking at

1 serious adverse events, these were more common in
2 the device patients, in fact, they were 2.3 times
3 more common, a high significant difference.

4 Particular types of adverse events, namely
5 neurologic dysfunction and bleeding, not
6 surprisingly were also more common in the device
7 patients, but interestingly, complications like
8 infection, sepsis, and thromboembolic events, these
9 were not statistically significantly different
10 between the two groups.

11 [Slide.]

12 Also, of interest is the fact that adverse
13 events are generally concentrated early in the
14 postoperative course of these patients, and decay
15 off to a lower incidence over time. It does not
16 reach zero, but it does decrease over time.

17 [Slide.]

18 Looking in particular at neurologic
19 events, there were 28 neurologic events in 67 VAD
20 patients, a total of 40 events in those 28
21 patients, but very importantly, only a quarter of
22 those events were permanent or disabling. The
23 overwhelming majority of these events were toxic
24 encephalopathy typically early in the intensive
25 care unit after the operation, or transient

1 ischemic attacks.

2 [Slide.]

3 Looking at the sum total of serious
4 neurologic events, there were 5 ischemic strokes,
5 one intracranial hemorrhage, and 2 patients who had
6 serious morbidity from air embolism.

7 [Slide.]

8 Also looking at this particular adverse
9 event, we see that the majority of events or the
10 highest incidence occurs early in the postoperative
11 course and falls off over time.

12 [Slide.]

13 In terms of bleeding, the majority of
14 events were associated with VAD implant or
15 reimplantation, which is quite similar to the
16 bridge experience.

17 Infection was a specific complication of
18 VAD use. There was initially in this trial an
19 unappreciated association of infection with
20 malnutrition. Patients who were nutritionally
21 depleted generally could not heal the drive line
22 sites well, and investigators only began to pay
23 specific attention to this late in the course of
24 the trial.

25 Infection guidelines were developed in the

1 midpoint or in the earlier course of the trial with
2 the adoption of specific guidelines that
3 investigators adopted on the recommendation of the
4 Surgical Management Committee.

5 [Slide.]

6 There were 156 malfunctions of the device
7 reported, 70 were confirmed by actual analysis of
8 the device component, 50 of these were external
9 components, 20 internal components. The most
10 common malfunction was the controller, malfunction
11 with broken lead wires in 27 percent, 14 percent
12 had the serious complication of inflow valve
13 incompetence seen in 14 percent of patients in this
14 trial, and 9 percent of patients had a broken
15 Y-connector.

16 The top 1 and 3 of these were external
17 device malfunctions, which allowed their
18 replacement.

19 [Slide.]

20 Median time spent in and out of the
21 hospital was dramatically different between the two
22 groups. As I said before, median survival of 408
23 days compared to 150 at the time of the 92nd death.

24 VAD patients enjoyed almost a full year of
25 days out of the hospital during a two-year period

1 of observation, where, control patients enjoyed
2 approximately 100 days out of hospital.

3 VAD patients also spent more time in the
4 hospital with readmissions for device complications
5 or other complications, higher than controls, and
6 index hospitalization days, as would be expected
7 for the major procedure of VAD replacement, the
8 length of hospitalization as 29 days for the VAD
9 patients, which was virtually identical to the
10 length of stay that we typically see for bridge to
11 transplant patients.

12 [Slide.]

13 With regard to quality of life, again, our
14 hypothesis was that quality of life with the VAD
15 should equal or exceed the OMM group. Toward that
16 end, we carefully chose the instruments that we
17 used.

18 In particular, we used the SF-36 Health
19 Survey, a general health measure, and prespecified
20 two very specific domains - physical functioning
21 and role/emotional scores. These were prespecified
22 before we even began the trial that these were the
23 particular SF-36 portions we were going to look at.

24 The Minnesota Living with Heart Failure
25 scale is a disease-specific quality of life measure

1 for patients with heart failure.

2 The New York Heart Association functional
3 class is probably the most broadly used functional
4 status estimator for heart failure in the world.

5 The Beck Depression Inventory is a widely
6 employed scale for measuring clinical depression,
7 and the EuroQOL scale for patient preferences.

8 We imputed no values for quality of life
9 for dead patients. Had we done so, it would have
10 created an even greater benefit documented by the
11 device patients, so we specifically did not input
12 these values in order not to further bias the data.

13 [Slide.]

14 With regard to role/emotional scores, in
15 this slide and the succeeding slide, the VAD
16 patients are in yellow, OMM in purple. A higher
17 score here is better, reflects improved quality of
18 life. We have very little data after one year, but
19 we see that by 12 months, there is a highly
20 statistically significant difference between VAD
21 and OMM patients with regard to role/emotional
22 functioning.

23 [Slide.]

24 Similarly, with regard to physical
25 functioning, at 3, 6, and 12 months, again, a

1 higher number is better quality of life, and what
2 this means in terms of the questionnaires is can
3 you walk a block, can you walk up a flight of
4 stairs. There were significantly more positive
5 answers to those questions in the VAD patients
6 compared to the OMM patients, and at 3, 6, and 12
7 months, this P was less than 0.05.

8 [Slide.]

9 With the Minnesota Living with Heart
10 Failure scale, we did see at one time point
11 significant improvement, and at 3, 6, and 12
12 months, a trend to improvement for the VAD
13 patients. On this scale, improved quality of life
14 is a lower score. The 75 at baseline, to our
15 knowledge, is the highest MLHF score in a heart
16 failure population subjected to a randomized trial.

17 [Slide.]

18 In terms of New York Heart Association
19 functional class, the percentage of patients in
20 Class IV at the time of observation is plotted
21 here. There were only three patients alive at 24
22 months in the OMM group, one of whom had improved
23 out of Class IV. Otherwise, at virtually all other
24 times, the Class IV representation in the control
25 group was almost 100 percent compared to a marked

1 decrement, statistically significant decrement in
2 the VAD group.

3 [Slide.]

4 In the Beck Depression Inventory, both
5 groups at the time of enrollment met the definition
6 of clinical depression with scores of 17 or higher.
7 There was a highly significant difference between
8 the VAD and OMM groups at 1 and six months, and the
9 p-value was 0.055 at 12 months between these two
10 groups, suggesting that these patients were indeed
11 less depressed.

12 [Slide.]

13 To summarize these Quality of Life
14 findings, VAD scores were never worse than the OMM
15 group. I think the argument that these devices
16 prolong death is simply not tenable based on this
17 data set. They prolong meaningful life.

18 The only negative Quality of Life impact
19 was the issue of short-term, postoperative pain,
20 which is an obvious result of the operation that
21 the patients had.

22 The LVAD general Quality of Life was
23 better than OMM at 12 months in the key,
24 prespecified SF-36 domains, a physical functioning
25 and in role/emotional scores.

1 The LVAD disease-specific Quality of Life
2 measurement with the Minnesota scale was improved,
3 but not statistically significant at a year.

