U.S. FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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THURSDAY
MARCH 1, 2007

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The Panel convened at 8:00 a.m. at the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, William H. Maisel, M.D., M.P.H., Chairperson, presiding.

PRESENT:

WILLIAM H. MAISEL, M.D., MPH	Chairperson
EUGENE H. BLACKSTONE, M.D.	Consultant
JEFFREY S. BORER, M.D.	Consultant
JEFFREY A. BRINKER, M.D.	Consultant
MICHAEL J. DOMANSKI, M.D.	Consultant
GREGORY A. EWALD, M.D.	Consultant
PAUL J. HAUPTMAN, M.D.	Consultant
NORMAN S. KATO, M.D.	Consultant
SHARON-LISE NORMAND, Ph.D.	Voting Member
RICHARD L. PAGE, M.D.	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
JOHN R. TEERLINK, M.D.	Consultant
MARCIA S. YAROSS, Ph.D.	Industry Representative
MIKE FLEMING, DDS, P.A.	Consumer Representative

2007-4284 +1

FDA PARTICIPANTS:

JAMES P. SWINK	Executive Secretary
BRAM ZUCKERMAN, M.D.	Director, Division of Cardiovascular Devices
NILSA LOYO-BERRIOS, Ph.D.	Epidemiology Branch, Division of Postmarket Surveillance Office of Surveillance and Biometrics
RANDALL BROCKMAN, M.D.	FACC Division of Cardiovascular Devices, Office of Device Evaluation
MATTHEW HILLEBRENNER, MSE	Division of Cardiovascular Devices, Office of Biostatistics and Biometrics

SPONSOR PRESENTERS:

WILLIAM T. ABRAHAM,M.D.	Davis Heart & Lung Research Institute
PHILIP B. ADAMSON,M.D.	Director, The Heart Failure Institute at Oklahoma Heart Hospital
ROBERT C. BOURGE, M.D.	UAB Heart and Vascular Research Center, University of Alabama at Birmingham
JACK GERMANSON	
CHARLES J. LOVE, M.D.	Ohio State University
VEN MANDA	
BRANDON SPARKS, Ph.D.	
DAVID M. STEINHAUS, M.D.	Vice President and Medical Director, Medtronic, Inc.
LYNNE WARNER STEVENSON, M.D.	Harvard Medical School
MICHAEL ZILE, MD.	Medical University of South Carolina

I-N-D-E-X

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

2 (8:00 a.m.)

3 CHAIRPERSON MAISEL: Good morning.

4 I would like to call this meeting of the

5 Circulatory System Devices Panel to order.

6 I am Dr. William Maisel and Chair

7 of this Panel. I am a cardiologist from Beth

8 Israel Deaconess Medical Center in Boston.

9 If you haven't already done so,

10 please sign the attendance sheets that are on

11 the tables by the doors. If you wish to

12 address this Panel during one of the open

13 public sessions today, please provide your

14 name to Ms. AnneMarie Williams who is out at

15 the registration table.

16 If you are presenting in any of

17 the open public sessions today and have not

18 previously provided an electronic copy of your

19 presentation to the FDA, please arrange to do

20 so with Ms. Williams.

21 I note for the record that the

22 voting members present constitute a quorum, as

1 required by 21 CFR Part 14. I would also like
2 to add that the Panel participating in the
3 meeting today has received training in FDA
4 device law and regulations.
5 I would like to remind the
6 attendees here today to silence their
7 cellphones and pagers, please, and at this
8 point I will invite the Executive Secretary of
9 the Circulatory System Devices Panel, James
10 Swink, to make some introductory remarks.
11 MR. SWINK: I will read into the
12 record the conflict of interest statement.
13 The Food and Drug Administration
14 has convened today's meeting of the
15 Circulatory system Devices Panel of the
16 Medical Devices Advisory Committee of the
17 Center for Devices and Radiological Health
18 under the authority of the Federal Advisory
19 Committee Act of 1972.
20 With the exception of the industry
21 representative, all members and consultants of
22 the Panel are Special Government Employees or

1 regular Federal employees from other agencies
2 and are subject to Federal conflict of
3 interest laws and regulations.
4 The following information on the
5 status of this Panel's compliance with Federal
6 ethics and conflict of interest laws covered
7 by, but not limited to, those found at 18
8 U.S.C., Section 208, are being provided to
9 participants in today's meeting and to the
10 public. FDA has determined that members and
11 consultants of this Panel are in compliance
12 with Federal ethics and conflict of interest
13 laws.
14 Under 18 U.S.C., Section 208,
15 Congress has authorized FDA to grant waivers
16 to Special Government Employees who have
17 financial conflicts when it is determined that
18 the agency's need for a particular
19 individual's service outweighs his or her
20 potential financial conflict of interest.
21 Members and consultants of this Panel who are
22 SGEs have been screened for potential

1 financial conflicts of interests of their own
2 as well as those imputed to them, including
3 those of their employee, spouse or minor
4 child, related to the discussion of today's
5 meeting.
6 These interests may include
7 investments, consulting, expert witness
8 testimony, contracts, grants, CRADAs,
9 teaching, speaking, writing, patents and
10 royalties, and primary employment.
11 Today's agenda involves the review
12 and discussion of a pre-market approval
13 application sponsored by Medtronic, Inc. for
14 the Chronicle Implantable Hemodynamic Monitor
15 System. This implantable device is intended
16 to reduce hospitalization events or equivalent
17 events for worsening heart failure in patients
18 with moderate to advanced heart failure.
19 Based on the agenda for today's
20 meeting and all financial interests reported
21 by the Panel members and consultants, a
22 conflict of interest waiver has been issued in

1 accordance with 18 U.S.C, Section 208(b)(3) to
2 Dr. Gregory Ewald.
3 The waiver for Dr. Gregory Ewald
4 was issued for his employer's pending grants
5 with the sponsoring firm for which he has no
6 involvement in the amount of funding that is
7 to be determined. The waiver allows this
8 individual to participate fully in today's
9 deliberations.
10 Copies of this waiver may be
11 obtained by visiting the agency's web site at
12 www.fda.gov or by submitting a written request
13 to the agency's Freedom of Information Office,
14 Room 6-30 of the Parklawn Building.
15 A copy of this statement will be
16 available for review at the registration table
17 during this meeting, and will be included as
18 part of the official transcript.
19 Marcia S. Yaross, Ph.D., is
20 serving as the industry representative, acting
21 on behalf of all related to industry, and is
22 employed by Biosense Webster, a Johnson &

1 Johnson company.

2 We would like to remind members
3 and consultants that, if the discussions
4 involve any other products of firms or firms
5 not already on the agenda for which the FDA
6 participant has a personal or imputed
7 financial interest, the participants need to
8 exclude themselves from such involvement, and
9 their exclusion will be noted for the record.

10 FDA encourages all other
11 participants to advise the Panel of any
12 financial relationships that they may have
13 with any firms at issue. Thank you.

14 I will now read the temporary
15 voting members statement.

16 Pursuant to the authority granted
17 under the Medical Devices Advisory Committee
18 charter dated October 27, 1990, and amended
19 August 18, 2006, I appoint the following as
20 voting members of the Circulatory System
21 Devices Panel for the duration of this meeting
22 on March 1, 2007: Dr. Eugene H. Blackstone;

1 Dr. Jeffrey A. Brinker; Dr. Michael J.
2 Domanski; Dr. Gregory A. Ewald; Dr. Paul J.
3 Hauptman; Dr. Norman S. Kato.
4 For the record, these people are
5 Special Government Employees and are
6 consultants to this Panel or another panel
7 under the Medical Devices Advisory Committee.
8 They have undergone the customary conflict of
9 interest review and have reviewed the material
10 to be considered at this meeting.
11 This is signed by Daniel G.
12 Schultz, M.S., Director, Center for Devices
13 and Radiological Health, dated February 22,
14 2007.
15 Pursuant to the authority granted
16 under the Medical Devices Advisory Committee
17 charter of the Center for Devices and
18 Radiological Health dated October 27, 1990,
19 and as amended August 18, 2006, I appoint
20 Jeffrey S. Borer, M.D., and John R. Teerlink,
21 M.D., as voting members of the Circulatory
22 System Devices Panel for the duration of the

1 meeting on March 1, 2007.

2 For the record, Dr. Borer and Dr.
3 Teerlink serve on the Cardiovascular and Renal
4 Drugs Advisory Committee of the Center for
5 Drug Evaluation and Research. Dr. Teerlink is
6 a member, and Dr. Borer is a consultant to the
7 committee. They are Special Government
8 Employees and have undergone the customary
9 conflict of interest review and have reviewed
10 the material to be considered at this meeting.

11 This is signed by Randall Lutter,
12 Ph.D., Associate Commissioner for Policy and
13 Planning. Thank you.

14 CHAIRPERSON MAISEL: Thank you,
15 James.

16 Today, the Panel will be making a
17 recommendation to the Food and Drug
18 Administration on the pre-market approval
19 application P050032 for the Medtronic
20 Chronicle Implantable Hemodynamic Monitoring
21 System.

22 The Chronicle Implantable

1 Hemodynamic Monitor System is indicated for
2 the chronic management of patients with
3 moderate to advanced heart failure who are in
4 New York Heart Association Class 3 or 4 to
5 reduce hospitalizations for worsening heart
6 failure in these patients.
7 Before we go around and introduce
8 the Panel members, I would like to remind the
9 Panel that to press the button on the front of
10 your microphone, the red light will come on,
11 and that means your mike is live. Turn it off
12 when you are done speaking. Only four
13 microphones can be on at a time. So you need
14 to remember to turn them off or I will remind
15 you.
16 At this point, I would like to
17 introduce our Panel members, or have them
18 introduce themselves, and I will start on my
19 left with Dr. Zuckerman.
20 DR. ZUCKERMAN: Bram Zuckerman,
21 Director, FDA Division of Cardiovascular
22 Devices.

