

AT

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

CIRCULATORY SYSTEM DEVICES PANEL  
OPEN SESSION

**This transcript has not  
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Tuesday, March 5, 2002

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1                    P R O C E E D I N G S

2                    **Call to Order**

3                    DR. LASKEY: I would like to call us to  
4 order. My name is Warren Laskey. I am pleased to  
5 be chairing this morning's session, discussing the  
6 premarket application for the Medtronic InSync ICD  
7 System. I would like to begin by having Dr. Ewing  
8 read the conflict of interest statement.

9                    **Conflict of Interest Statement**

10                   DR. EWING: Good morning. I would like to  
11 welcome everyone to this morning's session.

12                   The following announcement addresses  
13 conflict of interest issues associated with this  
14 meeting, and is made part of the record to preclude  
15 even the appearance of an impropriety.

16                   To determine if any conflict existed, the  
17 agency reviewed the submitted agenda for this  
18 meeting and all financial interests reported by the  
19 committee participants. The conflict of interest  
20 statutes prohibit special government employees from  
21 participating in matters that could affect their or  
22 their employers' financial interests. The agency  
23 has determined, however, that the participation of  
24 certain members and consultants, the need for whose  
25 services outweighs the potential conflict of

1 interest involved, is in the best interest of the  
2 government.

3           Therefore, a limited waiver has been  
4 granted for Dr. Tony Simmons for his interest in  
5 firms that could potentially be affected by the  
6 panel's recommendations. The waiver, allowing him  
7 to participate only in the panel discussions,  
8 involves grants or contracts to his employer. The  
9 first is for competitors competing products study,  
10 funded at less than \$100,000 per year, in which he  
11 has limited involvement in data generation, with no  
12 data analysis. The second is for competitors.  
13 competing technology study, funded at less than  
14 \$100,000 per year, in which he is not involved in  
15 data generation or analysis. Copies of this waiver  
16 may be obtained from the agency's Freedom of  
17 Information Office, Room 12A-15 in the Parklawn  
18 Building.

19           We would like to note for the record that  
20 the agency took into consideration other matters  
21 regarding Drs. Tony Simmons, Salim Aziz, Mitchell  
22 Krucoff, Jeffrey Brinker, Mark Haigney and Marvin  
23 Konstam. Each of these panelists reported  
24 interests in firms at issue but in matters that are  
25 not related to today's agenda. The agency has

1 determined, therefore, that they may participate  
2 fully in all discussions.

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

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

14 DR. LASKEY: I would like to have us all  
15 introduce ourselves.

#### 16 Introductions

17 DR. ZUCKERMAN: Bram Zuckerman, Acting  
18 Director, Division of Cardiovascular and  
19 Respiratory Devices, FDA.

20 DR. WITTES: Janet Wittes, statistician,  
21 Statistics Collaborative, D.C.

22 DR. DOMANSKI: Mike Domanski, I am a  
23 cardiologist at NHLBI.

24 MR. HAIGNEY: Mark Haigney, I am staff  
25 electrophysiologist at National Naval Medical

1 Center. 1  
2 DR. KONSTAM: Marv Konstam, Tufts  
3 University, New England Medical Center.  
4 DR. OSSORIO: Pilar Ossorio, University of  
5 Wisconsin Law School and Medical School.  
6 DR. EWING: Lesley Ewing, Executive  
7 Secretary, FDA.  
8 DR. LASKEY: Warren Laskey, interventional  
9 cardiologist, University of Maryland.  
10 DR. SIMMONS: Tony Simmons, cardiac  
11 electrophysiologist, Lake Forest University.  
12 DR. NISSEN: Steve Nissen, cardiologist,  
13 Cleveland Clinic.  
14 DR. AZIZ: Salim Aziz, cardiac surgeon,  
15 University of Colorado.  
16 DR. PINA: Ileana Pina, cardiology, Case  
17 Western Reserve University in Cleveland.  
18 MR. KRUCOFF: Mitch Krucoff, cardiology at  
19 Duke University.  
20 DR. BRINKER: Jeff Brinker, cardiology,  
21 Johns Hopkins.  
22 MR. DACEY: Robert Dacey, consumer  
23 representative, from Boulder, Colorado.  
24 MR. MORTON: Michael Morton, I am employed  
25 by Alcon Labs and I am the industry rep.

1 DR. LASKEY: Dr. Ewing, would you be so  
2 kind as to read the voting status statement?

3 DR. EWING: Thank you. Pursuant to the  
4 authority granted under the Medical Devices  
5 Advisory Committee Charter of the Center for  
6 Devices and Radiologic Health, dated October 27,  
7 1990 and as amended August 18, 1999, I appoint the  
8 following individuals as voting members of the  
9 Circulatory System Devices Panel for the meeting on  
10 March 5, 2002: Steven E. Nissen, Ileana Pina,  
11 Marvin A. Konstam. For the record, Dr. Nissen is a  
12 voting member and Drs. Pina and Konstam are  
13 consultants to the Cardiovascular Renal Drugs  
14 Advisory Committee of the Center for Drug  
15 Evaluation and Research. They are special  
16 government employees who have undergone the  
17 customary conflict of interest review, and have  
18 reviewed the material to be considered at this  
19 meeting.

20 Additionally, pursuant to the authority  
21 granted under the Medical Devices Advisory  
22 Committee Charter, dated October 27, 1990 and as  
23 amended August 18, 1999, I appoint the following  
24 individuals as voting members of the Circulatory  
25 System Devices Panel for this meeting on March 5,

1 2002: Pilar Ossorio, Michael Domanski, Mitchell  
2 Krucoff, Mark Haigney, Jeffrey Brinker. For the  
3 record, these people are special government  
4 employees and are consultants to this panel under  
5 the Medical Devices Advisory Committee. They have  
6 undergone the customary conflict of interest  
7 review, and have reviewed the material considered  
8 at this meeting.

9 In addition, I appoint Dr. Warren Laskey  
10 to serve as panel chair for the duration of this  
11 meeting.

12 DR. LASKEY: Thanks, Lesley. We are going  
13 to move on to the open public hearing portion of  
14 this morning's session. Is there anyone in the  
15 audience who wishes to come forward and address the  
16 panel on today's topic? If not, then I will close  
17 this portion of the open hearing to move on to the  
18 sponsor's presentation.

19 DR. EWING: As people are coming up to the  
20 microphone, I want to again recommend or ask that  
21 people introduce themselves clearly for the  
22 transcriptionist and state your conflict of  
23 interest.

24 **Sponsor Presentation**

25 **Introductory Comments**

1 MR. MANDA: Good morning.

2 [Slide]

3 My name is Ven Manda. I am with  
4 Medtronic. I am the Director of the Cardiac  
5 Resynchronization Program at Medtronic. On behalf  
6 of Medtronic and the participants in the InSync ICD  
7 study, I thank you for the opportunity to be here  
8 today to present results of the InSync ICD trial.

9 [Slide]

10 The clinicians that are in attendance  
11 today represent the study, including investigators  
12 that have been part of the InSync or the InSync ICD  
13 study. They are Dr. William Abraham, from the  
14 University of Kentucky; Dr. Bruce Wilkoff, from the  
15 Cleveland Clinic Foundation; Dr. Angel Leon, from  
16 Emory University; Dr. James Young, from the  
17 Cleveland Clinic Foundation; and Dr. Milton Packer,  
18 from Columbia University.

19 [Slide]

20 Our agenda today will start with Dr.  
21 William Abraham giving the background introduction  
22 for the trial, followed by the study design and  
23 methodology discussion by Dr. James Young.  
24 Subsequently, Dr. Leon will summarize the results  
25 of the safety and left ventricular lead

1 effectiveness results; followed by Dr. James Young  
2 who will summarize the InSync ICD primary and  
3 secondary efficacy results. Finally, Dr. William  
4 Abraham will then provide concluding comments with  
5 comparison to InSync results.

6 With this, I take the pleasure of inviting  
7 Dr. William Abraham.

8 **Introduction and Background**

9 DR. ABRAHAM: Thank you.

10 [Slide]

11 For the record, my name is William  
12 Abraham, from the University of Kentucky. I am an  
13 investigator and consultant to Medtronic, Inc.

14 Chairman Laskey, panel members, I would  
15 like to begin with a brief review of the background  
16 which supports the evaluation of cardiac  
17 resynchronization therapy in patients with heart  
18 failure, ventricular dysynchrony and an implantable  
19 cardioverter defibrillator.

20 [Slide]

21 As you are well aware, more than one-third  
22 of heart failure patients with moderate to severe  
23 disease have ventricular dysynchrony as evidenced  
24 by QRS duration of at least 130 ms. In heart  
25 failure, ventricular dysynchrony has been

1 associated with limited exercise tolerance,  
2 impaired quality of life and functional capacity,  
3 and poor left ventricular systolic function.

4 [Slide]

5 When one considers potential candidates  
6 for the evaluation of cardiac resynchronization,  
7 there are perhaps an infinite number of ways to  
8 stratify patients or study populations. In the  
9 InSync ICD clinical trials program we chose to  
10 stratify patients based on their indication for an  
11 implantable cardioverter defibrillator.

12 The first trial initiated was the InSync  
13 trial. The InSync evaluated patients with New York  
14 Association Class III or Class IV heart failure due  
15 to LV systolic dysfunction with ventricular  
16 dyssynchrony, inclusive of patients with QRS  
17 restoration of greater than or equal to 130 ms and,  
18 importantly, no indication for an ICD.

19 [Slide]

20 The design of the trial is reviewed on  
21 this slide. You recall that this was a  
22 prospective, randomized, double-blind, parallel-  
23 controlled evaluation of cardiac resynchronization  
24 therapy in these patients. Following a period of  
25 stable and optimal drug therapy and baseline

1 evaluation, patients underwent an implant attempt.  
2 If the implant was successful they underwent a pre-  
3 discharge randomization to a control group, or no  
4 cardiac resynchronization therapy, or to active  
5 resynchronization therapy. They then underwent  
6 evaluation at one, three and six months, with six  
7 months representing end of study evaluation.  
8 Patients who were randomized to the control group  
9 were then crossed over to the active  
10 resynchronization therapy. All patients were  
11 followed until this device was approved by the FDA  
12 in August of last year.

13 [Slide]

14 The results of the InSync study are  
15 summarized on this and the next three slides. This  
16 slide summarizes the primary endpoints of the  
17 InSync study. Recall that the InSync study  
18 demonstrated an improvement in quality of life, New  
19 York Heart Association class and six-minute hall  
20 walk seen with cardiac resynchronization therapy.  
21 For example, the median difference between groups  
22 in quality of life was 9.5 points, a value that is  
23 comparable to or better than most forms of heart  
24 failure therapy.

25 [Slide]

1           In addition, there were a number of  
2 important secondary clinical endpoints evaluated in  
3 the InSync study, and they were also markedly  
4 improved with cardiac resynchronization therapy.  
5 Peak VO2 and exercise time determined during  
6 treadmill exercise testing and, importantly, a  
7 clinical composite heart failure response score was  
8 also significantly improved with cardiac  
9 resynchronization therapy.

10           [Slide]

11           These improvements in primary and  
12 secondary endpoints were associated with a reduced  
13 risk of a combined endpoint of death or worsening  
14 heart failure, as defined on the top of this slide.

15           [Slide]

16           Finally, the InSync trial demonstrated or  
17 met all of its prespecified safety endpoints. It  
18 achieved all primary six-month safety objectives,  
19 including implant success rate, freedom from device  
20 lead and system complications, and demonstrated  
21 excellent pacing threshold across six months.

22           [Slide]

23           So in summary, the InSync trial  
24 established the role for cardiac resynchronization  
25 therapy in this group of patients, patients with

1 moderate to severe systolic heart failure and  
2 ventricular dysynchrony without an indication for  
3 an implantable cardioverter defibrillator.

4 [Slide]

5 Now let's take a look at a group of  
6 patients who have an indication for a cardioverter  
7 defibrillator. Currently, these therapies may be  
8 provided to patients through the implantation of  
9 two devices, an InSync device and a separate  
10 implantable cardioverter defibrillator. However,  
11 there are a variety of both clinical and  
12 electrophysiological reasons for concerns or risks  
13 that preclude such an approach.

14 For example, the implantation of both of  
15 these devices requires two surgical procedures, two  
16 pockets, the implantation of two devices and two  
17 lead systems and, thus, the inherent risks that go  
18 along with two separate surgical procedures.