4 LVAD functional status measured by the New
5 York Association classification was significantly
6 better, and VAD patients had reduced depressive
7 symptoms to normal range, below that of clinical
8 depression, a phenomenon which was not seen in the
9 OMM groups.

10 [Slide.]

11 To put this in context, the LVAD physical
12 function scores, while improved, were not normal,
13 but these scores are analogous to patients who were
14 receiving long-term hemodialysis, of which there
15 are 300,000 now in the United States, and moderate
16 heart failure patients.

17 Similarly, the role/emotional scores are
18 better than those reported for clinical depression
19 and similar to those with moderate heart failure.

20 [Slide.]

21 The most recent Kaplan-Meier plot is
22 depicted in this slide with very little difference
23 essentially in the shapes of these curves. The
24 area between them is now significant at the 0.001
25 level, and the difference at two years, the p-value

1 here is now 0.054.

2 [Slide.]

3 In terms of efficacy, REMATCH has shown
4 that the VE LVAS exceeded the primary objective of
5 the trial by demonstrating a reduction in all-cause
6 mortality of 46 percent in patients who were not
7 candidates for cardiac transplantation.

8 With regard to safety, the incidence of
9 adverse events associated with implantation is
10 higher than OMM patients, but the incidence of
11 overall adverse events we believe is clearly
12 acceptable when compared to the natural history of
13 this terminal illness.

14 In addition, even in this small early
15 experience, multiple opportunities for improvement
16 have been identified.

17 [Slide.]

18 To return to Lynne's question as what is
19 clinically meaningful benefit, we did see an
20 absolute reduction in one year mortality of 27
21 percent in this patient population, which in terms
22 of simple magnitude is obviously more than
23 comparable, more than favorably comparable with
24 those that we have seen for other heart failure
25 therapies that are now considered standard.

1 [Slide.]

2 Now, we also would like to address the
3 seven questions which were posed to the panel by
4 the FDA to offer our views of these very important
5 issues that were raised by the FDA examiners.

6 [Slide.]

7 First, there was the question of whether
8 or not there now are good end of pump life
9 indicators. Before I speak to this about the VADs,
10 I think it is important to recognize that it is not
11 just the mechanical circulatory support that has
12 the issue of end of pump life indicators. Heart
13 failure itself, we have difficult issues with
14 regard to end of life indicators, whether or not
15 serum sodium or creatinine or inotrope dependency
16 themselves are absolute indicators of end of life
17 is something that is under intense investigation
18 and deserves further, but even in the context of
19 this trial, there are patient indicators that can
20 suggest that a person is reaching end of life of
21 the device.

22 For example, increased alarm frequency and
23 changing pump sounds are just simple clinical
24 indicators, and there are device indicators. This
25 device's motor current waveforms can be measured on

1 an ongoing basis and the waveforms analyzed to
2 indicate earlier forms of wear in the device, and
3 in addition, particulate matter can be analyzed in
4 the filters from the air vent side of the device.

5 [Slide.]

6 In terms of device reliability, are we
7 seeing enough reliability with this device, so that
8 is appropriate for destination therapy? In the
9 context of the available alternative therapies and
10 the terminal illness, the observed failure rates in
11 the REMATCH trial essentially define what is
12 acceptable at this time.

13 The reliability, even though flawed, is
14 sufficient to produce a very measurable survival
15 benefit. Furthermore, we see multiple
16 opportunities that address device improvements,
17 patient selection, and patient management.

18 [Slide.]

19 The other important question, is the
20 survival benefit that we documented clinically
21 meaningful? Now, this was the guiding question for
22 the REMATCH trial. Before we embarked on this, we
23 tried to reach a consensus among many groups as to
24 what would be a clinically meaningful indicator and
25 what could be done practically.

1 There was agreement between the REMATCH
2 investigators at 20 sites, the NHLBI, the FDA, and
3 Thoratec that the endpoint that we defined for
4 mortality was indeed a clinically meaningful
5 benefit if we could document it.

6 We documented that as a 33 percent
7 reduction in mortality during two years with
8 Quality of Life that was greater than or equal to
9 that of OMM.

10 Indeed, we found that median survival more
11 than doubled in this two-year observational trial.

12 [Slide.]

13 The other question raised, is the
14 effectiveness of the system on functional status
15 clinically meaningful, in particular because the
16 data with regard to a test like six- minute walk
17 and PPO₂ were confusing.

18 The trends with regard to all of the
19 Quality of Life indicators that were used, that are
20 subjective, admittedly subjective, are consistent
21 favorable. With regard to peak VO₂ and 6-minute
22 walk, there are not benchmarks available that have
23 been validated in order to look at those and
24 compare them to patient's assessment of Quality of
25 Life or survival.

1 The New York Heart Association class,
2 while flawed, is still the most widely used
3 classification of functional status of heart
4 failure patients in the world, and the prespecified
5 physical function domains and role/emotional
6 scores, again admittedly subjective, we are asking
7 the patients how did you do or how do you feel were
8 highly significant at 12 months.

9 To quote the President's Commission for
10 the Study of Ethical Problems in Medicine and
11 Biomedical and Behavioral Search, "Quality of life
12 is an ethically essential concept that focuses on
13 the good of the individual. What kind of life is
14 possible given the person's condition and whether
15 that condition will allow the individual to have a
16 life that he or she views as worth living, not
17 whether some dispassionate third party views the
18 life as worth living," and to make the judgment
19 that on the basis of a 6-minute walk or a peak VO₂,
20 a life is not worth living, I think is more than a
21 stretch.

22 [Slide.]

23 In terms of destination therapy - do the
24 benefits outweigh the risks?

25 The adverse events in this trial were not

1 calculated independent of survival and Quality of
2 Life. Their impact is calculated into the survival
3 and Quality of Life analyses, and even in the
4 presence of those adverse events, it is clear that
5 the risks outweigh the benefits.

6 [Slide.]

7 With regard to the labeling, is it
8 adequate? We feel that reasonable labeling has
9 been proposed, but certainly I think anyone
10 reasonable will view that recommendations for
11 improvement would be well accepted.

12 [Slide.]

13 In terms of postmarket evaluation, I do
14 believe there is a widely held view in this field
15 that this is essential going forth and that
16 Thoratec shares in that belief.

17 I thank you for the opportunity and am
18 proud, on the part of the REMATCH investigators, to
19 present this work, and turn it back to Don
20 Middlebrook.

21 **Summary and Closing Remarks**

22 **Donald A. Middlebrook**

23 MR. MIDDLEBROOK: Thank you, Lynne, Eric,
24 and Victor for an excellent presentation.

25 [Slide.]

1 I would like to summarize and conclude
2 with the following remarks. It is our belief that
3 this study has scientifically validated the safety
4 and effectiveness of the HeartMate VE LVAS for the
5 proposed indication.