1 DR. DOMANSKI: Mike Domanski, and
2 I am a cardiologist at the National Heart,
3 Lung and Blood Institute and Chief of the
4 Atherothrombosis and Coronary Artery Disease
5 Branch.
6 DR. PAGE: Richard Page, head of
7 Cardiology at University of Washington in
8 Seattle.
9 DR. BLACKSTONE: Eugene
10 Blackstone, head of clinical research at
11 Department of Thoracic Cardiovascular Surgery
12 at Cleveland Clinic.
13 DR. TEERLINK: John Teerlink,
14 Director of Heart Failure at the San Francisco
15 VA Medical Center and on the faculty at UCSF.
16 DR. SOMBERG: John Somberg,
17 Professor of Medicine and Pharmacology, Rush,
18 Chicago.
19 DR. KATO: Norman Kato, private
20 practice, cardiothoracic surgery, Los Angeles,
21 California.
22 MR. SWINK: James Swink, Executive

1 Secretary for the Circulatory System Devices
2 Panel.
3 DR. NORMAND: Sharon-Lise Norman.
4 I am a Professor of Health Care Policy and
5 Biostatistics in Harvard Medical School and in
6 Harvard School of Public Health.
7 DR. EWALD: Gregory Ewald. I am
8 the Director of the Heart Failure and
9 Transplant Program at Washington University in
10 St. Louis.
11 DR. BRINKER: Jeff Brinker,
12 Professor of Medicine and Radiology, Johns
13 Hopkins University.
14 DR. BORER: I am Jeff Borer. I am
15 a cardiologist at Cornell in New York where I
16 direct the Division of Cardiovascular
17 Pathophysiology and the Howard Gillman
18 Institute.
19 DR. HAUPTMAN: Paul Hauptman,
20 cardiologist, St. Louis University School of
21 Medicine.
22 DR. FLEMING: Dr. Mike Fleming.

1 I'm the consumer representative on the Panel
2 today.
3 DR. YAROSS: Marcia Yaross, Vice
4 President, Clinical Quality Regulatory and
5 Health Policy, Biosense Webster in Diamond
6 Bar, California, and I am the industry
7 representative.
8 CHAIRPERSON MAISEL: Thank you.
9 At this point, we will proceed with the open
10 public hearing portion of the meeting.
11 Both the Food and Drug
12 Administration and the public believe in a
13 transparent process for information gathering
14 and decision making. To ensure such
15 transparency at the open public hearing
16 session of the Advisory Committee meeting, FDA
17 believes that it is important to understand
18 the context of any individual's presentation.
19 For this reason, FDA encourages
20 you, the open public hearing or industry
21 speaker, at the beginning of your written or
22 oral statement to advise the committee of any

1 financial relationship that you may have with
2 the sponsor, its product and, if known, its
3 direct competitors.
4 For example, this financial
5 information may include the sponsor's payment
6 of your travel, lodging or other expenses in
7 connection with your attendance at the
8 meeting.
9 Likewise, FDA encourages you at
10 the beginning of your statement to advise the
11 committee if you do not have any such
12 financial relationships. If you choose not to
13 address this issue of financial relationships
14 at the beginning of your statement, it will
15 not preclude you from speaking.
16 At this point, I would like to ask
17 if there is anyone who would like to speak at
18 the open public hearing portion of this
19 meeting. Seeing no one, we will close the
20 open public portion session and proceed on to
21 the sponsor presentation for the Medtronic
22 Chronicle Implantable Hemodynamic Monitoring

1 System.

2 I would like to remind public
3 observers at the meeting that, while this
4 meeting is open for public observation and
5 there are portions during which the public may
6 participate, public attendees may not
7 participate except at the specific request of
8 the Panel.

9 So I would like to invite the
10 sponsor to begin their presentation.

11 DR. STEINHAUS: Good morning. My
12 name is David Steinhaus. I am the Vice
13 President and Medical Director of the Cardiac
14 Rhythm and Disease Management Division at
15 Medtronic.

16 On behalf of the company and all
17 the Chronicle investigators, we appreciate the
18 opportunity to review our clinical experience
19 with the Chronicle Implantable Hemodynamic
20 Monitoring System.

21 Our journey with hemodynamic
22 monitoring began 15 years ago when Medtronic

1 initiated research with a novel pressure
2 sensing lead placed in the right ventricle.
3 Early feasibility studies demonstrated that we
4 could measure and retrieve accurate long term
5 intracardiac pressure data from an implanted
6 sensor. These early studies also served as
7 the foundation for future sensor based lead
8 design, development and implantation.
9 In 1998, Medtronic initiated
10 chronic human studies to confirm the accuracy,
11 reliability, and safety of a new implantable
12 hemodynamic monitoring system called the
13 Chronicle IHM.
14 This system was developed, because
15 physicians expressed the need for a better
16 approach to monitor volume status in heart
17 failure patients. Today's presentation
18 reflects many years of research and commitment
19 to fulfilling this goal.
20 We recognize the challenge, given
21 that our pivotal trial, the COMPASS-HF, did
22 not meet its primary pre-specified

1 effectiveness endpoint. It is not our intent
2 to discount the statistical findings of this
3 study. However, the clinical experience that
4 will be presented today confirms the
5 physiologic basis underlying Chronicle IHM and
6 provides reasonable assurance that the system
7 is safe and effective.
8 The Chronicle Implantable
9 Hemodynamic Monitoring System provides
10 clinicians with accurate information on
11 continuous intracardiac pressure as a measure
12 of volume status in the ambulatory setting.
13 Therefore, the proposed indication for use is
14 as follows:
15 The Chronicle IHM system is
16 indicated for the chronic management of
17 patients with moderate to advanced heart
18 failure who are New York Heart Association
19 Class III or IV to reduce hospitalizations for
20 worsening heart failure.
21 It is my pleasure to introduce the
22 following COMPASS-HF investigators: Dr.

1 William Abraham from the Ohio State
2 University; Dr. Philip Adamson from the
3 Oklahoma Heart Hospital; Dr. Robert Bourge
4 from the University of Alabama at Birmingham -
5 - Dr. Bourge also served as our Chairman of
6 the COMPASS-HF study; Dr. Charles Love from
7 the Ohio State University; Dr. Lynne Stevenson
8 from Brigham and Women's Hospital; Dr. Michael
9 Zile from the Medical University of South
10 Carolina.
11 Dr. Stevenson will begin today's
12 agenda by highlighting the current state of
13 volume management in the treatment of chronic
14 heart failure.
15 Next, Dr. Adamson will describe
16 the components of the Chronicle system and
17 review the clinical experience gained during
18 the Phase I and II study.
19 Dr. Bourge will then review the
20 COMPASS-HF study, a randomized, controlled
21 trial that evaluated the clinical impact of
22 IHM guided care.

1 It is now my pleasure to invite
2 Dr. Lynne Stevenson to discuss the physiologic
3 basis for volume management.
4 DR. STEVENSON: Thank you very
5 much, Dr. Steinhaus.
6 I am a consultant for Medtronic,
7 an investigator in the Chronicle program. I
8 have received research support, and have no
9 financial interest in the company.
10 To provide a background for
11 today's discussion, my presentation will
12 highlight the following points: Symptoms of
13 congestion and elevated filling pressures
14 dominate the clinical picture of heart failure
15 hospitalizations, regardless of ejection
16 fraction.
17 Reduction of these elevated
18 filling pressures improves symptoms during
19 hospitalization. Serial assessment and
20 therapy for elevated filling pressures in the
21 outpatient setting is a Level I recommendation
22 for chronic heart failure management, leading

1 to the most common intervention that we make
2 after heart failure hospitalization, which is
3 in diuretics, but is currently is based on
4 unreliable information.
5 Recurrent heart failure events
6 contribute to disease progression and worse
7 prognosis.
8 Finally, I will suggest that a new
9 strategy for volume management is needed.
10 Data from the acute decompensated
11 heart failure registry and the European heart
12 failure survey in over 120,000 consecutive
13 patients show that over 75 percent of
14 admissions for heart failure are due to
15 worsening of chronic heart failure rather than
16 to a new presentation of heart failure.
17 Although heart failure is often
18 assumed to be primarily a low output state,
19 the minority of overall admissions are
20 characterized by clinical hypoperfusion, and
21 most often we find ourselves dealing with a
22 congestive syndrome rather than a low output

1 state.

2 The ADHERE Registry has shown us
3 that most of these patients exhibit evidence
4 of volume overload, as indicated by dyspnea at
5 rest or minimal exertion, pulmonary congestion
6 and peripheral edema.

7 Interestingly, about half of the
8 patients who present with heart failure have
9 preserved ejection fraction, but even among
10 those with low ejection fraction the average
11 systolic blood pressure at the time of
12 admission is 140 millimeters of mercury,
13 highlighting once more the relative
14 infrequency of a low output state in this
15 population.

16 In addition to triggering the
17 symptoms in hospitalizations, elevated cardiac
18 filling pressures and related measures are
19 consistent prognostic factors. They define
20 Class IV heart failure, and they are
21 associated, although not linearly or
22 predictably, with naturitic peptide levels

1 which also predict poor outcome.

2 The high filling pressures that we
3 measure predict worse outcome, whether they
4 are measured in the right atrium, the
5 pulmonary artery, or the pulmonary capillary
6 wedge position.

7 The echocardiographic features of
8 elevated filling pressures are all predictors
9 of worse outcome as well, including mitral and
10 tricuspid regurgitation.

11 So the goal of treatment during
12 and after a heart failure hospitalization
13 should be to relieve these elevated filling
14 pressures.

