

UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES PANEL
OF THE MEDICAL DEVICES ADVISORY COMMITTEE

+ + + + +

PMA DISCUSSION, RECOMMENDATIONS,
AND VOTING

+ + + + +

WEDNESDAY,
JULY 28, 2004

+ + + + +

The above-entitled Advisory Panel Meeting convened in the Grand Ballroom of the Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, pursuant to notice, at 9:00 a.m., Warren K. Laskey, M.D., Acting Chairperson, presiding.

PANEL MEMBERS PRESENT:

WARREN K. LASKEY, M.D., Acting Chairperson, Uniformed Services University of Health Sciences
MITCHELL KRUCOFF, M.D., Voting Member, Duke University
Medical Center
WILLIAM H. MAISEL, M.D., M.P.H., Voting Member, Brigham & Women's Hospital
SHARON-LISE T. NORMAND, Ph.D., Voting Member, Harvard School of Public Health
JEFFREY A. BRINKER, M.D., Consultant, Johns Hopkins Hospital
NORMAN S. KATO, M.D., Consultant, Cardiac Care Medical Group
JOHN C. SOMBERG, M.D., Consultant, American

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Institute of Therapeutics

PANEL MEMBERS PRESENT: (cont'd)

ALBERT L. WALDO, M.D. (via telephone), Consultant,
University Hospitals of Cleveland
CLYDE YANCY, M.D., University of Texas Southwestern
Medical Center
MICHAEL MORTON, Industry Representative, Cardiac
Surgery, North America Sorin Group
CHRISTINE MOORE, Consumer Representative
GERETTA WOOD, Executive Secretary
BRAM ZUCKERMAN, Division Director, FDA

PRESENTERS:

Sponsor Presentation - Guidant Panel Attendees:

JOHN P. BOEHMER, M.D.
MICHAEL R. BRISTOW, M.D., Ph.D.
PETER E. CARSON, M.D.
DAVID L. DeMETS, Ph.D.
ARTHUR M. FELDMAN, M.D.
LESLIE A. SAXON, M.D.

U.S. Food and Drug Administration Presentation:

OWEN P. FARIS, Ph.D.
BARBARA KRASNICKA, Ph.D.
SCOTT PROESTEL, M.D.

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A-G-E-N-D-A

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

2 (9:01 a.m.)

3 ACTING CHAIR LASKEY: Well, good morning.

4 It being 9:00, I'd like to call us to order.

5 This morning we meet discussing the pre-
6 market application for the Guidant Cardiac
7 Resynchronization Therapy Defibrillators, P010012,
8 Supplement 26.

9 And we'll begin as usual with Ms. Wood
10 reading the conflict of interest statement.

11 MS. WOOD: The following announcement
12 addresses conflict of interest issues associated with
13 this meeting and is made a part of the record to
14 preclude even the appearance of an impropriety. To
15 determine if any conflict existed, the agency
16 reviewed the submitted agenda and all financial
17 interests reported by the committee participants.

18 The conflict of interest statutes
19 prohibit special government employees from
20 participating in matters that could affect their or
21 their employers' financial interests. However, the
22 agency has determined that participation of certain

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1 members and consultants, the need for whose services
2 outweighs the potential conflict of interest
3 involved, is in the best interest of the government.

4 Therefore, waivers have been granted for
5 Drs. Jeffrey Brinker, Mitchell Krucoff, William
6 Maisel, John Somberg, and Albert Waldo, for their
7 interests in firms that could potentially be affected
8 by the panel's recommendations.

9 The waivers for Drs. Brinker, Krucoff,
10 Maisel, Somberg, and Waldo involve a grant to their
11 institution for the sponsor study. The panelists had
12 no knowledge of the funding and had no involvement in
13 data generation or analysis. Dr. Krucoff's waiver
14 also involves consulting for the sponsor on unrelated
15 matters for which he receives an annual fee of less
16 than \$10,001, and consulting with a firm that has a
17 financial interest in a competitor or unrelated
18 matters for which he receives an annual fee of less
19 than \$10,001.

20 The waivers allow these individuals to
21 participate fully in today's deliberations. Copies
22 of these waivers may be obtained from the agency's

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1 Freedom of Information Office, Room 12A-15 of the
2 Parklawn Building.

3 We would like to note for the record that
4 the agency took into consideration other matters
5 regarding Drs. Brinker, Krucoff, and Dr. Clyde Yancy.

6 These panelists reported past or current interest
7 involving firms at issue but in matters that are not
8 related to today's agenda.

9 The agency has determined, therefore,
10 that these individuals may participate fully in the
11 panel's deliberations. The agency also would like to
12 note that Dr. Warren Laskey has consented to serve as
13 chair for the duration of this meeting. In the event
14 that the discussions involve any other products or
15 firms not already on the agenda for which an FDA
16 participant has a financial interest, the participant
17 should excuse him or herself from such involvement,
18 and the exclusion will be noted for the record.

19 With respect to all other participants,
20 we ask in the interest of fairness that all persons
21 making statements or presentations disclose any
22 current or previous financial involvement with any

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1 firm whose products they may wish to comment upon.

2 ACTING CHAIR LASKEY: I'd like to have
3 the panel members introduce themselves, beginning on
4 my right.

5 DR. ZUCKERMAN: Dr. Waldo, can you hear
6 us?

7 DR. WALDO: Yes, I can.

8 DR. ZUCKERMAN: Can you introduce
9 yourself, please?

10 DR. WALDO: I'm Dr. Albert Waldo from
11 Case Western Reserve University.

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

14 DR. KATO: Norman Kato, private practice,
15 Encino, California.

16 DR. YANCY: Clyde Yancy, UT Southwestern,
17 Dallas.

18 DR. MAISEL: William Maisel,
19 Cardiovascular Division, Brigham & Women's Hospital
20 in Boston.

21 DR. BRINKER: Jeff Brinker, Johns
22 Hopkins.

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1 DR. NORMAND: Sharon-Lise Normand,
2 Statistician, Harvard Medical School and Harvard
3 School of Public Health.

4 ACTING CHAIR LASKEY: Warren Laskey. I'm
5 an Interventional Cardiologist, the Uniformed
6 Services University.

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

9 DR. KRUCOFF: Mitch Krucoff, Cardiologist
10 at Duke. I'm Director of the Cardiovascular Devices
11 Unit at the Duke Clinical Research Institute.

12 DR. SOMBERG: John Somberg, Rush
13 University.

14 MS. MOORE: Christine Moore, Consumer
15 Representative.

16 MR. MORTON: Michael Morton. I'm the
17 Industry Representative. I'm employed by Sorin
18 Group.

19 ACTING CHAIR LASKEY: Thank you.

20 And, Geretta, could you please read the
21 voting status statement.

22 MS. WOOD: Pursuant to the authority

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1 granted under the Medical Devices Advisory Committee
2 charter, dated October 27, 1990, and as amended
3 August 18, 1999, I appoint the following individuals
4 as voting members of the Circulatory System Devices
5 Panel for this meeting on July 28, 2004: Warren
6 Laskey, M.D., serving as Chairperson; Norman S. Kato,
7 M.D.; Clyde Yancy, M.D.; John C. Somberg, M.D.;
8 Albert L. Waldo, M.D.; Jeffrey A. Brinker, M.D.

9 For the record, these individuals are
10 special government employees and are consultants to
11 this panel under the Medical Devices Advisory
12 Committee. They have undergone the customary
13 conflict of interest review and have reviewed the
14 material to be considered at this meeting.

15 This is signed by Daniel G. Schultz,
16 M.D., Director, Center for Devices and Radiological
17 Health, and dated July 23, 2004.

18 ACTING CHAIR LASKEY: Thank you.

19 Before we begin the open public hearing
20 portion, I'd like to read the following statement.
21 Both the Food and Drug Administration and the public
22 believe in a transparent process for information-

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1 gathering and decision-making. To ensure such
2 transparency at the open public hearing session of
3 the Advisory Committee meeting, FDA believes it is
4 important to understand the context of an
5 individual's presentation.

6 For this reason, FDA encourages you, the
7 open public hearing speaker, at the beginning of your
8 written or oral statement to advise the committee of
9 any financial relationship that you may have with the
10 sponsor, its product, and, if known, its direct
11 competitors. For example, this financial information
12 may include the sponsor's payment of your travel,
13 lodging, or other expenses in connection with your
14 attendance at the meeting.

15 Likewise, FDA encourages you at the
16 beginning of your statement to advise the committee
17 if you do not have any such financial relationships.

18 If you choose not to address this issue of financial
19 relationships at the beginning of your statement, it
20 will not preclude you from speaking.

21 That being said, I'd like to ask the
22 audience if there's anyone who wishes to address the

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1 panel on today's topic, or any other topic. If not,
2 then I'm delighted to close the open public hearing
3 portion and proceed with the sponsor's presentation.

4 DR. WALDO: Excuse me. This is Al Waldo.
5 It's very, very hard for me to hear you.

6 DR. ZUCKERMAN: Okay.

7 DR. WALDO: I can hear you. Is that you,
8 Bram?

9 DR. ZUCKERMAN: Yes.

10 DR. WALDO: I can hear you very well, but
11 anyone distant from the mike is very hard for me to
12 hear.

13 DR. SOMBERG: You have to put the
14 telephone receiver near where the speaker is.

15 DR. ZUCKERMAN: Okay.

16 DR. SOMBERG: It's not going to work near
17 the microphone. It's --

18 DR. ZUCKERMAN: Yes. We're about to get
19 a better telephone. Let me check on that.

20 (Pause.)

21 MS. WOOD: We would just like to remind
22 the sponsor to please introduce yourself and state

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1 your connection with the company and any conflict of
2 interest that you might have.

3 (Pause.)

4 Go ahead and get set up, but we'll try to
5 wait just a minute to make sure we can patch Dr.
6 Waldo in where he can hear your presentation.

7 (Pause.)

8 ACTING CHAIR LASKEY: Please forgive the
9 appearance of chaos up here. If you would, proceed.

10 DR. FELDMAN: Thank you.

11 Good morning. I'm Arthur Feldman from
12 Jefferson Medical College in Philadelphia, and I'm
13 very pleased to be able to be here this morning to be
14 one of the panel that will be presenting to you data
15 this morning from the COMPANION trial.

16 My conflict of interests include the fact
17 that I'm a consultant for numerous companies, both in
18 general cardiology and in the heart failure arena,
19 including I received travel expenses and room and
20 board to come here today, as well as a modest
21 honorarium.

22 I was an investigator for the COMPANION

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1 trial, and I served as the co-chairman of that trial.

2 I'd like to begin by introducing to you
3 the members of the trial that are here today and will
4 be presenting to you first. First is Dr. John
5 Boehmer who is an Associate Professor of Medicine and
6 Surgery at the Penn State College of Medicine; Dr.
7 Michael Bristow, who is the Gilbert Blout Professor
8 of Medicine and co-Director of the Cardiovascular
9 Institute at the University of Colorado; Dr. Peter
10 Carson, who chaired the Morbidity and Mortality
11 Committee and is Associate Professor of Medicine at
12 Georgetown. Dr. Bristow is also the co-chair of the
13 Steering Committee.

14 Dr. David DeMets, who directed the
15 Statistical Data Analysis Center for this trial and
16 is professor and chair of the Department of
17 Biostatistics and Medical Informatics at the
18 University of Wisconsin; Dr. Leslie Saxon, a member
19 of the Steering Committee, who is Professor of
20 Medicine and Director of Cardiac Physiology -- or
21 Electrophysiology, excuse me, at the University of
22 Southern California; and Dr. Jonathan Steinberg who

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1 is a member of the Morbidity and Mortality Committee
2 and is Chief of the Division of Cardiology at
3 Roosevelt/St. Luke's Hospital in New York.