6 Every aspect of this study has been
7 thoroughly planned and carefully executed. The
8 REMATCH study has demonstrated strong scientific
9 evidence of clinically meaningful survival benefit.

10 If you take a look at the experience we
11 have in the previous clinical trials in our
12 commercial use and in this REMATCH study, the VE
13 LVAS is a well characterized and a proven
14 technology.

15 It is our belief also that the REMATCH
16 trial has demonstrated reasonable evidence for
17 safety particularly in the context of terminal
18 illness. As Eric said, even in the fact that the
19 REMATCH patients faced a higher opportunity for an
20 adverse event, all of the Quality of Life
21 instruments showed sustained improvement trends
22 over the optimal medical management group.

23 The device, as Dr. Lynne Warner Stevenson
24 alluded to, provided unprecedented reduction in
25 mortality in end-stage congestive heart failure

1 patients when compared to the landmark drug
2 studies.

3 The VE LVAS is now the only proven
4 alternative therapy for non-transplantable
5 end-stage congestive heart failure patients.

6 [Slide.]

7 The threshold for PMA approval is
8 reasonable assurance of safety and effectiveness.
9 If you consider all of the data we have presented
10 here this morning, and contained in the PMA in
11 relation to the patient population, the conditions
12 of use, the probable benefit versus the probable
13 injury, and the demonstrated reliability, we
14 strongly believe that there is clear and compelling
15 scientific evidence that the HeartMate VE LVAS
16 should be approved as a new treatment option for
17 end-stage heart failure patients ineligible for
18 cardiac transplantation.

19 Thank you very much for your time and
20 attention. This concludes our presentation.

21 DR. LASKEY: Thank you all for a most
22 informed and articulate presentation.

23 I would like to move now to the FDA
24 presentation starting with Dr. Berman.

25

FDA Presentation

1 **Michael Berman, Ph.D.**

2 DR. BERMAN: Good morning. My name is
3 Michael Berman. I am the FDA lead reviewer for
4 this PMA supplement. For the record, this is
5 Supplement 16 to PMA P920014. It is being brought
6 by the Thoratec Corporation for the their Thoratec
7 HeartMate VE LVAS System.

8 I will be speaking to the engineering
9 review for this PMA supplement. I will be followed
10 by Dr. Swain, who will address the clinical review,
11 and then by Dr. Gray, who will address the FDA
12 statistical review.

13 After that, I will read the questions to
14 the panel into the record.

15 [Slide.]

16 These are the folks on the FDA review team
17 for this supplement.

18 [Slide.]

19 In this supplement, the sponsor is
20 proposing an expanded indication for use for the
21 currently approved VE LVAS system. The current
22 approval is as a bridge to transplantation in
23 patients who are transplant-eligible. This is the
24 language the sponsor is proposing.

25 "The HeartMate VE LVAS is indicated for

1 use as a bridge to transplantation in cardiac
2 transplant candidates at risk of imminent death
3 from non-reversible left ventricular failure."
4 That is the approved language.

5 This is what the sponsor wishes to add.
6 "The HeartMate VE LVAS is also indicated for use in
7 patients with end-stage left ventricular failure
8 who are ineligible for cardiac transplant." And
9 for both indications, "The HeartMate VE LVAS is
10 intended for use both inside and outside the
11 hospital."

12 [Slide.]

13 This is what the FDA has to do during this
14 review. We have to determine if the sponsor has
15 provided a reasonable assurance of safety and
16 effectiveness. That is the law. And we are
17 obligated to consider the following factors: the
18 patient population, in whom will this device be
19 used, the conditions of use, how will it be used,
20 what is the probable benefit versus the probable
21 injury to the patients using the device, and
22 finally, what is the reliability of the device when
23 used as indicated.

24 [Slide.]

25 I would like to remind you of the device

1 description. The device basically has implanted
2 and external components, the implanted components
3 being the blood pump, the valved conduits, and part
4 of the percutaneous tube.

5 The external components are the
6 controller, the battery packs, and what we will
7 call accessories. The accessories are described in
8 your panel pack in Tab 3.2, pages 5 and 6. It is
9 just external components.

10 [Slide.]

11 This is a figure which the sponsor allowed
12 me to use. This is their figure. Just to remind
13 you, this is the blood pump. It sits in the chest.
14 It is a rigid titanium shell. It is divided into
15 two halves internally. One half contains the
16 electric motor and is connected by means of a vent
17 tube to the outside.

18 The other half is the blood side. Blood
19 comes from the apex of the left ventricle through
20 the valve conduit into the pump. The electric
21 motor rotates. There is a cam that converts that
22 rotation to linear motion, pushes a pusher plate,
23 pushes the blood out of the blood side into the
24 aorta. This also is a valve conduit. So, this is
25 all implanted.

1 The percutaneous tube carries an air line
2 and an electric line out. This is the skin
3 breakthrough site. There is a connector here.
4 There is a vent line which allows air to vent in
5 and out of the motor side of the pump. There is an
6 electric line, which connects to the controller,
7 which has alarms, which conditions power, and so
8 on.

9 There are two battery packs, only one of
10 which is shown. The system can also be powered
11 from a bedside console. The system also comes with
12 a battery charger with a system monitor, and so on.

13 [Slide.]

14 This is a very complex system, as you
15 might well imagine. During the review of such a
16 complex system, these are the things that the FDA
17 will consider. In this case, the sponsor is asking
18 for an expanded indication for use for an existing
19 system which is currently approved for a bridge to
20 transplant, so all of the things shown here have
21 been reviewed in detail, and we have no concerns.
22 Nothing will change for these things for the
23 proposed expanded indication for use, the longer
24 term use. We have already reviewed this, and we
25 have no concerns.

1 [Slide.]

2 These are the things that we do have
3 concerns with: the difference between the proposed
4 long-term use, the destination therapy versus
5 bridge. The thing that we looked at very hard was
6 device system reliability, in particular the
7 reliability of the internal components since they
8 would require that the patient have surgery should
9 anything go wrong with them. We are less concerned
10 about the externals. It has been demonstrated
11 quite readily that they can be changed out rather
12 easily and aren't a problem.

13 In particular, we are concerned with the
14 motor, this is what pumps the blood, and the valved
15 conduits as Mr. Poirier spoke to and I will speak
16 to again, and we are concerned about a Device End
17 of Life Indicator. The sponsor noted that there
18 are several things which could indicate end of pump
19 life, but there are no objective indicators or at
20 least nothing the sponsor has proposed by which you
21 can tell that this particular pump is at end of
22 life and should be replaced and that particular
23 pump has six months left.

24 [Slide.]

25 I would like to address the reliability

1 testing, the bench testing that was performed by
2 the sponsor, which was described briefly by Mr.
3 Poirier.

4 Fifteen units were put on test. All of
5 them were VE LVAS, none of them were VE SNAP. They
6 were put on test on a mock circulatory loop. The
7 implanted components of the system were in water at
8 37 degrees Centigrade to simulate the environment
9 they would see in the patient, the temperature.
10 They were pumping water.

