

1 traction that is necessary to extract?

2 DR. LOVE: I believe I have the
3 world's largest extraction experience on these
4 leads. I think we have taken three or four of
5 them out at Ohio State that have been
6 referred in from other places, and your
7 analysis is correct. The stylette does not go
8 beyond the pressure sensor. It just goes to
9 the pressure sensor.

10 The lead is constructed well, and
11 in two cases I did need to use stylettes in
12 order to lock into the lead and apply traction
13 to the lead to get a sheathe over it. In the
14 other cases, the leads just pulled right out.
15 That's number one.

16 Number two: The lead is
17 constructed robustly so that, even though I
18 was only able to lock at the pressure sensor,
19 the lead held together very nicely. I was
20 able to get my sheath beyond the pressure
21 sensor, apply my counter-traction and pop the
22 lead free.

1 Another issue is the actual
2 position of the lead, which is kind of
3 interesting. It actually lends itself better
4 to extraction, because not being laying on the
5 floor of the right ventricle and having the
6 opportunity to fibrose into the apex and along
7 the floor of the ventricle, this lead is kind
8 of hanging up in the outflow tract, which
9 actually prevents the fibrosis from occurring
10 and plastering it against the wall of the
11 ventricle.

12 So there is actually less
13 fibrosis, at least at this point. It is
14 relatively in the maturation process and the
15 fibrotic process, but our experience was that
16 these leads are hanging there. The pressure
17 sensor does not become attached to the wall.
18 It is kind of hanging out in the body of the
19 ventricle. As a result, we don't get as much
20 fibrosis, and we don't have as much difficulty
21 removing the lead.

22 DR. PAGE: Thank you.

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1 CHAIRPERSON MAISEL: Thank you.

2 Dr. Somberg.

3 DR. SOMBERG: Thank you. I was
4 troubled by the presentation of the sponsor in
5 terms of the different duration, different
6 composite endpoints of the -- and not able to
7 follow how many patients were seen at each
8 different time point, and sort of a follow-up
9 on what Jeff Borer mentioned of the difference
10 between FDA's material, your material, and
11 material given to us and now the presentation
12 materials.

13 I hope, in the follow-up later on,
14 you can give us consistent data on how many
15 patients are followed for that duration
16 between the two groups in your COMPASS study,
17 and give us consistent endpoints, and also if
18 you could give us those people at Class III
19 versus Class IV in that two different subsets,
20 which may be very important as well.

21 So I just thought, the more I
22 think about it, the more difficult it is to

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1 follow, and it seems, you know, you can argue,
2 well, it's just differences, we are showing
3 you what is right. But you can argue the
4 other side of it: Well, you're giving the
5 best foot forward, and the other stuff is
6 highly selected.

7 So I think we are not given the
8 right data to make a judgment at this point.

9 DR. BOURGE: Bob Bourge again. We
10 certainly have all of the data, like to share
11 all of it. Remember that the randomized part
12 of the COMPASS-HF study was the first three
13 months -- the first six months, I'm sorry. At
14 the end of six months, all data was available
15 to everyone in the study. So we were able to
16 utilize that data.

17 For certain, to apply the
18 physiology and to show you the application of
19 the physiology, we thought it was important to
20 show the longer term data also. That's why
21 there is different numbers, but every patient
22 who got the device, all 274, are followed out,

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1 and still now. We are still following those
2 exact same patients.

3 Slide on, please. If you look at
4 the primary --

5 DR. SOMBERG: Can I just ask a
6 clarification of that? So you're saying,
7 after a certain point of three months, did you
8 say?

9 DR. BOURGE: Six months.

10 DR. SOMBERG: Six months. After
11 that point the physicians were able to utilize
12 the hemodynamic data for decision making for
13 both groups?

14 DR. BOURGE: Yes.

15 DR. SOMBERG: But you are giving
16 us follow-up at a year's time when there is no
17 difference between the two groups in terms of
18 what the physician can -- in terms of
19 assessing the hemodynamic monitoring data?

20 DR. BOURGE: Correct.

21 DR. SOMBERG: Why are you doing
22 that?

1 DR. BOURGE: Because it supports
2 the application of the physiology. We have
3 some back-up slides to show you that. Indeed,
4 the randomized part, we did show you, and here
5 it is here. On the screen is the primary
6 effectiveness endpoint out to six months for
7 the Chronicle versus the control group.

8 One of the reasons to do this type
9 of trial and to get a patient to go into the
10 trial and have a device is a benefit. It is
11 extremely difficult to get a patient to have a
12 device put in with no long term benefit
13 whatsoever, and having 27 years of clinical
14 trials experience, a big part of this was to
15 allow patients to know that we would be able
16 to look at their pressure, which we thought
17 would be useful down the line.