19 In addition, there are some  
20 electrophysiological considerations in,  
21 importantly, unwanted or maladaptive device-device  
22 interaction which precludes the use of these two  
23 devices in most patients. That is, the functioning  
24 of one of these devices may adversely affect the  
25 functioning of the other device.

1 [Slide]

2 Thus, an approach has been developed to  
3 deliver these therapies with a combined device  
4 which has been developed to avoid these problems  
5 and inherent risks, and this is the InSync ICD  
6 device.

7 [Slide]

8 The characteristics of this device are  
9 summarized on this slide. Typical for implantable  
10 cardioverter defibrillators, the device provides VT  
11 and VF detection, as well as antitachycardia pacing  
12 and cardioversion and defibrillation therapies. In  
13 addition, it is a dual chamber pacemaker which is  
14 capable of providing simultaneous biventricular  
15 pacing and, importantly, while providing  
16 biventricular pacing it senses only the RV.

17 The importance of this is that RV sensing  
18 only in the setting of a delivery of biventricular  
19 pacing eliminates the risk of inappropriate  
20 defibrillator therapy that may be associated with  
21 sensing of both the LV and the RV lead. This is  
22 more than just a theoretical consideration. There  
23 are other ways of delivering biventricular pacing  
24 in association with defibrillation which have been  
25 reported to result in inappropriate sensing and

1 inappropriate defibrillation in these patients.  
2 The problem is eliminated with the InSync ICD  
3 device.

4 [Slide]

5 So, as we lead in now to our discussion of  
6 methodology for this trial, these are the two  
7 central questions to be addressed: Could an  
8 indication for an ICD influence the efficacy of  
9 resynchronization? That is, we perceived that  
10 there was a need to ensure that patients with an  
11 ICD indication respond favorably to  
12 resynchronization, just as those patients without  
13 an ICD indication do.

14 The second is, could the presence of  
15 resynchronization therapy in some way influence the  
16 efficacy of the ICD? That defines the need to  
17 ensure that the coexistence of resynchronization  
18 function does not adversely affect the ICD  
19 function.

20 With that background, I would now like to  
21 introduce Jim Young, from the Cleveland Clinic, to  
22 talk about study design, methodology and the  
23 patient population.

24 **Study Design, Methodology and Patient Population**

25 DR. YOUNG: Thank you very much, Bill.

1 [Slide]

2 Mr. Chairman, ladies and gentlemen of the  
3 panel, good morning. My name is Jim Young and I am  
4 from the Cleveland Clinic Foundation. I have been  
5 a consultant for Medtronic and have received  
6 research grants from Medtronic. Along with Dr.  
7 Abraham, I am currently the co-principal  
8 investigator of the ICD trial.

9 [Slide]

10 Patients enrolled in the InSync ICD study  
11 were adults with moderate to severe heart failure  
12 due to systolic left ventricular dysfunction, with  
13 evidence of ventricular dyssynchrony manifest by a  
14 wide QRS complex. A stable heart failure medical  
15 regimen was require, including an ACE inhibitor or  
16 substitute if tolerated, and if the patient was on  
17 a beta-blocker, the dose had to be therapeutic for  
18 three months prior to enrollment. The only  
19 differences between InSync and InSync ICD patient  
20 entry criteria were that InSync ICD patients had an  
21 ICD indication and could be New York Heart  
22 Association Class II.

23 [Slide]

24 As Bill mentioned, the design of the  
25 InSync ICD study was very similar to the InSync

1 study design. An InSync ICD implant was attempted  
2 in patients who met the inclusion and exclusion  
3 criteria within seven working days of their  
4 baseline evaluation. Randomization was  
5 accomplished in block groups for each center in  
6 order to ensure a one-to-one balance of therapy to  
7 control assignments at each participating  
8 institution.

9 Randomization and cardiopulmonary exercise  
10 testing occurred within seven days after a  
11 successful implant. Patients were randomized for a  
12 period of six months to either the control arm with  
13 cardiac resynchronization off, or the treatment arm  
14 with cardiac resynchronization on. Off patients  
15 were programmed to CRT on after completion of the  
16 six-month follow-up visit.

17 [Slide]

18 One important difference between InSync  
19 and InSync ICD was the timing of baseline exercise  
20 testing. In the InSync ICD study the  
21 cardiopulmonary exercise test was done after the  
22 randomization. Concerns about performing a maximal  
23 exercise stress test and patients having an IC  
24 indication but no ICD support dictated this  
25 approach. On the other hand, the baseline

1 submaximal exercise test was done before device  
2 implantation in both studies.

3 [Slide]

4 InSync ICD was a double-blind clinical  
5 trial. Patients and their heart failure caregivers  
6 were blinded to CRT status and were not to review  
7 EKG data. The blinded heart failure staff were  
8 responsible for collecting the patient self-  
9 administered quality of life sheets, the patient  
10 global self-assessment, performing physical  
11 examinations and determining New York Heart  
12 Association symptomatic class.

13 Cardiopulmonary exercise testing was not  
14 performed by the blinded heart failure staff.  
15 Electrophysiology staff, responsible for management  
16 of pacing ICD issues, were unblinded but CRT status  
17 was not to be divulged to the heart failure  
18 management team.

19 [Slide]

20 Primary efficacy endpoints for InSync ICD  
21 were quality of life, New York Heart Association  
22 classification and six-minute hall walk. They were  
23 designed to assess functional status, and all of  
24 these endpoints are commonly employed in heart  
25 failure clinical trials.

1           As prespecified in the investigational  
2 plan, this therapy will be considered effective if  
3 all three endpoints are met at p less than or equal  
4 to 0.05, or two endpoints are met at p equal to or  
5 less than 0.25, or one endpoint is met at p equal  
6 to or less than 0.167. The significance level was  
7 determined according to the Hochberg multiple  
8 comparison procedure with an overall significance  
9 of alpha equals 0.05.

10           [Slide]

11           Secondary effectiveness endpoints in  
12 InSync ICD may be generally classified into two  
13 categories. First, clinical endpoints included  
14 maximal exercise performance, as measured by  
15 cardiopulmonary exercise testing, a clinical  
16 composite response and hospitalization. Second,  
17 physiological endpoints included echocardiographic  
18 parameters, LV volumes, diameters, filling times,  
19 mass, ejection fraction, MR severity, E and A wave  
20 flow velocities and select neurohormonal values.

21           [Slide]

22           This slide demonstrates InSync study  
23 milestones. The PMA submission, on May 3, 2001,  
24 was triggered when 100 New York Heart Association  
25 Class III and IV patients had completed a six-month

1 follow-up. As prespecified in the investigational  
2 plan, these 100 InSync ICD were pooled with InSync  
3 Class III and IV patients for the PMA submission.

4           The PMA update submission was in November,  
5 2001 and was triggered when 224 New York Heart  
6 Association Class III and IV patients had completed  
7 a six-month follow-up. This number was, again,  
8 prespecified and based on the fact that the  
9 Minnesota Living with Heart Failure Quality of Life  
10 tool we used required the largest total sample  
11 size, the three efficacy endpoints in power  
12 calculations.

13           [Slide]

14           This slide shows the total number of  
15 patients in InSync ICD. Out of 636 total implant  
16 attempts, 421 were New York Heart Association Class  
17 III and IV patients and, as prespecified, this  
18 group comprises the primary study cohort for  
19 efficacy analysis.

20           [Slide]

21           In New York Heart Association Class III  
22 and IV patients, 421 underwent an implant attempt,  
23 with 371 or 88 percent successfully receiving an  
24 InSync ICD system. Of the 362 patients who were  
25 randomized, 176 were control and 186 were treatment

1 patients.

2 [Slide]

3 Of the 176 patients in the control group,  
4 124 reached their six-month follow-up visit at the  
5 database cut-off date for the PMA update  
6 submission. Thirty-five patients were still in  
7 double-blind follow-up; 15 patients died; and 2  
8 patients missed their six-month follow-up visit.

9 Of the 186 patients in the treatment  
10 group, 133 reached their six-month follow-up visit.  
11 Thirty-six patients were still in double-blind; 12  
12 died and 5 missed their six-month follow-up visit.

13 [Slide]

14 For safety analysis, as prespecified in  
15 the study protocol, data from New York Heart  
16 Association Class II, III and IV patients were  
17 submitted to the FDA. Subsequently, as requested  
18 by the FDA, only safety data from New York Heart  
19 Association Class III and IV patients were included  
20 in the panel pack and in this presentation.

21 [Slide]

22 The InSync ICD protocol prespecified that  
23 the primary efficacy analysis was to be based on  
24 New York Heart Association Class III and IV  
25 patients, with paired data at baseline and six

1 months excluding crossovers. Today, however, we  
2 are presenting results based on an intention-to-  
3 treat analysis for patients with paired data at  
4 baseline and six months but including crossovers.  
5 We will also briefly summarize results of the  
6 prespecified analysis, as well as results of the  
7 last observation carried forward analysis that  
8 includes crossovers.

9 [Slide]

10 As one would expect, baseline patient  
11 characteristics are indicative of a population with  
12 a significant congestive heart failure problem, and  
13 they are balanced. Patients had substantive  
14 cardiomegaly, depressed ejection fraction and  
15 intraventricular conduction delay.

16 [Slide]

17 Note that the peak VO<sub>2</sub> was 13.5 in each  
18 group. Medication therapies in this population  
19 were typical of a congestive heart failure cohort,  
20 with about 93 percent on a diuretic, 90 percent on  
21 an ACE inhibitor or ARB, and 60 percent on a beta-  
22 blocker.

23 Next we will cover the safety data results  
24 and my colleague, Dr. Angel Leon, will cover that  
25 area.



1 observation. The investigational plan defines a  
2 complication as an adverse event requiring invasive  
3 intervention or that results in the death of or  
4 serious injury to the patient, or in termination of  
5 a significant device function. It classifies an  
6 observation as an adverse event not requiring  
7 invasive intervention or that resolves  
8 spontaneously.

9           Additionally, a system-related  
10 complication is a classification of a device-  
11 related complication attributable to the combined  
12 device and not only the left ventricular lead but  
13 the right ventricular and right atrial leads, not  
14 necessarily attributable to any single component of  
15 the system.

16           [Slide]

17           The lead effectiveness objectives include  
18 total implant success with the model 4189, 2187 and  
19 2188 leads; the electrical performance of the model  
20 4189 left ventricular lead and the electrical  
21 performance of the model 2187 and 2188 left  
22 ventricular leads.

23           [Slide]

24           The evaluation of the integrity of the ICD  
25 function includes determination of the efficacy of

1 antitachycardia treatment by the defibrillator  
2 device; the comparison of ventricular tachyrrhythmic  
3 event rate; and a comparison of ventricular  
4 tachyrrhythmic event rates in the control and  
5 treatment arm; and a look at the efficacy of  
6 biventricular antitachycardia pacing for  
7 spontaneous episodes of ventricular tachycardia.

8 [Slide]

9 This figure illustrates the recommended  
10 transvenous lead positions as specified in the  
11 investigational plan. You can see a single lead in  
12 the right atrium. This represents the ventricular  
13 defibrillating electrode, located at the apex; and  
14 the left ventricular lead passed into the coronary  
15 sinus and then into one of the tributaries to the  
16 coronary sinus. The investigational plan  
17 recommends implantation of the left ventricular  
18 lead into one of the veins draining the free wall  
19 of the ventricle, such as the lateral,  
20 posterolateral or anterolateral vein.

21 The inset picture shows the  
22 investigational model number 4189 transvenous lead,  
23 which the investigational plan designated as the  
24 primary lead to be used by the investigator in this  
25 clinical evaluation. Only upon failing to obtain

1 an adequate lead position with the 4189 lead could  
2 the implanter then choose either the 2187 or the  
3 2188 as an alternative.

4 [Slide]

5 And, 421 patients underwent an implant  
6 attempt. The implants succeeded in 371 of those  
7 patients. The implant was unsuccessful in 50 of  
8 those 421.

9 [Slide]

10 Here we list the reasons, which are not  
11 mutually exclusive, for the failure or the  
12 unsuccessful implants. These can be categorized  
13 into three general groups: either an unstable lead  
14 position or one that dislodged within the  
15 procedure; unfavorable venous anatomy; or  
16 unsuccessful implants caused by coronary sinus  
17 trauma.