4 This morning, the agenda as seen before
5 you here, I'm going to start by reviewing some of the
6 background for the COMPANION trial and for giving you
7 a study overview of the COMPANION trial.

8 Dr. Peter Carson will then speak to data
9 handling from the trial and the adjudication process.

10 Dr. Michael Bristow will present the effectiveness
11 results. Dr. David DeMets will present the
12 statistical considerations. And then, Dr. Saxon will
13 present the safety data and will summarize the study
14 conclusions on behalf of the Steering Committee.

15 I'd like to first just preface my remarks
16 with a little bit of the regulatory history for this
17 trial. You can see here that the pre-IDE meeting was
18 held in June of 1999. The FDA sent an agreement
19 letter in September of '99, and the first patient was
20 enrolled in this trial in January of 2000. The study
21 was stopped on the recommendation of the Data and
22 Safety Monitoring Committee on 11/18/02, and

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1 subsequent notices were filed with the FDA.

2 This next slide just makes the point that
3 there were numerous and extensive interactions
4 between the sponsor and the FDA during the course of
5 this trial. These include reviewers' memos, which
6 are found in your packets, and also systems safety
7 communications with the approval of CONTAK CD and
8 EASYTRAK lead systems; in May of '02, the renewal TR
9 approval based on CONTAK TR substudy data in 104.

10 Next slide.

11 Now, I think many of you are aware of the
12 background to this study, but I think it's worthwhile
13 to review it in brief. I think this panel is
14 certainly aware of the fact that heart failure is a
15 disease of epidemic proportions in the United States
16 affecting nearly six million people, that it's a
17 progressive disease, and that it's characterized by
18 very high morbidity and mortality.

19 Over the past two decades, a number of
20 pharmacologic therapies have been evaluated and have
21 proven salutary in both prolonging survival and
22 improving outcomes in patients with this disease.

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1 However, it has been recognized now for over a decade
2 that approximately 30 percent of patients with heart
3 failure have a prolongation in conduction that
4 results in a dysynchrony in cardiac contractility,
5 and it further impairs myocardial function as well as
6 adversely affecting the biology of the already-
7 failing myocardium. And, unfortunately,
8 pharmacologic agents do not address this
9 pathophysiologic problem.

10 Resynchronization through electrical
11 stimulation of both ventricles, or cardiac
12 resynchronization therapy, has been shown to improve
13 myocardial function, reverse ventricular remodeling,
14 and actually improve the biology of the failing
15 heart.

16 Next slide.

17 So how does CRT therapy work? Well, this
18 is a diagrammatic drawing. You can see a blockage
19 right here in the conduction system, and CRT therapy
20 works by simply placing electrodes on the surface of
21 the heart and then having these both -- having these
22 timed appropriately to synchronize the contraction of

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1 the two ventricles.

2 Initially, about eight to nine years ago,
3 these pacemakers were placed, or these leads were
4 placed, on the surface of the heart using an approach
5 through a thoracotomy. This was found to be
6 beneficial in terms of improving cardiac
7 hemodynamics. However, obviously, the morbidity
8 associated with a thoracotomy was somewhat
9 problematic in this group of patients.

10 More recently, leads have been developed
11 which were used in this study, which allowed a
12 totally percutaneous implantation by placing a lead
13 through the coronary sinus, then down the great
14 coronary vein, and approaching the surface of the
15 left ventricle, with the right ventricular lead being
16 placed consistent with standard lead placements for
17 pacemaker devices.

18 Next slide.

19 We'll use some new terminology in the
20 presentation that has come into the world of heart
21 failure over the past few years. This includes CRT
22 or cardiac resynchronization therapy. This is a

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1 generic term that describes the therapy independent
2 of the device; CRT-P, which describes a device with
3 biventricular pacing capabilities alone; and then,
4 CRT-D, which describes a device with both
5 biventricular pacing and defibrillation capabilities.

6 Now, we had a number of rationales for
7 the COMPANION trial. The first was that CRT-P or
8 CRT-D devices have the potential, because of their
9 effects on remodeling, to reduce mortality in a heart
10 failure hospitalization's in-patients with advanced
11 heart failure.

12 Now, at the time that COMPANION was
13 started -- in fact, up 'til today -- there have been
14 no appropriately powered clinical trials that were
15 designed on an intention-to-treat basis that have
16 prospectively investigated the effect of CRT on
17 mortality or on hospitalizations.

18 Now, this was important because it was
19 really these two endpoints which were keys to
20 understanding the efficacy of this treatment and the
21 importance of this treatment for the heart failure
22 population, and specifically for the heart failure

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1 physician.

2 Next slide.

3 So the COMPANION trial was designed to
4 determine if CRT-P or CRT-D resulted in a significant
5 reduction of a composite of time to first all-cause
6 hospitalization or all-cause mortality when compared
7 with optimal pharmacologic therapy alone. Combined
8 endpoints incorporating both mortality and
9 hospitalization are a standard for primary endpoints
10 to receive a robust heart failure clinical trial
11 endpoint.

12 The motivation behind this composite
13 endpoint was the desire to address both mortality and
14 morbidity. Incorporating all-cause hospitalization
15 into a composite endpoint helps to address the
16 challenge of competing risk and raises the bar for
17 demonstrating effectiveness of CRT when compared to
18 other heart failure trials.

19 This is the study design of the COMPANION
20 trial. You can see that after enrollment patients
21 underwent baseline testing. They were then
22 randomized to one of three arms -- either to optimal

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1 pharmacologic therapy or OPT, OPT plus CRT-P, and OPT
2 plus CRT-D.

3 The randomization was one to two to two,
4 and I make this point so that you will recognize
5 during later presentations the fact that there were
6 twice as many patients in the OPT/CRT-D group as in
7 the OPT group.

8 Another important feature of this trial
9 was that the clock started ticking at the time of
10 randomization. So, in other words, if an event
11 occurred between randomization and device implant in
12 any of these patients, that was considered as an
13 endpoint for the trial, despite the fact that the
14 device had not yet been implanted. So this was a
15 very conservative approach to analysis of the trial.

16 A two-day window was set for
17 implantation. The randomization was stratified, both
18 by site and by beta blocker therapy, and the
19 hospitalizations associated with the investigational
20 device -- in other words, hospitalizations to implant
21 a device -- were not considered as a study endpoint,
22 because obviously if they were then each patient, at

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1 the time of randomization, would actually be a study
2 endpoint.

3 Next slide.

4 I would point out also that we will
5 concentrate today -- we will focus exclusively today
6 -- on this OPT and CRT-D group and its comparison
7 with OPT alone. And the reason for that was that the
8 OPT and CRT-P data was previously supplied to the
9 agency and was used in the approval for this device.

10 Now, the indications currently for a CRT-
11 D device are seen here. They include New York Heart
12 Association Class III or IV symptoms despite optimal
13 pharmacologic therapy, a QRS greater than or equal to
14 120 milliseconds, an ejection fraction less than or
15 equal to 35 percent, and an indication for
16 conventional ICD.

17 We are proposing, based on the data that
18 you'll see today, that these indications should be
19 expanded to now include the same patient population
20 -- that is, symptomatic patients with QRSs greater
21 than or equal to 120 milliseconds and an ejection
22 fraction of less than or equal to 35 percent, but

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1 also a current ICD indication or COMPANION patient
2 population criteria.

3 Now, the composite primary endpoint for
4 this trial was the composite of time to first all-
5 cause hospitalization or all-cause mortality event.
6 This composite endpoint included mortality to account
7 for mortality as a competing risk. It was analyzed
8 as time to first event as measured, again, from the
9 randomization visit, not from the implantation.

10 The analysis was intended to treat
11 from the time of randomization, and per agreement
12 with the FDA, and in order to preserve
13 hospitalization as a valid, morbidity clinical
14 endpoint, the investigational device implant was not
15 considered to be a hospitalization event.

16 Next slide.

17 So the primary endpoint consisted of a
18 composite of death from any cause and hospitalization
19 for any cause. However, it also included IV
20 inotropes or vasoactive drugs being administered for
21 four hours in an outpatient hospital or physician
22 office, because this was viewed as an instance of the

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1 primary endpoint with respect to hospitalization.

2 Now, secondary endpoints for the trial
3 included all-cause mortality with the highest order
4 secondary endpoint being all-cause mortality, and
5 this was analyzed by intention to treat and it was
6 analyzed as time to event as measured from the
7 randomization visit, and cardiac morbidity also
8 analyzed by intention to treat.

9 This slide shows the main entry criteria
10 for the COMPANION trial. It included New York Heart
11 Association Class III or IV symptoms, optimal
12 pharmacologic therapy which was defined as loop
13 diuretics, beta blockers, ACE inhibitors, and
14 spironolactone.

15 Patients could be enrolled if they were
16 found to be intolerant of these agents. However, if
17 they were on a beta blocker or an ACE inhibitor, it
18 needed to be at a stable dose for greater than three
19 months in the case of beta blockers, and for greater
20 than one month in the case of ACE inhibitors.
21 Spironolactone also had to be at a stable dose for
22 greater than one month.

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1 The ejection fraction had to be less than
2 or equal to 35 percent with a left ventricular end
3 diastolic dimension of greater than or equal to 60
4 millimeters. And the QRS had to be greater than or
5 equal to 120 milliseconds with a PR interval of
6 greater than 150 milliseconds.

7 Each patient was required to have had a
8 heart failure hospitalization between one and 12
9 months prior to enrollment, and there could be no
10 indication for either a pacemaker or for an ICD.

11 This, again, shows the study design.
12 Again, I'd point out that after randomization
13 patients were randomized to one of three arms. I
14 think it's important to also note that the patients
15 who received the device had a hospitalization or a
16 visit with both the physicians and the study nurse at
17 this point, and then subsequently all patients were
18 seen at one week, one month, and then every three
19 months.

20 We made a number of statistical
21 assumptions in establishing the goals for this trial.

22 The trial was powered to detect a 25 percent

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1 relative reduction in 12-month event rates in each
2 device arm versus optimal pharmacologic therapy for
3 both the primary and the secondary all-cause
4 mortality endpoints.

5 Alpha allocation was set at 0.02 for CRT-
6 P versus OPT and at 0.03 for CRT-D versus OPT. This
7 shows you down in the bottom part -- portion of the
8 slide the assumed event rate for mortality or
9 hospitalization in the control group and in terms --
10 and mortality endpoint in the control group, this
11 being 24 percent mortality and 40 percent event rate
12 for mortality or hospitalization.

13 This was the expected absolute reduction
14 or the assumed absolute reduction -- 10 percent in
15 mortality or hospitalizations, and six percent in
16 mortality -- to give a power of greater than 90
17 percent for the primary endpoint and 80 percent for
18 the mortality endpoint.

19 This was an event-driven trial with a
20 target number of 1,000 first events to be detected
21 for a 25 percent reduction for the primary endpoint.

22 There was sequential monitoring of both the primary

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1 and the secondary all-cause mortality endpoint events
2 performed by the DSMB every six months during the
3 course of the trial.

4 Now, the management of the trial is seen
5 on this slide, and it was independent of the
6 sponsors. The Steering Committee was charged with
7 providing overall guidance and leadership of the
8 study. The Morbidity and Mortality Committee
9 developed a process and the precise operational
10 criteria for adjudication of the study endpoints, and
11 then reviewed and adjudicated deaths and
12 hospitalizations.