11 The external components were in air at
12 room temperature as they would be in clinical use,
13 and the pumps were run at what is described as
14 worst, average, and minimum operating conditions,
15 and they were cycled from condition to condition to
16 condition every week, and so cycled around and
17 around throughout the course of the test.

18 The things that were changed were beat
19 rate, outlet pressure, and flow that the pumps were
20 generating. This is the way it is done. This is
21 the way this reliability testing is done. The
22 number of units is good, the conditions chosen were
23 reasonable or apparently reasonable. This testing
24 was conducted in a most appropriate way.

25 [Slide.]

1 This is the results of the testing, which,
2 by the way, is still ongoing. As of this past
3 summer--this testing began in 1997--as of this past
4 summer, 10 pumps had failed, 8 of those failures
5 were main bearing failures, 1 was a diaphragm
6 failure, 1 was a commutator failure. The
7 commutator is part of the motor. Five units, as of
8 last summer remained on test. That is, they still
9 continue to function.

10 [Slide.]

11 Looking at the main bearing failures, this
12 is the motor. If the bearing fails, if the motor
13 fails, you don't have electric pumping. The mean
14 run time before the observed failure was about 136
15 million cycles at 75 beats a minute, that comes to
16 about three and a half years. That is roughly 40
17 million cycles a year at 75 beats a minute. The
18 standard deviation for that was about half a year.

19 The soonest a bearing failed was at about
20 2.25 years, the longest one ran before failing
21 other than the ones still running was about 4
22 years. The median is about 3.5 years. What I
23 would like you to look at, look at the mean and
24 look at the median. It is out at around 3.5 years.

25 The sponsor has initiated a corrective and

1 preventive action to address the problem of the
2 bearing failures. This is an investigation, there
3 is no mitigation yet. This is an open
4 investigation, no steps have been taken to address
5 the failures, no specific engineering changes have
6 been made that we are aware of.

7 [Slide.]

8 Using these numbers and using a
9 mathematical model, a Ybel [ph] model, one can
10 predict what the reliability of the system should
11 be. This is a prediction. 86 percent reliability
12 at 2 years with a 60 percent confidence, 76 percent
13 reliability at 2 years with a 90 percent
14 confidence.

15 The mean time to failure for the pump with
16 90 confidence should be 3 years. Keep those
17 numbers in mind, 3 years.

18 [Slide.]

19 These are observed end of pump life
20 events. They occurred at times ranging from 460 to
21 779 days. These are events observed in patients in
22 the clinical trial.

23 The cycles are in million of cycles. For
24 instance, looking here, this is about 50 million
25 cycles at 75 beats a minute. At 100 beats a

1 minute, it is about 67 million, and what was
2 observed, there was dust, and when the pump was
3 looked at, it was a bearing failure.

4 Similarly, for the other ones, the number
5 in parenthesis is either the higher estimated rate
6 or, here, for these two, these are numbers of
7 cycles estimated by the sponsor based on records of
8 what the beat rate was when those patients were
9 seen at follow-up.

10 The point here is that these occurred
11 early in the process compared to what the bench
12 testing predicted. The sponsor is saying the bench
13 testing predicts end of life at between 80 and 120
14 cycles for the pump, and these are occurring early.
15 The clinical observation is they occur early.

16 [Slide.]

17 Another malfunction, not failure, a
18 malfunction, is inflow valve incompetence that Mr.
19 Poirier spoke of. This has been confirmed, 12
20 events in 11 patients. One patient experienced
21 this twice. Six of those devices were VE, five
22 were VE SNAP, which calls into concern the
23 effectiveness of the 90-degree elbow, which is one
24 of the things that differentiates the VE SNAP from
25 the VE.

1 The idea was to not allow the outflow
2 valve graft to kink, so that the pump would not
3 develop high pump pressure and thereby high back
4 pressure across the inflow valve. Roughly half of
5 the events observed were in the modified pump.

6 We wonder whether this might be related to
7 end of pump life. One of the symptoms of inflow
8 valve incompetence is an increase in pump rate up
9 to on the order of 100 to 120 beats a minute. That
10 means for a given absolute length of time, for a
11 day, the pump will undergo more cycles at the
12 higher rate than at 75.

13 Consequently, the pump will reach its end
14 of life sooner in time. The clinical consequences
15 of inflow valve incompetence can be surgery for
16 replacement of the inflow conduit, and so that, by
17 definition, puts the patient at some risk.

18 [Slide.]

19 The engineering summary is that the bench
20 testing, in our eyes, did not account for all of
21 the observed clinical conditions. In particular,
22 it did not account for the elevated pump chamber
23 pressure which was seen clinically and/or for the
24 high beat rate which was seen clinically, the
25 elevated pump chamber pressure could well be

1 I would like to present our review today.
2 The clinical review was performed by Dr. Ewing,
3 cardiology, and Dr. Sapirstein and I in
4 cardiothoracic surgery.

5 [Slide.]

6 As Dr. Berman has said, the indication is
7 an expanded use for patients with end-stage left
8 ventricular failure who are ineligible for cardiac
9 transplantation.

10 [Slide.]

11 The primary effectiveness endpoint was
12 survival benefit, as Dr. Rose has said.

13 [Slide.]

14 This was estimated based on mortality at 2
15 years, and the estimates were based on the
16 literature, as Dr. Stevenson has said, based on a
17 mortality of 75 percent in the OMM group and 50
18 percent in the LVAS group, calculated for 92 study
19 deaths.

20 The worst case power calculation for a
21 power at 80 percent was calculated as 60 and 40, so
22 a 30 percent improvement in survival. When you
23 look at the results of the study, the observed
24 Kaplan-Meier curves, the mortality was 91 and 76
25 percent at the two-year mark.

1 [Slide.]

2 The data that I will be showing you are
3 based on three separate submissions from the
4 sponsor. The first was in June, and in each slide,
5 I will attempt to have that marked, a June
6 submission. There was an update on mortality
7 curves in November, and another update in February.

8 So, the survival will be based on the
9 February update from the sponsor. We received the
10 serious adverse event update about three working
11 days ago. It was too late to include in the
12 presentation, but on first pass, it appears to be
13 not substantially different.

14 [Slide.]

15 The inclusion criteria used originally for
16 when the study was designed, which was used for 124
17 of the 129 patients, is as shown, that the patients
18 were ineligible for transplantation, NYHA Class IV
19 for greater than 90 days, 70 percent of these
20 patients turned out to be on inotropes, intensive
21 medical therapy, LVEF lower than 25 percent, VO_2
22 max less than 12. VO_2 max was performed at
23 baseline on about 50 percent of the patients in the
24 study.

25 [Slide.]