18 [Slide]

19 This slide shows a listing of adverse  
20 events that occurred during the implant procedure,  
21 both in the successful implants and in the  
22 unsuccessful implants. Again, one can categorize  
23 these into coronary sinus trauma or coronary venous  
24 trauma, arrhythmia or conduction block, or heart  
25 failure decompensation. You can see that nearly

1 all these events resolved with therapy.

2 [Slide]

3 Left ventricular lead implantation appears  
4 to be particularly associated with trauma to the  
5 coronary sinus and to the coronary venous system.  
6 We observed 22 events in 22 patients of the 421  
7 implant attempts. The clinical sequelae or the  
8 resolution of these events included  
9 pericardiocentesis in two patients; abandonment of  
10 the procedures in seven; echocardiography; ICU  
11 observation; explant of the lead; or repositioning  
12 of the lead. In eight cases no intervention was  
13 required, and we must note that there was no  
14 patient death associated with these complications.

15 [Slide]

16 We will now go over the primary safety  
17 results.

18 [Slide]

19 The device met its prespecified safety  
20 objective with an observed three-month, 98.6  
21 percent freedom from complications, with a lower 95  
22 percent confidence bound of 97.6 that meets the  
23 predetermined safety objective. There were seven  
24 events described or observed in seven patients.  
25 These are typical of ICD implantation and, again,

1 these resolved with therapy.

2 [Slide]

3 The model 4189 lead also met its  
4 predetermined performance objective, with an  
5 observed freedom from LV-related complications of  
6 85.1 percent at a lower 95 percent confidence bound  
7 of 81.7 percent that met the prespecified  
8 performance objective. There were 49 events in 44  
9 patients, and when we look at these more closely we  
10 can see that the great majority were either lead  
11 dislodgement, extra cardiac stimulation, or exit  
12 block, again, most of which resolved with therapy.

13 [Slide]

14 The model 2187 and 2188 leads, which are  
15 now commercially approved, also met their  
16 prespecified performance objective during the  
17 InSync ICD clinical evaluation. Freedom from lead-  
18 related complications was 89.9 percent, with a  
19 lower 95 percent confidence bound of 82.9 percent,  
20 again, meeting the prespecified objective that this  
21 should exceed 75 percent.

22 [Slide]

23 There were five events in five patients.  
24 Again, most of these resolved.

25 [Slide]

1           The system, including the ICD device, the  
2 left ventricular lead and the right atrial and  
3 right ventricular leads, also met their  
4 prespecified performance objective, achieving an  
5 event-free survival of 81.1 percent at a lower  
6 bound confidence interval of 77.6 percent and, once  
7 again, met the prespecified objective of 67 percent  
8 or greater.

9           [Slide]

10           When we summarize the primary safety  
11 results we see that the device, the left  
12 ventricular leads and the combination of device,  
13 left ventricular and right ventricular and right  
14 atrial lead met all the prespecified performance  
15 objectives for safety.

16           [Slide]

17           The secondary safety objectives, again,  
18 are characterize the complication rate, the  
19 observation rate, and also patient survival.

20           [Slide]

21           This slide shows complications that  
22 occurred during the six months randomization phase.  
23 You see that the events in the control and in the  
24 therapy arm do not greatly differ from each other,  
25 and most of the events are not device related.

1 [Slide]

2 When we look at the observation during the  
3 same six-month randomized period, we see that  
4 although there is a larger number of observed  
5 events in the therapy group, they do not differ  
6 from those in the control group and, again, are  
7 primarily neither device nor therapy related.

8 [Slide]

9 This slide summarizes patient survival.  
10 The event rate is too low to determine any  
11 statistical analysis or difference between them,  
12 but they do appear comparable.

13 [Slide]

14 We will now move on to the lead  
15 effectiveness results.

16 [Slide]

17 The first was implant success rate. The  
18 overall implant success for the model 4189, 2187  
19 and 2188 resulted in an observed rate of 88.1  
20 percent, with a lower limit of the confidence  
21 interval of 84.6 percent that, again, met the  
22 prespecified performance objective of 83 percent or  
23 higher.

24 [Slide]

25 For the model 4189 lead, the electrical

1 performance objective was met, with an observed  
2 pacing threshold of 1.5 Volts with a confidence  
3 interval at 1.7 Volts that met the prespecified  
4 performance objective that the voltage threshold be  
5 below 3 Volts.

6 [Slide]

7 When we look at pacing threshold for the  
8 model 4189 lead throughout not only the six-month  
9 randomization period but also in those individuals  
10 that reach 18 months of follow-up, we see that the  
11 left ventricular pacing threshold remained stabled  
12 throughout the interval.

13 [Slide]

14 For the model 2187 and 2188 leads, they  
15 also met the prespecified performance objective for  
16 electrical performance. The observed pacing  
17 threshold was 1.9 Volts, with a confidence interval  
18 limit of 2.2 Volts. That meets the prespecified  
19 performance objective that the threshold be below 3  
20 Volts. Again, these are the two commercially  
21 released leads.

22 [Slide]

23 When we graph voltage threshold over time,  
24 we see that through the randomization period  
25 voltage threshold by the end of the six-month

1 period remains stable, and also remains stable in  
2 those individuals who have reached 18 months of  
3 follow-up.

4 [Slide]

5 The last part of my presentation involves  
6 the evaluation of the integrity of ICD function in  
7 the InSync ICD clinical evaluation.

8 [Slide]

9 This slide shows the InSync ICD's overall  
10 efficacy in terminating spontaneous ventricular  
11 tachyarrhythmias. The device classifies episodes  
12 as either fast ventricular tachycardia, ventricular  
13 fibrillation or ventricular tachycardia. There  
14 were 78 patients who had a total of 1,125  
15 spontaneous ventricular tachyrrhythmia events. The  
16 overall efficacy of terminating spontaneous  
17 ventricular tachycardia or ventricular fibrillation  
18 episodes was 99.1 percent. The ten unsuccessfully  
19 terminated events, based upon device definition and  
20 device reporting, all eventually terminated. We  
21 can see that six episodes of ventricular  
22 tachycardia or ventricular fibrillation terminated  
23 after all therapies were delivered, and four  
24 episodes of fast ventricular tachycardia and  
25 ventricular tachycardia terminated after re-

1 detection but before additional therapies could be  
2 delivered. The last line is an error on the slide  
3 that is already incorporated into the first bullet  
4 listing the six ventricular tachycardia  
5 fibrillation episodes.

6 [Slide]

7 This slide compares the incidence of  
8 spontaneous ventricular tachycardia and ventricular  
9 fibrillation events in the control and treatment  
10 group patients who completed the six-month follow-  
11 up, and it only shows those episodes that occurred  
12 during the six-month randomization period. The  
13 treatment group had fewer patients experience  
14 ventricular tachycardia or ventricular  
15 fibrillation. These reductions, however, do not  
16 achieve statistical significance.

17 [Slide]

18 One additional concern dealing with the  
19 addition of cardiac resynchronization therapy to a  
20 ventricular defibrillator is that one must ensure  
21 that biventricular pacing does not adversely affect  
22 the ICD's ability to detect ventricular  
23 fibrillation or delay ventricular fibrillation.  
24 This slide indicates that regardless of the program  
25 ventricular fibrillation detection algorithm--these

1 are the two options available--there is no  
2 difference in detection time between the control  
3 groups and those that have active biventricular  
4 stimulation.

5 [Slide]

6 Now we will move back to Dr. Jim Young,  
7 who will present the effectiveness results in the  
8 InSync ICD evaluation.

9 **Effectiveness Results**

10 DR. YOUNG: Thank you.

11 [Slide]

12 We will now summarize the InSync ICD  
13 effectiveness results.

14 [Slide]

15 To remind everyone, the primary efficacy  
16 objectives of InSync ICD were the change from  
17 baseline to six months in quality of life score,  
18 measured by the Minnesota Living with Heart Failure  
19 questionnaire, New York Heart Association  
20 functional class assessed by the blinded heart  
21 failure clinician, and six-minute hall walk  
22 distance.

23 [Slide]

24 Quality of life data are presented on this  
25 slide. In the left-hand panel you see the median

1 quality of life scores at one-, three- and six-  
2 month time points. While there is a significant  
3 improvement from baseline to one month in both  
4 groups, improvements through six months are seen  
5 only in the treatment group.

6 On the right-hand panel are the median  
7 results for the control and treatment groups at  
8 baseline and six-month follow-up. The boxes above  
9 and below each median represent the 75th and 25th  
10 percentiles. The quality of life score decreased  
11 by 10 points in the control group and 19 points in  
12 the CRT group. The p value of 0.0098 is consistent  
13 with a highly significant improvement.

14 [Slide]

15 This slide demonstrates the change in New  
16 York Heart Association functional class from  
17 baseline to six-month follow-up, and 63 percent of  
18 the treatment patients improved at least one class,  
19 compared to 47 percent of the control patients,  
20 with a p value of 0.028.

21 [Slide]

22 These histograms depict the distribution  
23 of New York Heart Association class at baseline and  
24 then again at six months, and 90 percent of  
25 patients in both group were New York Heart

1 Association Class III at baseline. At six months  
2 60 percent of the treatment patients were in Class  
3 I or II compared to 44 percent of the control  
4 patients.

5 [Slide]

6 The six-minute hall walk data, on the  
7 right, is again presented as the median result for  
8 each of the control and treatment groups at  
9 baseline and six-month follow-up with the 25th and  
10 75th percentiles. There was no significant  
11 difference between the two groups for this  
12 submaximal exercise parameter.

13 [Slide]

14 Up to now the data presented has been  
15 based on the intention-to-treat, crossovers  
16 excluded, analysis. Those results for the primary  
17 efficacy endpoints are shown as p values here, in  
18 the first column. This slide also presents the  
19 protocol prespecified analysis, in the middle  
20 column, which excluded crossovers. In the right-  
21 hand column, a last observation carried forward  
22 analysis, including crossovers, and data for the  
23 most recent follow-up is presented.

24 The latter analysis is the more  
25 conventional approach taken in heart failure

1 clinical trials. Regardless of the approach, the  
2 study met at least one prespecified endpoint and,  
3 in particular, when the protocol prespecified and  
4 last observation carried forward analysis are  
5 looked at, two of the three endpoints were  
6 satisfied at the prespecified values.

7 [Slide]

8 As already presented, secondary  
9 effectiveness endpoints can be categorized in the  
10 clinical and physiologic endpoint groups.

11 [Slide]

12 Peak VO<sub>2</sub> data, on the left, represents the  
13 median and inter-quartile range for the control and  
14 treatment groups at baseline and six-month follow-  
15 up. There was a significant improvement in peak  
16 VO<sub>2</sub> for the treatment group, increasing 1.1  
17 ml/kg/minute, and no change seen in the control  
18 group. This between group difference is  
19 significant, with a p value of 0.05. On the right  
20 is exercise time data which also demonstrated  
21 significant improvement. The CRT group increased  
22 their exercise time by nearly a minute, while the  
23 control group decreased their exercise time by 26  
24 seconds. The between group difference of almost a  
25 minute and a half was highly significant, with a p

1 value less than 0.001.

2 [Slide]

3 The heart failure clinical composite  
4 response has emerged as an important endpoint for  
5 clinical heart failure treatment trials. In this  
6 study it is the only endpoint, other than  
7 mortality, that takes into account all randomized  
8 patients. A patient is defined as improved if they  
9 decreased New York Heart Association functional  
10 class by one or more level, or if the patient  
11 indicated a moderate or marked improvement in their  
12 patient global self-assessment score.

13 The patient is said to have worsened if  
14 they died, were hospitalized for worsening heart  
15 failure, if they crossed over from the assigned  
16 group because of worsening heart failure, if they  
17 withdrew consent for follow-up, if they had a  
18 worsening of New York Heart Association functional  
19 class, or if they indicated a moderate or markedly  
20 worse ranking on the global assessment. A patient  
21 is said to have no change if the improved or  
22 worsening conditions were not met.

23 [Slide]

24 This slide demonstrates that the CRT group  
25 had a significantly better clinical composite

1 response than did the control group. Fifty-five  
2 percent of the CRT patients improved compared to 40  
3 percent in the control patients, and 33 percent of  
4 the control patients worsened by this definition  
5 compared to 26 percent of the CRT patients. This  
6 between group difference was statistical  
7 significant at a p value of 0.038.