13 The Data and Safety Monitoring Board
14 reviewed study outcomes, including safety at
15 prescribed intervals. The independent statistical
16 group provided statistical support as well as
17 guidance, and the contract research organization
18 administrated the study and acted as a clearinghouse
19 for CRFs and study monitoring.

20 This shows the relationships between the
21 various entities that were part of this study. You
22 can see that the contract research organization

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1 received information from the independent statistical
2 group. It gave data from patient centers to the
3 Morbidity and Mortality Committee for their
4 adjudication. It interacted with the sponsor.

5 The independent statistical group
6 provided information to the Data and Safety
7 Monitoring Board, who in turn made recommendations to
8 the Steering Committee. And there was also
9 interaction between the sponsor and the Steering
10 Committee, and the sponsor communicated with the Food
11 and Drug Administration.

12 During the context of this study, there
13 were three occasions or approximately three occasions
14 when there was direct interaction between components
15 of the study outside of this diagram. First, the
16 Morbidity and Mortality Committee communicated with
17 the Steering Committee to clarify hospitalization as
18 a calendar date change.

19 Second, the Data and Safety Monitoring
20 Board communicated with the Food and Drug
21 Administration regarding instances of coronary venous
22 trauma and to provide information about changes that

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1 were made in the protocol for administration of these
2 devices as a result of this finding.

3 And then, finally, the independent
4 statistical group interacted with the Steering
5 Committee in recommending gathering of post-
6 withdrawal data.

7 Next slide.

8 I'd like to now turn the podium over to
9 Dr. Peter Carson, who will discuss data handling and
10 the adjudication process.

11 DR. CARSON: Thank you, Dr. Feldman.

12 I'm Peter Carson, and I am speaking to
13 you this morning as the Chairman of the Morbidity and
14 Mortality Committee of COMPANION. My conflicts are
15 as chairman of that committee and also as a member of
16 the panel for Guidant today. I have no other
17 relationship to the sponsor.

18 The slide that is up at this point is
19 looking at the data flow process from the standpoint
20 of the Morbidity and Mortality Committee. A patient
21 event that occurred would be reported on a clinical
22 report form to the CRO, and all hospitalizations,

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1 four-hour inotrope use as an outpatient and deaths
2 would then be assembled as a dossier and sent to the
3 Morbidity and Mortality Committee to adjudicate.

4 The Morbidity and Mortality Committee
5 then would meet in a process that I'll describe a
6 little more later, adjudicate these events,
7 communicate them back to the CRO, which would then
8 further communicate them to the statistical group.
9 There would be a final report that would then go to
10 the sponsor.

11 The Morbidity and Mortality Committee
12 communicated only with the CRO and with the Steering
13 Committee. The Steering Committee communication was
14 through me, and I was an ex officio member of the
15 Steering Committee. And I would emphasize that the
16 M&M Committee had no contact with the sponsor through
17 the course of the trial.

18 Next slide.

19 The Morbidity and Mortality Committee was
20 composed of seven cardiologists, and I want to take
21 special mention of them. This was a remarkable
22 group, and I feel like I'm a position to say so as I

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1 have chaired or been a member of virtually every
2 Endpoint Committee in heart failure over the last 12
3 years. This group had great expertise in heart
4 failure, clinical trials, regulatory experience, and
5 also electrophysiology.

6 And it is well that this group had this
7 expertise -- if we could go to the next slide --
8 because the committee performed a number of
9 functions, developed the process and precise
10 operational criteria for adjudication of study
11 endpoints. We reviewed and adjudicated deaths and
12 hospitalizations. For those deaths, we defined and
13 adjudicated a mode of death, and we also adjudicated
14 the relationship of death to device implant.

15 Regarding hospitalization, further, we
16 defined and adjudicated specific causes of
17 hospitalization. And, finally, we adjudicated
18 cardiac morbidity.

19 Next slide.

20 In consideration of -- regarding
21 operational definitions, some of the committee's
22 criteria involved these thoughts. For a

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1 hospitalization event, an event should be of
2 sufficient morbidity to enter a composite with
3 mortality, and should also have verifiable
4 components.

5 For cause-specific mortality, we assessed
6 that the cause of death would be the event that
7 defined the patient's clinical course or altered it,
8 and it should be definitions that have been used in
9 previous clinical trials.

10 For cause-specific hospitalizations,
11 similarly, we wanted to indicate the primary reason
12 for hospitalization. With evidence from specific
13 treatment and response, we again wanted definitions
14 that had been used in other clinical trials. I
15 should note that, per protocol, we did not adjudicate
16 elective implants or reimplant hospitalizations.

17 Next slide.

18 For mode of death analysis, as said, the
19 primary mode of death related to the event that led
20 to death. We did not usually adjudicate according to
21 the terminal event.

22 We principally assessed cardiac deaths,

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1 because that's what occurred in COMPANION. The two
2 principal causes are sudden, unexpected, and pump
3 failure, and you see short descriptions of these
4 modes of death on this slide. As with other
5 parameters on this slide, fuller definitions are in
6 the Morbidity and Mortality Committee manual.

7 Other causes, as you see, for cardiac
8 deaths include ischemic deaths in two ways -- cardiac
9 procedure, other cardiac. Vascular deaths, non-
10 cardiac deaths. And for those cases in which there
11 was simply no data available, these cases would be
12 assessed as unknown or unclassifiable.

13 In terms of the relation of device
14 implant to mortality, we used a schema that was
15 typical of intervention trials -- pre-operative,
16 after randomization but before implant; peri-
17 operative, within 30 days; post-operative, after 30
18 days. We assessed the relationship as non-applicable
19 if this was a patient in the OPT arm or a CRT-D
20 patient who never received a device. Procedure-
21 related and device-related were also assessed, and
22 these details are once again in the operations manual

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1 of the committee.

2 For hospitalizations, let me principally
3 say a word about heart failure hospitalizations. We
4 were looking for a principal diagnosis of heart
5 failure. We looked for increases signs or symptoms
6 of heart failure. And treatment had to include
7 intravenous therapy, either diuretic or another type
8 of vasoactive drug, or it could be other parenteral
9 therapy on occasion, or we also assessed its
10 significant alteration in oral therapy could also be
11 included in the diagnosis of a heart failure
12 hospitalization.

13 We adjudicated many other causes of
14 cardiac hospitalization. I should also add that we
15 also adjudicated all non-cardiac hospitalizations
16 also, and that is quite unique for any heart failure
17 trial.

18 The cardiac morbidity index is seen on
19 this slide. This is from the protocol. Please
20 recall that hospitalization was assessed as the
21 primary reason when we looked at it, and, therefore,
22 one of the purposes of the cardiac morbidity scale

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1 was to pick up other morbidities that might have
2 happened during the hospitalization or other
3 important components of that initial reason for
4 hospitalization.

5 Bear in mind that all of these aspects of
6 cardiac morbidity would be reflecting cardiac
7 worsening. That was their design, and that was the
8 way the committee adjudicated them.

9 Next slide.

10 The M&M Committee adjudication process
11 involved the CRO collating clinical summary and event
12 information from investigational centers. This was
13 to involve hospitalizations. It involved a calendar
14 date change, and I'll show you the hospitalization
15 CRF for that later. Also, outpatient IV or
16 vasoactive drug use for greater than four hours on
17 another CRF, and, of course, all deaths.

18 Please note the committee did not screen
19 adverse experiences. All AEs in submission were
20 reported by center, reviewed by the CRO, and
21 submitted to the Data and Safety Monitoring Board in
22 a summary format.

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1 A little further detail on the
2 adjudication process in terms of what we received
3 from the CRO, and I should point out that the
4 documentation in the COMPANION trial was among the
5 best I've seen in any clinical trial I've been
6 associated with.

7 This involved hospitalization data,
8 admission summary and physical, discharge summary,
9 lab reports, progress notes when we needed them.
10 Death data included a physician narrative, clinic
11 notes, and a discharge summary if the patient had had
12 a recent previous hospitalization.

13 A primary and secondary reviewer were
14 assigned to each event, and they reviewed, presented
15 the cases to the committee, and a vote was taken for
16 each adjudication. It should be pointed out that the
17 patient ID, randomization arm, physician center,
18 etcetera, were all removed from the documentation
19 that both reviewers and the committee saw. The
20 process for each committee meeting was documented
21 with meeting minutes.

22 I should make a statement about M&M

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1 Committee blinding. I think as you probably all
2 realize, in a device trial such as COMPANION,
3 blinding is largely problematic. For mortality
4 events, the committee adjudicated the relation of
5 device and implant procedure to death, so, therefore,
6 the committee had to be unblinded to whether the
7 patient had a device or not.

8 For hospitalization events, while, as I
9 said, all identifying data was removed to the degree
10 possible, the nature of a hospitalization or the
11 events themselves or statements in the narrative,
12 even if you black them out, might reveal or hint the
13 presence of a device.

14 However, please keep in mind that the
15 committee functions in equipoise regarding the study
16 hypothesis, and, therefore, the knowledge of the
17 treatment arm should not interfere or influence
18 adjudication of individual events. And the committee
19 at no time had knowledge of cumulative events or
20 assembled data.

21 Further, while CRO members were present
22 at committee meetings, no sponsor representative was

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1 ever present, and all communication was to the CRO or
2 to the Steering Committee.

3 Next slide.

4 Now, there has been concern about the
5 definition of hospitalization adjudication, and just
6 a few comments to make here. The committee believed
7 that the protocol intended that an event be
8 significantly or sufficiently morbid to enter into a
9 composite endpoint with death.

10 It is also true that all trials prior to
11 COMPANION had used a parameter of a 24-hour duration
12 hospitalization. For these reasons, the committee
13 initially used a 24-hour duration as the descriptor
14 of an all-cause hospitalization.

15 Now, the largest experience in this area
16 prior to COMPANION was MERIT heart failure and
17 VALHeFT. In both of those trials, the committees
18 ultimately used a descriptor of a calendar date
19 change, and they did so for the same reasons as we
20 did, which is that early in the adjudication process
21 it became apparent that discharge times were not
22 uniformly available.

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1 Therefore, the committee agreed to adopt
2 what was a more verifiable and precise approach of a
3 calendar date change. This operational criteria was
4 approved by the Steering Committee and utilized for
5 all hospitalizations and included in all analyses.

6 There were 113 hospitalizations
7 adjudicated prior to the adoption of this criteria.
8 All were reviewed, none changed. If you look on the
9 next slide, you see two things that are quite
10 important. One is the flow of events through the
11 course of the trial, noting that the first Endpoint
12 Committee meeting was 3/16/01, and that on 1/19/01,
13 after 113 events, we particularly used to use -- we
14 used a calendar date change.

15 Then, for a hospitalization, this is the
16 overall stream of events that occurred through the
17 course of the trial. This is why I particularly
18 compliment this committee. I should also say that
19 the hospitalization CRF was in place at the start of
20 the trial, and it was the same hospitalization CRF
21 for the entire trial.

22 If you go to the next slide, this is the

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1 hospitalization CRF. What this hospitalization CRF
2 asked the site to report was what day the patient was
3 admitted and what day the patient was discharged. It
4 did not ask for times. The committee did realize
5 during the course of adjudicating that first 113
6 events that we could not accurately ascertain always
7 the discharge summary.