1 Later, in order to increase enrollment in
2 the study, the criteria were changed slightly, and
3 this was for five of the patients in the study. It
4 was NYHA Class IV for greater than 60 days as
5 opposed to 90, and added NYHA Class III or IV for
6 greater than 28 days, and inotropic therapy or
7 balloon pump. Also, increased VO₂ criteria to less
8 than 14 rather than 12.

9 [Slide.]

10 The exclusion criteria are as shown, in
11 particular, patients smaller than 1.5m², history of
12 stroke, neurological complications, things of that
13 sort.

14 [Slide.]

15 Baseline characteristics were equal
16 between the two groups or nearly equal in the
17 number of patients able to do the 6-minute walk,
18 the distance of the walk, NYHA IV, 65 and 2 in
19 Class III versus 60 and 1, so, in general, this was
20 a study of NYHA Class IV patients.

21 [Slide.]

22 This is based on the February 02 data, and
23 the study design, as Dr. Rose has said, 968
24 patients were screened as possible enrollees in
25 this trial, and patients enrolled, 129. That gives

1 you a ratio of 7.5 to 1. You will see slight
2 differences in our slides, 128 versus 129 patients,
3 67 versus 68. This reflects one patient who was
4 consented for the trial before the end of the
5 trial, but received his device after the end of the
6 trial, and these are included in the survival data,
7 this one particular patient.

8 What we see is that 7 patients reached the
9 two-year end of study mark in the left ventricular
10 assist group, 45 patients died at less than two
11 years, and there are, as of February 02 data, 16
12 patients alive less than two years.

13 For the medical management group, 3
14 patients survived to the two-year mark, 5 are alive
15 less than two years, and 53 patients have died.

16 [Slide.]

17 All of my slides that have percents are
18 zero to 100 scale, those with number of patients
19 are zero to 70 scales just to keep things
20 consistent.

21 Looking at the Kaplan-Meier curves for the
22 data that you just saw, one-year survival, n equals
23 16 for medical management, and medical management
24 in my slides are in gold as the gold standard, and
25 blue for the device, and 33 patients were the basis

1 of the KM curve, survival curve at one year at 57
2 percent.

3 At two years, the curves are based on 3
4 patients and 7 patients respectively in the two
5 groups. By 12 weeks later, at the end of the
6 trial, this is the February 02 data again, 4 of the
7 7 device patients had died, and all 3 of the
8 medical management patients had died by 12 weeks
9 past the end of the two-year trial.

10 [Slide.]

11 Serious adverse events occurred in 64 of
12 68 of the device patients, 36 of 61 of the medical
13 patients, P less than 0.001.

14 [Slide.]

15 Then, comparing for safety, the use of
16 this device in destination patients versus bridge
17 to therapy patients, there are several problems as
18 the sponsor has pointed out in making the
19 comparisons. They are certainly different patient
20 populations, different definition for many of the
21 SAE's, the studies were done in different times
22 periods with a different patient care team, which
23 makes comparison of SAE's between the bridge data
24 set and the current data set to somewhat
25 problematic.

1 [Slide.]

2 I am going to discuss just a few of the
3 SAE's, and the slides all contain two graphs. One
4 is the percent of patients experiencing the event,
5 the other is per 100 patient days, as Dr. Rose has
6 shown. I think it is important to do it both ways.

7 There are certain complications like the
8 need for transfusion that would probably be more
9 appropriate looking at patient days, events per 100
10 patient days. However, other complications, such
11 as a stroke, it might be more important or
12 clinically more important I think to look at the
13 percentage of patients experiencing the event it
14 would tend to overshadow other events occurring,
15 and not be able to detect lesser strokes and lesser
16 neurologic dysfunctions in this case.

17 Also, for situations like sepsis, a
18 patient who has sepsis and then has sepsis for the
19 remainder of the time in the study would not be
20 reflected in events per 100 days, but probably
21 would be reflected more clinically relevant in
22 percent of patients.

23 So, when we look at neurologic
24 dysfunction, we find a statistically significant
25 difference between device versus medical therapy,

1 27 percent of the patients having a serious adverse
2 event in neurologic dysfunction.

3 It is important to note that this study
4 was designed in the early-to-mid-nineties when we
5 had less of a knowledge of neurologic events than
6 we do now in cardiac surgery, so the definitions of
7 neurologic events are really based on the NIH
8 stroke score and a clinical examination, there are
9 virtually no cognitive function being done other
10 than what is present in the NIH stroke score, which
11 is truly a stroke score, and that is really two
12 questions relating to alertness and ability to
13 function.

14 These are the results of neurologic
15 dysfunction.

16 [Slide.]

17 When you look at local infections, we also
18 look at a P equals 0.07 difference, less of a
19 difference between the two groups, and less than
20 0.1 when look at it per 100 patient days.

21 [Slide.]

22 When you look at sepsis, and you look at
23 the individual patient summaries, you will see very
24 often that local infections may lead to implant
25 infection, sepsis, and that sort, so a lot of these

1 SAE's are not independent at all. They are very
2 much interrelated.

3 When you look at sepsis, the difference is
4 31 percent versus 13 in the two groups, and percent
5 of patients, which is a 0.02 difference
6 significantly. Likewise, when you look at per 100
7 days, a P less than 0.2 difference in that
8 particular SAE.

9 [Slide.]

10 Now, for complications that only the
11 device patients could have, looking at percutaneous
12 or pocket infections, 24 percent of the patients
13 and a 0.11 event per 100 day level, and this is
14 again based on the June data.

15 [Slide.]

16 Looking at pump housing inflow or outflow
17 tract infections, which could be extremely serious,
18 13 percent of the patients had that complication.

19 [Slide.]

20 Look at bleeding. This is not
21 perioperative bleeding, this is bleeding after the
22 perioperative period, a statistically significant
23 difference between the two groups here with the
24 device patients having 25 percent versus 3 percent
25 incidence of bleeding, and again, a statistical

1 difference when you look at event rate.

2 [Slide.]

3 Perioperative bleeding, which obviously
4 can only be present in the device patients, 34
5 percent of the patients and this event rate.

6 [Slide.]

7 When we look at SAE's of all types, and
8 look at operations, and this excludes the original
9 implant operation obviously, it includes all
10 operations in the medical group and every operation
11 after the original implant in the left ventricular
12 assist group, we can see the number of
13 reoperations, the number of patients having 1, 2,
14 and up to 10 reoperations. This includes all
15 reoperations, everything from a Hickman catheter to
16 replacement of the device itself.

17 [Slide.]

18 What about the device malfunction analysis
19 that Dr. Berman has mentioned? When you look at
20 the various types, implant, as he has explained,
21 which is the most serious, external element
22 replacement, and then device malfunctions, and the
23 definition of malfunction, 20 elements in 19
24 patients had implant element replacement. Of the
25 12 pumps removed, 8 pumps were replaced, 7 of those

1 8 patients died, 6 of those 7 in the postoperative
2 period.