8 [Slide]

9 With regard to all-cause hospitalization,  
10 79 patients in the control group had 134  
11 hospitalizations during six months of double-blind  
12 follow-up compared to 75 patients that had 127  
13 hospitalizations. Fewer patients in the CRT group  
14 had hospitalizations for worsening heart failure  
15 compared to the control group, 39 versus 47. These  
16 CRT patients had 31 percent fewer total days  
17 hospitalized for heart failure than control  
18 patients but neither of these reductions reached  
19 statistical significance.

20 [Slide]

21 Echocardiographic variables are summarized  
22 in this slide, LV end systolic and diastolic  
23 volumes, and E and A wave velocity changes were  
24 significantly reduced at six months compared to  
25 baseline in the treatment group, with p less than

1 0.05. Also, the treatment group experienced a  
2 marginal improvement in left ventricular ejection  
3 fraction, p value equal to 0.06.

4 [Slide]

5 Other interesting physiologic changes,  
6 including left ventricular filling time, were  
7 significantly improved at six months and QRS width  
8 which was also decreased significantly from  
9 baseline to six months in the treatment group. The  
10 fact that the QRS was significantly narrowed at the  
11 long-term follow-up further confirms biventricular  
12 pacing in the treatment group.

13 [Slide]

14 Here we see the neurohormonal levels  
15 measured in the InSync ICD study. As the FDA  
16 reviewer pointed out, the neurohormonal data  
17 trended in the direction of improvement, with the  
18 exception of norepinephrine. These changes were,  
19 however, in reality all quite small and clinically  
20 insignificant.

21 [Slide]

22 In conclusion, in patients with moderate  
23 to severe heart failure, ventricular dysynchrony  
24 and an ICD indication the InSync ICD study  
25 demonstrates that the InSync ICD system improves

1 patient quality of life, functional status and  
2 exercise tolerance and, importantly, with an  
3 acceptable safety profile.

4 Next, we will move on to summarization  
5 with Dr. Abraham.

6 **Comparison of InSync and InSync ICD**

7 DR. ABRAHAM: Well, to conclude this  
8 presentation, I would like to present a brief  
9 comparison of the InSync and InSync ICD trials and  
10 make a few concluding comments. Like the InSync  
11 trial, the InSync ICD trial met its prespecified  
12 efficacy and safety endpoints and may be considered  
13 as a positive study.

14 [Slide]

15 Though you have seen this slide before, I  
16 show it again just to remind you that the InSync  
17 ICD trial was designed to be identical or nearly  
18 identical to the InSync trial. In fact, the key  
19 difference between the studies was the exclusive  
20 inclusion in the InSync ICD study of a group of  
21 patients who had an indication for an implantable  
22 cardioverter defibrillator. But, otherwise, the  
23 mechanics of these trials were very similar.

24 [Slide]

25 There was one notable exception, and that

1 is shown on this slide, a slide that you have also  
2 seen. That was in the timing of baseline  
3 assessments. An attempt was made to keep this  
4 timing as similar between InSync and InSync ICD as  
5 possible, but there were concerns about performing  
6 a maximal exercise treadmill test in patients with  
7 an ICD indication who did not yet have an ICD  
8 implanted. It was felt to be both unwise and  
9 unsafe to do that study prior to implantation of  
10 the device.

11 So, in the InSync trial cardiopulmonary  
12 exercise testing was done prior to implantation of  
13 the device, and in the InSync ICD trial the  
14 exercise test was done following implantation of  
15 the InSync ICD device. In fact, in retrospect,  
16 perhaps the same thinking should have been applied  
17 to the timing of the six-minute hall walk test  
18 because, as I will point out in a moment, it is  
19 possible that by performing this test prior to  
20 implantation of the ICD the patients were perhaps  
21 hesitant in some way to provide a true effort,  
22 reflective of their baseline six-minute hall walk  
23 distance.

24 [Slide]

25 Let's look at some of the baseline

1 demographic data comparing these two patient  
2 populations, and you will see that in many ways the  
3 populations are similar with perhaps the major and  
4 expected exception of an increased prevalence of  
5 ischemic heart disease as the etiology of heart  
6 failure in the InSync ICD study. This is not  
7 surprising and, as noted, as expected.

8 [Slide]

9 This slide, however, I think provides some  
10 insight into the question of the six-minute hall  
11 walk distance. You will see that the two groups,  
12 the InSync ICD and InSync populations were very  
13 well matched in general in terms of quality of life  
14 and functional status at baseline. For example,  
15 peak VO<sub>2</sub>, New York Heart Association class and the  
16 quality of life scores were nearly identical.  
17 There was one major difference, and that was seen  
18 in the baseline six-minute hall walk distances,  
19 with a very substantial, approximately 50 m less  
20 six-minute hall walk distance in the InSync ICD  
21 patients. Again, what this tells us, or may tell  
22 us, is that these patients in some way gave a poor  
23 effort that was not reflective of a true baseline  
24 value.

25 [Slide]

1           Now let's take a look at the data in a  
2 comparative sense, and this slide and the next two  
3 are set up in a similar fashion. Results from the  
4 InSync ICD trial are shown on the left-hand panel  
5 of the slide. Those from the InSync trial are  
6 shown on the right-hand panel of the slide. We  
7 will look at each of the three primary endpoints  
8 from these InSync studies.

9           As you have seen in the InSync ICD trial,  
10 cardiac resynchronization therapy produced a highly  
11 significant improvement in quality of life score.  
12 You will note from these slides that the pattern of  
13 improvement and the magnitude of benefit is similar  
14 in these two trials.

15                     [Slide]

16           This slide looks at the change in New York  
17 Heart Association class seen in InSync ICD versus  
18 the InSync trial. Among the pair of bars, the  
19 left-hand bar depicts control data; the right-hand  
20 bar treatment data. You will see that the change  
21 in New York Heart Association class seen in  
22 association with resynchronization in these two  
23 trials is also strikingly similar. For example, in  
24 the InSync ICD trial 63 percent of patients at six  
25 months improved their New York Heart Association

1 classification by at least one class. This is  
2 comparable to a value of 68 percent in the InSync  
3 trial.

4 [Slide]

5 Finally, let's take a look at the six-  
6 minute hall walk data, the one discordant piece of  
7 data between these two trials. What happened here?  
8 Well, I don't know that I know the answer, and we  
9 all know that sometimes these sorts of endpoints  
10 move in a discordant fashion in heart failure  
11 clinical trials.

12 But there are some interesting  
13 observations or conclusions that can be drawn from  
14 this slide. Looking first at the InSync data, you  
15 will see that in the InSync trial the six-minute  
16 hall walk test was relatively resistant to a  
17 placebo effect and resynchronization therapy was  
18 associated with a highly significant improvement in  
19 the six-minute hall walk distance.

20 What happened in InSync ICD? You will  
21 recall that these patients started off at a  
22 substantially lower baseline, and you will see that  
23 there is this marked improvement in six-minute hall  
24 walk distance seen between baseline and one-month  
25 evaluation not only in the treatment group but also

1 in the control group. This may be a placebo effect  
2 but this may be more than a placebo effect, and  
3 this may indicate that patients felt less  
4 constrained in performing true six-minute hall walk  
5 following implantation of the defibrillator device.

6 [Slide]

7 The results of these two trials in regard  
8 to primary endpoints are summarized on this table  
9 to show you again the striking similarity between  
10 at least two of the three primary endpoints,  
11 specifically quality of life and New York Heart  
12 Association class, which were improved to a nearly  
13 identical order of magnitude in these two trials.

14 [Slide]

15 In addition, as shown on this slide, some  
16 of the important secondary clinical endpoints of  
17 these trials were also similarly improved:  
18 improvement in peak oxygen consumption, exercise  
19 time and the important clinical heart failure  
20 composite response measure.

21 [Slide]

22 Finally, these trials demonstrated a  
23 decrease in risk of the combined endpoint of death  
24 or worsening heart failure, defining worsening  
25 heart failure requiring hospitalization or IV

1 medications. The effect seen in InSync ICD is  
2 shown on this slide.

3 [Slide]

4 On this slide is the Kaplan-Meier analysis  
5 from the InSync trial. However, I will caution you  
6 to not overinterpret this data as this was a post  
7 hoc analysis and the studies were not prospectively  
8 designed, nor powered, to these endpoints.

9 [Slide]

10 In conclusion, in New York Heart  
11 Association Class III and Class IV systolic heart  
12 failure patients, with an intraventricular  
13 conduction delay and an indication for an ICD  
14 cardiac resynchronization, as demonstrated in the  
15 InSync ICD trial improves quality of life  
16 functional status and exercise tolerance in  
17 association with an acceptable safety profile.

18 The benefits of resynchronization in  
19 patients with an ICD indication are similar in both  
20 direction and magnitude to the effects seen in  
21 patients who do not have an ICD indication.

22 On behalf of my colleagues, I would like  
23 to thank you for your attention.

24 DR. LASKEY: Thank you very much. I would  
25 like to move on to the FDA's presentation this

1 morning.

2 DR. EWING: Before the FDA presentation, I  
3 would like to ask the sponsor representatives to  
4 rejoin the audience. Thank you.

5 **FDA Presentation**

6 **Lead Reviewer**

7 MS. TERRY: Good morning. My name is  
8 Doris Terry. I am the primary reviewer for P010031  
9 to the Circulatory Devices Panel.

10 [Slide]

11 Ladies and gentlemen, the manufacturer,  
12 Medtronic, Inc. is seeking marketing approval for  
13 the Medtronic InSync implantation cardioverter  
14 defibrillator model 7272 system.

15 [Slide]

16 These are acknowledgements to the PMA  
17 review team, which was essential in completing the  
18 review of the PMA application.

19 [Slide]

20 Two PMA modules were submitted. The first  
21 module was for the model 7272 preclinical testing  
22 software validation and animal testing. The second  
23 module included the preclinical tests on the leads  
24 and the sterilization information. The test data  
25 presented in the modules demonstrated that the

1 system met the acceptance criteria and performed to  
2 specifications. Both modules were approved.

3 [Slide]

4 The InSync PMA application, which included  
5 pooled data from the MIRACLE trial, was filed on  
6 May 4, 2001. The data were found by FDA as not  
7 poolable with the MIRACLE study data. On November  
8 13, 2001 the PMA application was amended with the  
9 current data set.

10 [Slide]

11 The InSync ICD model 7272 system consists  
12 of the InSync model 7272 pulse generator which has  
13 a five-port header, RV sensing and accommodates  
14 independent RV/LV leads. The system includes the  
15 Attain model 4189 LV lead, which is a 4F unipolar  
16 lead, smaller than the commercially available 2187  
17 and 2188 LV leads which were approved in the  
18 MIRACLE trial. The system also consists of the  
19 9969 software and other commercially available  
20 leads and accessories.

21 [Slide]

22 The preclinical testing consisting of  
23 component and subassembly qualification tests,  
24 design verification testing, device qualification  
25 testing and animal testing. In all cases the

1 results demonstrated that the components and  
2 finished device met the acceptance criteria and the  
3 device performed as intended.

4 [Slide]

5 A detailed software development plan was  
6 submitted, and hazard analysis and  
7 verification/validation tests were performed. The  
8 results reported that the system met the acceptance  
9 criteria and performed to specifications.

10 [Slide]

11 Preclinical tests were also done with the  
12 Attain model 4189 LV lead. The test consisted of  
13 environmental, mechanical, electrical,  
14 biocompatibility and sterilization qualification  
15 tests. Also, in these cases the results  
16 demonstrated performance to specifications.

17 [Slide]

18 The clinical data will now be presented by  
19 Dr. Helen Barold, followed by the questions for the  
20 panel.

21 **Clinical Data Statistical Summary**

22 DR. BAROLD: Good morning. I am Helen  
23 Barold.

24 [Slide]

25 This presentation will be the clinical and

1 statistical summary for the Medtronic InSync ICD.  
2 It was put together by myself and Dr. Gerry Gray  
3 who is our biostatistician.

4 [Slide]

5 I would like to read to you the sponsor's  
6 indications for use for this device. The InSync  
7 ICD system is indicated for the reduction of the  
8 symptoms of moderate to severe, New York Heart  
9 Association Functional Class III or IV heart  
10 failure, in those patients who remain symptomatic  
11 despite stable, optimal medical therapy, as defined  
12 by the trial inclusion criteria, and have a left  
13 ventricular ejection fraction less than or equal to  
14 35 percent and a QRS duration greater than or equal  
15 to 130 ms.