18 Indeed, the one slide that I
19 showed -- slide on, please -- if you look at
20 the long term effects of guided care, you can
21 see on the left is the randomized part of the
22 Chronicle IHM system where we saw a difference

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1 between the control group and the Chronicle
2 group. These are all patients.

3 If you go then to the six to 12
4 months when the control patients were able to
5 see the pressures, indeed the event rate drops
6 to virtually the same as the Chronicle group
7 throughout the entire 12 month period.

8 Am I answering the question?

9 CHAIRPERSON MAISEL: It would be
10 up to Dr. Somberg to decide, but I think that
11 was a welcome clarification. So Dr. Normand,
12 and I would also remind the Panel members to
13 shut off their microphone until they are
14 called on, because we can't have too many
15 mikes on. So thank you.

16 DR. NORMAND: Thank you. I have
17 two questions. One, I think, is simple to
18 clarify.

19 The speaker who was just up said
20 the patient -- where the patient got the
21 information on the pressures -- Does the
22 patient actually get the information or does

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1 it just go to the physician? That's the first
2 question.

3 DR. BOURGE: I'm sorry. I
4 misspoke. The physician gets the information.
5 The patient doesn't see it.

6 DR. NORMAND: Okay. Thank you,
7 because it's an important design issue.

8 Then the second question is one
9 also of clarification about your design and
10 the thought that went into your design.

11 In the Panel packet you, and you
12 also presented today information that in your
13 design you powered your study to find a 30
14 percent absolute difference. I wanted to get
15 some sense from you as to why you chose the 30
16 percent and just some thinking about that;
17 because it will help me later on with some
18 questions I have about that.

19 So why 30 percent? Is that
20 clinically meaningful, a 30 percent reduction,
21 absolute reduction, because that is what you
22 picked?

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1 DR. BOURGE: In choosing, as I
2 alluded to in my presentation, and developing
3 this particular protocol, we didn't have a
4 reference. There is no study that I am aware
5 of that looked at this, and we were also, as I
6 said, worried that the intervention -- because
7 we didn't know -- could we make patients
8 worse, knowing this information? Could we
9 over-diurese them, over-responding to
10 ambulatory pressure changes?

11 Although we had four years of
12 experience in Class III and IV in utilizing
13 the pressure information, we wanted to show
14 and track if we made things worse. That's why
15 we used this composite endpoint.

16 Indeed, in looking at this
17 composite endpoint, we thought that
18 hospitalizations would be the primary driver
19 in a positive effect. So we tried to choose a
20 population which we had data on, a similar
21 population, and indeed in a Class I and II
22 patients in some other studies in patients

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1 that have had a prior hospitalization six
2 months prior to entry into a study, the events
3 rates ran from 1.6 to 1.8 over six months.

4 We chose 1.2, being conservative,
5 thinking that indeed we set the bar very high
6 in this study by insisting that the blind not
7 be broke, every patient was contacted on
8 average of once a week. In fact, when you add
9 the clinic visits into that, it's even more
10 contacts than any other patient trial that I
11 am aware of.

12 So those number of contacts, we
13 thought, would lower the overall event rate,
14 and it did. It lowered it more than we
15 thought it would.

16 So in calculating the power, we
17 assumed the event rate of 1.2 over six months,
18 and with 80 percent power it came out to be 30
19 percent.

20 DR. NORMAND: So I don't think I -
21 - I'm sorry. I probably wasn't clear about my
22 question.

1 DR. BOURGE: I'm sorry.

2 DR. NORMAND: No, it's my fault.

3 Of course, you wanted to show a benefit and
4 worried about directionality.

5 My question really was one of why
6 did you look at absolute versus relative,
7 given that you just said you had no idea,
8 apparently, of what the baseline rates were,
9 but I want to get -- because, obviously, if
10 you look at a relative difference versus an
11 absolute difference, as we have seen, you are
12 getting a different answer.

13 I just want the clinical gestalt
14 of why 30 percent was a clinically meaningful
15 -- Forget about the statistics. It really is,
16 because you chose specifically to look at an
17 absolute difference as opposed to a relative
18 difference, and I don't know if you want a
19 statistician to answer this question or what.

20 DR. BOURGE: Be glad to have
21 someone else.

22 DR. NORMAND: But it really is a

1 clinical answer. I'm seeking a clinical
2 answer to a question.

3 DR. BOURGE: Well, my clinical
4 answer is I think that both 20 and 30 percent
5 are different -- are clinically relevant.