15 During hospitalization for
16 worsening heart failure, as tracked during the
17 NHLBI ESCAPE trial, on average there was a net
18 loss of about 3.5 kilograms of fluid,
19 reduction of jugular venous pressure to normal
20 levels, resolution of edema and dyspnea as
21 demonstrated, and when measured, the filling
22 pressures were lowered as indicated here by

1 the wedge pressure with reduction of 8
2 millimeters in right atrial pressure with a
3 reduction of 4 millimeters.
4 These reductions were associated
5 with a 25-point improvement in the Worst
6 Symptom Score on a scale from 1 to 100.
7 The degree of improvements in
8 symptoms correlated closely with the reduction
9 in pulmonary capillary wedge pressure. This
10 is shown here for shortness of breath, for
11 improvement in the Worst Symptom, whatever
12 that was, and for improvement in the global
13 score.
14 As you can see here, the biggest
15 improvement in symptoms is shown here in the
16 green bar. These were patients who had a
17 reduction of pulmonary capillary wedge
18 pressure of at least 33 percent during
19 hospitalization, which was about half of the
20 patients.
21 Once patients are discharged from
22 the hospital, the goal is to try to keep their

1 volume status in check. If we look at what
2 actually happens, we do make a lot of
3 interventions for fluid management.
4 This is a study done in patients
5 following discharge from heart failure
6 hospitalization, looking at all the
7 interventions that were made during the next
8 three months.
9 As you can see here, the vast
10 majority of interventions made related to
11 fluid balance, which may have been increasing
12 or decreasing diuretics. The next most common
13 change was in potassium supplementation, which
14 is related to diuretic doses.
15 The use of ACE inhibitors and beta
16 blockers is of critical importance for long
17 term outcome in heart failure. However, these
18 drugs are not the main target of dosing
19 changes after discharge from a heart failure
20 hospitalization.
21 In the latest version of the
22 ACC/AHA guidelines, which represent exhaustive

1 expert review and consensus, it is recommended
2 as Level I that volume status should be
3 assessed at each visit. In addition to volume
4 assessment, diuretics and salt restriction are
5 indicated in symptomatic patients who exhibit
6 evidence of volume retention.
7 This recommendation is further
8 emphasized for patients with advanced disease
9 in whom meticulous identification and control
10 of fluid retention is recommended as the first
11 priority.
12 The major problem that we face is
13 that we don't know how best to determine our
14 patients' volume status. We make our best
15 guess prior to an intervention, but then we
16 have to make another set of guesses to decide
17 when we have achieved the desired endpoint of
18 the change in fluid.
19 So this is the major challenge
20 that we face on a day to day basis with our
21 patients after hospitalization for heart
22 failure and between clinic visits.

1 So how well do we assess volume
2 status? Let's look first at the optimal
3 situation, when the patient is right in front
4 of us, right in front of a heart failure
5 expert in the hospital or clinic.
6 As presented here by Dr. Drazner
7 and Dr. Leier, we are not too bad at it when
8 we can take account of all those parameters
9 that we see in clinic. But at the best we get
10 to a sensitivity of about 70 percent for
11 elevated pulmonary capillary wedge pressures,
12 and that is through assessment of jugular
13 venous pressure. However, the bigger question
14 is how well do we assess volume status at
15 home?
16 Bear in mind, the typical patient
17 is seen fewer than five percent of the days
18 after hospital discharge. Most of the time,
19 he is at home.
20 Well, at home we have edema and
21 weight to go by, but they are unreliable.
22 When edema does occur, it is usually after two

1 or more liters of fluid retention have already
2 occurred. Many patients in middle age never
3 get edema, while older patients may develop
4 edema related to peripheral factors, even when
5 central filling pressures are normal.
6 We know this. What we didn't know
7 is how weak the weights are as a reflection of
8 chronic volume status. We frequently
9 encounter patients who go into severe heart
10 failure without any change in weight. This is
11 because the weight may stay stable when fluid
12 increases and heart failure worsens if the
13 appetite falls, which can then lead to
14 decreased nutrition.
15 On the other hand, we sometimes
16 put patients into renal failure by aiming at a
17 target weight that is no longer accurate,
18 because the real body weight may increase over
19 time when patients eat better due to improved
20 clinical status.
21 In this study from Europe, weight
22 gains were highly specific, but had very low

1 sensitivity for decompensation, as shown here,
2 whether you look at 2 kilograms of weight gain
3 or 2 percent of weight gain.
4 Interestingly, in this study the
5 BNP levels were also of limited sensitivity,
6 even for clinical decompensation. So these
7 are clinical decompensation events. Much less
8 are these useful for an early warning sign.
9 Hospitalizations are an indicator
10 of worsening disease, as shown here, through
11 the course of heart failure, but they may
12 themselves play a role in accelerating disease
13 progression.
14 When exacerbation of fluid
15 retention becomes severe enough to require
16 hospitalization, there is often a leak of
17 troponin which suggests further myocyte loss.
18 Further damage may occur as a result of
19 aggressive therapies instituted to bring about
20 the rapid relief of symptoms once
21 hospitalization has occurred.
22 These may be intravenous inotropic

1 agents, vasodilators, and always high doses of
2 intravenous diuretics, which may be more toxic
3 when given in large boluses in the hospital as
4 opposed to modest increases instituted earlier
5 at home.
6 The adverse outcomes associated
7 with rehospitalization are shown here in an
8 analysis of 14,000 patients after heart
9 failure hospitalization in British Columbia.
10 The median survival decreased by
11 almost half after each subsequent
12 hospitalization from the first to the fourth
13 hospitalization.
14 The impact of subsequent
15 hospitalizations on mortality was demonstrated
16 also in the CHARM trial following the first,
17 the second, and the third hospitalization.
18 This is the hazard ratio for mortality on the
19 y axis.
20 This data also highlights the
21 importance of delaying the time to
22 hospitalization, as the highest mortality was

1 noted in those patients who had
2 rehospitalization early after their previous
3 discharge.
4 In conclusion, it is clear that
5 symptoms of congestion resulting from elevated
6 filling pressures dominates the clinical
7 picture of acute heart failure and
8 hospitalizations, and this is regardless of
9 ejection fraction.
10 Elevated filling pressures predict
11 poor outcomes, and a reduction of elevated
12 filling pressures improves symptoms during
13 hospitalization.
14 The importance of serial
15 assessment and therapy for elevated filling
16 pressures in the outpatient setting is clearly
17 emphasized in heart failure guidelines as a
18 Level I recommendation, and the most common
19 intervention. This is an ongoing challenge
20 for heart failure experts when patients are
21 right in front of us, but reliable assessment
22 of volume is not available using weights or

1 symptoms at home where most diuretic
2 interventions are made.
3 The critical part of heart failure
4 management then is currently based on
5 unreliable information. We are flying without
6 instruments. This issue is even more critical
7 for primary care clinicians who care for the
8 majority of patients with heart failure.
9 I would, therefore, propose that a
10 new strategy is needed for the assessment and
11 management of volume in the ambulatory
12 setting.
13 I will now turn it over to Dr.
14 Philip Adamson.
15 DR. ADAMSON: Thank you, Dr.
16 Stevenson. I am a consultant for Medtronic,
17 an investigator in the Chronicle programs, and
18 I have received research support from the
19 sponsor, but I have no financial interest in
20 the company.
21 In the following section I will
22 describe in detail the Chronicle Implantable

1 Hemodynamic Monitoring System and the early
2 clinical experience with that system.
3 I will begin my presentation by
4 providing an overview of the Chronicle IHM
5 system and its various components. I will
6 then highlight the key results of the
7 Chronicle Phase I and II study, and end with
8 the genesis of IHM Guided Care as a heart
9 failure management strategy.
10 This slide provides a high level
11 description of the flow of information from
12 the Implantable Hemodynamic Monitor to the
13 clinician. The device is interrogated
14 remotely by the patient using a specialized
15 monitor that transmits the data to a secured
16 server. These data are then accessible by a
17 clinician using standard Internet access.
18 This process will be described in much more
19 detail in the coming slides.
20 The Chronicle IHM System is
21 comprised of implantable and external
22 components necessary to acquire, transmit and

1 display hemodynamic information. The monitor
2 itself is a programmable, battery powered
3 device, similar in appearance to the pulse
4 generator of a cardiac pacemaker, and it
5 continuously monitors and stores various
6 physiologic parameters, including intracardiac
7 pressures.
8 Data are collected on a beat-to-
9 beat basis, but the device typically commits
10 to memory one data point every eight minutes.
11 The pressure sensing lead is a
12 transvenous right ventricular lead with a
13 dedicated pressure sensor, a capsule near its
14 tip. The Chronicle IHM measures numerous
15 pressure related parameters, including right
16 ventricular systolic and diastolic pressures
17 and an estimation of the pulmonary artery
18 diastolic pressure, which serves as an
19 estimate of left ventricular filling
20 pressures.
21 In addition, the device records
22 several non-pressure related parameters,

1 including heart rate, core temperature, and
2 patient activity levels.
3 The following tracing was obtained
4 by an investigational Chronicle device to
5 illustrate how pressure measurements are
6 obtained by the system.
7 The tracing shows concurrent
8 recordings of the surface electrocardiogram,
9 the electrogram as measured by the device
10 itself, the right ventricular pressure wave
11 form, and the derivative of the pressure wave
12 form known as the change in pressure or a
13 change in time or dP/dt.
14 Point one on this tracing is the
15 pressure at the time of QRS detection by the
16 device, which defines right ventricular
17 diastolic pressure. Point number two is the
18 pressure at the peak of the wave form
19 corresponding to right ventricular systolic
20 pressure, and point number three is the
21 pressure at the time of maximal dP/dt,
22 corresponding to the opening of the pulmonary

1 valve and providing an estimate of the
2 pulmonary artery diastolic pressure.
3 The implant procedure of the
4 Chronicle IHM is similar to that of a cardiac
5 pacemaker, whereby the IHM is positioned
6 subcutaneously in the pectoral area with the
7 lead positioned transvenously in the right
8 ventricular outflow tract. Average implant
9 time is approximately one hour.
10 Since the IHM records absolute
11 pressure, the patient must carry a small pager
12 sized external pressure reference device that
13 continuously measures barometric pressure,
14 shown in this slide.
15 Intracardiac pressure is
16 calculated by deducting ambient pressure from
17 the absolute pressure measured by the
18 implanted IHM.
19 Patients then download the
20 information from the device at least weekly
21 using a remote monitor that interrogates both
22 the implantable device and the external

1 pressure reference, and then transmits the
2 data via standard telephone line to a secure
3 server.
4 In the clinic setting, a standard
5 device programmer can be used to access
6 Chronicle data, which will include also real
7 time wave form analysis.
8 Data is then displayed on the
9 Chronicle IHM website, which is a secure
10 application that allows remote review of
11 consolidated and trended pressure data by
12 clinicians.
13 In addition to heart rate, patient
14 activity, the website also displays trended
15 data related to these four pressure
16 parameters: Right ventricular diastolic
17 pressure; right ventricular systolic pressure;
18 estimated pulmonary artery diastolic pressure;
19 and estimated mean pulmonary artery pressure.
20 This stream shows one month's
21 worth of data, but time periods can be
22 displayed and changed to one day, one week or

1 one year.