16 The ICD is intended to provide ventricular  
17 antitachycardia pacing and ventricular  
18 defibrillation for automated treatment of life-  
19 threatening ventricular arrhythmias.

20 [Slide]

21 It is important to keep in mind that the  
22 primary function of this device is that of an ICD.  
23 It is indicated for those patients who need an ICD,  
24 and it will be necessary to distinguish between the  
25 biventricular pacing features and the ICD features,

1 and to ensure that the biventricular pacing does  
2 not in any way interfere with the primary function  
3 of the ICD or the ability to adequately program the  
4 ICD functions.

5 [Slide]

6 Here is the InSync ICD study design that  
7 has already been gone over by the sponsor, but I  
8 would just like to review it quickly. There was a  
9 baseline evaluation done, and that consisted of  
10 baseline New York Heart Association testing,  
11 quality of life and a six-minute hall walk, as well  
12 as echo indices and neurohormones. The patient was  
13 then implanted and, as the sponsor has stated,  
14 after the implantation the patient then underwent  
15 the cardiopulmonary testing. At that point, the  
16 patients were then randomized to either the  
17 biventricular pacing on or biventricular pacing off  
18 for a period of six months. Then, at the end of  
19 six months it was up to the physician's discretion  
20 as to whether or not to turn the patients on. Just  
21 to remind you, at all times the ICD was on in all  
22 patients.

23 [Slide]

24 Again, the sponsor has already presented  
25 this information. It just goes over the timing of

1 the testing, and just to point out that the  
2 cardiopulmonary testing was done after implantation  
3 but prior to randomization.

4 [Slide]

5 This was a somewhat double-blinded study  
6 in that the EP physicians were unblinded to the  
7 randomization, for obvious reasons--they needed to  
8 test the device. The congestive heart failure  
9 physicians and staff, who were responsible for  
10 collecting the endpoints, were blinded to the  
11 randomization, and the patients were also blinded.

12 [Slide]

13 There were three co-primary effectiveness  
14 endpoints in the study, the New York Heart  
15 Association classification, quality of life scores  
16 as measured by the Minnesota Living with Heart  
17 Failure questionnaire and the six-minute hall walk  
18 distance. The statistical analysis performed was  
19 the Hochberg adjustment for multiplicity, and that  
20 works at all three endpoints. If they met all  
21 three endpoints they needed to have a p value of  
22 less than 0.05. Any two endpoints could have p  
23 values of less than 0.024; or any one p value, if  
24 they met one endpoint, would have a p value of less  
25 than 0.0165. This gives an experiment-wise error

1 rate of a p value less than 0.05.

2 [Slide]

3 The primary safety objectives, the sponsor  
4 has already gone over those, the InSync ICD  
5 generator complications at three months; the InSync  
6 system related complications at six months; and  
7 then the Attain model 4189 complications.

8 [Slide]

9 This is a listing of the secondary  
10 objectives. They include mortality, congestive  
11 composite response, the healthcare utilization,  
12 which is another name for hospitalization,  
13 cardiopulmonary testing, echo indices, plasma  
14 neurohormones, adverse events, lead performance,  
15 VT/VF episodes and defibrillation criteria.

16 [Slide]

17 I am not going to go through these  
18 completely, but just to point out that in the  
19 inclusion criteria these patients were indicated  
20 for an ICD. Patients were allowed to be enrolled  
21 if they had Class II, III or IV heart failure but  
22 today we will only be presenting the Class IIIs and  
23 IVs because that is what the device is to be  
24 indicated for.

25 [Slide]

1           The exclusion criteria are listed here.  
2 Just to point out that patients could not have an  
3 indication for standard cardiac pacing.

4           [Slide]

5           This is a tree of the patient  
6 accountability. There was a total of 659 patients  
7 that were enrolled in the study. Out of those  
8 patients, 554 were actually randomization. There  
9 were 282 patients in the control group and 272  
10 patients in the treatment group. But, remember,  
11 Class IIs, IIIs and IVs could be enrolled and we  
12 will only be looking at IIIs and IVs. So, of  
13 those, there were 176 patients in the control group  
14 that were IIIs and IVs and 186 in the treatment  
15 group.

16           Today we will be presenting data on 124  
17 patients in the control group. There was  
18 approximately 30 percent of patients who had not  
19 reached the six-month follow-up, and approximately  
20 the same numbers in the treatment group.

21           [Slide]

22           This is just another listing of patient  
23 accountability. There was approximately 20 percent  
24 of patients who were administratively censored.

25           [Slide]

1 I would like to talk a little bit about  
2 the blinding issues and crossovers that occurred  
3 during this study. The sponsors are required to  
4 give us a listing of all the protocol deviations  
5 that occur in a study, and they are done by a line  
6 listing. If you went through the line listings,  
7 there were approximately 69 protocol deviations  
8 that were attributed specifically by the sponsor to  
9 the blinding issues. Of those protocol deviations  
10 specifically for blinding, there 49 that were  
11 related to the collection of a primary endpoint.  
12 These protocol deviations include the Class IIs,  
13 IIIs and IVs because they were not broken down for  
14 the agency into IIIs and IVs.

15 During the study there were 25 patients in  
16 Class III and IV that crossed over to the other  
17 treatment category. There were ten patients that  
18 had pacing off that crossed over to pacing on  
19 because of worsening heart failure. The majority  
20 of those happened within the first month. There  
21 were no patients in the pacing on group who had  
22 worsening heart failure that had their device  
23 turned off. The patients who had their device on  
24 that were then turned off, the majority of those  
25 reasons were for some lead issues, lead

1 dislodgement or lead performance issues. Again,  
2 there were no patients that had the device turned  
3 on that then were turned off because of worsening  
4 heart failure.

5 [Slide]

6 The sponsor has gone over the baseline  
7 characteristics. I have listed some of the more  
8 important clinical characteristics on this slide.  
9 I would just like to point out some of the  
10 characteristics here for you. The average age is  
11 typical of an ICD patient, approximately 68 years  
12 old. The overwhelming majority of them are male.  
13 You can see that most of the patients here were in  
14 Class III. There was a limited number of patients  
15 in Class IV.

16 I would also like to point out the  
17 ischemic etiology of the patients. This was the  
18 one baseline characteristic that was statistical  
19 significantly different between the two groups.  
20 Obviously, they look at a wide variety of variables  
21 and you are bound to have something, but this one  
22 is potentially important. You can see in the  
23 control group that 74 percent of patients had an  
24 ischemic etiology for their cardiomyopathy. In the  
25 treatment group there was a statistically

1 significantly lower percentage of patients that had  
2 an ischemic etiology for their heart failure.

3 I would also like to point out that in  
4 this study they were allowed to take patients that  
5 currently had an ICD and then upgrade them to a  
6 biventricular ICD, and there was approximately 30  
7 percent in each group that had an actual upgrade.

8 Lastly, I would like to point out that  
9 approximately 13 percent of patients in each group  
10 had right bundle branch block.

11 [Slide]

12 These are the primary safety objectives  
13 and results. You can see the ICD generator  
14 complications at three months. There was only one  
15 case of electrical rest. The Attain model 4189  
16 complications, there were 31 lead dislodgements  
17 with this lead. The lower 95 percent confidence  
18 interval for complications was 81.7 percent. The  
19 ICD system complications at six months, those  
20 numbers were basically driven by the Attain model  
21 4189 complications, and you can see that the 95  
22 percent lower confidence interval was 77.6 percent.

23 [Slide]

24 I am going to be presenting the results on  
25 an intention-to-treat analysis, and that will be

1 the only analysis that we will be presenting from  
2 the FDA. So, I am going to start now with the  
3 primary effectiveness results.

4 Here are the results for the quality of  
5 life. You can see here that patients in both  
6 groups did have an improvement in their quality of  
7 life. As the score goes down, it improves. There  
8 is a significant difference between the two groups  
9 for quality of life.

10 [Slide]

11 This is a slide that shows all of the  
12 individual values for patients and their quality of  
13 life at baseline, three months and six months for  
14 both the control and treatment groups. The colored  
15 lines are the averages, which was presented on the  
16 previous slide, but you can see the wide variation  
17 in the numbers in both groups.

18 [Slide]

19 This is an overall assessment of the  
20 quality of life. You can see that in both groups  
21 there is a large percentage of patients who do  
22 improve in their quality of life, with the pacing  
23 group on having more improvement.

24 [Slide]

25 These are the New York Heart Association

1 class results. These are median results. The  
2 median baseline values, obviously, are going to be  
3 three as that was really the enrollment for this,  
4 and there was a difference between the two groups  
5 and then at six months the median for the off group  
6 stayed at three and for the on group it decreased  
7 to two.

8 [Slide]

9 This slide, which is in the FDA memo, just  
10 shows a breakdown of where the patients moved in  
11 their New York Heart Association classification.  
12 It just points out again that patients did improve  
13 in the pacing on, 62 percent of the patients did  
14 improve. It also just shows the number of  
15 worsenings, approximately three to five percent of  
16 patients had a worsening of their heart failure  
17 classification.

18 [Slide]

19 These are the six-minute hall walk  
20 results. You can see that there is really no  
21 difference between the two groups as far as the  
22 six-minute hall walk.

23 [Slide]

24 Here is another slide, similar to the  
25 quality of life slide, where it shows individual

1 results, with the colored lines representing the  
2 medians. You can see that there is no difference  
3 between the hall walk distance.

4 [Slide]

5 This is, again, just a summary of those  
6 patients that had total improvement in the amount  
7 of distance that they walked versus worsening or no  
8 change. There is little difference between the two  
9 groups.

10 [Slide]

11 Again, just to tell you that the three  
12 primary endpoints, and you have heard this several  
13 times, are the New York Heart Association class,  
14 quality of life and six-minute hall walk. The  
15 device meets the third criteria, meaning that their  
16 p value was less than 0.0165 for one of their  
17 endpoints, the quality of life. You can see the  
18 three p values and this, again, is the intention-  
19 to-treat analysis. The question is how do we  
20 interpret this significant result?

21 [Slide]

22 I would like to move on to the LV lead  
23 effectiveness. There were 636 attempts and 69  
24 failures to implant the LV lead, approximately 10  
25 percent. The electrical performance was fine. The

1 thresholds were stable; the sensing was stable; and  
2 we don't have information on the impedance. I  
3 would like to point out that FDA did request that  
4 we receive information from the Class IIIs and IVs  
5 as those are the patients that are indicated for  
6 the device, and we have not reviewed that data yet.

7 [Slide]

8 Now I am going to move on to some of the  
9 secondary objectives and we will start with the  
10 peak VO<sub>2</sub>. This slide shows the number of patients  
11 that underwent the peak VO<sub>2</sub> testing at both  
12 baseline and six months. You can see here the  
13 differences between the pacing off group and the  
14 pacing on group, with a p value of 0.05.

15 Remember, when you do peak VO<sub>2</sub> testing, it  
16 is cardiopulmonary testing so there is a variety of  
17 variables that are collected along with this and I  
18 just want to bring up some of the other pieces of  
19 information associated with that testing. The RER,  
20 or the respiratory exchange ratio, shows that there  
21 was a significant difference between the groups at six  
22 months. The RER was higher for the pacing on group  
23 versus the pacing off group. The VE/VCO<sub>2</sub> slope  
24 showed no difference between the two groups. The  
25 anaerobic threshold, a very small number of

1 patients had this done but there was no difference  
2 between the two groups. The rest of the data is in  
3 your panel pack.

4 [Slide]

5 The CHF composite--the sponsor has already  
6 gone over what that entails. There was an  
7 improvement in the treatment group over the control  
8 group. Then, if you break down part of the CHF  
9 composite, there is something called the patient  
10 global assessment score and that is basically if  
11 the patients feel better, and there was no  
12 difference between the two groups in the patient  
13 global assessment score. In hospitalizations,  
14 there was no difference between the two groups as  
15 far as hospitalizations and even for  
16 hospitalizations for congestive heart failure.

17 [Slide]

18 The echocardiographic results have also  
19 been presented. There was no improvement in the  
20 ejection fraction, cardiac index or the E/A ratio.  
21 There were decreases seen in the LVED and the LVES.  
22 For the plasma neurohormones the data set is  
23 incomplete. We don't have data on all the  
24 patients. We only have a small percentage, and  
25 there was no difference between the groups.