6 DR. NORMAND: Absolute difference.
7 I'm sorry?

8 DR. BOURGE: I think a 20 percent
9 and a 30 percent difference is clinically
10 important. However, if the event rate is two
11 per year --

12 DR. NORMAND: So it's not
13 absolute. You're thinking it should be
14 relative.

15 DR. BOURGE: I think it should be
16 relative.

17 DR. NORMAND: Okay. That's all I
18 wanted to know your thinking on. Thank you.

19 CHAIRPERSON MAISEL: Dr. Brinker.

20 MR. MANDA: May I just -- Is it
21 okay if I just clarify?

22 CHAIRPERSON MAISEL: Sure.

1 MR. MANDA: I think your question
2 is valid, Dr. Normand. Our assumptions are
3 actually on the relative -- That 30 percent
4 was expected to be a relative reduction in the
5 event rate.

6 DR. NORMAND: But you didn't --
7 You didn't look at -- You were looking at
8 absolute -- Your analysis looks at absolute.
9 So how would you -- There is a difference
10 between what you designed and what you
11 analyzed.

12 MR. MANDA: Right. Yes. We
13 analyzed it. We compared the average event
14 rates in the two groups, and we looked at the
15 reduction to see if it was -- But in the power
16 calculations, we assumed that there would be a
17 30 percent reduction of an average rate of
18 1.2.

19 DR. NORMAND: I understand what
20 you are saying. Okay. Thank you.

21 CHAIRPERSON MAISEL: Dr. Brinker.

22 DR. BRINKER: I, too, have two

1 questions. The first one is a fairly short one
2 as well.

3 Table 65 in the Panel pack, days
4 alive outside of hospital by Heart Association
5 class -- One would assume that the goal would
6 be keeping people alive, first, and second, to
7 keep them out of the hospital. When you look
8 at this, the mean days out of the hospital
9 over six months, you would assume that 180
10 would be the max. Was basically the same days
11 alive and out of the hospital, 175 for both
12 the control and the device group in Class III,
13 and actually a little bit better in the Class
14 IV group.

15 I understand there is an issue
16 about maybe the Class IV group wasn't
17 stratified appropriately, so that there were
18 sicker patients in it. But let's just take
19 the Class III group. What does that mean to
20 you all?

21 CHAIRPERSON MAISEL: Dr. Brinker,
22 what page in the Panel pack are you looking

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1 at?

2 DR. BRINKER: It's page 6-122.

3 CHAIRPERSON MAISEL: I'm sorry?

4 Six?

5 DR. BRINKER: 122.

6 DR. BOURGE: 6-122. Indeed, part
7 of this days alive outside the hospital -- I
8 agree with your comments. We want to keep
9 people alive, and we want to keep them out of
10 the hospital alive is very important.

11 If you look at the survival
12 curves, we don't believe that death
13 contributed to changes in the distribution of
14 total days as a mean for a patient out of the
15 hospital.

16 There were, however, in both the
17 Class III and Class IV some sicker patients,
18 we do believe, and some patients contributed
19 to what I call outliers. Some of them had
20 more than 30 days of hospitalization, and
21 those patients tended to be in the Chronicle
22 group, for whatever reason. So that is why I

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1 believe that the total days and the mean days
2 didn't show any significant difference between
3 the Class IIIs or the Class IVs.

4 DR. BRINKER: So could it be
5 possible that some of those days in the
6 hospital in the Chronicle group might have
7 been related to some of the device
8 complications? Certainly, some people had --
9 or weren't they counted?

10 DR. BOURGE: They were counted.

11 DR. BRINKER: So some of those
12 people had extractions and --

13 DR. BOURGE: They did.

14 DR. BRINKER: -- a couple had
15 infection.

16 DR. BOURGE: But the average time
17 for the resolution of a problem -- the median
18 time was one day. So it contributed, but not
19 a lot, I don't believe, 20 days.

20 DR. BRINKER: Okay. Fine. I have
21 my second question, which sort of relates to
22 this. But that is: How many patients --

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1 encounters in which decisions were made for
2 medical change were made strictly over the
3 telephone, and how many involved patients
4 being called back in to see the doctor or
5 nurse practitioner personally, and was there a
6 difference between somebody actually seeing a
7 patient as opposed to calling them in the two
8 groups?

9 DR. BOURGE: Indeed, the majority
10 -- and we have the data, which will come up in
11 a second. The majority of hospitalizations or
12 urgent care visits were patient initiated,
13 two-thirds, I believe, and we will have that
14 up in a second.

15 There was no differences between
16 the Chronicle group and the control group as
17 to who initiated that hospitalization or that
18 emergency department visit. We have that
19 data.