2 The next slide actually shows a
3 magnified view of trended estimated pulmonary
4 artery diastolic pressure. Median values are
5 noted by the black line, while the sixth and
6 94th percentiles of these measurements are
7 denoted by the red lines.

8 I will now move on to describe the
9 Chronicle Phase I and II study. Extensive
10 clinical experience has been amassed with
11 this implantable hemodynamic monitor spanning
12 more than 15 years. As described in the PMA,
13 this novel concept of continuous intracardiac
14 pressure monitoring was first tested in acute
15 feasibility studies in the early 1990s.

16 Beginning in August of 1998,
17 chronic evaluation of this system was
18 initiated under the Chronicle Phase I and II
19 study. Today's discussion will be based on
20 the Chronicle Phase I and II study and the
21 COMPASS-HF trial. Both IDEs remain open, and
22 patients are still being followed.

1 The Chronicle Phase I and II study
2 incorporated a prospective multi-center, non-
3 randomized design. The first enrollment
4 occurred in August of 1998. Phase I enrolled
5 32 patients, and data were used to establish
6 the accuracy of the Chronicle IHM system.
7 Patients enrolled in Phase I and
8 those subsequently enrolled in Phase II
9 contributed data to just system safety and
10 pressure sensor performance, as I will shortly
11 describe. Overall data during the Phase I and
12 II study formed the foundation for the
13 COMPASS-HF study, which will be reviewed in
14 detail by Dr. Bourge.
15 Several objectives were tested
16 during the Chronicle Phase I and II study.
17 Listed here are the key primary objectives
18 that will be discussed in the next few slides
19 related to accuracy, performance, and safety
20 of the system.
21 A consistent data collection and
22 testing methodology was applied to assess the

1 accuracy of the Chronicle IHM compared to a
2 Swan-Ganz catheter system. Simultaneous
3 hemodynamic measurements were performed in 32
4 patients at implant, three, six and 12 months.
5 Each visit entailed eight paired
6 measurements performed during supine and
7 sitting rest, Valsalva maneuver and exercise
8 testing.
9 Overall, approximately 700 data
10 points were collected in over 100 right heart
11 catheterizations. Correlation coefficients
12 were estimated using Pearson's method and
13 bootstrap analyses. Drift rate was analyzed
14 using linear mixed methods. For the safety
15 objective, survival analyses were performed
16 using the Kaplan-Meier method.
17 I will begin by describing each of
18 the effectiveness objectives in more detail.
19 The first key objective was to
20 measure the accuracy of the Chronicle IHM
21 compared to a Swan-Ganz catheter, defined as
22 the average paired difference in right

1 ventricular systolic pressure between the two
2 systems.
3 Average difference was -1.2
4 millimeters of mercury with a narrow 95
5 percent confidence interval, well within the
6 predetermined performance criterion.
7 The second key objective was to
8 assess the correlation between right
9 ventricular systolic pressure measurements
10 obtained by the Chronicle IHM and a Swan-Ganz
11 catheter.
12 The observed correlation
13 coefficient was 0.95 with a 95 percent lower
14 confidence bound of 0.92, exceeding the
15 performance criterion.
16 Plotted here are paired IHM and
17 Swan-Ganz measurements of RV systolic, RV
18 diastolic, and estimated pulmonary artery
19 diastolic pressures. While the correlation
20 effectiveness objective was based only on RV
21 systolic pressure, these graphs demonstrate
22 that very high correlations were observed in

1 other hemodynamic parameters as well.

2 Although not pre-specified as an
3 effectiveness objective, this analysis
4 demonstrates consistently high correlation
5 coefficients comparing right ventricular
6 systolic pressure measurements taken by the
7 Chronicle IHM and the Swan-Ganz catheter at
8 implant three months, six months, and 12
9 months.

10 For the first time, these results
11 establish with reasonable assurance that the
12 device is effective in measuring long term
13 intracardiac pressures.

14 The third key objective was to
15 assess the drift rate of the Chronicle IHM,
16 defined as a change in average difference
17 between right ventricular systolic pressure
18 measurements recorded by the Chronicle IHM and
19 a Swan-Ganz catheter.

20 The change in average difference
21 was -0.12 millimeters of mercury with a 95
22 percent confidence interval, well within the

1 performance criterion.

2 The fourth key objective was to
3 assess the reliability of pressure sensor,
4 defined as the freedom from complete pressure
5 sensor failures after the system had been
6 successfully implanted.

7 Twenty-eight pressure sensor
8 failures were reported during the Phase I and
9 II study, resulting in a freedom rate and
10 corresponding 95 percent lower confidence
11 bound that did not meet the pre-specified
12 performance criterion. However, 25 of the 28
13 pressure sensor failures were ultimately
14 traced to a common root cause that I will
15 discuss in detail in the next few slides.

16 Those 25 pressure sensor failures
17 with a common root cause were limited to four
18 manufacturing lots and were characterized by
19 an abrupt downward shift in all pressure
20 parameters, as shown on this slide.

21 Since the failure pattern was
22 readily identifiable by clinicians,m erroneous

1 data was not used in the management of the
2 patients. Importantly, other than the
3 procedures performed to resolve these sensor
4 failures, no further clinical sequelae were
5 noted in the patients.
6 The FDA was informed of the
7 decision to suspend implants and perform a
8 root cause analysis, which was found to be
9 compromised hermeticity of the pressure sensor
10 capsule.
11 FDA was notified of design and
12 manufacturing process changes implemented to
13 correct the root cause. Clinical enrollment
14 resumed following FDA approval with no
15 subsequent pressure sensor failures in over
16 300 patients to date, including patients
17 enrolled in the COMPASS-HF study.
18 I will now describe in more detail
19 the safety objectives of the Chronicle Phase I
20 and II study.
21 The first safety objective was to
22 assess the freedom from a severe device

1 related adverse event, defined as an event
2 that is incapacitating, life threatening,
3 causes death, requires urgent treatment or an
4 inpatient hospitalization, prolongs an
5 existing admission, or results in persistent
6 or significant disability.
7 Three severe device related
8 adverse events were reported through three
9 months following implantation of the IHM,
10 meeting the pre-specified performance and
11 safety criterion.
12 The description of the events is
13 listed here for your convenience. All three
14 were successfully resolved.
15 A second safety objective was to
16 assess the freedom from device related
17 complication, defined as an event that
18 requires invasive treatment or a device
19 explant, causes death or a permanent loss or
20 significant device function.
21 Fourteen device related
22 complications were reported through three

1 months following implantation, meeting the
2 pre-specified performance criterion. Only
3 seven of the 28 pressure sensor failures
4 qualified as a device related complication,
5 because they occurred during the three months
6 after implantation. The description of the
7 other complications is listed here for your
8 convenience.
9 In summary, the Chronicle Phase I
10 and II study demonstrated that continuous
11 intracardiac pressure monitoring is feasible
12 in the ambulatory setting with reasonable
13 assurance that the system is accurate and that
14 the system is safe.
15 While early reliability was
16 compromised by some sensor failures, the root
17 cause was identified and corrected, and no
18 subsequent recurrence has been seen.
19 So after establishing that
20 intracardiac pressures and pressure monitoring
21 was safe and accurate, the Phase I and II
22 investigators sought to develop and test a

1 heart failure management strategy based on
2 ambulatory intracardiac pressures, and we
3 termed this strategy IHM Guided Care.
4 As was previously described,
5 congestion is the hallmark of worsening heart
6 failure, but symptoms typically develop late
7 in the decompensation process, and often
8 require acute intervention or even
9 hospitalization, shown here at the dotted
10 white line at Day Zero.
11 Treatment, therefore, is reactive
12 in nature with the goal of relieving patients
13 of their volume overload and accompanying
14 symptoms. But we learned that the congestion
15 process typically begins many days prior to
16 the appearance of symptoms, and is associated
17 with an increase in cardiac filling pressures
18 as volume is accumulated.
19 It was hypothesized then that the
20 ability to continuously monitor intracardiac
21 pressures would provide an opportunity to
22 intervene in a proactive manner prior to the

1 development of symptoms.

2 To validate this premise, the
3 study investigators conducted a retrospective
4 review of Phase I data at a time when IHM
5 information was not used to guide patient
6 management. The goal of the analysis was to
7 characterize pressure changes prior to
8 clinical events and following medical
9 intervention.

10 As anticipated, there was a
11 consistent rise in intracardiac pressures in
12 the days leading to heart failure
13 hospitalization at Day Zero, with a sharp
14 decline toward baseline following initiation
15 of successful treatment.