1 However, as the sponsor did bring up, we did notice  
2 that the norepinephrine level seemed to be very  
3 discordant with the rest of them, and was elevated  
4 in the pacing on group. Again, we don't have the  
5 complete data set for those patients.

6 [Slide]

7 Sensing of the LV lead was fine. There  
8 was a shortening of the QRS with biventricular  
9 pacing, which is expected. There was no difference  
10 in the incidence of VT or VF between the pacing on  
11 and the pacing off groups.

12 [Slide]

13 Here is a tree of the mortality. Again,  
14 it just says there were 659 patients that were  
15 enrolled. There were three deaths that occurred  
16 prior to implantation. There were 13 deaths that  
17 occurred between the time the patients had the  
18 implant attempted, the successful implants. There  
19 were 8 deaths that occurred prior to the actual  
20 randomization time. Then, if you look down below,  
21 here, there is no difference in the number of  
22 deaths between both groups.

23 [Slide]

24 Here are just the Kaplan-Meier curves with  
25 the 95 percent confidence intervals, just to show

1 that there is no difference between the two groups  
2 as far as mortality is concerned.

3 [Slide]

4 One of the issues that has been brought up  
5 with this technology is that you have a new lead  
6 location, which is a little different for us so we  
7 would like to talk about what the potential adverse  
8 events are that are associated with the new lead.  
9 That lead is placed in the coronary sinus. Here is  
10 a slide that just shows the number of adverse  
11 events that happened as a result of placing a lead  
12 in the coronary sinus.

13 [Slide]

14 Again, when a sponsor gives us an  
15 application for a device, they give us all the  
16 adverse events. So, we get an alphabetical listing  
17 of all of the adverse events that happen. The  
18 sponsor has nicely gone through the difference  
19 between a complication and observation.

20 I just pulled out from that line listing  
21 some of the things that may be related to  
22 congestive heart failure and/or ICD therapy. You  
23 can see that there is no difference between the two  
24 groups. I pulled out things like heart failure  
25 decompensation and there is no difference between

1 the two groups. This "other" is something that we  
2 will be asking the sponsor about because there are  
3 quite a few "other" things going on that we are not  
4 quite sure of. But otherwise there is really no  
5 difference in the adverse effects in pacing on or  
6 off.

7 [Slide]

8 I would like to switch gears a little bit  
9 now and talk about some of the additional issues  
10 that are associated with the ICD function. In the  
11 beginning we mentioned that we have to ensure that  
12 biventricular pacing does not in any way interfere  
13 with the primary function of the ICD. So, what are  
14 some variables that we look at to make sure that  
15 that does not happen?

16 One of them is the VF detection time. We  
17 do that to ensure that the addition of  
18 biventricular pacing does not interfere in any way  
19 with the ability to sense ventricular fibrillation.  
20 This information has been requested by the FDA.  
21 Before the meeting the sponsor did show me that  
22 they did present some of this information but it is  
23 only on a few patients, and the FDA has requested  
24 that we get this information on a larger cohort of  
25 patients.

1           Another thing to look at is the number of  
2 inappropriate shocks because we want to make sure  
3 that it is not because of the addition of the  
4 biventricular lead. There are always going to be  
5 inappropriate shocks with ICDs but you want to look  
6 at what those causes are, and are they associated  
7 in any way with having an additional lead there  
8 and/or having continuous pacing on. They did give  
9 us some information but it doesn't answer that  
10 question.

11                       [Slide]

12           Another important variable to look at is  
13 the percentage of time that the patients are being  
14 biventricular paced. The goal of cardiac  
15 resynchronization therapy is to deliver continuous  
16 biventricular pacing. So, we need to ensure,  
17 number one, that they are delivering continuous  
18 biventricular pacing and also to ensure that there  
19 is continuous biventricular capture because, again,  
20 we have an additional lead there and we need to  
21 make sure that that lead is functioning concordant  
22 with the RV lead.

23           We also need to make sure that the ICD  
24 programming does not interfere in any way with the  
25 ability to deliver continuous biventricular pacing.

1 Again, the FDA has requested this information from  
2 the sponsor.

3 [Slide]

4 As the sponsor has pointed out, this is  
5 really a combination of two devices. It is a  
6 biventricular pacer and an ICD. So, an  
7 electrophysiologist, we talk about things like  
8 device-device interaction and what the potential  
9 limitations are if you have two devices that are  
10 combined into one. Remember, the goal is to have  
11 continuous biventricular pacing.

12 If you look at how the patients were  
13 programmed during this study, the VT zone  
14 programming, and ICDs are programmed under  
15 different zones; you can have VF only zone and you  
16 can have the addition of a VT zone, 44 percent of  
17 the patients in the study had the VT detection  
18 turned off so those patients were a VF only zone,  
19 ventricular fibrillation only; 81 percent of the  
20 patients were programmed to have a VT zone of 140  
21 ms. or faster. So, the question is what do you do  
22 with the patient that has a slow ventricular  
23 tachycardia, and does having a slow ventricular  
24 tachycardia in some way limit the flexibility of  
25 your ability to program the biventricular pacing

1 on? You have to remember that with this device you  
2 cannot have biventricular pacing at a rate that is  
3 higher than the VT detection rate.

4 [Slide]

5 Some of those issues relate to the upper  
6 tracking rate for a biventricular pacer. Forty-  
7 eight percent of the patients in this study were  
8 programmed to have an upper tracking rate of 120  
9 beats per minute. The question is how can should  
10 this upper tracking rate be programmed to optimize  
11 the amount of biventricular pacing and to limit  
12 something called the upper rate phenomenon, which  
13 has the potential to cause detrimental  
14 hemodynamics?

15 In this study it was recommended that mode  
16 switching was turned off. Eighty-six percent of  
17 the patients did have this feature turned off. The  
18 question then becomes how do we take care of some  
19 patients who may need to have the feature turned  
20 on?

21 At this point, I am going to turn it back  
22 to Doris Terry to go over questions for the panel.

23 **Questions for the Panel**

24 [Slide]

25 MS. TERRY: These are the panel questions

1 that we would like the panel to consider.

2 [Slide]

3 Number one, please comment on the  
4 sponsor's study design. Specifically, please  
5 address the following issues in your discussion:

6 Part a), please comment on the adequacy of  
7 the sample size that contributed data in support of  
8 the primary endpoints. In particular, are there  
9 any concerns related to the administrative  
10 censoring of 20 percent of the enrolled patients  
11 who had not passed the six-month point at the time  
12 of the submission?

13 [Slide]

14 Part b), please discuss the benefits and  
15 limitations associated with the six-month follow-up  
16 duration for the primary endpoints.

17 Part c), please discuss any concerns about  
18 the propensity for crossovers and any additional  
19 issues related to blinding.

20 [Slide]

21 Part d), the intent-to-treat analysis on  
22 NYHA class, quality of life and six-minute hall  
23 walk produced nominal p values of 0.027, 0.009 and  
24 0.407 respectively. Thus, the study results meet  
25 the prespecified Hochberg criteria for statistical

1 significance in that one of the endpoints, quality  
2 of life, produced a p value less than 0.0167. In  
3 light of this, please comment on the possible  
4 interpretation of the results for each of the co-  
5 primary endpoints individually.

6 [Slide]

7 Number two, the primary endpoints of the  
8 study were improvement in NYHA class, quality of  
9 life and six-minute hall walk. Please discuss the  
10 clinical relevance of these endpoints for  
11 evaluating a therapy for congestive heart failure.

12 Number three, please discuss the clinical  
13 relevance of the sponsor's choice of secondary  
14 endpoints for evaluating a therapy for CHF. Are  
15 there specific secondary endpoints, such as peak  
16 VO<sub>2</sub>, that should be more heavily weighted in the  
17 assessment of the device?

18 [Slide]

19 Number four, please comment on whether the  
20 results of the clinical study support the  
21 effectiveness of the device for the treatment of  
22 patients with medically stable Class II/IV CHF.

23 [Slide]

24 Number five, when evaluating the safety of  
25 the device, one concern is whether the treatment

1 contributes to the worsening of CHF. The sponsor  
2 has identified several measures designed to capture  
3 this, including the CHF composite response,  
4 hospitalizations, medication changes and mortality.  
5 Please comment on whether the results support the  
6 safety of the system for treating CHF in the  
7 population studied.

8 [Slide]

9 Number six, please comment on whether the  
10 sponsor has provided adequate information to assure  
11 that there is no interference of proper ICD  
12 functionality with the addition of biventricular  
13 pacing and that both biventricular pacing and ICD  
14 therapy can be delivered simultaneously.

15 Number seven, please discuss whether you  
16 have any comments or recommendations regarding  
17 programming considerations for the device.

18 [Slide]

19 Number eight, for the model 6262 ICD pulse  
20 generator, the sponsor has provided analyses of the  
21 ICD system-related complications at three months.  
22 Please comment on whether the results provide a  
23 reasonable assurance of the safety of the model  
24 7272 ICD pulse generator.

25 Number nine, for the model 4189 lead, the

1 sponsor has provided analyses of lead-related  
2 complications at six months. Please comment on  
3 whether the results provide a reasonable assurance  
4 of the safety of the model 4189 lead.

5 [Slide]

6 Number ten, the sponsor has provided  
7 analyses of the system-related complications at six  
8 months and the adverse effects, complications and  
9 observations, reported in the clinical study.  
10 Please comment on whether the results provide a  
11 reasonable assurance of the safety of the InSync  
12 ICD system.

13 [Slide]

14 Number 11, FDA defines safety as  
15 reasonable assurance that the probable benefits to  
16 health outweigh any probable risks. Effectiveness  
17 is defined as reasonable assurance that in a  
18 significant portion of the population the use of  
19 the device for its intended uses will provide  
20 clinically significant results. Please discuss the  
21 overall risk-benefit of the system.

22 [Slide]

23 Number 12, one aspect of the premarket  
24 evaluation of a new product is the review of its  
25 labeling. The labeling must indicate which

1 patients are appropriate for treatment, identify  
2 potential adverse effects with the use of the  
3 device, and explain how the product should be used  
4 to maximize benefits and minimize adverse effects.  
5 If you recommend approval of the device, please  
6 address the following questions regarding product  
7 labeling:

8 Part a), do the indications for use  
9 adequately define the patient population studied?

10 [Slide]

11 Part b), based on the clinical experience,  
12 should there be additional contraindications,  
13 warnings and precautions for the use of the in  
14 model 7272 ICD system? Do the indications for use  
15 adequately define the patient population studied?

16 Part c), please comment on the operator  
17 instructions as to whether they adequately describe  
18 how the device should be used to maximize the  
19 benefits and minimize the adverse events.

20 [Slide]

21 Part d), please provide any other  
22 recommendations or comments regarding the labeling  
23 of this device.

24 [Slide]

25 Number 13, with approval of the Medtronic

1 InSync biventricular pacing system, FDA and the  
2 sponsor agreed on the following post-approval  
3 conditions: a), obtaining 12-month mortality data  
4 on the IDE cohort and, b), performing a three-year  
5 evaluation or mortality and chronic lead  
6 performance, including electrical performance and  
7 adverse events, on 1000 patients. If you recommend  
8 approval, please comment on whether additional  
9 clinical follow-up or post-market studies are  
10 necessary for this device.

11 This concludes our questions. Thank you.

12 DR. LASKEY: Thanks very much. At this  
13 point, I think we could all use a break. I would  
14 like to reconvene in exactly 15 minutes. I have  
15 9:40. Actually, let's reconvene at ten o'clock  
16 sharp. Thank you.

17 [Brief recess]

18 DR. LASKEY: Thank you very much for  
19 keeping ahead of schedule. That will pay off this  
20 afternoon. The next portion of this panel meeting  
21 will be the committee discussion, and we would like  
22 Dr. Pina to lead off as one of the co-lead  
23 reviewers. Ileana?

24 **Open Committee Discussion**

25 DR. PINA: Yes, thank you. I want to go

1 over the deaths that were listed at the beginning  
2 of our packet. I counted 12 sudden deaths. Of  
3 those 12 sudden deaths, there were seven who had  
4 the pacer turned on. Now, everybody had the AICD  
5 turned on. How many of those did the AICD, in  
6 fact, fire and was unable to change the arrhythmia,  
7 or do you have documentation that, in fact, the  
8 sudden death was a ventricular event?