8 We felt we would be vulnerable to the
9 issue of the times, and, therefore, we felt this was
10 clearly verifiable. Note that this form was in place
11 at the very beginning of the trial.

12 Next slide.

13 In terms of -- Dr. Feldman talked to you
14 about four-hour inotrope or vasoactive therapy use.
15 We used this definition for the adjudication of these
16 events. This is actually the wording of the
17 definition that is out of the cardiac morbidity area
18 of the protocol.

19 I should comment that four-hour endpoint
20 of IV inotrope or vasoactive therapy use has really
21 been the only way that this endpoint has ever been
22 used in clinical trials, and it provides assurance

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1 that the administration of IV therapy is clinically
2 meaningful and is a hospitalization equivalent.

3 Next slide.

4 And just like with the hospitalization
5 CRF, this was the CRF that the sites always used that
6 had the four-hour distinction for IV vasoactive or
7 inotrope use. So this was also used from the
8 beginning of the trial onward.

9 Next slide.

10 Let me conclude by saying that the
11 COMPANION Endpoint Committee provided operational
12 criteria for events occurring during the study. The
13 classifications used were those used in previous
14 clinical trials. They provided verifiable data and
15 maximized capture of significant events.

16 The adjudication process consisted of
17 activities that are the standard practice for
18 clinical trials in heart failure.

19 Thank you.

20 ACTING CHAIR LASKEY: Thank you.

21 Dr. Bristow, if you would kindly indulge
22 us for a moment, we're going to try and get Dr. Waldo

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1 back online. So can we just take a minute?

2 I was just told it wasn't going to take a
3 while, so either we move ahead or -- five-minute
4 break? Mike, is that all right?

5 DR. BRISTOW: Sure.

6 ACTING CHAIR LASKEY: All right. Five-
7 minute break, please, and we'll -- we will regroup.

8 Thank you.

9 (Whereupon, the proceedings in the
10 foregoing matter went off the record at
11 9:44 a.m. and went back on the record at
12 10:00 a.m.)

13 ACTING CHAIR LASKEY: Thank you for your
14 indulgence. I guess we're functional, as we say. So
15 we'll continue with Dr. Bristow's presentation.

16 DR. BRISTOW: Thank you, Dr. Laskey.

17 It's my privilege to present the
18 effectiveness results of COMPANION. I'm Mike Bristow
19 from the University of Colorado. I was a co-chairman
20 of the Steering Committee. My other relevant
21 conflicts are that I'm a consultant to Guidant, and I
22 also receive research support to Guidant.

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1 MS. WOOD: Sir, pull the mike up just a
2 little.

3 DR. BRISTOW: The first slide is the
4 geographic location of the study centers. This was
5 entirely a U.S. study conducted in 120 U.S. centers
6 averaging 12 patients enrolled per center. This
7 gives some of the baseline demographics and other
8 historical data in the two treatment groups.

9 The first point in the baseline data is
10 that none of these parameters that we're going to be
11 describing are different between the two treatment
12 groups. So the age is late sixties, which is a
13 little older than standard heart failure clinical
14 trials that have reported lately.

15 We had a substantial number of women, a
16 little higher than most heart failure clinical
17 trials, so 67, 69 percent male. And the New York
18 Heart Class -- all Class III and IV. This was an
19 advanced heart failure study.

20 Duration of heart failure is typical for
21 a heart failure -- chronic heart failure clinical
22 trial, three to four years. Severe LD dysfunction,

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1 average EF, 22 percent. Dilated chrome EPI
2 phenotype, as mandated in the protocol, was 6.7
3 centimeter ventricles.

4 Heart rate a little lower than is usually
5 seen in heart failure clinical trials, reflecting a
6 background therapy of beta block aid -- one of the
7 lowest, if not the lowest, systolic blood pressure at
8 a heart failure clinical trial reporting at least
9 oral agents -- in this case, obviously, a device
10 trial at 112.

11 Next slide.

12 Moderate exercise, six-minute walk, on
13 the high side PR intervals and QRS durations based on
14 the protocol, 55 to 60 percent ischemic typical for a
15 heart failure trial enriched in diabetes, also
16 typical for a heart failure trial, 45 percent.
17 Seventy percent left bundle.

18 Background therapy shown here --
19 approximately 90 percent of patients on an ACE or an
20 ARB, 66 or 68 percent on a beta blocker, virtually
21 all patients on a loop diuretic, and 55 percent on
22 spironolactone, probably representing the upper limit

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1 of tolerability of this agent in an advanced heart
2 failure population.

3 This slide gives some of the details on
4 trial termination. On November 18, 2002, the DSMB
5 recommended to the Steering Committee that enrollment
6 be stopped for two reasons. First and foremost, this
7 was an event-driven trial with a target number of
8 events of 1,000, and it was the opinion of the DSMB
9 at that time that that target had been reached, based
10 on the number of endpoints that they were reviewing
11 at that time -- 941.

12 And then, projecting the number of
13 endpoints that had not yet come in -- and, in fact,
14 the final number of endpoints analyzed in COMPANION
15 was 1,020. The second point was that the
16 effectiveness boundaries for the primary endpoint and
17 mortality had been crossed in the CRT-D group at that
18 time.

19 So the Steering Committee followed this
20 recommendation, stopped enrollment at 1,520
21 randomized patients on that date, and established a
22 study cutoff date for gathering efficacy data as

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1 November 30, 2002.

2 These are the sequential monitoring
3 Z values that the DSMB was observing over time, and
4 you can see out here at the end of the trial the
5 boundary for the primary endpoint being crossed.

6 These are the Kaplan-Meier curves for the
7 primary endpoint, which is a composite of time to
8 mortality or all-cause hospitalization. And the OPT
9 or control group is in red. The interrupted line and
10 the solid blue line is CRT-D.

11 The first point is that the 12-month
12 event rate in the OPT group was 68 percent, which is
13 somewhat higher than we had projected. In the CRT-D
14 group, the 12-month event rate was reduced to 56
15 percent. That's a 12 percent absolute reduction.

16 The hazard ratio for these two curves is
17 .80, statistically significant, relative risk
18 reduction of 20 percent. Therefore, a P value
19 adjusted for sequential monitoring ending up being
20 .011, which is under the critical value of .03.

21 Now, in terms of the components of this
22 primary endpoint, if -- taking both groups together,

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1 90 percent of the primary endpoints were
2 hospitalization. Seven and a half percent were
3 mortality, approximately. And only two and a half
4 percent were the IV inotrope use.

5 Next slide.

6 This adds on to the Kaplan-Meier curve
7 the results in the CRT-P group for the primary
8 endpoint. And you can see that the CRT-P group
9 actually is virtually superimposable to the CRT-D
10 group. In other words, the treatment effect for the
11 primary endpoint heavily driven by hospitalization,
12 is virtually identical in the CRT-D and CRT-P group.

13 Next slide.

14 These are some subgroup analyses, hazard
15 ratios for standard subgroups that are looked at for
16 the -- in heart failure trials for the primary
17 endpoint, and the important point is that all of
18 these point estimates lie to the left of unity,
19 indicating homogeneity, essentially, of treatment
20 effect for the primary endpoint.

21 Next slide.

22 This is the sequential monitoring data

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1 for the Z statistic that DSMB was following for all-
2 cause mortality. And you can see the boundary
3 effectiveness, boundary being crossed here at the end
4 of the trial for mortality.

5 These are the Kaplan-Meier curves for the
6 secondary endpoint of all-cause mortality.
7 Obviously, these curves are very different. The 12-
8 month event rate in the OPT group was 19 percent -- a
9 little less than predicted -- down to 12 percent in
10 the CRT-D group, absolute risk reduction of seven
11 percent. The hazard ratio for these curves is .64.
12 That's a 36 percent relative risk reduction, highly
13 statistically significant P value.

14 Next slide.

15 This adds on the mortality results for
16 the CRT-P group. And unlike for the primary
17 endpoint, these curves are somewhat different. So
18 this is CRT-P, which has a hazard ratio of .76
19 compared to the .64 for CRT-D. And so two-thirds of
20 the reduction in mortality in this trial was achieved
21 in the CRT-P group compared to the CRT-D group.

22 Next slide.

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1 This gives some of the subgroup analysis
2 data for all-cause mortality. And much like the
3 primary endpoint, the vast majority of these point
4 estimates lie to the left of unity, indicating
5 homogeneity of treatment effect across subgroups.

6 Next slide.

7 This is some of the death classification
8 data from Dr. Carson's Morbidity and Mortality
9 Committee. The majority of deaths in this study, as
10 you would imagine, are cardiac -- around three-
11 fourths. So here is the crude mortality rate in the
12 OPT arm versus CRT-D, 18.8 versus 12.8 percent,
13 statistically significant.

14 Here is the subdivision by the two major
15 types of cardiac death -- adjudicated pump failure
16 and sudden death. There are either trends or
17 statistically significant reductions in both of these
18 modes of death, with a greater degree of reduction
19 perhaps, for sudden death. And here are the other
20 more minor modes of death that were classified.

21 Next slide.

22 So this slide gives the projected event

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1 rates and treatment results based on what actually
2 happened. So as we've already said, we projected
3 that the primary endpoint event rate would be 40
4 percent at 12 months, and 24 percent for the
5 secondary endpoint -- the event rate at 12 months,
6 the actual -- in the OPT group.

7 The actual event rates achieved are shown
8 here -- 68 percent, greater obviously, for OPT for
9 primary endpoint, and a little bit less for all-cause
10 mortality. So going down here to the relative
11 reductions, we assumed that we would get 25 percent
12 relative risk reduction, and we -- for the primary
13 endpoint, and we ended up with 20.

14 We assumed 25 percent for mortality,
15 ended up with 36. What really counts for statistical
16 significance is a combination of the event rate and
17 the absolute risk reduction. And in the case of the
18 primary endpoint and mortality, the absolute risk
19 reduction was a little greater than we anticipated --
20 10 versus 12 for the primary endpoint, six versus
21 seven for all-cause mortality.

22 We measured cardiac morbidity by protocol

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1 in this trial. So there was a cardiac morbidity
2 index designed to encompass all significant events
3 that could happen to a heart failure patient --
4 significant clinical events, including in this case
5 serious device-related hospitalizations.

6 Now, there is no standard definition for
7 cardiac morbidity for advanced heart failure trials.

8 You can't reach into the bucket and pull out a
9 standard definition for this. So the protocol
10 defined cardiac morbidity for the COMPANION trial,
11 and this endpoint was intended to measure frequency
12 and duration of all cardiac morbid events as defined
13 in the protocol.

14 So these are data for the aggregate of
15 the cardiac morbidity index, in terms of frequency
16 per patient, frequency per patient per year, and
17 duration. OPT is in red, and CRT-D is in blue. And
18 you can see there's a reduction in these morbidity
19 measurements in the CRT-D group for all three of
20 these types of measures.

21 And this breaks it out by component of
22 the morbidity index. And for the -- at least for the

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1 high prevalence components of this index, there is a
2 reduction in the CRT-D group. For example,
3 hospitalization for a acute decompensation heart
4 failure, you see the degree of reduction here.
5 Statistically significant.

6 Next slide.

7 COMPANION, I'll have to say, after
8 working in heart failure clinical trials for nearly
9 25 years, was a bit of a challenging study to
10 conduct, and for that matter to design. The first
11 sort of hurdle that had to be overcome, as we knew
12 that we were not going to be successful with every
13 implant, but we also wanted to conduct this as
14 intention to treat with randomization triggering
15 essentially the tabulation of endpoints. We didn't
16 want to wait for successful implants and then start
17 tabulating, which typically has been done in device
18 trials.