16 The observed pressure pattern
17 reinforced the idea that timely detection of
18 meaningful changes in filling pressures may
19 provide an opportunity to intervene and
20 prevent the onset of clinical decompensation.
21 With this insight, IHM Guided Care was
22 developed to standardize the approach by which

1 clinicians can utilize intracardiac pressure
2 data.
3 In order to identify clinically
4 meaningful changes in intracardiac pressures,
5 the first step in the management strategy
6 calls for a definition of a patient-specific
7 pressure range associated with an optimal
8 volume state.
9 Optivolemia was defined as the
10 pressure range corresponding to optimal
11 balance between the signs and symptoms of
12 congestion and of those of low output.
13 As represented in this
14 illustration, since pressure ranges satisfying
15 this definition varied by patient, optivolemia
16 was coined as a patient-specific
17 individualized measure as opposed to
18 euvolemia, which reflects populational based
19 definitions of normal.
20 Once the patient's optivolemic
21 range was determined, subsequent periodic
22 review of pressure data was used to determine

1 the patient's volume status by classifying
2 pressures as reflecting either optivolemia,
3 hypervolemia, or hypovolemia.
4 Then based on this volume
5 assessment, the application of appropriate
6 evidence based therapies was recommended,
7 consistent with the published ACC/AHA
8 guidelines for heart failure management.
9 This schematic summarizes the
10 patient management strategy developed and
11 tested within the Phase I and II study, which
12 again was termed IHM Guided Care.
13 The overall goal of this
14 management strategy is to maintain optivolemia
15 through ongoing assessment and proactive
16 management based on intracardiac pressures.
17 Deviations from targeted pressure ranges
18 require adjustment of medications,
19 modifications in dietary restrictions or more
20 acute intervention as deemed appropriate by
21 clinicians.
22 This is an actual website image

1 that illustrates the practical application of
2 IHM Guided Care. The trend describes a two-
3 week period of time that began with a patient
4 eating salted popcorn and becoming
5 hypervolemic.
6 At the first blue vertical line,
7 we detected changes intracardiac pressures in
8 the direction of hypervolemia. At the second
9 notation, the patient continued to be
10 noncompliant, and remote intervention was
11 initiated.
12 The final notation represents the
13 return of this patient to optivolemic pressure
14 ranges after successful remote management of
15 the episode.
16 Following the development of IHM
17 Guided Care, the investigators examined the
18 effect of this management strategy on heart
19 failure hospitalization. Data from 67
20 patients who completed six months of IHM
21 Guided Care and provided consent were included
22 in a retrospective chart review which was

1 conducted by an independent clinical research
2 organization.
3 We found that using IHM Guided
4 Care, we could achieve a 53 percent reduction
5 in hospitalizations. These results formed the
6 basis for the hypothesis tested in the
7 COMPASS-HF study, as Dr. Bourge will describe
8 shortly.
9 The clinical Phase I and II study
10 represented the culmination of significant
11 research and clinical effort, starting with a
12 rigorous assessment of the accuracy,
13 reliability, and long term safety of a
14 permanently implanted intracardiac pressure
15 monitoring system.
16 For the first time, clinicians
17 were able to observe changes in underlying
18 heart failure progression as represented by
19 trends and ambulatory pressures while patients
20 were at home pursuing their daily lives.
21 This insight enabled investigators
22 to identify a consistent pattern of rising

1 intracardiac pressures in the days and weeks
2 leading up to hospitalization for worsening
3 heart failure.
4 The investigators then developed
5 an IHM Guided Care plan, a heart failure
6 management strategy based on the use of
7 intracardiac pressures to assess volume status
8 and prevent acute heart failure exacerbations.
9 When implemented in a non-
10 randomized setting during the Phase I and II
11 study, IHM Guided Care was found to positively
12 impact heart failure morbidity in ambulatory
13 patients. A randomized controlled trial was
14 then designed to further assess the clinical
15 impact of IHM Guided Care.
16 I will now turn it over to Dr.
17 Robert Bourge, who served as the Chairman of
18 the COMPASS-HF study.
19 DR. BOURGE: Thank you, Dr.
20 Adamson.
21 I am a consultant for Medtronic,
22 an investigator on the Chronicle program, and

1 I have received research support, but I have
2 no financial interest in the company.
3 Now that you have heard about the
4 early clinical experience with the Chronicle
5 IHM, I'd like to describe in more detail the
6 COMPASS-HF study.
7 I will begin by outlining the
8 study's objectives, design and methodology,
9 continue with the presentation of the study
10 results, and end by summarizing the findings
11 and overall clinical experience with the
12 Chronicle IHM System.
13 COMPASS-HF was designed to test
14 the hypothesis that a management strategy
15 based on continuously monitored intracardiac
16 pressures in heart failure patients already
17 receiving standard medical therapy would
18 further decrease morbidity.
19 The COMPASS-HF Steering Committee
20 faced several critical challenges in designing
21 a trial that would evaluate a novel management
22 strategy as opposed to a therapeutic device.

1 We wrestled with many questions, such as:
2 What is the appropriate endpoint to evaluate a
3 monitoring device? What is the relevant
4 control group to test a management strategy?
5 How should patients be blinded? What centers
6 should be selected?
7 To meet these challenges, the
8 following objectives in study design were
9 implemented.
10 The study's overall objective was
11 to assess the effectiveness and safety of the
12 Chronicle IHM System. The effectiveness
13 objective was to demonstrate a reduction in
14 heart failure related hospital equivalence,
15 defined as heart failure hospitalizations as
16 well as emergency department and urgent clinic
17 visits requiring intravenous therapy.
18 These events are collectively
19 referred to as heart failure events throughout
20 this presentation.
21 The safety of the system was
22 evaluated using standard device performance

1 criteria, but given the importance of pressure
2 data integrity in this study, a separate
3 endpoint was used to monitor the reliability
4 of the pressure sensor.
5 Sites involved in COMPASS-HF were
6 carefully selected to include those with
7 established multi-disciplinary heart failure
8 clinics. These sites had comprehensive
9 patient management programs involving
10 specialized heart failure physicians, nurses,
11 and staff.
12 Key inclusion criteria included
13 New York Heart Association Class III or IV,
14 the requirement to be on standard medical
15 therapy for at least three months prior to
16 baseline evaluation, and each patient had to
17 have experienced at least one heart failure
18 event in the six months prior to study entry.
19 Other inclusion criteria are
20 described in detail on the protocol, and are
21 provided to you as part of the panel package.
22 Key exclusion criteria included

1 patients with severe pulmonary disease,
2 patients with concomitant devices from other
3 manufacturers, patients receiving cardiac
4 resynchronization therapy but not on optimized
5 programming, patients with a recent
6 cardiovascular event, and patients with severe
7 kidney dysfunction.
8 Following baseline evaluation and
9 successful implantation, patients were
10 randomized to either a total clinician arm,
11 called the Chronicle Group, where the
12 Chronicle system was used to guide care, or a
13 blocked clinician access arm called the
14 control group where Chronicle data were not
15 used to guide care.
16 Protocol mandated visits were
17 performed at one, three and six months post-
18 randomization, in addition to other visits as
19 clinically indicated. It is important to note
20 that best available heart failure management
21 strategies were utilized in both groups during
22 the study.

1 Randomization assignments were
2 stratified at each center by left ventricular
3 ejection fraction to account for potential
4 differences in event rates between patients
5 with preserved versus depressed ejection
6 fraction.
7 For patients randomized to the
8 Chronicle Group, clinicians gained immediate
9 access to intracardiac pressure data. For
10 patients randomized to the control group,
11 clinicians did not have access to Chronicle
12 data. Following the six-month visit, access
13 to Chronicle data in the control group was
14 also enabled, and it was used thereafter in
15 patient management.
16 Patients in both the Chronicle and
17 control groups were required to transmit data
18 using the home-based monitor previously
19 described by Dr. Adamson at least once a week
20 for clinician review and interpretation.
21 Following clinician review of
22 intracardiac pressure data, IHM Guided Care

1 was implemented, with the goal of maintaining
2 patients within their predetermined
3 optivolemic ranges, consistent with the
4 management of patients studied during the
5 Phase I and II study.
6 Documentation from all
7 hospitalizations, emergency department and
8 urgent clinic visits were reviewed by an
9 independent endpoint review and adjudication
10 committee.
11 Patients were blind to their
12 randomization assignment to minimize the
13 potential impact on symptom reporting and
14 self-initiated access to medical care.
15 Blinding could have been compromised by either
16 an increased call rate to the Chronicle
17 patients or inadvertent disclosure by the
18 clinician.
19 Therefore, call schedules were
20 generated for each control patient to
21 replicate the increased frequency of
22 communication observed in the Chronicle group.

1 In addition, standardized communication
2 scripts were employed when interacting with
3 patients in both groups.
4 The rate of heart failure events
5 was compared between the Chronicle and control
6 groups using the Poisson regression analysis.
7 However, as indicated in the statistical plan
8 of the study protocol, should the results
9 reflect an overdispersion in the distribution
10 of heart failure events at the time of the
11 final analysis, the data would be analyzed,
12 and was analyzed, using the negative binomial
13 regression method.
14 The attention to treat principle
15 was used for analyzing all study objectives,
16 and finally, pre-specified subgroups were
17 evaluated for interaction with outcome, but no
18 hypotheses were specified.
19 This slide shows the sample size
20 determinants for each of the three study
21 objectives. One hundred fifty-five patients
22 ensured that both pre-specified safety

1 objectives could be tested with adequate
2 power.
3 The sample size and power
4 calculations for the primary effectiveness
5 objective were based on the assumption that
6 the control group would experience an average
7 of 1.2 heart failure events over a six-month
8 period. This assumption did not hold true.
9 It may have affected the ability
10 of the study to meet its primary effectiveness
11 objective in a statistically significant
12 manner.
13 Analyses reported in the Panel
14 package and the presentation today are based
15 on 1,620 randomized patient months of follow-
16 up when all patients completed their six-month
17 follow-up visit.
18 Of the 301 patients that were
19 evaluated for participation in the study, 24
20 patient withdrawals occurred prior to implant
21 for typical reasons, such as patients
22 withdrawing consent.