9           Subsequent to that, of the 75 deaths that  
10 are listed there, ten of those are, in fact, in the  
11 patients who crossed over who were randomized to  
12 off but who, at the time of death, were in the on  
13 mode?

14           DR. WILKOFF: Let me be clear, you want to  
15 know how many times the defibrillator went off or  
16 didn't go off?

17           DR. PINA: Yes. In other words, there are  
18 12 deaths that are classified as sudden cardiac  
19 death, and then there is something about  
20 ventricular arrhythmias. Everybody had their AICD  
21 function on. Were those failures of the AICD to,  
22 in fact, convert? Do you have data on what the  
23 terminal event was? Were you able to interrogate  
24 the box?

25           DR. LASKEY: Excuse me, I am sorry to

1 interrupt but before you begin could you identify  
2 yourself?

3 DR. WILKOFF: Yes, I am Bruce Wilkoff,  
4 from the Cleveland Clinic Foundation,  
5 electrophysiologist, and I am a consultant and have  
6 done research funded by Medtronic.

7 We don't have information about all of the  
8 patients. For four of the patients we had no  
9 interrogation of the device so we don't know what  
10 happened at that time. There were no VT/VF  
11 episodes that were recorded on that day, or the  
12 VT/VF episodes that were recorded were terminated  
13 by the device but later on there was not something  
14 at that point in time.

15 I will have to count them up for you, but  
16 there were instances where there was a shock just  
17 prior to death. I don't know if there were any  
18 ineffective shocks. Let me see. There were no  
19 tachycardias that were treated with shocks that did  
20 not convert the patient out of the tachyrrhythmia,  
21 and there were no failures to detect the  
22 tachycardia but that is a difficult thing to say;  
23 if it didn't detect it, then the device would not  
24 have recorded it. But there is no evidence of it  
25 here.

1 DR. PINA: You may not have the data on  
2 some of these 12 patients if they died outside of  
3 hospital.

4 DR. WILKOFF: Right. We have the device  
5 interrogations for all but four devices. For those  
6 four patients we don't have the interrogations so  
7 we don't have that information.

8 DR. PINA: I am kind of concerned about  
9 this dissociation. I want to go back to quality of  
10 life and hospitalizations. Yesterday we had a  
11 discussion about quality of life and  
12 hospitalization, and I went back to a recent  
13 clinical trial that has equated the improvement in  
14 quality of life, or the lack of worsening of  
15 quality of life with a decrease in  
16 hospitalizations. Why do you think there is a  
17 disparate finding here? Quality of life looks like  
18 it gets better; hospitalizations don't decrease.

19 DR. PACKER: Ileana, I don't think there  
20 is a disparity. Quality of life was improved in  
21 patients who were randomized to resynchronization  
22 compared to the control group. The hospitalization  
23 data are directionally concordant with that.  
24 Remember, the trial was powered for quality of life  
25 but not powered to detect a p less than 0.05 value

1 for hospitalizations. So, I think the data are  
2 internally consistent and concordant.

3 DR. LASKEY: In order that we conform to  
4 parliamentary procedure, even though everyone knows  
5 who you are, Milton, would you introduce yourself?

6 [Laughter]

7 DR. PACKER: I apologize. I am Milton  
8 Packer, from Columbia University. I am a heart  
9 failure cardiologist, and have received research  
10 grants and am a consultant to Medtronic.

11 DR. PINA: Let's go into the lead implant  
12 failure. I want to spend a little time on the  
13 cardiopulmonary testing but let me go into the lead  
14 implant failures. Is there a sense that the lead  
15 implant failure is more common in the sicker  
16 patients with the bigger LVEDDs? Do you know that?  
17 I mean, since the indication for CRT has III/IV who  
18 are well medicated, etc., etc.

19 DR. LEON: In general, the sense is that  
20 it is not. I am Angel Leon, from Emory University  
21 and I introduced myself and said my disclosures  
22 previously.

23 If we look at a comparison between the  
24 Class III and IV patients implant success rates in  
25 all the patients, we do not have all the EDD

1 information and cannot tell you, based upon LVEDD,  
2 if you define a sick heart by using that criterion,  
3 that having an increased diameter necessarily makes  
4 the lead implant less successful. But the answer  
5 to your question is we don't have any information  
6 that it is more difficult to implant the lead in  
7 the sicker patients beyond what I just told you.

8 DR. PINA: Do you have any data on who the  
9 patients are who would be likely to either get  
10 dislodged? I mean, as you are giving advice to a  
11 patient about the pacer you would like to be able  
12 to tell them what their chances are of becoming  
13 dislodged or of inability to implant and find a  
14 good placement for the coronary sinus lead.

15 DR. WILKOFF: I just want to address your  
16 question a little more directly. We have analysis  
17 of the operative times for the Class III and IV  
18 patients, then also looking at the patients that  
19 include functional Class II, and there was no  
20 difference in implant times for whether functional  
21 Class II were included in that or not. And, you  
22 would presume that the functional Class II patients  
23 may be a little bit less sick. We don't have  
24 diameter information but we do have, in terms of  
25 the functional status, that information.

1 DR. LEON: Going back to the second  
2 question with respect to being able to predict lead  
3 dislodgement, we have to remember that in this  
4 particular clinical evaluation we were required by  
5 the protocol, unless there was an obvious medical  
6 reason, to use a specific electrode first. That  
7 makes a proper answer to your question possibly--  
8 you know, we cannot give it to you because if one  
9 starts getting a hint that that lead may more  
10 likely dislodge we wouldn't know that because we  
11 were having to use that lead first. I don't know  
12 whether I answered your question in that manner.

13 DR. PINA: That addresses it. The VO2s  
14 that were done at the six-month time interval, what  
15 was the relationship between the quality of life  
16 assessment and the cardiopulmonary test? In other  
17 words, was the quality of life acquired or the six-  
18 minute walk acquired after the VO2 or before the  
19 VO2?

20 DR. YOUNG: It could have varied. There  
21 would have been a window when the VO2 was done and  
22 the QOL measurement was done. It could have been  
23 done in the same setting.

24 DR. PINA: It could have been done on the  
25 same day, in other words?

1 DR. YOUNG: Correct.

2 DR. PINA: So, the QOL could, in fact,  
3 have followed the cardiopulmonary test?

4 DR. YOUNG: Yes.

5 DR. PINA: The reason I am asking is  
6 because I am concerned about the blinding issue  
7 with the cardiopulmonary test, and I would imagine  
8 that it wasn't administered by the  
9 electrophysiologist; I would imagine it was  
10 administered by the heart failure physician who was  
11 blinded.

12 DR. YOUNG: The quality of life or--?

13 DR. PINA: No, no, the cardiopulmonary  
14 test.

15 DR. YOUNG: No, in actuality the vast  
16 majority of the cardiopulmonary tests were done in  
17 an exercise laboratory, a physiology laboratory,  
18 and some even in laboratories where the pulmonary  
19 people were running the cardiopulmonary exercise  
20 testing.

21 DR. PINA: So, the pulmonary people  
22 applied the test?

23 DR. YOUNG: Yes, and the test was also  
24 interpreted at an independent site. The data was  
25 reviewed at a core exercise testing laboratory,

1 Lynne Wagner at Cincinnati.

2 DR. PINA: One of the reasons I am  
3 questioning this is because, first of all, your  
4 baseline numbers are not bad at all for this age  
5 group. As a matter of fact, this is a little bit  
6 older age group than your InSync population. So,  
7 13.5 really represents 52, 54 percent of predicted  
8 which is not that bad for that age group.

9 DR. YOUNG: Well, that is still a  
10 functional aerobic impairment of about 50 percent.

11 DR. PINA: I understand, but the prognosis  
12 goes with percent prediction. Then, the control  
13 group has a lower RER at a follow-up visit with a  
14 similar VO2 which, in fact, tells me that those  
15 patients probably had a higher VO2; they just went  
16 pushed to that point, with a wide standard  
17 deviation.

18 DR. YOUNG: Ileana and I quibble about  
19 this sometimes.

20 DR. PINA: All the time!

21 DR. YOUNG: First of all, I think we both  
22 agree that MVO2s are doggone good measures of peak  
23 exercise capacity and perhaps one of the things  
24 that is least variable in clinical trials. So, to  
25 get there with an interpretable test, whether or

1 not the RER goes over 1.0 or 1.10 is a little bit  
2 arguable. We did require for the first test that  
3 they go over 1.0.

4           The way I look at the REF is they did  
5 achieve getting across the 1.0 mark on average, and  
6 if you look at the components of the exercise test,  
7 including time, the treatment did better and there  
8 is consistency there. So, RER is a little better,  
9 MVO2 significantly better, exercise time is better,  
10 and if you look at some of the other parameters  
11 associated with things, blood pressure was higher  
12 in the treatment group. So, my interpretation of  
13 the global exercise testing is that it was actually  
14 very positive in the group that had CRT on compared  
15 to those off.

16           DR. PINA: I don't necessarily agree since  
17 exercise time is a very poor surrogate for VO2 at  
18 that level, and the blood pressure would be higher  
19 because they did more and blood pressure is related  
20 to the work load. But the ventilatory threshold,  
21 even though it was measured in a smaller percentage  
22 of the patients, was identical.

23           DR. YOUNG: The anaerobic threshold?

24           DR. PINA: The anaerobic threshold, the  
25 ventilatory threshold does not, you know, push me

1 to think that there was actually a significant  
2 difference.

3           Let me go on with some of the medication  
4 therapy. The beta-blocker used was pretty good  
5 across both groups, but there was a stipulation in  
6 the protocol that no beta-blocker could be  
7 initiated in six months. Did that cause a problem  
8 with any of the investigators since we are all  
9 trying to kind of push the beta-blocker use in this  
10 population?

11           DR. YOUNG: Yes, I can talk to that issue  
12 because this was something that was discussed at  
13 the time of the protocol design. It was also  
14 something that, coming off InSync, was an issue.  
15 You have to remember that the time period of  
16 protocol design occurred before the presentation of  
17 an awful lot of beta-blocker data. I think at this  
18 table today we all recognize that beta-blockers are  
19 extraordinarily important. Some of us felt that  
20 way at the outset of this trial; others did not  
21 necessarily feel as compelled about the beta-  
22 blocker question. But we did push clinicians to  
23 have patients on beta-blockers as best as they  
24 could, and wanted them on a "therapeutic" dose, and  
25 we can argue about, you know, which dose might or

1 might not be therapeutic, for a stable period of  
2 time before going into the trial. There were many  
3 patients who were eligible for the study from every  
4 other aspect, except that they had just been  
5 started on a beta-blocker and so actually didn't  
6 get into the trial. So, I think the issue is a  
7 very important one and, at the end of the day,  
8 having 60 percent on beta blockers I think was  
9 pretty doggone good.

10 DR. PACKER: Ileana, maybe I can give you  
11 some more information about this. There was a  
12 strong guidance to the investigators in this trial  
13 to keep background therapy constant. As in all  
14 heart failure trials, that is generally followed  
15 but not invariably followed. So, in the course of  
16 this study there were some patients who were  
17 initiated on a beta-blocker during the course of  
18 the trial. The numbers are actually strikingly  
19 small. I am just trying to read this; I am trying  
20 to see if I got this right.

21 DR. PINA: Is that in our packet, Milton?

22 DR. PACKER: I believe it is on page 157  
23 in the packet. The number of patients who were not  
24 on a beta-blocker initially, who were initiated on  
25 a beta-blocker were 15, 10 in the control group and

1 five in the treatment group. There were 10  
2 patients who were on a beta-blocker at baseline who  
3 came off a beta-blocker during the course of the  
4 randomized study period, and that is five in each  
5 group. So, there was, in fact, very good stability  
6 of background medication and, if anything, beta-  
7 blocker therapy was initiated a little bit more  
8 frequently in the control arm than the treatment  
9 arm.