20 DR. BRINKER: I was referring,
21 actually, to clinic visits and where a change
22 in medicine -- not a -- In other words, your

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1 doctor finds that the estimated diastolic
2 pulmonary pressure is up, and he calls and he
3 says how are you doing? Not so well. Let's
4 up your diuretic by a half a pill a day, as
5 opposed to him saying, gee, I saw something on
6 your tracing; why don't you come into the
7 clinic and let us look at it.

8 So the real question is how many
9 times did a doctor actually, or a nurse, set
10 eyes on a patient in each group as opposed to
11 just telephone?

12 DR. BOURGE: We will how that, but
13 let me clarify. In the randomized part of the
14 study, patients were blinded. We couldn't
15 tell the patient I saw something on your
16 tracing. We used the phrase specifically,
17 based on all data available to us today, this
18 is what you need to do.

19 DR. BRINKER: Okay. So based on
20 that, telling the patient that, how many
21 physician/professional encounters versus
22 telephone?

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1 DR. STEVENSON: We don't have the
2 data right now on that proportion. In
3 general, in every study that's been done and
4 our impression from this, it's about three-
5 quarters of direct interventions are made by
6 phone. I don't have the exact data for us in
7 this case, but that is the general that's
8 done.

9 DR. BRINKER: So you don't know,
10 really -- So my point that I'm getting at, as
11 I'm sure you understand, is that could part of
12 the difference be that there were more signals
13 to actually see the patient by the implantable
14 monitoring system as opposed to just by the
15 sort of pseudo-control of calling them every
16 week?

17 DR. STEVENSON: No. The patient
18 contacts, both in clinic and by phone, are
19 equivalent between the two groups.

20 DR. BRINKER: They're equal.
21 Okay, that's the answer to the question.

22 CHAIRPERSON MAISEL: Thank you.

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1 At this point, we are going to take a short
2 break of 15 minutes, and we will reconvene.
3 Thank you.

4 (Whereupon, the foregoing matter
5 went off the record at 9:49 a.m. and went back
6 on the record at 10:05 a.m.)

7 CHAIRPERSON MAISEL: Welcome back.

8 I would like to call the meeting back to
9 order and to invite the FDA to make their
10 presentation.

11 MR. HILLEBRENNER: My name is Matt
12 Hillebrenner, and I am the lead reviewer for
13 this PMA, and first of all, I would like to
14 thank the Panelists for their time and effort
15 in reviewing the Panel packs in today's
16 proceedings, and also to thank the sponsor for
17 their presentation today.

18 Now I would like to provide a
19 brief introduction to FDA's review of this
20 submission.

21 This PMA is a first-of-a-kind
22 device, as we have discussed, and has actually

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1 taken up a considerable amount of resources on
2 FDA's part. You will be hearing later from
3 our clinical and statistical team. Dr. Randy
4 Brockman was the primary clinical reviewer,
5 and Ileana Pina, who is a heart failure
6 cardiologist and a consultant to the FDA, has
7 also helped out with that review.

8 George Koustenis is the
9 statistical reviewer. Vivianne Holt performed
10 the review of the pressure sensing lead for
11 this device, and Jim Cheng reviewed all of the
12 software, which was extensive for this
13 technology.

14 As of January 1, 2005, all PMA
15 submissions that were received after that
16 date, original PMAs, we conducted an
17 interactive review for the condition of
18 approval study on those applications in an
19 effort to have those studies in pretty good
20 shape and hope to approve them along with the
21 PMA, should the PMA end up being approved.

22 So to that effect, we have had

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1 Nilsa Loyo-Berrios, an epidemiologist,
2 reviewing the condition of approval study that
3 the sponsor is proposing.

4 Sharon Lappalainen has reviewed
5 the sterilization for this device. Mike
6 Mendelson and his group has worked with the
7 sponsor to improve their patient labeling and
8 also conduct human factors testing for the
9 system.

10 Melissa Torres in the Office of
11 Compliance has led the manufacturing review,
12 which included an inspection of the sponsor's
13 manufacturing facilities, and also ensuring
14 that their manufacturing processes live up to
15 good manufacturing practice regulations. And
16 Connie Braxton was the bioresearch and
17 monitoring reviewer when they conducted an
18 audit of the selected clinical sites that were
19 involved in the investigation.

20 Just a brief reminder of the
21 device description. The sponsor has gone
22 through this in detail. The system, in

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1 conjunction with the pressure sensing lead,
2 measures and stores the hemodynamic data,
3 heart rate, activity, and temperature in
4 ambulatory patients.

5 The lead is placed in the right
6 ventricular outflow tract, designed to sense
7 right ventricular pressure and R-wave, and is
8 not intended for pacing.