3 Of 4 devices removed, but not replaced,
4 all of those patients died, 3 of them were removed
5 for unrelenting sepsis, and 1 patient chose not to
6 have the device replaced.

7 [Slide.]

8 When we look at withdrawal from treatment
9 in the two groups, 4 of the medical management
10 patients chose to have the treatment withdrawn
11 within one month of randomization, of choosing to
12 be in the study and being randomized to medical
13 therapy, they chose to have treatment withdrawn.
14 Eight others chose to have treatment withdrawn at
15 some time later in the study. So, a total of 12 of
16 the 61 patients in optimum medical management chose
17 to have their treatment withdrawn.

18 In the left ventricular assist group, 7
19 patients or their family chose to have the device
20 turned off or did not agree to replacement when
21 replacement was recommended, and 6 more chose to
22 have treatment withdrawn, so a total of 13 of the
23 68 patients chose to have their treatment on the
24 device withdrawn.

25 [Slide.]

1 Now we look at secondary endpoints, which
2 were originally part of the study design, and that
3 includes NYHA class, QoL's, functional status by
4 way of 6-minute walk, VO₂ max, number of
5 hospitalizations, and what we have just spoken
6 about, adverse events and device malfunction.

7 [Slide.]

8 When you look at NYHA class, as Dr. Rose
9 has shown, there is an excellent result in
10 comparing the device, that is statistically
11 significant at 6 and 12 months, and there was very
12 little data after 12 months. It is important, as
13 Dr. Rose said, that no values were imputed. We
14 standardly looked for values that are imputed, and
15 that can either be done by taking the last result
16 in the chart that was done and imputing results,
17 which would give you different results from here,
18 very good, or to look at data that was not
19 collected because the patient died or could not do
20 the test and impute the worst possible result,
21 which would also give you very different results
22 from shown here.

23 So, no data was imputed, these are all the
24 real data that were collected.

25 [Slide.]

1 When you looked at Quality of Life
2 results, the problem in an unblinded study, and
3 necessarily this was unblinded to both physicians
4 and to patients, and what is the effect on both the
5 physicians and the patients of not being selected
6 for the test device or the test therapy.

7 We are often concerned about the placebo
8 effect in any unblinded study, and this may be very
9 important, up to a 30 percent difference in
10 results.

11 There may be sample bias for missing data.
12 A patient who has had a large CVA would not
13 necessarily be expected to be able to complete any
14 of the QoL questionnaires or the walk or VO₂ data.

15 We also expect consistency, statistical
16 consistency between the Quality of Life and
17 functional measures, and clinical concordance, you
18 expect things to move in the same direction with
19 the same relative magnitude.

20 [Slide.]

21 What about the data, what amount of data
22 do we have for Quality of Life? When you look at
23 the questionnaires, we can see these number of
24 patients had completed QoL questionnaires. At one
25 year, the LVAS patients, 22 of them, and 4 at two

1 years, 6 and 3 in the OMM patients completing the
2 questionnaires, of which we are looking at the QoL
3 data.

4 [Slide.]

5 When we look at 6-minute hall walk, the
6 number of tests performed, 37 of the 68 patients in
7 LVAS either never or only once had a 6-minute hall
8 walk, and 29 had multiple performances, two or more
9 performances of this test.

10 OMM patients, 44, and 17 had multiple
11 performances of the test. So, there really are
12 inadequate data for a comparison of these groups.

13 [Slide.]

14 When you look at the data, this is clear.
15 Of the patients who did have the test performed,
16 these are the median distances in meters performed.

17 [Slide.]

18 Look at peak VO_2 data, which is one of the
19 inclusion criteria for the study. About half of
20 the patients in both groups had baseline
21 performance of data. When we look out to one year
22 and two years, 15 of the LVAS groups and 3 of the
23 OMM group had data, 2 and 1 at two years, and you
24 look at the data obtained, and again no statistical
25 difference in this small sample size.

1 [Slide.]

2 Another way of look at hospitalization is
3 the percent of the remainder of life out of the
4 hospital. According to the June 01 data, when we
5 look at the average and median for the device
6 group, 50 percent of the remainder of their life
7 after randomization was found out of the hospital,
8 median of 64 percent.

9 On the OMM group, 71 percent of the
10 remainder of their life was spent out of the
11 hospital versus 83 in the median numbers.

12 [Slide.]

13 Death during hospitalization, 20 of the
14 LVAS patients and 6 of the OMM patients died during
15 their initial hospitalization. Of the OMM patients
16 who died, of the 6 who died, several had treatment
17 withdrawn, 1 patient had ventricular fibrillation
18 on the day of randomization and died on that day.
19 Another patient within a week of randomization was
20 found to have critical aortic stenosis, underwent
21 urgent cardiac valve replacement, and died in the
22 postoperative period.

23 [Slide.]

24 Our clinical summary is that in a very
25 advanced heart failure population, the device used

1 produced a survival benefit. The mortality and
2 morbidity associated with use of the LVAS was
3 considerable.

4 Interpretation of functional testing data
5 is limited by the amount of data available.

6 Thank you.

7 **Gerry Gray, Ph.D.**

8 DR. GRAY: Good morning. My name is Gerry
9 Gray. I was the statistical reviewer for this
10 device.

11 [Slide.]

12 Just give a synopsis of a couple of things
13 you have already seen in this study so far,
14 patients were randomized in this study 1 to 1 to
15 Optimal Medical Management versus Left Ventricular
16 Assist System.

17 The primary endpoint of the trial was
18 two-year mortality. By that, I mean the trial was
19 designed to detect a difference in survival over
20 the course of the two-year period between the two
21 arms of the trial.

22 There were three interim analyses designed
23 into the trial at 23 deaths, the trial was designed
24 to stop after 92 deaths.

25 For the survival analyses we have complete

1 follow-up. There is no missing data for survival.

2 As of the end of last June, there were 128
3 patients enrolled, 61 OMM, 67 LVAS. At that time,
4 we had 40 deaths in the LVAS arm, and the remaining
5 52 in the OMM arm.

6 Some of my slides will use the updated
7 survival data, that was updated as of the beginning
8 of February of this year.

9 [Slide.]

10 The primary endpoint for the trial was all
11 cause mortality. This is a graph of the survival
12 curves showing the all cause mortality for the two
13 arms of the trial. The X axis shows months since
14 randomization, the Y axis, the estimated survival
15 probability.

16 The thick red line is the LVAS arm, the
17 thick black line is the OMM arm. The thin line
18 show 95 percent confidence intervals at each point
19 over the course of the trial. The blue circles
20 indicate the estimated median survival for the two
21 groups. That was 150 days for the OMM arm versus
22 408 days for the LVAS arm.

23 Below the graph are the numbers of
24 patients who survived up to 0, 6, 12, 18, and 24
25 months. So, all the results past that are

1 primarily on those patients.