1 An implant was attempted in 277
2 patients, with 274 successfully receiving
3 their Chronicle device. The three
4 unsuccessful implants were due to complete AV
5 block in one patient, inability to gain venous
6 access in another, and tricuspid entrapment of
7 the pressure sensing lead in the last patient,
8 resulting in a system that was programmed off.
9 The 274 patients that successfully
10 received a Chronicle device were then
11 randomized to either the Chronicle or control
12 group. On average, at baseline the two groups
13 were well balanced with respect to the
14 baseline characteristics listed here.
15 Of note, 35 percent were female,
16 and patients were of diverse ethnicity. Forty
17 percent of patients had a concomitant
18 implanted device. Utilization of heart
19 failure medications was appropriately high for
20 this patient population at baseline
21 evaluation, with more than 90 percent of
22 patients on diuretics, more than 80 percent an

1 ACE inhibitor and/or an ARB, and more than 80
2 percent on a beta blocker.
3 Overall patient and clinician
4 compliance in the COMPASS-HF study was
5 extremely high. During the randomized follow-
6 up period, only one patient was lost to
7 follow-up, and 99.6 percent of protocol
8 required follow-up visits were completed.
9 Study patients were required to
10 transmit IHM data at least once a week. A
11 study deviation was noted if data transmission
12 was not received within 10 days of the
13 previous transmission. Only 138 deviations
14 were noted, compared to the 14,835
15 transmissions that were received on time.
16 Finally, once transmissions were
17 received, clinicians applied IHM Guided Care
18 in 96 percent of the cases reviewed. In the
19 instances when IHM Guided Care could not be
20 implemented, the most common reason was the
21 inability of the clinician to communicate a
22 treatment decision or gather more clinical

1 information from the patient. This high
2 degree of study compliance underscored the
3 excellent quality with which this difficult
4 and novel trial was executed.
5 The two primary safety objectives
6 were freedom from system related complications
7 and freedom from pressure sensor failures
8 through six months.
9 A system related complication was
10 defined as an adverse event related to the
11 system, which consists of the implantable
12 monitor and the pressure sensor lead, and
13 satisfied at least one of the following
14 criteria: Treated by invasive means; resulted
15 in the death of the patient; resulted in the
16 explant of device or caused a permanent loss
17 of significant function of the system.
18 All 277 patients that underwent an
19 implant attempt contributed to the analysis of
20 system related complications. Overall, 23
21 patients experienced 24 complications in the
22 six-month follow-up period. Twenty-three of

1 the complications were lead related, and most
2 of those were attributable to lead
3 dislodgements.
4 All system related complications
5 were solved with no subsequent clinical
6 sequelae. Four complications resulted in
7 either a system explant or a capped lead. In
8 20 of the 24 complications, resolution
9 resulted in a fully functioning system.
10 Freedom from system related
11 complications through six months was 91.5
12 percent, with a lower 95 percent confidence
13 bound of 88.7 percent meeting the pre-
14 specified performance criteria.
15 A pressure sensor failure, as
16 observed in Phase I and Phase II studies, was
17 defined as a significant downward
18 nonphysiological shift in all pressure
19 parameters, with no associated compatible
20 changes in other IHM derived variables.
21 There were no pressure sensor
22 failures through the six-month randomized

1 follow-up period, resulting in a freedom from
2 pressure sensor failure of 100 percent.
3 As previously described, the
4 primary effectiveness objective was to
5 demonstrate a reduction in heart failure
6 events, defined as hospital admissions lasting
7 more than 24 hours where the primary reason
8 for admission was worsening heart failure, and
9 heart failure emergency department and urgent
10 care visits requiring IV therapy.
11 This unique composite endpoint was
12 chosen, because the impact of IHM Guided Care
13 on each of these types of heart failure events
14 was unclear a priori. Therefore, the study's
15 Steering Committee recognized that, while
16 reducing hospitalization was the primary goal
17 of the strategy, the possibility existed that
18 inappropriate use of information from the IHM
19 system could actually increase other types of
20 heart failure events.
21 This slide illustrates the
22 distribution of events by randomization

1 groups. One hundred eight-one patients
2 experienced a total of 473 events during the
3 six-month randomized follow-up period.
4 Of the 125 cardiovascular events
5 in Chronicle patients and 156 in control
6 patients, the blinded independent events
7 committee determined that 84 events in the
8 Chronicle group and 113 in the control group
9 met the pre-specified definition of the
10 primary endpoint. Importantly, the number of
11 both volume overload and dehydration events
12 was lower in the Chronicle group.
13 Overall, fewer patients
14 experienced an event in the Chronicle group
15 compared to the control group. The observed
16 event rate in the control group was 0.85 over
17 the six month randomized follow-up period,
18 much less than a hypothesized event rate of
19 1.2 events per six months.
20 This lower control event rate
21 negatively impacted the statistical power of
22 the trial. Acknowledging this limitation of

1 the study, IHM Guided Care beyond standard
2 medical management reduced the overall event
3 rate by 21 percent, a result that did not
4 reach statistical significance.
5 Two key assumptions were made in
6 estimating the sample size requirements of
7 COMPASS-HF that may have affected the ability
8 of the study to meet its primary effectiveness
9 endpoint.
10 The first assumption was that the
11 average heart rate event -- or heart failure
12 event rate in the control group would be 1.2
13 over a six-month period. In actuality, the
14 observed average event rate in the control
15 group was 0.85 during the six-month randomized
16 follow-up period.
17 This lower observed event rate may
18 have been a consequence of the diligent
19 efforts to maintain blinding in the control
20 group, which included matching the intensive
21 rate of patient contact observed in the
22 Chronicle group.

1 Indeed, as this slide
2 demonstrates, an excellent balance was
3 achieved when comparing average call rates
4 between the two groups. Remote patient-
5 clinician contact occurred in both groups on
6 average at a rate of almost once a week, which
7 is not typical in routine heart failure
8 management.
9 Since frequent patient contact of
10 heart failure management teams has previously
11 been shown to reduce hospitalizations, it is
12 likely that this increased level of
13 interaction contributed to the lower than
14 anticipated event rate in the control group.
15 The second assumption was that
16 heart failure events would follow a Poisson
17 distribution, with the mean equal to the
18 variance. In actuality, the observed variance
19 was nearly three times the average event rate
20 of 0.85.
21 As shown in this slide, departure
22 from the hypothesized assumptions related to

1 the average event rate, and the associated
2 variance resulted in an overall loss of power
3 that likely hindered the ability of the trial
4 to meet its primary effectiveness endpoint.
5 In addition to the reported
6 primary safety and effectiveness endpoints,
7 COMPASS-HF pre-specified numerous secondary
8 objectives to further characterize the impact
9 of IHM Guided Care on routine measures of
10 patient safety and heart failure status.
11 There were no pre-specified performance
12 criteria or hypotheses for these secondary
13 objectives.
14 In this section of my
15 presentation, I will review the objectives
16 listed here. Information on other secondary
17 objectives is included in your Panel package.
18 Cumulative days hospitalized for
19 worsening heart failure is a useful measure of
20 overall morbidity and hospital resource
21 utilization. This slide shows the
22 distribution of cumulative days in the

1 hospital for heart failure in 10-day
2 increments by randomization group.
3 Overall, there was a significant
4 difference in the distribution of cumulative
5 days in the hospital for heart failure in
6 favor of the Chronicle group with a p-value of
7 0.04.
8 While the composite response
9 endpoint was not significantly different
10 between the two groups, the analysis trended
11 in favor of IHM patient care with more
12 Chronicle patients improving and fewer
13 Chronicle patients worsening.
14 Quality of life as measured by the
15 Minnesota Living with Heart Failure Score was
16 compared between the two groups. This slide
17 shows the median apparent differences at three
18 and six months compared to baseline. On this
19 scale, a lower number is associated with an
20 improvement in quality of life.
21 The magnitude in the improvement
22 in the Chronicle group was higher compared to

1 control, but this result did not reach
2 statistical significance.
3 Six-minute hall walk distance was
4 compared between the Chronicle and control
5 groups. This slide shows the median of paired
6 differences at three and six months compared
7 to baseline. Overall, patients in the
8 Chronicle group tended to walk greater
9 distances at three and six months compared to
10 the control group. This result did not reach
11 statistical significance.
12 Mortality is a commonly reported
13 outcome in heart failure trials. In the
14 COMPASS-HF study there was no pre-specified
15 hypothesis related to mortality. During the
16 six-month randomized follow-up period, there
17 were 13 deaths in the Chronicle group and 11
18 in the control group. These mortality rates
19 are comparable to those seen in trials
20 enrolling similar patients.
21 As shown on this slide, there was
22 no difference in long-term mortality between

1 the two study groups.

2 This post hoc effectiveness
3 analysis section includes a Cox proportional
4 hazards analysis to estimate the reduction in
5 the relative risk of a heart failure
6 hospitalization, the predominant component of
7 the primary effectiveness objective.

8 In addition, since randomization
9 in the study was stratified by baseline
10 ejection fraction, results were reported for
11 patients with preserved or depressed ejection
12 fraction separately.

13 Results for New York Heart
14 Association Class III and IV patients as well
15 as multi-variable analyses stemming from
16 specific outcome related observations made in
17 New York Heart Association Class III and IV
18 patients are summarized in the Panel package
19 as supporting evidence. There were no a
20 priori alpha adjustments pre-specified in the
21 protocol for these post hoc effectiveness
22 analyses.