19 We knew we had to drag along the upfront
20 implant lack of success rate, and so in the CRT-D
21 group the success rate was 91 percent. So right up
22 front, we're dragging along nine percent of patients

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1 who did not get a device and could not have a
2 treatment effect. So we have to overcome that with
3 efficacy over time.

4 Another major challenge here that wasn't
5 fully anticipated when the trial began, because I
6 don't believe it could have been, was that there were
7 several devices that were approved and, in fact,
8 marketed while this trial was in progress -- several
9 CRT devices. So a CRT-P device was approved, a CRT-D
10 device, and there were expanded indications for ICD
11 based on the beta trial, beta II trial, that came on
12 the scene. And, of course, this created competition
13 essentially for enrollment.

14 And so these challenges slowed enrollment
15 and made maintaining patients in the study somewhat
16 of a challenge. So this is enrollment by month over
17 time in COMPANION, and you can see up until mid 2001
18 we're kind of zinging along here with increasing
19 rates of enrollment. And then these devices started
20 being approved and marketed, and this is probably no
21 coincidence -- that our enrollment rate begins to
22 drop.

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1 Next slide.

2 So we had to have a response to that as a
3 trial in terms of how to cope with this and deal with
4 this. So CRT device approval while COMPANION was in
5 progress clearly influenced investigator equipoise.
6 Investigators were faced with the difficult choice of
7 continuing to enroll and treat patients in COMPANION
8 or basically put a device in them in an open label
9 fashion or drop them into that therapy if they were
10 COMPANION patients.

11 So the Steering Committee strongly
12 discouraged that and, through direct communication
13 with investigators, made them aware that the only way
14 this could happen in COMPANION -- that is, a patient
15 could get an open label drop-in device -- would be if
16 they had progressive heart failure to the point of
17 having a heart failure hospitalization -- in other
18 words, would be endpointed first in COMPANION.

19 And the investigators were required to
20 consult with a Steering Committee member prior to
21 implanting device and produce on paper the evidence
22 that this patient had progressive heart failure.

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1 Next slide.

2 Nevertheless, we did experience a
3 disproportionate withdrawal rate in COMPANION in the
4 OPT group. And when this was first fully
5 appreciated, early 2003, the numbers were a
6 withdrawal rate in the OPT group, in-patients who had
7 not previously had a primary endpoint of 13 percent,
8 versus two percent in the CRT-D group.

9 The study, of course, was based on
10 intention to treat, and due diligence in this setting
11 requires accounting for as many patients as possible.

12 So Dr. DeMets, the independent statistician in
13 COMPANION, recommended to the Steering Committee to
14 obtain vital status and hospitalization status on all
15 of the withdrawn patients.

16 In order to do that and be in compliance
17 with HIPAA regulations, we essentially had to write a
18 new protocol and re-consent patients that had
19 withdrawn prior to 11/30/02, who had not had a
20 primary endpoint.

21 Next slide.

22 And so we did that, and this was a very

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1 painful process requiring a total of seven months,
2 delaying publication of COMPANION and delaying this
3 meeting today. So IRB-approved protocol had to occur
4 in each center. The patients had to sign a written
5 consent.

6 And, therefore, data-gathering was just
7 as it had been in patients who had not been
8 withdrawn. That is, case report forms for the
9 withdrawal contact were filled out, but -- which is
10 in addition to the standard, but also that the
11 standard hospitalization, the CRFs were filled out,
12 and the data were handled and adjudicated just as
13 other data were thereafter.

14 Next slide.

15 So here is what happened in terms of
16 withdrawals. So in terms of all patients withdrawn,
17 26 percent in the OPT group versus 6.6 in the CRT --
18 now, these are final numbers, not the preliminary
19 numbers I showed you earlier. So in terms of
20 patients who had not had a primary endpoint, which is
21 the important issue, 14 percent in OPT versus 1.5
22 percent in CRT-D. This is prior to the re-consent

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1 process.

2 And so then we go through the re-consent.

3 We end up finding these extra endpoints, identifying
4 these extra endpoints, 14 in the OPT group, or 4.5
5 percent of the total, and .7 percent CRT-D. And then
6 the real issue is: what are you left with at the end
7 of all this?

8 These are the number of patients with no
9 ascertainment -- that is, truly withdrawn, no
10 ascertainment -- after that withdrawal, which is down
11 to four percent in the OPT group and .7 percent in
12 the CRT-D group. And the important number here is
13 actually what happens in the CRT-D group, because if
14 we missed endpoints there obviously we -- we might
15 bias the results in favor of the therapy.

16 And as you can see, this number is
17 extremely small and certainly in keeping with dropout
18 and withdrawal rates in heart failure clinical trials
19 that are conducted in the most rigorous manner.

20 Next slide.

21 So this is what happened in terms of
22 withdrawals for mortality. Same numbers up here,

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1 starting with 26 and six. It ends up being 14 for
2 patients who have had a primary -- or have not had a
3 primary endpoint. And the bottom line is we end up
4 with only 4.9 percent withdrawn with no ascertainment
5 percentage for OPT, and one percent for CRT-D. And
6 so 95 percent of patients in the OPT arm basically
7 are followed to a conclusion.

8 Next slide.

9 And so the bottom line on this
10 differential withdrawal is shown here. The measures
11 taken -- an IRB-approved reconsent process, minimize
12 the impact of withdrawals. In addition, the more
13 complete data -- these more complete data -- that is,
14 the data that included the withdrawal -- as it turns
15 out were not qualitatively different from data
16 censored at time of withdrawal.

17 The data really didn't change. It's just
18 more robust. As a result, we do not believe
19 withdrawals adversely affected the results of
20 COMPANION.

21 Next.

22 In summary, the COMPANION patient

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1 population was well balanced across groups. There is
2 no baseline imbalance that could explain the
3 treatment outcomes. In COMPANION, there were
4 statistically significant and clinically meaningful
5 reductions in the primary endpoint of first all-cause
6 mortality or all-cause hospitalization by 20 percent,
7 a 36 percent reduction in all-cause mortality, and a
8 reduction in various cardiac morbidity measurements.

9 And as I just said, the re consent process
10 we don't believe jeopardized the trial and did not
11 create important bias.

12 Thank you.

13 Now, Dr. DeMets will present some
14 statistical considerations.

15 DR. DeMETS: Thank you. I was asked by
16 the Steering Committee to join you today to make a
17 few comments on some of the statistical
18 considerations that were raised in the view of
19 COMPANION.

20 My primary role in this study was to
21 serve as the independent statistician for COMPANION.
22 That was done through a contract between Guidant and

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1 the CRO with the University of Wisconsin. That's my
2 only financial involvement other than payment for the
3 trip to be with you today.

4 So, as I said, my primary role is to
5 support the COMPANION Data Monitoring Committee. I
6 did have the opportunity to be involved a bit with
7 the protocol design at the beginning, and our
8 statistical center was the primary source of data for
9 the New England Journal publication. Some of the
10 analyses that we did were in fact included in the --
11 in your -- in the submission.

12 So I listed here five issues that sort of
13 were raised to some extent during the review process,
14 and I'm going to comment on each of them
15 sequentially.

16 The issue of proportional hazards was
17 raised, and I'd like to just make a few comments.
18 First of all, the Kaplan-Meier curves, which are
19 traditional ways to present time to event, did not
20 make any assumptions about proportional hazards.
21 And, furthermore, the proportional hazards assumption
22 is really not required for the log rank test.

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1 That's testing the null hypothesis.
2 That's a well-known result in sequential literature.

3 So that is not a requirement. There are certainly
4 some -- certain properties where that's not required.

5 As a footnote, the cost proportional
6 hazards model is -- the only covariate in treatment.

7 In fact, it is algebraically identical to the log
8 rank tests. So even for that particular case it's
9 not required.

10 Now, the log rank test certainly has good
11 statistical properties for something we call a
12 stochastic ordering. To the non-statistician, one
13 manifestation of that is that the survival curves
14 don't cross.

15 So if you look at the primary endpoint,
16 which Dr. Bristow just presented to you, the
17 important feature here is that these two survival
18 curves don't cross. This is for all-cause mortality
19 and all-cause hospitalization. And the second slide
20 -- next slide -- for all-cause mortality is -- also,
21 they do not cross.

22 So with regard -- next -- with regard to

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1 the proportional hazards function, one, it's not
2 required for the log rank test. But even so, the
3 hazards are not drastically non-proportional. We
4 looked at this pretty carefully, fitting models,
5 looking at log plots.

6 But, in addition, the sponsor asked Dr.
7 Kenny Larntz, who is a consultant to them, to do some
8 further analysis looking at what he called Schoenfeld
9 residuals, and the correlation between those
10 residuals in time shows no correlation. So from my
11 perspective, as an independent statistician, there
12 really aren't any concerns about applying the log
13 rank test to this particular set of data.

14 Now, we often use hazard ratios as a
15 handy statistic to summarize treatment effect. And,
16 of course, if it's -- if the model, as appropriate,
17 then, is -- as I said, it's a very useful statistic.

18 But even if the hazard ratio is not constant, the
19 simple hazard ratio is still an average of those
20 hazards that may perhaps be changing.

21 However, one could look at other summary
22 statistics. And so relative risk at, say, one year

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1 is one particular way you could summarize the
2 effects. So I've done that for both mortality and
3 mortality plus hospitalization. And as you can see
4 here, the -- whether you look at the hazard ratio or
5 the relative risk at one year, these results don't
6 change a whole lot.

7 Next.

8 Another sometimes common way to summarize
9 time to event data is to look at the median time to
10 failure, and the proper way to do that is to use the
11 Kaplan-Meier curves and look at the 50th percentile.

12 For this particular trial, for mortality, we don't
13 have 50 percent mortality for the patients in this
14 time, so you can't do that.

15 I'll just make the comment that you can't
16 just simply take the observation -- observed failure
17 times and take an average, because that methodology
18 doesn't take into account staggered entry, censoring,
19 and all of those aspects that are factors in real
20 survival time in terms of event trials.

21 Next.

22 The issue of hospitalization is another

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1 important topic. In survival analysis, all of the
2 methods that we use make a very important assumption
3 that the censoring that we look at is independent of
4 the risk -- underlying risk. Well, in COMPANION,
5 clearly mortality is a competing risk for
6 hospitalization, or for any other cause-specific
7 hospitalization for that matter.

8 Thus, the rationale which is traditional
9 in heart failure trials at this point in time, is to
10 look at death plus all-cause hospitalization, or
11 perhaps death plus a cause-specific. You can look at
12 hospitalization alone, and we are often tempted to do
13 that, but just -- you have to keep in mind that in a
14 formal sense there is a potential for bias because of
15 the competing risk, and that's certainly the case
16 here in COMPANION.

17 Mike -- Dr. Bristow talked a little bit
18 about the post-withdrawal events. Again here you
19 have to look at the assumptions that we used to do
20 the analysis. Both the log rank test and the Kaplan-
21 Meier survival curves assume, again, that censoring
22 is independent of the disease process.

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1 Furthermore, intention to treat requires
2 that all patients randomized in all events for the
3 specified endpoint are counted. The definition is
4 consistent with the ICH guidelines in Document E-9.

5 We certainly agree that COMPANION has had
6 informative censoring due to the disproportionate
7 withdrawal in the censoring related to the treatment
8 arm. Therefore, if you just take the data without
9 following the patients up post-withdrawal, you really
10 don't have analysis that is in some sense unbiased.
11 And in a strict sense, it's not valid.