9 The indication for use being
10 sought in this application is as follows: The
11 Chronicle Implantable Hemodynamic Monitor
12 system is indicated for the chronic management
13 of patients with moderate to advanced heart
14 failure who are in NYHA Class III or IV to
15 reduce hospitalizations for worsening heart
16 failure in these patients.

17 As I discussed before, there was
18 an extensive preclinical review done for this
19 submission, and I just want to let the Panel
20 know that we have worked interactively with
21 the sponsor to resolve any concerns that we
22 had related to this portion of the submission,

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1 and that is why we have focused our
2 presentation and Panel pack on the clinical
3 and statistical issues that remain.

4 In the Phase I study Dr. Adamson
5 covered most of the results. I just also
6 wanted to point out that a secondary objective
7 was to compare the pressure measurements for
8 the estimated pulmonary artery diastolic
9 pressure, and those were very similar to those
10 obtained with the Swan-Ganz catheter.

11 Again, there was a reasonably high
12 degree of correlation, with a correlation
13 coefficient of 0.84, and a small degree of
14 drift with .37 millimeters of mercury per
15 month.

16 In addition to their presentation,
17 Section 5 of the Panel pack covers these
18 results in detail.

19 Finally, I just want to introduce
20 the presentation team for the FDA. George
21 Koustenis, Randy Brockman and Nilsa Loyo-
22 Berrios will be assisting in today's

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1 presentation. With that, I will turn it
2 over to George Koustenis.

3 MR. KOUSTENIS: Good morning, Dr.
4 Maisel, ladies and gentlemen of the Panel.
5 It's very nice to be here with you this
6 morning. Thanks, Matt.

7 I thought Dr. Bourge did a really
8 great job of summarizing much of the clinical
9 trial. So if you will bear with me, some of
10 this is going to be redundant, but we will go
11 through the slides as opposed to just saying
12 ditto to what he said.

13 A prospective, multi-center,
14 randomized, single-blind, controlled trial,
15 274 patients enrolled at 28 sites. All
16 patients received the Chronicle implant.
17 Randomization involved physician access to the
18 Chronicle data versus physicians having no
19 access to the Chronicle data.

20 As was mentioned before,
21 stratified by left ventricular ejection
22 fraction, and that was already explained

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1 clinically.

2 It has been discussed that
3 communication can frequently have an impact on
4 getting patients into the clinic, which can,
5 in and of itself, provide some improvement in
6 treatment.

7 The sponsor tried to assure some
8 balance here. What they did was designed a
9 communication program where they had both
10 random and scheduled surveillance calls to the
11 patients in the control group, with the idea
12 of trying to match frequency of communication
13 that would be expected with physicians who had
14 access to their data in the treatment group.

15 This slide shows the breakdown of
16 clinician initiated, patient initiated calls,
17 overall call rates. As you can see, they
18 achieved a pretty good balance on that end,
19 with no significant differences.

20 Here is a breakdown. You have
21 seen this slide as well. Twenty-four patients
22 who were withdrawn prior to implantation, the

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1 various reasons presented; three patients who
2 were unsuccessful implants. So a total of 274
3 patients went on to randomization, 134 to the
4 treatment group and 140 to the control group.

5 Quite a bit of patient demographic
6 data was presented and analyzed. I didn't
7 want to take up a lot of time here. There are
8 extensive tables presented on pages 6-62
9 through 6-65 in your Panel pack. In addition,
10 there is going to be some clinical discussion
11 on some of these variables with Dr. Brockman.

12 Lost to follow-up: They achieved
13 a very high compliance rate of 99.6 percent.
14 In fact, only one patient out of 274 was
15 reported lost to follow-up, which is a very
16 acceptable rate.

17 Here is a rationale of the reasons
18 for study exits. Analysis showed that there
19 were no differences between the treatment and
20 the patient group with regard to reasons for
21 exit.

22 As has already been discussed,

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1 there were preliminary estimates made on some
2 earlier data with regard to what the mean and
3 variance would be for the different groups.
4 It was underestimated for the mean and
5 overestimated for the variance. This resulted
6 in a drop in power to 68 percent for the
7 overall effect.

8 The pre-specified primary safety
9 objective, freedom from system related
10 complications at six months is at least 80
11 percent; and as you have seen earlier, they
12 had a lower 95 percent one-sided bound of 88.7
13 percent, which was, in fact, above the pre-
14 determined performance criterion.

15 Similarly, the pre-specified
16 safety objective was freedom from pressure
17 sensor failure at six months is at least 90
18 percent. The sponsor reported zero pressure
19 sensor failures and, of course, the lower one-
20 sided confidence bound did, in fact, exceed
21 the pre-specified value.

22 The primary effectiveness

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1 objective was to evaluate the impact of the
2 system on reducing heart failure related
3 hospital equivalents compared to a control
4 group.