1 As described earlier, the primary
2 endpoint in COMPASS-HF was a composite of
3 heart failure events. As shown here, heart
4 failure hospitalizations accounted for 87
5 percent of all events contributing to this
6 composite endpoint.
7 The relative risk of a heart
8 failure related hospitalization is one of the
9 most commonly used endpoints measuring
10 morbidity in heart failure studies. Since
11 hospitalizations accounted for the vast
12 majority of heart failure events in this
13 study, a Cox proportional hazards analysis was
14 performed to further assess the impact of IHM
15 Guided Care on heart failure morbidity.
16 As shown here, there was a 36
17 percent reduction in the relative risk of a
18 heart failure hospitalization with a p-value
19 of 0.03.
20 This analysis demonstrates the
21 consistency of the effect of IHM Guided Care
22 on patients with preserved or depressed

1 ejection fraction. As shown, 70 patients or
2 26 percent of the study population had a
3 preserved left ventricular ejection fraction
4 at baseline. These patients demonstrated a 20
5 percent reduction in the rate of heart failure
6 events, which is comparable to the observed 22
7 percent in patients with depressed ejection
8 fraction.
9 In the acute setting, evidence to
10 date clearly underscores the strong
11 relationship between changes in underlying
12 physiology and clinical signs and symptoms of
13 decompensated heart failure.
14 The Chronicle IHM System for the
15 first time provides insight into changes in
16 ambulatory hemodynamic parameters and their
17 relationship to impending worsening heart
18 failure.
19 Information collected during the
20 COMPASS-HF study allowed us to perform several
21 analyses that support the physiological basis
22 of IHM Guided Care and its relevance as a

1 heart failure volume management strategy.

2 In this section, analysis will be
3 presented that reinforce the relationship
4 between dynamic intracardiac pressures and
5 heart failure events. In addition, I will
6 discuss medication interventions performed
7 during the study and their relationship to
8 volume status. Finally, the long term effect
9 of IHM Guided Care beyond the six-month
10 randomized follow-up period will be shown.

11 In COMPASS-HF volume overload
12 events accounted for over 90 percent of all
13 heart failure events. This analysis was
14 performed to evaluate the relationship between
15 volume overload an intracardiac pressure, this
16 case estimated pulmonary diastolic pressure
17 and RV diastolic pressure.

18 Based on a total of 163
19 hypervolemic events, these data illustrate a
20 significant and consistent rise in
21 intracardiac pressure starting at four weeks
22 prior to hospital admission or initiation of

1 IV therapy for worsening heart failure.

2 Pairwise comparisons between
3 average pressures at seven, four and two weeks
4 before the event and five days following event
5 were all significantly lower than peak
6 pressure, with a p-value under 0.01.

7 To evaluate the relationship
8 between the occurrence of heart failure events
9 and the magnitude of intracardiac pressures,
10 average daily and nighttime minimum e-PAD were
11 compared between patients with or without
12 heart failure events.

13 Only patients with at least 90
14 days of intracardiac pressure data contributed
15 to this analysis, amounting to 254 out of a
16 possible 274 patients. Patients who
17 experienced heart failure events recorded
18 significantly higher average daily and
19 nighttime minimum e-PAD compared to patients
20 who did not experience such events.

21 This slide shows the relationship
22 between RV diastolic pressure and body weight

1 in the days and weeks preceding a heart
2 failure event. The analysis included only
3 patients for whom paired data of weight and
4 pressure were available in association with a
5 volume overload event.
6 On average, body weight did not
7 change prior to a heart failure event. In
8 contrast, RV diastolic pressure gradually
9 increased to a peak that was reached around
10 the day of admission or initiation of IV
11 therapy.
12 Average pressures at seven, four
13 and two weeks prior to the event, as well as
14 average pressure five days following the
15 event, were all significantly lower than the
16 peak average pressure.
17 These results do not discount the
18 value of monitoring weight changes in the
19 heart failure population. Rather, this
20 observation is consistent with previous
21 reports demonstrating the high specificity but
22 relatively low sensitivity of weight changes

1 immediately prior to a heart failure
2 decompensation.
3 Our analysis suggests that changes
4 in intracardiac pressure constitute a more
5 sensitive tool than changes in weight in the
6 days and weeks preceding a heart failure
7 event.
8 Shown here are the changes in
9 medications made throughout the study by
10 randomization group. A significant difference
11 was noted between the two groups in all drugs
12 and all cardiovascular drugs.
13 These differences were attributed
14 primarily to the changes in diuretics where
15 the Chronicle group experienced 54 percent
16 more adjustments in diuretics than the control
17 group. No differences were observed in other
18 categories of heart failure medications.
19 These data provide further support
20 that IHM Guided Care is a management strategy
21 enabling more frequent changes in medications
22 that effect volume status.

1 This slide shows the average daily
2 and nighttime minimum e-PAD by volume state as
3 determined by the commission managing
4 Chronicle patients during the six-month
5 randomized follow-up period. As shown,
6 average pressures were significantly lower
7 during hypovolemia and significantly higher
8 during hypervolemia compared to the optimal
9 volemic state.
10 As expected, the termination of
11 volume status was, in fact, based on objective
12 changes in intracardiac pressures measured by
13 the Chronicle IHM.
14 Importantly, as shown here with
15 the green bars, diuretics were adjusted nearly
16 three times more often when patients deviated
17 from their optivolemic state to either hyper
18 or hypovolemia. Similar to pressures,
19 difference in the frequency of medication
20 changes were also highly significant, with p-
21 values of less than 0.01.
22 These results clearly demonstrate

1 that the more frequent diuretic adjustments in
2 the Chronicle group were performed
3 appropriately in association with the
4 patient's volume status as assessed using
5 pressure information.
6 Frequent adjustments in diuretics
7 may raise the concern of over-diuresis and the
8 associated complications it may produce. As I
9 alluded to earlier and as shown here, the
10 Chronicle group experienced fewer dehydration
11 events than the control group during the
12 randomized follow-up period.
13 Moreover, when comparing the serum
14 creatinine levels of both groups at baseline
15 and six months, it is clear that neither group
16 experienced a meaningful change in renal
17 function over the course of the randomized
18 follow-up period.
19 Finally, this analysis provides
20 insight into the impact of IHM Guided Care
21 beyond the six-month randomization period when
22 IHM data became available for patient

1 management in the control group as well.
2 These results are based on 240 patients for
3 whom paired data were available from both the
4 six-month randomized period and the subsequent
5 six months.
6 Only heart failure
7 hospitalizations, which constitute the
8 majority of heart failure events during the
9 randomized follow-up period, were included in
10 this analysis, and all events were
11 investigator adjudicated in this analysis.
12 As shown here, the Chronicle group
13 remained low and stable beyond the randomized
14 follow-up period. That is, the event rate in
15 the Chronicle group remained low and stable.
16 In addition, once IHM data became
17 available for the management of control
18 patients, their event rate, when we were able
19 to look at the data, declined from 0.81 to
20 0.55 in the subsequent six months, very
21 similar to that of observed in the Chronicle
22 group, very consistent also.

1 In summary, the COMPASS-HF study
2 demonstrated the following: The Chronicle IHM
3 System is safe and reliable. Cardiac filling
4 pressures rise steadily, beginning as early
5 as four weeks prior to a heart failure event,
6 and reach a peak around the day of admission
7 for worsening heart failure.
8 Clinicians made nearly three times
9 as many adjustments in medications to achieve
10 and maintain stable volume status in Chronicle
11 patients, with no evidence of complications
12 associated with over-diuresis.
13 IHM guided heart failure
14 management strategy was associated with a 21
15 percent reduction in heart failure events
16 beyond currently available heart failure
17 therapies. This result did not reach
18 statistical significance.
19 IHM Guided Care resulted in a 36
20 percent reduction in the relative risk of a
21 heart failure related hospitalization, based
22 on a post-hoc analysis of these events, which

1 were the major contributor to the primary
2 effectiveness endpoint of the study.
3 Finally, IHM Guided Care resulted
4 in a long term reduction in heart failure
5 events beyond the randomized follow-up period.
6 These findings suggest that IHM
7 Guided Care may have a durable, positive
8 effect on heart failure hospitalizations.
9 Well, we began today's
10 presentation by noting that, despite advances
11 in the treatment of heart failure, volume
12 overload and congestion continue to result in
13 acute decompensation and significant heart
14 failure morbidity. Neither increased filling
15 pressures nor volume status can be reliable
16 assessed over time using current approaches.
17 Therefore, our interventions to
18 control volume are currently based in
19 inaccurate surrogate estimates of fluid
20 status, particularly in the ambulatory
21 setting.
22 After extensive testing of the

1 Chronicle IHM System in 422 patients over the
2 last eight years, we conclude the following:
3 The Chronicle IHM is an accurate
4 pressure monitoring system that expands the
5 intermittent snapshot assessment of volume in
6 the hospital and clinic to that of continuous
7 remote monitoring in the ambulatory setting.
8 While COMPASS-HF did not meet its
9 primary objective, all analyses performed
10 throughout the clinical experience with the
11 Chronicle IHM System consistently support the
12 physiological premise and clinical utility of
13 this IHM guided heart failure management
14 strategy.
15 For the first time, clinicians can
16 optimize the application of proven heart
17 failure treatment strategies in individual
18 patients, with the goal of reducing the burden
19 of heart failure decompensation.
20 In conclusion, the totality of
21 clinical experience with the Chronicle IHM
22 system provides a reasonable assurance that a

1 strategy based on continuous hemodynamic
2 monitoring is safe and effective in the
3 management of heart failure.
4 Dr. Steinhaus will now provide his
5 closing remarks on behalf of the sponsor.
6 Thank you.
7 DR. STEINHAUS: Well, thank you,
8 Dr. Bourge, and thank you, by the way, to all
9 of our physician presenters.
10 Medtronic recognizes that the use
11 of longitudinal trended pressure data in the
12 ambulatory is a novel concept. We are,
13 therefore, committed to ensuring adequate
14 training and education of clinicians.
15 To that end, a comprehensive
16 training plan has been developed to address
17 the multiple health professionals in the
18 integration of this technology.
19 In the event of FDA approval, we
20 are committed to continue the collection of
21 clinical evidence in support of this
22 management strategy. The goal of the proposed

1 conditions of approval study would be to
2 confirm the long term safety and effectiveness
3 of IHM Guided Care.
4 Specific emphasis will be placed
5 on overall mortality, system related adverse
6 events, and the impact of IHM Guided Care on
7 heart failure events. A detailed study
8 protocol has been submitted to the DDA, and
9 Medtronic continues to work with the agency to
10 finalize its details.
11 The first primary objective of the
12 study is to assess all-cause mortality, with
13 the hypothesis that mortality among patients
14 managed using IHM Guided Care will be no worse
15 than that observed in a concurrent control
16 group through 24 months of follow-up.
17 Key assumptions to test this
18 hypothesis are listed on this slide for your
19 reference.
20 The second primary objective of
21 the study is to assess system related
22 complications, with the hypothesis that