2 Some features to note in this graph, you
3 might note the survival up until the 30-day point
4 was pretty much identical for the two groups at
5 which point they diverged. The LVAS arm stayed
6 above OMM up until maybe around 22 months, where
7 there was somewhat of a decline in LVAS survival,
8 but again, that is only based on a very few
9 patients. I think there were only 11 patients who
10 survived up to 22 months.

11 As has already been stated, the log-rank
12 test for the overall difference is significant with
13 a p-value of 0.003. The two median survival times
14 of 150 and 408 days are significantly different.
15 At the one-year point in the June 2001 data, there
16 is a significant difference in survival.

17 [Slide.]

18 The updated survival curves shown on this
19 graph are pretty much the same. I am going to go
20 back and go forward, and you see that the only real
21 difference is that the confidence bounds got
22 slightly smaller because we had more follow-up.

23 This data of February 2002 had seven
24 months more follow-up than the previous. The basic
25 features are still unchanged. We still have a

1 significant difference between the two curves using
2 the log-rank test. We still have potential
3 drop-off in LVAS survival around the 22-month
4 point.

5 Using these data at 24 months, pointwise,
6 there is a marginal difference in survival. The
7 p-value is around 0.05.

8 [Slide.]

9 One of the secondary endpoints of the
10 trial was cardiac mortality. This graph shows the
11 deaths due to cardiac mortality in the two arms of
12 the trial. Again, red line is LVAS, black is OMM.

13 In this analysis, deaths that are not due
14 to cardiac causes are considered to be censoring.
15 Those patients are censored. When you look at the
16 data in this way, the LVAS arm is very much
17 superior to OMM. There still might be a drop-off
18 in LVAS survival at 22, but again, this is very,
19 very few patients.

20 There is a problem in looking at this kind
21 of analysis. In this case, the cardiac and
22 non-cardiac mortality are not independent. In
23 statistical terms, you would say that the censoring
24 is independent of the mortality.

25 [Slide.]

1 This graph shows the converse of the
2 previous mortality due to non-cardiac causes. When
3 you look at it this way, the OMM arm looks to be
4 superior to the LVAS arm. You will recall that only
5 1 out of 52 deaths at the stopping point were due
6 to non-cardiac causes in the OMM arm, whereas, 29
7 of the 40, about three-quarters of the LVAS deaths,
8 were non-cardiac causes.

9 So, you have to look at these two graphs
10 sort of together to interpret meaningfully. So,
11 again, it would appear that the causes or
12 mortality, at least cardiac versus non-cardiac, are
13 not independent, and it would appear that the LVAS
14 device reduces the cardiac mortality and, at the
15 same time, increases the non-cardiac mortality to
16 some degree.

17 [Slide.]

18 So, to summarize the mortality results,
19 there is a significant increase in the median
20 survival time, 150 days versus 408 days. There is
21 a significant difference between the two survival
22 curves using the log-rank test with a p-value of
23 0.003.

24 There is a significant difference in the
25 mortality at one year, 50.8. That says

1 "mortality," it should say "survival." The
2 survival at one year was 50.8 percent versus 24.4.

3 Using the updated data, updated as of
4 early February, there is marginal statistically
5 significant difference in mortality at the two-year
6 point.

7 The cardiac and non-cardiac mortality
8 don't look to be independent, and there might be a
9 drop-off in LVAS survival starting at around 22
10 months, but again, that is based on only 11
11 patients who survived after that point.

12 [Slide.]

13 Also, as has been previously noted,
14 survival benefits didn't come without a cost.
15 There were significant increases in the number of
16 adverse events and serious adverse events per
17 person and in the rates per 100 days in the LVAS
18 arm.

19 [Slide.]

20 This graphic shows the death and serious
21 adverse event rates per 100 days in the two arms of
22 the trial, the red bars on the left LVAS, the gray
23 bars the OMM arm.

24 The top five bars in here are
25 device-related events that could only have happened

1 in the LVAS patients. Overall, as has also been
2 stated, the LVAS rates were significantly higher
3 than the OMM, especially the bleeding and
4 neurologic dysfunction down at the bottom were very
5 different.

6 [Slide.]

7 Cutting the time at 30 days or less versus
8 events that happened at more than 30 days is shown
9 in this graph here, the lefthand side being what
10 you might call peri-operative events that happened
11 at 30 days or less, the righthand side being events
12 after 30 days.

13 Again, these show rates per 100 patient
14 days, so they are adjusted for the different
15 survival times for the two arms of the trial.

16 You will note that the X axes are not the
17 same in these two, and that is because the rate per
18 100 days did drop off significantly for both groups
19 after 30 days. Bleeding and neurologic dysfunction
20 stayed high in the LVAS arm, and for both of these
21 time periods, the event rates were significantly
22 higher for the LVAS patients.

23 The mortality at the bottom, the death
24 rate for the two arms was nearly identical for the
25 first 30 days. After that, the LVAS rates were much

1 better.

2 [Slide.]

3 Associated with this increase in serious
4 adverse event rates, the hospitalization time was
5 significantly higher for the LVAS arm, a median of
6 61 days in the hospital versus 16, 24 percent of
7 the total days in the LVAS arm were spent in the
8 hospital versus 15 percent in the OMM arm.

9 I am not sure about this 141. I got it
10 out of the panel pack, and the sponsor seemed to
11 indicate that was more like 300 days, so I am not
12 totally clear why that says 141.

13 [Slide.]

14 One of the panel questions asks the panel
15 how to combine or how to make the tradeoff between
16 mortality benefit and adverse events.

17 I am going to take a little sidetrack here
18 and talk about two possible ways that you might
19 formally try to combine those into one analysis,
20 the first one being an analysis based on a
21 hierarchical ranking of patients, the second one
22 being survival to not just death, but death or some
23 other bad thing. These are by no means the only
24 two possibilities.

25 [Slide.]

1 First, using a hierarchical ranking, what
2 you might think of doing is trying to rank patients
3 by whatever the most important outcome is, and then
4 if there are any ties, to break those ties using
5 secondary outcomes.

6 In this trial, the obvious example is to
7 first rank patients by how long they survived, and
8 if they survived to the end of the trial, to try to
9 rank them by some other secondary objective like
10 how many days they spent in the hospital or perhaps
11 how many serious adverse events they had.

12 The bottom line here is if you believe in
13 this kind of analysis and you can meaningfully rank
14 patients using this hierarchical method, if you use
15 the death time as the first ranking factor, then,
16 regardless of how ever else you rank patients after
17 that, there is always a significant improvement in
18 favor of the device.

19 So, if you like this kind of analysis, the
20 device would always look better.

21 [Slide.]

22 The other method you might do is to try to
23 combine death and other serious adverse events into
24 one analysis. This is again Kaplan-Meier survival
25 curve that shows the survival up until the time of

1 the first serious adverse event or death. In this
2 analysis, death and serious adverse events all
3 count the time, there is no differential.