5 As you have seen before, this was,
6 in fact, the definition for the hospital
7 equivalents: Hospitalizations over 24 hours,
8 ER or urgent care visits where the primary
9 reason for admission was worsening heart
10 failure, defined by the variables, as you see
11 on the slide here.

12 The primary effectiveness analysis
13 was concerned with the rate of heart failure
14 related equivalents through six months, and
15 they were hypothesizing that the Chronicle
16 treatment group is equal to the control group
17 and, conversely, the null hypothesis would be
18 that they were not equivalent.

19 As had been stated before, early
20 on it was assumed that the distribution would
21 be a Poisson. However, there was some concern
22 on the part of the sponsor. So they added the

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1 negative binomial as another pre-specified
2 analysis in case there were any problems.

3 Given that, and using the negative
4 binomial -- Well, first of all, you can see
5 here the differences in the number of events
6 with the patients, and then the total hospital
7 equivalents broken down by category.

8 The analysis revealed a 21 percent
9 differential, but the likelihood ratio tests
10 showed no significance. This would be broken
11 down as a -- distributed as a chi square value
12 which approached approximately one and, as you
13 can see, the p-value was non-significant at
14 .33. So as Dr. Steinhaus and Dr. Bourge have
15 also acknowledged, the sponsor did not meet
16 their primary effectiveness endpoint.

17 A number of secondary objectives
18 were proposed early on. However, as has been
19 noted, there were no specific performance
20 criteria established for these secondary
21 objectives. There were no hypothesis tests
22 designed for them in advance.

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1 The sponsor acknowledges that they
2 are descriptive in nature and were evaluated
3 to gain additional information about how the
4 system performs.

5 I would like to add from the FDA's
6 perspective that it is always challenging to
7 interpret any secondary objectives, given the
8 failure of the primary endpoint. At that
9 point, you have overall power which in this
10 case was actually, in fact, underpowered. So
11 secondary endpoints never have the statistical
12 power the primary do, and also failing the
13 primary endpoint, which is supposed to be the
14 major clinical factor involved in any study,
15 that that is the most definitive, and
16 secondaries would be supportive in nature.

17 In addition, the FDA does ask that
18 any attempts to look at secondary objectives
19 also account for multiplicity. That is to
20 say, the more statistical tests that you
21 perform, the greater the likelihood that you
22 will, you know, hit one significant by chance

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1 alone. There are recognized and regularly
2 used methods to do this, was not done in this
3 case.

4 Now I don't want to imply that the
5 sponsor is saying that these secondary
6 endpoints they presented were, in fact, meant
7 to be interpreted. However, I couldn't help
8 but notice that they did present some p-values
9 as they tried to look at it. So I just wanted
10 to caution the Panel that, from the
11 statistical perspective, given the results --
12 in fact, most of the secondaries didn't show
13 anything significant anyway, but be that as it
14 may, those p-values are pretty questionable
15 and very difficult to interpret.

16 They also referred to some post
17 hoc analyses that they did. These were
18 designated to be exploratory. Again, they can
19 provide additional insight into system impact
20 on the relevant heart failure visit rates.

21 The sponsor also wanted to do some
22 of these to look at the different New York

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1 Heart Association classifications,
2 specifically Class III versus Class IV, to
3 see if there was any indication there.

4 These types of analyses, while not
5 statistically meaningful in the larger sense
6 of this trial, can be useful in trying to plan
7 future trials. And again, any of the p-values
8 that were presented for post hoc issues, I
9 would caution you, are extremely difficult to
10 make any statistical interpretation of.

11 So just to quickly wrap up, the
12 sponsor has shown that their primary safety
13 objectives were met. However, the primary
14 effectiveness objective was not met.

15 A number of post hoc exploratory
16 analyses have been performed, which may
17 provide a lot of fodder for possible clinical
18 implications and discussions, which I would
19 expect, and that brings me to the end of my
20 summary. To discuss the clinical
21 implications, I would like to introduce Dr.
22 Randall Brockman of the FDA staff.

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1 DR. BROCKMAN: Thank you, George.

2 Good morning. I am Randy Brockman. I am a
3 cardiologist with Food and Drug Administration
4 in the Division of Cardiovascular Devices, and
5 I was the lead clinical reviewer for the
6 Chronicle PMA.

7 I just want to review some of the
8 highlights of the COMPASS-HF trial. I want to
9 briefly go over the design, some demographics,
10 discuss the safety data, including the
11 survival data, discuss the pre-specified
12 primary effectiveness analysis, and then I
13 would like to discuss the New York Heart Class
14 III and IV subgroup analyses. There is some
15 redundancy here.