10 DR. PINA: I have no other questions at  
11 this time.

12 DR. LASKEY: Thank you. Dr. Haigney?

13 DR. ZUCKERMAN: Dr. Laskey, if I could  
14 make a point before Dr. Haigney starts? As with  
15 the last set of questions, there may be some  
16 questions from our electrophysiologist, Dr.  
17 Haigney, where data is not contained in the panel  
18 pack but the sponsor is using these data to respond  
19 to questions from the panel. If the sponsor's  
20 representatives can, one, be more exacting in  
21 indicating if the data are actually contained in  
22 the panel pack and, therefore, have been subject to  
23 prior FDA review, two, the panel needs to take into  
24 account the question of these new analyses versus  
25 data that has been previously reviewed in detail by

1 the FDA. Thank you.

2 DR. HAIGNEY: Thanks, Dr. Laskey. I want  
3 to congratulate you all on a positive study. You  
4 reached your primary prespecified endpoints and  
5 criteria for statistical effectiveness, and I think  
6 provided good prima facia evidence that  
7 biventricular pacing can be combined with an ICD.

8 I have some concerns though about the  
9 data. I think the magnitude of the effects that we  
10 are seeing is small when you compare the change in  
11 quality of life, for instance, to the standard  
12 deviation at baseline. There are a number of  
13 issues that Dr. Pina has brought up, and I am sure  
14 some of the other clinical trialists are going to  
15 have about the blinding of the data and the  
16 possible placebo effect on quality of life.

17 But I am going to set that aside. I am  
18 primarily interested in whether you all can help me  
19 identify which of the patients benefited from this  
20 study and whether we could have identified them  
21 before implanting the device. We know some things  
22 about biventricular pacing, or I think that we  
23 think we know some things about biventricular  
24 pacing and we have some ideas about who is going to  
25 benefit and who isn't.

1           Let me just give you a couple of the  
2 issues that I am interested in. Your QRS duration  
3 for your inclusion criteria was 130 ms. There is  
4 some evidence, Dave Cass' work and others', that  
5 the wider the QRS, the greater the degree of  
6 dysynchrony, the greater benefit to left  
7 ventricular pacing. Can you tell us--and I think  
8 this is not in the packet--whether the pre-pacing  
9 QRS correlated with a greater effect in terms of  
10 quality of life or any of the other things that you  
11 want to look at?

12           DR. ABRAHAM: This is Bill Abraham, and I  
13 would like to start off first by responding to the  
14 quality of life question and then Dr. Packer will  
15 talk about some of the analyses for predictors of  
16 responsiveness.

17           In regard to quality of life, I think,  
18 first of all, it might be perceived in the context  
19 of this study to be one of the more valid endpoints  
20 in terms of the blinding issue because this was  
21 assessed completely by the patient. While one  
22 might be concerned about unblinding of the  
23 practitioner, you know, every attempt was made to  
24 blind both the practitioner as well as the patient,  
25 and certainly the risk of patient unblinding was

1 probably lower among the two.

2           Secondly, I think the magnitude of effect  
3 demonstrated in this trial is really quite  
4 substantial, particularly when viewed in the  
5 context of other heart failure clinical trials that  
6 have evaluated this same endpoint. An in between  
7 group difference of 9.5 points, in fact, is every  
8 bit as good or better than the improvements in  
9 quality of life seen with virtually all other forms  
10 of heart failure therapy that are available.

11           DR. PACKER: This is Milton Packer. I  
12 just want to underscore what Bill has said. This  
13 is the magnitude of effect we see in heart failure  
14 trials, both in terms of quality of life and New  
15 York Heart Association class. This is what we see;  
16 this is what we get from drugs that we consider to  
17 be effective agents for the reduction of symptoms  
18 of patients with heart failure.

19           It is so funny, I had anticipated that  
20 there might be a question on subgroup analyses and  
21 ran a whole bunch of subgroup analyses prior to  
22 this meeting, but I didn't run the one that you  
23 just asked for. But we are capable of running it  
24 as we speak.

25                           [Laughter]

1           Let's see what I can do here. This is for  
2 quality of life and New York Heart Association  
3 class. Forgive me, I am reading this off a  
4 computer screen and have not seen this before. Let  
5 me just emphasize the size of the subgroups because  
6 that is relevant. I cut this off at 140. Is that  
7 okay?

8           DR. HAIGNEY: So, that is your lower  
9 limit?

10          DR. PACKER: No, no, no. I have two  
11 subgroups here, one from 130-140 and one from  
12 greater than 140. Is that okay?

13          DR. HAIGNEY: I guess I would take 150.

14          DR. PACKER: Hold on, we will come back  
15 with 150 in a few minutes. You can pick anything  
16 you want. The way to do this is to actually do  
17 this as a continuous variable and we can't do that  
18 right this minute but we can do any kind of cuts  
19 that you would like of the data. The problem is  
20 that the lower the cut, the smaller the subgroup  
21 will be and we get into all sorts of difficulties  
22 with trying to interpret treatment effects in very  
23 small subgroups. The right way to do this, and we  
24 will be happy to do this and present this to the  
25 FDA, is to look at it as a continuous function and

1 not as a dichotomous analysis.

2 DR. HAIGNEY: Yes, I appreciate that and I  
3 would like to see that analysis because I think  
4 that as an implanting physician or someone who is  
5 going to refer people for this procedure, I would  
6 like to be able to identify those people who are  
7 going to get the biggest benefit. My inclination  
8 is to think that the wider the QRS, the greater the  
9 benefit and that 130 ms. may be too narrow.

10 DR. PACKER: I would like to reassure you  
11 that we did do other subgroup analyses based on the  
12 baseline New York Heart Association, whether the  
13 patients were III or IV, whether the patients had  
14 ischemic or non-ischemic disease, whether they were  
15 on beta-blockers at baseline. Those were easy  
16 because they are dichotomous variables and the  
17 categories are easy to analyze.

18 DR. EWING: I am going to interrupt you  
19 for just a second and see if Dr. Zuckerman wants to  
20 say once again about presenting data that has not  
21 been evaluated by the FDA.

22 DR. ZUCKERMAN: Yes, again the same  
23 comments apply here, and probably will throughout  
24 this discussion. It is not that the sponsor can't  
25 mention these things but the panel will need to

1 recognize that when these analyses have not been  
2 seen and verified by FDA, they need to be taken in  
3 a different light.

4 DR. PACKER: All of these analyses will be  
5 submitted and subject to verification. We also did  
6 an age cut-off greater or less than 65. One could  
7 use a variety of ages, and men and women. I would  
8 be happy to share this with you and pass this  
9 around but, of course, it needs to be submitted,  
10 verified, etc. But there are no differences in  
11 the magnitude of the treatment effect based on the  
12 baseline variables that I just mentioned.

13 I just got 150 and, if I could, I would  
14 just like to look at this for a minute because I  
15 want to see what it says.

16 DR. LASKEY: Just from the standpoint of  
17 process up here, Dr. Zuckerman, if members of the  
18 panel want additional data that is not in our panel  
19 pack and we ask that of the sponsor, I think we  
20 recognize the fact that it has not been critically  
21 reviewed in-house, and so forth, but either we are  
22 allowed to ask for additional data or not. We need  
23 to decide on the level of acceptability of the  
24 answer.

25 DR. ZUCKERMAN: Again, there is the

1 opportunity here to ask additional questions and  
2 look for additional analyses, it is just that when  
3 it is done on the spot, as has been done this  
4 morning, one needs to, one, recognize that it is  
5 done on the spot and errors can be made as opposed  
6 to, you know, what is in the panel pack which has a  
7 different level of review and verifiability by both  
8 the sponsor and FDA. So, you should put these  
9 analyses in the proper context. That is the point  
10 that the agency is trying to make.

11 DR. PACKER: Does that mean you do or do  
12 not want to hear this?

13 [Laughter]

14 DR. LASKEY: We do, but I think you heard  
15 how we will interpret it.

16 DR. ZUCKERMAN: That is exactly the point.

17 DR. HAIGNEY: I certainly want to hear it.

18 DR. PACKER: With the caveats that have  
19 just been mentioned, and recognizing that this  
20 analysis has just been carried out and that my own  
21 feeling is that the appropriate analysis is to look  
22 at this as a continuous function, but addressing  
23 your request for a cut-off at 150, there are 56  
24 patients with a QRS duration equal to or less than  
25 150. Hold on a second. I just want to check the

1 Ns here because I think these are the Ns for the  
2 treatment. This is the kind of problem we get with  
3 doing it on the fly.

4 DR. HAIGNEY: It is very impressive that  
5 you can do it on the fly. I wasn't expecting that.  
6 I thought perhaps you had done this analysis or it  
7 could be done.

8 DR. PACKER: It can be done. It needs to  
9 be subject to verification--

10 DR. HAIGNEY: Right.

11 DR. PACKER: --both on the basis of the  
12 sponsor as well as the agency. I just noticed that  
13 some of these numbers don't make sense, and that is  
14 not surprising given the fact--I have to double  
15 them? Okay, fine. Can I try it again?

16 DR. LASKEY: Yes.

17 DR. PACKER: Good. There are a number of  
18 patients with a QRS less than or equal to 150.  
19 There are approximately 112. The number of  
20 patients with a QRS greater than 150 is  
21 approximately 250. I say approximately because  
22 right now I only have the numbers for the treatment  
23 groups but there was a 1:1 randomization so I am  
24 doubling them. The magnitude of the quality of  
25 life effects in the group less than or equal to 150

1 is minus 12 and minus 15 in the control and  
2 treatment; minus 9 and minus 20 in the group  
3 greater than 150. So, a delta of 3 in the group  
4 less than or equal to 150; a delta of 11 in the  
5 group greater than 150.

6 For New York Heart Association class,  
7 which is the other co-primary variable that  
8 achieved statistical significance in some analyses,  
9 the difference between control and treatment, the  
10 median change was 0 and minus 1 in the control and  
11 treatment for both the group less than 150 and the  
12 group greater than 150.

13 Let me emphasize that for New York Heart  
14 Association class there is no apparent difference  
15 in the efficacy of resynchronization therapy on New  
16 York Heart Association class whether patients had a  
17 QRS less than 150 or greater than 150. One has to  
18 explore further whether there is a difference based  
19 on quality of life. Again, ideally this needs to  
20 be done as a continuous variable.

21 DR. HAIGNEY: I would be very interested  
22 in seeing that data. I think that there are some  
23 other issues that might be helpful in deciding both  
24 for the labeling of the device and for patient  
25 selection. Please don't run these analyses now if

1 you haven't done them, but I wonder about the  
2 diluting effect of having right bundle branch block  
3 patients.

4 DR. PACKER: We did that analysis. Let me  
5 just say before even sharing this with you that the  
6 results are fairly parallel to what I just said.  
7 It has to be taken with a big grain of salt here.  
8 There are only 46 patients with right bundle branch  
9 block pattern in this study so we are getting to  
10 even bigger problems in terms of smaller subgroups.  
11 But for New York Heart Association class the effect  
12 is a minus 1 change in improvement in both  
13 subgroups. The treatment effect in quality of life  
14 is a little smaller than in the group without right  
15 bundle branch block but, again, the right bundle  
16 branch block subgroup is very, very, very small.

17 DR. LEON: If I can interject a comment  
18 regarding what is called the right bundle branch  
19 block in the resynchronization trials, pure right  
20 bundle branch block usually does not have a QRS  
21 duration that exceeds that limit which we used to  
22 enroll patients in this trial. Right bundle branch  
23 block that has a QRS duration exceeding 150 ms.  
24 should not be considered pure right bundle branch  
25 block, and does have a component of left

1 ventricular conduction system disease.

2 I cannot give you the mean QRS duration of  
3 the 46 patients who had the so-called right bundle,  
4 but to use the term right bundle in this patient  
5 population may be inappropriate when the QRS  
6 duration exceeds 130 ms. because they may have more  
7 than simple right bundle branch block.

8 DR. PACKER: I think that the ideal way to  
9 try to address the issue of subgroup analysis is to  
10 look at any prospectively defined or  
11 retrospectively defined subgroups of interest, and  
12 look primarily at the consistency of data across  
13 subgroups for the two primary measures that  
14 reflected a treatment effect. To do that, one  
15 would need to work with the agency to plot the data  
16 and verify the data so that everyone is agreeing to  
17 the numbers. It is hard to do this on the fly but  
18 we are doing this primarily to try to give you some  
19 information, but the right way to do this is to  
20 look for consistency of data across any subgroups  
21 of interest and to see if there are any subgroups  
22 that appear to differ markedly from the treatment  
23 effect seen in the overall study.

24 DR. HAIGNEY: The last issue I am going to  
25 raise that has to do with our ability to predict