4 The median LVAS survival time in this
5 analysis is much less, 13 days, versus 87 days in
6 the OMM arm. After about five or six months, the
7 rates level out to be about the time. The medians
8 again are shown by the blue dots.

9 [Slide.]

10 If you are wondering how we reconcile this
11 with the mortality results, remember that although
12 the time to the first bad event, the first serious
13 adverse event in the LVAS arm is much less, the
14 classification of that bad event is much different.

15 So, out of the 58 people who had death or
16 some serious adverse event, the first thing that
17 happened to them in the LVAS arm for two of those
18 people was death, whereas, in the OMM arm, the
19 first thing that happened to more than half of the
20 patients was they died, so although the rate was
21 higher in the LVAS arm, the seriousness of the
22 event I guess you would say was different.

23 [Slide.]

24 Now, there was a clinical impression from
25 the clinical reviewers that when they read the case

1 reports, that the first bad event initiates this
2 cascade of things that leads ultimately to the
3 death of the patient, and the question to me was,
4 is that impression borne out in some formal
5 analysis, and if it is, is there is some difference
6 between the two groups in the timing of those
7 subsequent events.

8 [Slide.]

9 This graph shows the results of such an
10 analysis. Again, it is Kaplan-Meier survival curves
11 of conditional survival to death or serious adverse
12 event. The two upper lines here are the time up
13 until the person had their first serious adverse
14 event, and those are the two lines that we have
15 already seen in a previous graph.

16 The two lower lines show if you survive
17 that first adverse event, how long was it until you
18 had some other bad thing happen to you. The point
19 here to note is that after the patient has their
20 first bad event, the second and third and fourth
21 events come very rapidly, and actually, they come
22 at about the same rate for the two arms.

23 So, the main difference between the two
24 groups is the time up until the first event. After
25 that, events occur rapidly at median times of about

1 three to five days, at about the same for the two
2 groups.

3 [Slide.]

4 This table summarizes the functional
5 status and Quality of Life results that we saw in
6 the trial. The entries in the table are the p
7 values for tests between OMM and LVAS improvement
8 over baseline.

9 These results generally favor the LVAS arm
10 especially for NYHA, where LVAS consistently
11 improved significantly more than the OMM arm. The
12 hall walk and the peak VO₂ are pretty much
13 inconclusive partly because there were very few
14 patients who could complete those.

15 The Quality of Life results somewhat favor
16 the LVAS especially for the EuroQOL, less so for
17 the Beck and less for the Minnesota Living With
18 Heart Failure and the SF-36.

19 I would note that the samples sizes are
20 very small at the 6- and 12-month point. At 6
21 months, there were 30 LVAS and 21 OMM patients, and
22 at 12 months, there were 22 LVAS and 6 OMM patients
23 who are represented here.

24 [Slide.]

25 To summarize the statistical results,

1 there was a significant decrease in mortality for
2 the LVAS arm whether you measure by median survival
3 time or you use a log-rank test, or compare
4 pointwise at one and two years.

5 The significant adverse event rates were
6 much higher in the LVAS arm. The LVAS treatment
7 resulted in decreased cardiac mortality rates and
8 increased non-cardiac mortality rates.

9 Survival much past two years was poor in
10 both groups.

11 There may be some indication of a relative
12 LVAS drop-off in survival at about 22 months, but
13 there were very few patients, only 11, that
14 survived that far.

15 The difference between the two groups is
16 almost entirely in the time up until their first
17 event, not to the time between subsequent events
18 after that, and any stage, the odds of death versus
19 some other serious adverse event is always higher
20 for the OMM arm.

21 The functional status results favor the
22 LVAS arm, but not consistently.

23 Thank you.

24 DR. LASKEY: Mike, did you want to read
25 the questions for the panel?

1 months, have enough patient data been reported to
2 demonstrate a clinically meaningful survival
3 benefit?

4 4. The New York Heart Association, the
5 Quality of Life, and the functional testing results
6 are not consistent. From these data, can we
7 determine that there is a clinically meaningful
8 improvement in functional status?

9 5. This device demonstrated an increase
10 in median survival time and showed an overall
11 difference in survival. However, this benefit
12 diminished at two years and was associated with
13 serious adverse events and hospitalizations
14 throughout the course of the study. Do the
15 benefits of this device outweigh its risks?

16 6. One aspect of the premarket evaluation
17 of a new product is the review of its labeling.
18 The labeling must indicate which patients are
19 appropriate for treatment, identify potential
20 adverse events with the use of the device, and
21 explain how the product should be used to maximize
22 benefits and minimize adverse events.

23 6(a). Please discuss the appropriateness
24 of the proposed indications for use for this
25 device, which reads:

1 "The HeartMate VE LVAS is indicated for
2 use as a bridge to transplantation in cardiac
3 transplant candidates at risk of imminent death
4 from nonreversible left ventricular failure. The
5 HeartMate VE LVAS is also indicated for use in
6 patients with end-stage left ventricular failure
7 who are ineligible for cardiac transplantation.
8 The HeartMate VE LVAS is intended for use both
9 inside and outside the hospital.

10 6(b). Does the labeling accurately inform
11 patients of the risks of the device?

12 6(c). Does the labeling adequately inform
13 patients of the expected duration of use for this
14 device?

15 6(d). Are there any other issues of
16 safety or effectiveness not adequately covered in
17 the labeling?

18 7. Based on the clinical data provided in
19 the panel pack, do you believe that additional
20 clinical follow-up or postmarket studies are
21 necessary to evaluate the long-term effects of this
22 device? If so, how long should patients be
23 followed, and what endpoints and adverse events
24 should be measured?

25 Thank you.

1 DR. LASKEY: Again, thank you all to the
2 presenters and the FDA reviewers. A well-deserved
3 lunch break, and we would like to reconvene
4 promptly at 1 o'clock. Thank you.

5 [Whereupon, at 12:00 noon, the proceedings
6 were recessed, to be resumed at 1:00 p.m.]

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AFTERNOON PROCEEDINGS

[1:10 p.m.]

Open Discussion

DR. LASKEY: I would like to start off the afternoon by having Drs. Aziz and Konstam deliver their reviews and ask questions of the sponsor.

Dr. Konstam, do you want to begin?

DR. KONSTAM: Sure. First, I just want to say a couple of things. One, I want to congratulate Dr. Rose and his colleagues and the sponsor for conducting this study. I think it is going to stand as a landmark study and showing that a study like this can be done, and I just want to compliment them for embarking on it and carrying it out as successfully as they did.

I also think that the FDA reviewers were fabulous. I think that they have hit all the critical issues, at least that I am aware of, and maybe some that I am not aware of, but I think they did a fabulous job of summarizing everything.

I find sort of six categories of discussion, and just to go through what I think they are. The first is the primary endpoint met. I think there is a little bit of discussion that is required here, maybe I can ask Eric.