16 So the COMPASS-HF trial was a
17 prospective, multi-center, randomized, single-
18 blind, controlled trial, enrolled 274 patients
19 at 28 sites. All patients received the
20 Chronicle implant. Randomization involved
21 physician access to the Chronicle data, which
22 was pressure data, not volume data, versus no

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1 access to the Chronicle data.

2 Enrolled subjects were New York
3 Heart Class III or IV at baseline. They were
4 on standard heart failure medical therapy for
5 at least three months prior to enrollment, and
6 they had had at least one heart failure
7 hospitalization or ER visit requiring IV
8 therapy within six months of enrollment.

9 A couple of -- or a key time point
10 was that both the primary safety and
11 effectiveness endpoints were analyzed at six
12 months. After six months, the blind was
13 broken, and clinicians had access to the
14 Chronicle data in all patients.

15 This is a standard subject
16 accountability flow chart. I just want to
17 remind you again that there were 277 attempted
18 implants, only three of which were
19 unsuccessful. Resulted in 274 patients who
20 were successfully implanted and randomized,
21 with 134 in the Chronicle group and 140 in the
22 control group.

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1 The baseline demographics in this
2 table are presented in terms of percentages.
3 About 85 percent of the subjects were in New
4 York Heart Class III. About 15 percent were
5 Class IV. About two-thirds of the patients
6 were male, meaning only a third of the
7 patients were female.

8 There was a little more
9 hypertension in the control group. I have
10 highlighted that, but overall I thought the
11 baseline cardiovascular medical conditions
12 were reasonably well matched between the two
13 arms.

14 This slide is just to point out
15 that the non-cardiovascular medical history
16 was also reasonably well matched between the
17 two arms.

18 There was a difference in the use
19 of diuretics at baseline, with a slightly
20 higher diuretic use in the control group.
21 This data accounts only for use of the
22 medication. It does not account for doses of

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1 the various medications. I do have several
2 back-up slides, if you want more information
3 about various types of medications used and
4 their doses.

5 Now I would like to move on to a
6 discussion of the results of the trial.

7 This shows the results of safety
8 objective number 1. the freedom from system
9 related complication rate for six months was
10 91.5 percent with a lower one-sided confidence
11 bound of 88.7 percent, which was above the
12 pre-determined performance goal of 80 percent.

13 this objective was met.

14 This is just to give you an idea
15 of what system related complications occurred.

16 I think you have already seen this slide. A
17 majority of the events consisted of lead
18 dislodgement. It was about 60 percent of the
19 events.

20 Of the 15 lead dislodgements, all
21 were either repositioned or replaced during
22 the randomized follow-up period. Lead

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1 dislodgement occurred in 14 out of 274
2 patients. That is about five percent of the
3 enrolled population.

4 As has been discussed, it is
5 likely due, at least in part, to the fact that
6 this lead was put in the right ventricular
7 outflow tract and is a passive fixation lead.

8 The right ventricular outflow tract is
9 generally not quite as stable as the apex.

10 The second pre-specified safety
11 hypothesis assessed freedom from pressure
12 sensor failures. No pressure sensor failures
13 occurred during the randomized follow-up
14 period, and they did meet this performance
15 objective as well.

16 Patient survival was reported in
17 terms of the number of deaths during the
18 randomized portion of the trial, which was the
19 first six months, and it was similar between
20 the two arms.

21 This graph shows the survival
22 curves for all randomized subjects for the

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1 first year. FDA chose to present this data
2 instead of the six-month curves, because the
3 number of patients at risk at the end of the
4 six-month curve or just beyond were quite low.

5 It was in the single digits.

6 I do have the six-month survival
7 curves as back-up slides, if you would like to
8 see it later.

9 So this graph shows the survival
10 curves for all randomized subjects through the
11 first year. The first 180 days do represent
12 the randomized portion of the trial. The dark
13 line represents the Chronicle group, and the
14 light line represents the control group. As
15 you can see, the survival curves are nearly
16 identical.

17 This graph shows the survival
18 curves for patients in the Class III subgroup
19 through one year. Again, the dark line is
20 Chronicle, and the light line is the control
21 group. Again, the survival curves are nearly
22 identical.

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1 This is the one-year survival
2 curves for the Class IV patients, and again
3 you can see that the curves cross multiple
4 times.

5 So next I am going to talk about
6 the effectiveness data. Before I do, I wanted
7 to also explain the way heart failure events
8 were defined.