1 freedom from such complications in Chronicle
2 IHM patients will be at least 80 percent
3 through 24 months of follow-up.
4 The third primary objective of the
5 study is to assess the impact of IHM Guided
6 Care on heart failure events, with the
7 hypothesis that implementation of this patient
8 management strategy will result in a 25
9 percent reduction in the risk of one or more
10 subsequent heart failure events compared to a
11 concurrent control group.
12 Participating sites will screen
13 for eligible patients based on indications as
14 provided by the FDA. At Chronicle centers,
15 indicated patients will be offered device
16 implantation or participation in the control
17 group.
18 Control patients will also be
19 recruited in non-Chronicle centers. Up to 100
20 sites will enroll 800 patients equally
21 distributed between the Chronicle and control
22 groups. Mortality and freedom from system

1 related complications will be analyzed using
2 the Kaplan-Meier method.
3 Reduction in the risk of heart
4 failure events will be analyzed using the
5 Anderson-Gill method, which is a
6 generalization of the Cox proportionate
7 hazards model to accommodate multiple events
8 in the same patient.
9 Three secondary objectives will be
10 analyzed using pre-specified performance
11 criteria in a hierarchical fashion, including
12 risk of a heart failure hospitalization, risk
13 of all-cause mortality or heart failure
14 hospitalization, and cumulative days in the
15 hospital for heart failure.
16 Additional secondary objectives
17 will be analyzed with no pre-specified
18 hypotheses, and will include standard heart
19 failure related endpoints such as quality of
20 life and six-minute hall walk.
21 In summary, Medtronic will
22 continue collaborating with the FDA to

1 finalize the details of the study protocols.
2 Centers participating in this proposed
3 conditions of approval study will be evaluated
4 for their ability to integrate this technology
5 into their heart failure practice.
6 This study, as outlined,
7 demonstrates a rigorous approach to post-
8 market evaluation and will provide additional
9 long-term clinical evidence to support IHM
10 Guided Care.
11 As I mentioned in my opening
12 remarks, we acknowledge the fact that COMPASS-
13 HF did not meet its primary effectiveness
14 endpoint. However, the clinical experience
15 presented today validates the physiologic
16 basis and clinical impact of volume management
17 using intracardiac pressures.
18 The consistency of the evidence
19 provides reasonable assurance that the
20 Chronicle IHM System is safe and effective in
21 the management of moderate to advanced heart
22 failure.

1 With that, I would like to
2 conclude our presentation. Thank you very
3 much for your attention.
4 CHAIRPERSON MAISEL: Thank you
5 very much for a very thorough and well
6 presented set of slides.
7 At this point, I would like to
8 open up for questions from the Panel. I will
9 remind the Panel that we will have ample time
10 later to question the sponsor, and we will --
11 Each individual member of the Panel will have
12 a chance to question the sponsor later. So i
13 would ask you to limit your comments to major
14 points of clarification. Dr. Borer.
15 DR. BORER: Thank you. I, too,
16 think that was a superb presentation and very
17 complete.
18 You showed a slide, 120, the
19 overall mortality slide. It differs from what
20 you sent us in our packet and what we shown in
21 the FDA summary. I think I can see why it
22 differs, but I'd like to hear why, what you

1 did for this.

2 It looks like the follow-up is

3 substantially longer in this slide than it

4 was in the slide that was originally presented

5 to us, and I'd like to understand those

6 differences.

7 MR. MANDA: Dr. Borer, my name is

8 Ven Manda. I am a Medtronic employee.

9 I think in the Panel pack that the

10 survival data you are looking at was through

11 six months of follow-up, and we actually

12 presented the longer term follow-up even

13 beyond six months. Throughout the Panel

14 review and discussions with the FDA, it was

15 felt it was important to actually reflect

16 survival beyond the six-month time point.

17 DR. BORER: Okay. So the

18 difference is only a longer follow-up in the

19 same group of patients.

20 MR. MANDA: That is correct. Same

21 group of patients. There are no new patients

22 here. It's all the same dataset.

1 DR. BORER: Okay. May I ask one
2 more question? You also presented some data
3 in the Panel packet that you didn't show in
4 this summary, and that's okay. But I thought
5 it was very useful and instructive, and I
6 wonder if you have a slide to put up.
7 That was the data about the
8 predictive value of the pressure measurements
9 for events in the control group.
10 MR. MANDA: Again, my name is Ven
11 Manda. I'm a Medtronic employee.
12 Dr. Borer, one of the -- When we
13 began this trial, we were also cognizant of
14 the fact that we needed to continue to develop
15 the algorithm development, if you will, of the
16 underlying detection of pressure, just as we
17 have for arrhythmia detection. So that was
18 the objective.
19 The intent of that endpoint really
20 was to help us get a better handle on the
21 accuracy of an automatic detection algorithm.
22 So that was what the second point was with

1 respect to the predictive value, or am I
2 missing your point?
3 DR. BORER: Yes, you are. The
4 issue here is that you looked at the rise in
5 pressure as a predictor of heart failure
6 events in the control group.
7 MR. MANDA: Right.
8 DR. BORER: And you presented that
9 to us very appropriately in the Panel packet.
10 MR. MANDA: That is correct.
11 DR. BORER: But you didn't show it
12 during the presentation, and I think a review
13 of that might be helpful, if you have a slide.
14 MR. MANDA: Yes, we do have a
15 slide. We can talk about it. I think,
16 actually, I am talking about the same point,
17 that the same predictive algorithm is in the
18 Panel pack. It is not part of the PMA
19 approval of that feature.
20 We included this, because it was a
21 pre-specified secondary endpoint. We wanted to
22 understand better how that algorithm would

1 perform, and that was what that secondary
2 endpoint that you are referring to is. We
3 will be happy to show that endpoint
4 subsequently, if you are interested.
5 CHAIRPERSON MAISEL: Do you have
6 that slide now? If not, we can show it later.
7 MR. MANDA: If it's okay, can we -
8 - I would prefer to revisit that maybe later
9 on, just because --
10 CHAIRPERSON MAISEL: That's fine.
11 We'll look at it later.
12 Other questions from the Panel?
13 Dr. Page?
14 DR. PAGE: A couple of brief
15 technical questions. The external device
16 correlates barometric pressure with the
17 pressure that is measured by the device.
18 There is no communication between that device
19 and the implanted device. Is that correct?
20 Then are those correlated when the
21 information is downloaded?
22 DR. BOURGE: It is correlated when

1 the patient uses the remote monitoring device
2 to interrogate his device. The EPR, the
3 external pressure reference, which is the size
4 of a beeper, is placed in the unit. There is
5 a time stamp. They are continued. So they
6 are both measuring at the same exact time.
7 That is when the data is correlated and
8 transmitted up to the network.
9 DR. PAGE: Thank you. And the
10 other questions I have, in part technical in
11 terms of -- I put in pacemakers, and I explant
12 them as well.
13 The lead that is being placed is a
14 tine lead in a non-right ventricular apical
15 spot, and as an implanter that is not the
16 fixation that I would choose to place a lead
17 anyplace other than the RV apex.
18 Could you address the issue of why
19 there is not an active fixation option, and
20 how that interferes with placement? You've got
21 close to a five percent dislodgement rate and
22 one entrapment, and I'm curious as to what

1 happened further with that entrapment.

2 DR. LOVE: Charles Love, the Ohio

3 State University. I'm a consultant to

4 Medtronic. I was one of the implanters of

5 these devices, and I'm a speaker as well.

6 Your question is right on. This

7 is a tine lead, and the issue has to do with

8 the comfort level, I think, of implanters with

9 exposed screws. Because of the design of the

10 pressure sensor, it prohibited the use of the

11 typical BISPING mechanism, which is the

12 extendable retractable helix that most

13 implanters are familiar with.

14 As a result, the tine lead was

15 felt to be the most widely acceptable to the

16 largest number of implanters as opposed to the

17 use of a fixed exposed helix. That was the

18 only other option at that time. That's the

19 reason the tines were chose, as far as my

20 understanding goes.

21 The other issue as far as

22 stability of the lead is the major issue here.

1 Most of the system complications, if you
2 will, were due to lead dislodgement or lead
3 migration. As a result, we learned from
4 experience better ways of putting it in,
5 better ways of adjusting slack and assuring
6 stability, and once we learned from our
7 experience, our dislodgement rates actually
8 dropped significantly.
9 As far as the entrapment in the
10 tricuspid apparatus goes, there were actually
11 two episodes. They were categorized
12 differently, but in any case, there were no
13 sequelae with that. The leads were left in
14 position and abandoned at that point.
15 DR. PAGE: So the lead actually
16 was abandoned. You could not extract that
17 without a surgical procedure. It was
18 entrapped to the point where further traction
19 on the lead, you felt, would be more dangerous
20 than helpful.
21 DR. LOVE: That was the decision
22 of the implanter. That did not occur under --

1 DR. PAGE: And the final question,
2 if I may: In terms of technically, your
3 stylette goes just shy of the tip of the lead,
4 if I understood the technical information
5 correctly. In fact, it is four centimeters
6 short of the tip.
7 Again, as an extractor, removing a
8 lead when it has been in place for a while,
9 typically in the setting of infection which
10 happens somewhere around one percent of
11 patients, part of the key is dislodging the
12 tip, and another part of the key to extraction
13 is being able to grab the lead, if you will.
14 Ideally, your extraction stylette grabs at the
15 very tip of the lead.
16 Do you have any suggestion of how
17 this lead would withstand the traction in case
18 of a lead that's been in five years or so with
19 a tined tip? If a patient had an infection,
20 the goal, obviously, is to remove the entire
21 lead. Do you have any information on how the
22 lead would withstand the sort of removal