12 The only solution to that problem, and
13 one that's, again, time-honored in clinical trials,
14 is to try to eliminate or minimize the censoring or
15 loss to follow-up. So that requires, as I
16 recommended to the Steering Committee at the
17 conclusion of COMPANION, that they do everything
18 possible to follow those patients up.

19 As Dr. Bristow has shown you -- next
20 slide -- for both the primary endpoint and mortality,
21 we started out with a number -- 80 in OPT arm and 300
22 in the CRT-D arm -- which was from my perspective an

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1 unacceptable high rate to leave on the table. So
2 through the process which you described, we got that
3 number down to the 12 in OPT and four in CRT-D.

4 So it's now down to a number that's --
5 while not perfect, it's certainly consistent with
6 other trials. And the important point, as you said,
7 is we have four -- potentially four patients for whom
8 ascertainment from the time of withdrawal to the end
9 of the study December 1st we don't know.

10 And for mortality, again, we whittled it
11 down to 15 versus six. So I think that I commend the
12 sponsor and the Steering Committee for pursuing this
13 with the vigor it took and the time it took, but I
14 think you need to get those numbers down to that
15 level to eliminate any potential for uncertainty.

16 The issue of alpha allocation, we have
17 two treatment arms to control here. One can divide
18 the .05 alpha in a variety of ways. You can divide
19 it in half. In COMPANION, it was divided .03 versus
20 .02, reflecting the priority and the focus of most
21 importance to the Steering Committee and to the
22 sponsor.

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1 It was stated in the protocol clearly,
2 and it was in the sample size section, and it was
3 discussed and agreed to between the sponsor and the
4 FDA. Survival is, in this study, the leading
5 secondary endpoint, and in some sense the ultimate
6 endpoint for heart failure trials. It has been
7 treated as though it had a separate alpha allocation,
8 and this, again, was discussed and agreed when the
9 sponsor and the FDA had their pretrial discussions.

10 The reason I think this is satisfactory
11 is that mortality is a special endpoint. It's not
12 one that's subject to interpretation, modifications,
13 definitions. And it's the only endpoint that I would
14 grant that special status to. So it is a secondary
15 endpoint with its own .05 alpha, as we have
16 interpreted and presented in the trial.

17 So from my perspective, the alpha
18 allocation for death and hospitalization is
19 appropriate, and the same is true for mortality.

20 The issue of subgroups -- subgroups are
21 intriguing, but they always must be done, analyzed,
22 and looked at cautiously. It's important to remember

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1 that subgroups must be defined properly, and by that
2 we mean using baseline data only. However, even in
3 this setting where we looked at baseline data, we
4 have had problems historically in our heart failure
5 trials.

6 Many of you are familiar with the
7 PRAISE I and PRAISE II trials -- properly-defined,
8 baseline-defined, subgroup was identify an ideology,
9 but, in fact, it was not able to be verified in its
10 subsequent trial in PRAISE II.

11 Well, why is that perhaps? Subgroups are
12 small. The estimates are not reliable, and you
13 expect some variation. From my perspective, you
14 should look at subgroups with what I consider an
15 eyeball test, general overall consistency, don't
16 demand perfect consistency -- you shouldn't expect
17 it. You can use it to validate previous hypotheses
18 and perhaps generate new ones.

19 As Dr. Bristow showed you in COMPANION
20 for the primary endpoint, these hazard ratios are
21 generally pretty consistent, all showing sort of a
22 positive effect with some variation, as you would

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1 expect.

2 Next.

3 Not only is there consistency across the
4 subgroups, but to me what was most remarkable is that
5 COMPANION, like other positive heart failure trials
6 we've seen, shows a remarkable consistency across the
7 primary and the whole portfolio of secondary
8 endpoints, whether it's mortality or mortality plus
9 hospitalization or cause-specific hospitalization,
10 quality of life, life functions, and so forth.

11 So this kind of consistency is what we've
12 seen in other trials that have been already alluded
13 to such as MERIT, CIBIS-II, COPERNICUS.

14 To summarize, the log rank analysis is
15 valid. Portionality hazards is not required.
16 Stochastic ordering is really the -- was really what
17 we really need. The bias from the informative
18 censoring was resolved to the extent possible by the
19 followup. I think the allocation of the alpha is
20 appropriate. Look at subgroups, but look at them
21 cautiously, and, as I said, the overall consistency
22 for me was impressive and consistent with other

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1 trials that I've been involved with.

2 Thank you very much.

3 DR. SAXON: My name is Leslie Saxon. I'm
4 from University of Southern California. My
5 disclosures include the fact that I receive research
6 funds from the sponsor and serve as an advisor. I
7 own no equity.

8 My task today is to describe, first, the
9 safety of CRT-D, the device used in this trial. As
10 way of background, the CONTAK CD device or the CRT-D
11 device used in COMPANION, and the EASYTRAK lead, have
12 been approved in a patient population with current
13 indications for both CRT-D therapy and an ICD. This
14 is based on the results of the CONTAK CD study.
15 There were no OTR or CRT-P device used in COMPANION,
16 and EASYTRAK lead have, in addition, been approved
17 for the COMPANION patient population based on
18 COMPANION exercise substudy data.

19 Nonetheless, adverse event reporting in
20 this trial was complete and inclusive, and adverse
21 events were defined as any undesirable clinical
22 event. Centers were required to report all adverse

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1 events, whether they were related to the device or
2 not. Complications, as a subclassification of AEs,
3 were defined as adverse events resulting in the need
4 for invasive intervention to correct, loss of
5 significant device function, death, or permanent
6 disability. And this was in accordance with FDA
7 guidelines that were established in 2000.

8 Observations were another category of AEs
9 that were defined as events that were resolved non-
10 invasively and were generally transient or
11 reversible. While system safety evaluation in
12 COMPANION was not predefined in the protocol, we did
13 evaluate CRT safety according to the system safety
14 definition, which is that system safety is defined as
15 complications related to any of the implanted
16 components or their -- or the associated implant
17 procedure in those patients who were successfully
18 implanted with the CRT-D system.

19 This is measured as the complication-free
20 rate, and this has been used in previous FDA approved
21 files, and it is measured over a six-month interval
22 post-randomization. It is considered to be

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1 acceptable at a lower bound of 95 percent confidence
2 interval, if the complication-free rate is greater
3 than 70 percent.

4 Other safety definitions utilized in this
5 trial and others include device safety. This is a
6 more inclusive definition than systems safety. It
7 includes both complications and observations related
8 to any of the implanted components or associated
9 implant procedures.

10 This was reported for all patients,
11 randomized to CRT-D devices as opposed to system
12 safety, which is all patients implanted. Patient-
13 related safety is an even broader category, referring
14 to complications or observations associated with the
15 patient's underlying medical condition. This AE is
16 reported for all patients randomized to CRT-D as well
17 as those randomized to optimal pharmacologic therapy,
18 and this excludes adverse events that are
19 attributable to the device or the procedure.

20 These, then, are the system safety
21 results. System-related complications were observed
22 in 12.6 percent. This is of successfully implanted

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1 patients. This gives a complication-free rate of
2 87.4 percent with a 95 percent lower bound of 85.1
3 percent. Those events that occurred in greater than
4 one percent frequency included loss of LV capture
5 observed in 4.6 percent of patients, los of right
6 atrial capture seen in 1.7 percent, and phrenic nerve
7 stimulation in 1.5 percent.

8 The graph to the right shows the percent
9 subsystem related complication-free rate at 87
10 percent, well above the lower acceptance boundary,
11 and equal to or exceeding that of other performed CRT
12 trials.

13 This slide provides the system and device
14 safety data. As I just stated, the system safety
15 percent of patients experiencing a system safety
16 event were 12.6. This number increases when
17 including the graph to the right showing device
18 safety as it includes all patients randomized, not
19 just successfully implanted, in terms of
20 complications but also expands the definition to
21 include observations listed to the right.

22 Patient-related safety -- the more

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1 inclusive category of all patients randomized
2 according to the total complications and
3 observations, are shown in this slide. That's why
4 the numbers are somewhat higher. This would include
5 a total of all complications and observations in the
6 OPT group versus the CRT-D group for more serious
7 complications, and then observations given on the
8 right.

9 This table illustrates the system-related
10 adverse events in all patients successfully implanted
11 through -- from randomization to six months that
12 occurred greater than one percent of the time. The
13 columns in yellow indicate -- I would draw your
14 attention there -- indicate those instances that
15 required an intervention or resulted in a loss of
16 therapy.

17 So while phrenic nerve stimulation was
18 observed in 60 patients, it only required invasive
19 intervention in three. And in one patient, it
20 resulted in loss of therapy due to the need to turn
21 or not to cause -- not to have LV stimulation due to
22 persistent stimulation.

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1 Loss of LV capture threshold was observed
2 in 36 patients, and the majority of this did require
3 a reintervention but was successfully resolved in all
4 but three instances. Loss of RV capture and loss of
5 right atrial capture were also seen and is consistent
6 with other device trials.

7 Okay. The next slide indicates
8 procedure-related adverse events in all patients
9 randomized, and includes things such as post-surgical
10 wound discomfort, hematomas, and coronary sinus
11 traumas. What should be noted, again, is those that
12 required invasive intervention or resulted in loss of
13 therapy. Coronary sinus venous trauma did result in
14 the need for invasive intervention in 1.2 percent of
15 patients but did not result in loss of therapy, only
16 an instance of device infection required, loss of
17 therapy due to the need to remove the device.

18 We'd now like to address the Steering
19 Committee's response -- we'd now like to provide the
20 Steering Committee's responses to the FDA questions.

21 The background to this is that the Steering
22 Committee felt strongly that it would be helpful to

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1 the FDA to comprehensively address the reviewers'
2 questions as part of our presentation.

3 The sponsor shared the FDA Director's
4 comments with the Steering Committee, and the FDA
5 encouraged the sponsor to address these questions
6 through the thoughts of the Steering Committee
7 members.

8 Let's start with the first question from
9 the FDA reviewers, which relates to the
10 hospitalization definition. Number one, please
11 comment on whether modifications to the
12 hospitalization definition impact the interpretation
13 of the primary endpoint. The Steering Committee
14 feels that the hospitalization definition has been
15 applied consistently throughout the trial.

16 The original case report forms dated
17 1999, and submitted with the initial IDE, have the
18 date of hospital admission and discharge and included
19 a note of four-hour need for IV inotrope or
20 vasoactive therapy. Therefore, the hospital data are
21 complete, and the definition was, in fact,
22 consistently applied for the entire study population.

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1 Further, the primary efficacy endpoint
2 hospitalization piece was not, in fact, modified
3 three times or changed three times as was mentioned
4 in one of the reviewer's comments. Rather, the
5 primary endpoint remained the same throughout and
6 included, again, any death, any hospitalization with
7 a calendar date change or use of IV inotropic or
8 vasoactive therapy lasting greater than four hours,
9 administered in an outpatient setting, to treat
10 decompensated heart failure.

11 Adjudicated events needs to have precise
12 definitions for verification and consistencies.
13 Endpoint Committees typically provide these
14 definitions, and these definitions are typically, in
15 addition, refined early in the trial as was the case
16 after four percent of the hospitalizations were
17 adjudicated in this trial.

18 Two, hospitalization definition impact.
19 Please comment on the impact of modifications to the
20 hospitalization definition on the interpretation of
21 the secondary endpoint of mortality. The independent
22 Steering Committee does not agree that the

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1 hospitalization definition was, in fact, modified.
2 The validity of the primary endpoint definition, and,
3 therefore, its statistical significance allow for
4 analysis of secondary endpoints.

5 Further, the all-cause mortality
6 endpoint, as Dr. DeMets suggested, represents a
7 particularly robust outcome and has been a historical
8 gold standard for heart failure device trials.

9 Three -- are the data from the COMPANION
10 clinical trial sufficient to support an expanded
11 patient population for the sponsor's CRT-D device?
12 The Steering Committee feels that this was a large,
13 multi-center clinical trial properly and rigorously
14 conducted under the guidelines of an independent
15 Steering Committee, Data Safety and Monitoring Board,
16 statistical group, and Mortality and Morbidity
17 Committee.

18 The trial design employed an endpoint of
19 all-cause mortality or all-cause hospitalization.
20 The conservative nature of this endpoint required a
21 higher standard of clinical evidence to demonstrate
22 effectiveness. The results are sufficient to support

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1 expanded indications as demonstrated by meeting both
2 the primary and secondary endpoint and, in addition,
3 demonstrating remarkably consistent, multiple
4 relevant positive endpoints across multiple
5 subgroups.

6 Four, indications for use. With respect
7 to statements in the indication for use regarding the
8 primary endpoint -- A) Are the data from COMPANION
9 sufficient to support claims based on the primary
10 endpoint results? This study demonstrated a
11 statistically significant 20 percent reduction for
12 the primary endpoint of all-cause hospitalization or
13 all-cause mortality and support the claims. The
14 secondary endpoint events were consistently
15 adjudicated by the independent Mortality and
16 Morbidity Committee.

17 B) If so, please comment on whether the
18 language of the proposed indications for use
19 statement adequately describes the endpoint. In
20 particular, please discuss whether the term "all-
21 cause hospitalization" is appropriate. We feel that
22 the language accurately describes this endpoint. The

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1 definition of all-cause mortality is identical to
2 that employed by the Morbidity and Mortality
3 Committee in the adjudication process.

4 In addition, we feel that it is a more
5 conservative and more comprehensive methodology than
6 what is typically used or may be used in other heart
7 failure trials such as a cardiovascular or heart
8 failure hospitalization endpoint, and, importantly,
9 is consistent with the pretrial mandate of the FDA.

10 Five, with respect to statements in the
11 indication for use regarding the secondary endpoint
12 of mortality, are the results from the COMPANION
13 clinical trial sufficient to support a mortality
14 benefit claim for the sponsor of CRT-D devices in the
15 COMPANION population?

16 The study demonstrated a statistically
17 significant reduction in time to all-cause mortality
18 of 36 percent. This improvement is in addition to
19 the benefit conferred by optimal pharmacologic
20 therapy. Therefore, the mortality results support
21 this indication.

22 Six, please comment on whether the CRT-D

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1 labeling should characterize the total number of
2 hospitalizations and length of time patients spent in
3 the hospital for the CRT-D and OPT arms of the
4 companion trial. No, we do not think the labeling
5 should reflect this, because the issue of competing
6 risk makes analysis of hospitalization days alone
7 problematic and inaccurate.

8 E) If so, please comment on whether
9 device implant hospitalization should be included as
10 part of that analysis. Again, no, in terms of device
11 implantations. The FDA did approve the study design,
12 which specifically excluded implant hospitalizations
13 from analysis, because to do so would be to give each
14 patient a primary endpoint event at the time that
15 they were admitted to receive device therapy.

16 However, adverse events reporting
17 occurred from the time of randomization and was
18 comprehensive and complete, not from successful
19 device implant as has been employed in other trials.

20 And, therefore, all adverse events were captured and
21 reported in the analysis. Thus, the implant
22 hospitalization and risks are adequately addressed in

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1 the proposed labeling.

2 Seven, please comment on whether the CRT-
3 D labeling should present adverse events from the
4 CRT-D and OPT arms of the COMPANION trial in a
5 consolidated manner that would allow their
6 comparison. The safety of previous CRT-D devices
7 that have been approved has traditionally been based
8 on the system safety definition -- that is,
9 complications related to the implanted system. It is
10 consistent with that methodology.

11 The proposed summary of safety and
12 effectiveness currently lists adverse events from
13 both groups. The sponsor has indicated to the
14 Steering Committee that they are willing to work with
15 the FDA to prepare an appropriate format for
16 accurately presenting adverse events. That is
17 consistent with the pre-agreed investigational plan.

18 Eight, please comment on whether data
19 obtained from patients after withdrawal should be
20 used in any of the analyses described in the device
21 labeling. Again, we emphasize that this trial was
22 designed as an intention to treat trial. Thus, all

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1 data must be included to avoid bias. And any
2 treatment comparison that does not include all events
3 is not valid.

4 In the COMPANION trial, these efforts to
5 complete the data set were designed, in fact, to
6 minimize bias, due to the differential withdrawal
7 rate observed in the OPT group. The Steering
8 Committee felt that it was obligated to make every
9 reasonable effort to ascertain the primary event
10 status of the withdrawn patients.

11 I'd like to conclude by stating that the
12 COMPANION study incorporated a primary endpoint of
13 all-cause mortality and all-cause hospitalization.
14 That is the most rigorous evaluation of CRT therapy
15 performed to date. When added to optimal
16 pharmacologic therapy in patients with moderate to
17 severe heart failure, left ventricular dysfunction,
18 and QRS delay, time to all-cause mortality or all-
19 cause hospitalization was significantly reduced by 20
20 percent.

21 Time to all-cause mortality was
22 significantly reduced by CRT-D therapy -- has a ratio

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1 of .64 by 36 percent.

2 Finally, CRT-D is safe for use in this
3 patient population, with a safety profile similar to
4 or exceeding that demonstrated in prior CRT-D studies
5 performed in less advanced heart failure patients.

6 That concludes our comments on the
7 Steering Committee.

8 ACTING CHAIR LASKEY: Thank you very
9 much, folks. That was all-encompassing.

10 I'd like to, at this point, ask the panel
11 -- we're actually right on schedule. So before we
12 take a break at 11:00, we potentially have a few
13 minutes up here to query the sponsor for the usual
14 burning issues.

15 Dr. Brinker?

16 DR. BRINKER: I realize and agree with
17 the concept that the initial hospitalization for
18 device implant did not count against hospitalization.

19 What I'm a little bit uncertain of is, if a patient
20 had an unsuccessful primary implant, and had as many
21 -- well, numerically many, maybe not proportionately
22 many, patients had one or two or even three more

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1 implant attempts, were the subsequent implant
2 attempts counted as hospitalizations?

3 DR. FELDMAN: Yes. We can actually show
4 you the absolute numbers on that. They are important
5 to look at -- if that's okay.

6 Leslie, do you want to --

7 DR. SAXON: In order to maintain
8 consistency related to this concept of not primary
9 endpoint of ND patients for devices, we, in fact, did
10 not count the second attempt. So there were
11 initially 15 percent of patients who were not
12 successfully implanted. Those that were taken back
13 included -- excuse me. I want to just look at this.

14 So reattempt was not done in 31. The
15 remainder -- 50 -- were taken back for a second
16 attempt, and that -- that was considered an index
17 hospitalization for implant and not counted.

18 DR. BRINKER: I can understand from a
19 physiologic point of view that studying the disease
20 while you review that -- it seems to me that the
21 impact of the second procedure has as much morbidity,
22 if you will, associated with it, possibly more, than

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1 a four-hour hospitalization for a vasoactive drug in
2 an emergency room. So I'm concerned a bit that the
3 bottom line doesn't reflect that.

4 DR. FELDMAN: Well, I think, first of
5 all, we're looking at endpoints not over a short
6 window of time, which is what you're looking at with
7 a reimplant. But in this trial we were really
8 looking at endpoints over a very long period of time.

9 And the two endpoints that we're most concerned with
10 in caring for a heart failure patient is either
11 mortality or hospitalization.

12 We want patients to live longer, and we
13 want them to feel better. So I think we recognize
14 the fact that upfront there is a certain procedural
15 intervention that is associated either with putting
16 the device in, or in a very small number of patients
17 putting a device in a second intervention if you
18 will. But over the long term we're looking at what
19 happens to these patients, and I think that's a more
20 appropriate comparator.

21 DR. BRINKER: Well, let me just take this
22 to -- a little further. I think that a second and

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1 third and perhaps even fourth reoperation for a
2 failed implant is not a short-term issue necessarily,
3 number one. Number two, we are looking at single
4 events as indices of an endpoint, in terms of
5 hospitalization.

6 So one issue would be that these single
7 events in some ways are used as surrogates for the
8 likelihood of the patient having a worsening -- a
9 worse clinical status that extends beyond that single
10 event. And that's one justification for treating in
11 a single hospitalization as an endpoint, if it got
12 heart failure therapy, let's say, for four hours
13 versus a second implant.

14 But I -- it's not absolutely clear to me
15 that one single hospitalization for four hours of
16 vasoactive therapy is, in fact, an issue that
17 indicates a worsened -- prolonged worsened state of
18 heart failure. So one question that I would ask you
19 is: do you have any information about cumulative per
20 patient hospitalizations?

21 Does one hospitalization always mean that
22 over a period, a year or two, that these people would

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1 be repeat? Or did many of them, in fact, have only
2 one hospitalization? And that would be equatable to
3 a repeat surgical procedure for implant.

4 DR. BRISTOW: Before we address that
5 issue, let me just add a little more comment on your
6 first point. The patients in the OPT group who
7 dropped in for devices, those hospitalizations, those
8 elected an implant hospitalization also didn't count.

9 So we consistently applied the standard that if it
10 was an implant hospitalization, done electively, out
11 of the context of any other reason to hospitalize,
12 that wouldn't count, just like it -- up front, so
13 that --

14 DR. BRINKER: Well, but again, I make the
15 differentiation between a primary implant, which
16 is --

17 DR. BRISTOW: Right.

18 DR. BRINKER: -- I agree should not be
19 counted against it.

20 DR. BRISTOW: Right.

21 DR. BRINKER: But second and third means
22 that there was a problem with the first, and that

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1 being assigned to that therapy imposes an additional
2 risk.

3 DR. BRISTOW: Well, and that could
4 possibly be. We'll try to comment further. But I
5 want to make the point, shown on this slide, that an
6 implant hospitalization is not the same thing as any
7 other kind of hospitalization for a heart failure
8 patient.

9 So this gives the duration in days of
10 hospitalization for implants. And notice the
11 implants in the OPT group. These are the drop-in
12 implants around three days versus what happens with a
13 medical hospitalization if you will, getting up close
14 to eight days' duration.

15 So it's a completely different thing in
16 terms of the impact on a patient and what it means in
17 terms of natural history, we would argue, whether
18 it's a device implant related or it's a real
19 medically-driven hospitalization.

20 Now, in terms of what happens, if you get
21 hospitalized once, does that set you up for
22 subsequent hospitalizations? The answer for a heart

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1 failure patient is yes. What can we provide from
2 COMPANION to support that? We have the multiple
3 hospitalization backup slide.

4 We don't have -- we probably can't give
5 you direct evidence that you're looking for. But as
6 you'll see on the clustering of number of
7 hospitalizations, there are many patients
8 hospitalized multiple times, which is the expected --
9 one hospitalization begets further hospitalization.
10 That's, in fact, why we have that as an inclusion
11 criteria, because we know it increases the event rate
12 for hospitalization to have a historical
13 hospitalization by two- to threefold in fact, as well
14 as a mortality rate.

15 DR. FELDMAN: While we're looking for
16 that, let me make one other comment, and then I think
17 Dr. Saxon wants to make a comment as well. You
18 mentioned the fact that there were three or four
19 attempts in patients. In fact, only three patients
20 had a second attempt. No patients had three or four
21 attempts, and --

22 DR. BRINKER: My reading of that was that

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1 -- you mean a second attempt after the first one.

2 DR. FELDMAN: Right. Here's the actual
3 data.

4 DR. BRINKER: So that's three. That's
5 three procedures.

6 DR. FELDMAN: Right.

7 DR. BRINKER: That's what I was referring
8 to.

9 DR. FELDMAN: But that only occurred in
10 three patients.

11 DR. BRINKER: Right.

12 DR. FELDMAN: And here is the data. So
13 you can see that --

14 DR. BRINKER: But two occurred in, what,
15 15 percent, did you say?

16 DR. FELDMAN: No, no, only -- excuse me
17 -- 8.4 percent. So here's the actual data. Here's
18 98.8 percent, here's the success rate for the first
19 attempt, here's a first reattempt and the success
20 rate, and here's the second reattempt and the success
21 rate. But here you only see three patients, and here
22 you only have 50 patients out of a total of 588

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1 patients. So a very small number had to be --

2 DR. BRINKER: Well, in here it's eight
3 percent had at least one more, and half a percent had
4 at least two more. So these, as you know from
5 watching some of these procedures, especially ones
6 that are complicated the first time, can be long
7 duration, high radiation exposure, a lot of other
8 morbidity, both on the patient and the physician.

9 So they're not easy things, and I was
10 just trying to equate this with the four-hour drug --
11 now, the fact has been brought up that the average
12 time in the hospital for events, where it was
13 actually quite long mean time, in the range of eight
14 days, suggests that actually the -- suggests to me at
15 least something that I didn't see quickly before in
16 your data, and that is that the absolute number of ER
17 or physician visits that resulted in a four-hour
18 infusion made up presumably a very small number of
19 the actual hospitalizations.

20 DR. BRISTOW: Yes, 2.5 percent of the
21 total primary endpoints. 2.5 percent on the average
22 between the two treatment arms was -- the IV was

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1 really a trivial number of events as a contributor to
2 the primary event.

3 DR. FELDMAN: Leslie, do you want to
4 comment?

5 DR. SAXON: Just a couple of additional
6 comments specific to your concern related to the
7 second first attempt. Number one, we did capture all
8 significant morbidities that may have occurred as a
9 result of that second attempt hospitalization. While
10 the hospitalization didn't count against the primary
11 endpoint, any badness or major morbidity associated
12 with that was, in fact, counted, as was every AE that
13 was then adjudicated by the Data Safety and
14 Monitoring Board.

15 The other piece is that because we
16 understood what this procedure involved, and I myself
17 have implanted many of these devices, what we
18 encouraged investigators to do in the trial was if
19 the trial exceeded four hours, or there were issues
20 related to difficulty in cannulating the cornerstones
21 or one of the other technical pieces, that they feel
22 free to bring the patient back.

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1 So a reattempt was considered something
2 that could occur in order to limit implant time,
3 limit potential morbidity, and this was the consensus
4 after looking at the early data and just with our
5 knowledge of the procedure itself. So I think that
6 the -- you know, to focus on that second attempt as
7 being a potentially more morbid event is, in fact,
8 not true in many of the cases, that we encourage
9 people to stop, think about the case, and take the
10 patient back, rather than -- if that patient had any
11 particular features that were --

12 DR. FELDMAN: Mike, did you find that
13 slide? Okay.

14 ACTING CHAIR LASKEY: Thank you.

15 Dr. Krucoff, do you have --

16 DR. KRUCOFF: Just a quick question about
17 the communication pattern. I'm sure, being as it's
18 you guys, you can understand one of the things we're
19 going to try and do or wrestle with is to understand
20 where all of these changing definitions or just
21 issues seem to have arisen between what you know is
22 coming in the FDA's view of the strong events, and

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1 ultimately have an understanding.

2 You had a couple of slides that were put
3 up on data flow process, and several of you have
4 commented on that. And I wonder, is anybody here
5 from the external CRO? Or can anybody help me
6 understand the background link of what data flowed
7 from the external CRO to the sponsor, and ultimately,
8 along the way, what the process was, then, for
9 communicating as definitions were refined or evolved
10 over the course of the trial in communicating back to
11 FDA?

12 MR. WHITE: Hi. I'm Bill White,
13 President and CEO of C2R. We were the external CRO
14 involved with this trial. As the slide presents,
15 what we were entailed with doing -- what we did for
16 the M&M Committee was very simple. We collected all
17 of the case report forms that came in from the
18 centers, and then we went through a laborious process
19 of accumulating the discharge summaries and the
20 supporting documentation and hospital records.

21 We prepared case narratives for every
22 case. That included a summary of the

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1 hospitalizations, all the case report forms, all of
2 the documentation, and we prepared those in booklets
3 for every meeting. The meetings were then scheduled
4 on a routine basis with the committee, at which time
5 we would send the books out from our office to the
6 members of the committee.

7 We would send individual booklets to the
8 primary and secondary reviewers, and they would make
9 all booklets available to the committee for the
10 meetings. During the meetings for the M&M
11 Committees, we were always present, minutes were
12 taken, all of the votes -- the material was reviewed,
13 the adjudication process was documented, case report
14 forms were filled out, all case report forms for the
15 adjudication process were then signed by the
16 Chairman, which is Dr. Carson.

17 At that point, all of the books were
18 retained by us, and brought back to our office. At
19 that point, what we did with the data was that data
20 became part of the official database, in our clinical
21 trial database, and that data was forwarded on a
22 period basis with our monthly transmittals to the

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1 independent statistician, Dr. DeMets' group.

2 We did not forward any data at any time
3 to the sponsor. The data always went from our
4 office, from the M&M Committee case report form, to
5 the independent statistician who did his analysis and
6 then reported it to the Data and Safety Monitoring
7 Board.

8 So that's what we did.

9 DR. KRUCOFF: Okay. So then, David, your
10 data would go directly to the DSMB, one way?

11 DR. DeMETS: Yes. We prepared sort of an
12 additional detailed monitoring report, which covered
13 things from recruitment to primary safety, the whole
14 double package, and we reported to the Monitoring
15 Committee. At no time did we communicate anything
16 about those reports to the sponsor. The only
17 communication was with the Data Monitoring Committee,
18 with the one exception that was noted when we had a
19 discussion with the FDA about a different matter.

20 DR. KRUCOFF: That was the coronary
21 sinus --

22 DR. DeMETS: Yes, that's right.

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1 DR. KRUCOFF: Okay. And then, is it fair
2 to say -- can somebody say the feedback from the line
3 from DSMB to Steering Committee is simply the sort of
4 go/no-go kind of communication, generic --

5 DR. DeMETS: Yes. The Chairman of the
6 Steering Committee wrote a very perfunctory letter
7 saying the committee met, reviewed the data, and
8 recommended to continue.

9 DR. KRUCOFF: And then, the Steering
10 Committee to the sponsor communications, can somebody
11 characterize what those were likely to be?

12 DR. BRISTOW: Yes. The sponsor had a
13 representative in an ex officio sense on Steering
14 Committee calls. And whenever the Steering Committee
15 -- in addition to that, whenever the Steering
16 Committee thought there was an issue requiring
17 sponsor input, we would communicate with them
18 directly.

19 DR. FELDMAN: Does that --

20 DR. KRUCOFF: That was very helpful.
21 Thanks. Maybe we can get --

22 ACTING CHAIR LASKEY: Yes, Dr. Yancy.

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1 DR. YANCY: Just two questions. The
2 first one is within the context of what Dr. Carson
3 shared with us. Looking at slide 56, it's evident
4 that the actual admit rates were higher than
5 projected. And so for clarification purposes, since
6 Dr. Saxon addressed the hospitalization question
7 quite substantially, was the change in
8 hospitalization more an operational change, so that
9 it would be easier for them to track and follow as
10 opposed to trying to enrich the event rate?

11 Because that has been a problem of a
12 number of heart failure trials, and has necessitated
13 a change in hospitalization. It looks as if this was
14 more for the purposes of accurate data tracking. If
15 you could just clarify that, if you would.

16 DR. CARSON: Yes. The change in the
17 completing of the definition, if you will, for
18 hospitalization, then, was related to trying to make
19 verifiable data possible. We had thought that a 24-
20 hour endpoint would be a reasonable one to use. And
21 as I had said in my comments, during the previous
22 trials that had used this endpoint -- maybe we could

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1 just go to backup slide 2.

2 This had been the endpoint that had been
3 used. This was the way the -- the definition,
4 really, for hospitalization has been an evolving one.

5 You are very well aware that all-cause mortality had
6 been the gold standard for trials for many years.

7 We didn't really see hospitalizations
8 being adjudicated or included in primary endpoints,
9 really, until the PRAISE trial in 1993. And that had
10 a -- CV morbidity was a hospitalization for life-
11 threatening CV cause, and it was for greater than 24
12 hours.

13 MERIT heart failure did all-cause
14 mortality and all-cause hospitalization, and they
15 started with a visit that was described in the
16 protocol as being greater than 24 hours. But yet, if
17 you look in their methods -- their methods paper, you
18 find that the Endpoint Committee added a calendar
19 date change if the dates -- if the times couldn't be
20 verified.

21 VALHeFT had nothing in the primary
22 protocol about time of hospitalization. The Endpoint

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1 Committee added on 24-hour duration, and then I
2 chaired that committee and we realized that we
3 weren't getting verifiable discharge times in many
4 patients, particularly foreign sites. So we went to
5 a calendar date change.

6 And then -- now, COMPANION fits in a
7 little bit between VALHeFT and -- I have Overture on
8 the bottom there. And we thought because we were at
9 U.S. centers that we might be able to get admission
10 and discharge times. The data, as you saw on the
11 adjudication form, was in terms of calendar date
12 change. When the committee looked within the records
13 and tried to find the discharge times, we found that
14 we couldn't always do that.

15 And we felt we were vulnerable, then, to
16 a group coming back and saying to us, "Well, could
17 you really verify that these were 24-hour times?
18 Could you really get the discharge times?" We would
19 have had to say we couldn't always get those.

20 So we felt that a 24-hour date change was
21 not something that was verifiable enough for this
22 endpoint, and we felt that a calendar date change,

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1 which had then been evolving into being really the
2 standard for clinical trials, was what we should use.

3 That was after a small number of events had been
4 done, so it was entirely for date clarity.

5 DR. DeMETS: Just a further comment. We
6 didn't convey any sense of event rates to anybody.
7 It would have been difficult for them to keep score.
8 They perhaps could have with a -- but they -- it
9 wasn't something they were aware of the dates, so
10 they didn't know anything about event rates at that
11 point in time.

12 DR. BRISTOW: Well, I will underscore
13 that. We have been under the assumption that it was
14 going to take 2,200 patients to achieve this 1,000
15 target events. And, in fact, when we were called in
16 to the DSMB in November 2002 and said that you've got
17 your target number of events, we were, frankly,
18 shocked that the event rate was that high. We had no
19 sense that the event rate was that high on the
20 Steering Committee.

21 DR. YANCY: One other question, Dr.
22 Carson. Given the threshold that you set for the

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