9 The primary effectiveness endpoint
10 was characterized in terms of heart failure
11 related hospital equivalents.

12 They were defined in the protocol
13 as one of three events. There are heart
14 failure related hospital admissions for 24
15 hours or longer, and the primary reason for
16 admission was worsening heart failure; heart
17 failure related emergency department visits,
18 which were defined as a visit to the emergency
19 department for worsening heart failure that
20 required invasive treatment, generally IV
21 diuretics; or heart failure related urgent
22 visits to the clinic, which were defined as a

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1 visit to the clinic which was not scheduled,
2 occurred on the same day that the patient
3 communicated heart failure related distress
4 and necessitated IV or invasive treatment,
5 again generally IV diuretics.

6 The pre-specified primary
7 effectiveness endpoint hypothesis -- this is
8 the alternate hypothesis -- was that the
9 Chronicle group will have a significantly
10 lower rate of heart failure related hospital
11 equivalents than the control group through six
12 months.

13 You have heard a little bit about
14 the different pre-specified statistical plans.

15 So I won't go into that any further.

16 In terms of the primary
17 effectiveness result, there were 44 patients
18 and 60 patients that experienced 84 and 113
19 heart failure related hospital equivalents in
20 the Chronicle group and the control group
21 respectively, which resulted in event rates of
22 0.67 in the Chronicle group and 0.85 in the

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1 control group. This was an absolute reduction
2 of 0.18 heart failure related hospital
3 equivalents per patient per six months in the
4 Chronicle group.

5 While there was a trend toward a
6 reduction in overall heart failure related
7 hospital equivalents, it was not statistically
8 significant, with a p-value of 0.33.

9 This is the same data presented in
10 a table format. You can see in the Chronicle
11 group 44 patients had 84 total hospital
12 equivalent events, most of which were
13 hospitalizations. In the control group 60
14 patients had 113 events, again most of which
15 were hospitalizations.

16 Interestingly, urgent heart
17 failure clinic visits were relatively few in
18 both arms. Now the PMA does report an
19 additional seven urgent clinic visits in the
20 Chronicle arm that resulted in
21 hospitalization. Those were accounted for in
22 the 72 events here, as well as five urgent

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1 clinic visits in the control arm that resulted
2 in hospitalization, also accounted for in this
3 number.

4 Nevertheless, if the Chronicle
5 data provides an early warning signal for
6 heart failure decompensation, we might have
7 expected to see an increase in the urgent
8 heart failure clinic visits in the Chronicle
9 arm compared to the control arm, but this
10 wasn't observed in the study.

11 Overall, this resulted in a six-
12 month event rate, as I have mentioned, of 0.67
13 in the Chronicle group, 0.85 in the control
14 group. This was an absolute reduction of 0.18
15 heart failure related hospital equivalents per
16 patient per six months.

17 Again, this was a trend toward the
18 reduction in heart failure events in the
19 Chronicle group, but it was not statistically
20 significant, with a p-value of .33. And just
21 to remind you, this was the pre-specified
22 primary effectiveness endpoint.

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1 Now there were several pre-
2 specified subgroup analyses to which alpha was
3 not prospectively attached. The pre-specified
4 subgroup analyses included outcomes based on
5 New York Heart Class, left ventricular
6 ejection fraction, etiology of cardiomyopathy,
7 presence or absence of coronary artery
8 disease, and whether or not another cardiac
9 rhythm device was implanted.

10 Most of these analyses indicated a
11 consistent outcome in subgroups, but there did
12 appear to be a difference in response between
13 the Class III and Class IV patients.

14 This table presents the heart
15 failure related hospital equivalents in the
16 New York Heart Class III subgroup only. There
17 was a trend toward reduction of the various
18 heart failure related events, especially
19 looking only at the hospital admission for the
20 Chronicle group compared to the control group.

21 This represents a reduction of
22 0.13 heart failure related hospital

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1 equivalents per patient per six months in the
2 Chronicle group. This was a 36 percent
3 reduction in the Class III subgroup. it
4 resulted in an unadjusted p-value of 0.58.
5 The significance of that p-value is unclear.

6 We can compare this result to the
7 same in the Class IV patients. So this table
8 presents the heart failure related hospital
9 equivalents in the Class IV subgroup. Please
10 note the trend toward an increase in heart
11 failure events of most types, including heart
12 failure hospitalization, in the Chronicle arm
13 compared to the control arm.

14 This represents an absolute
15 increase of 0.55 heart failure related
16 hospital equivalents per patient per six
17 months in the Chronicle group. This increase
18 was not statistically -- Well, I shouldn't say
19 that. This increase resulted in an unadjusted
20 p-value of 0.27. Again, the p-value here is
21 of unclear significance.

22 I do want to point out that three

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1 patients in the control group accounted for 16
2 out of the total 26 events in that group.
3 These three outliers may have skewed the
4 results.

5 In addition to the pre-specified
6 primary effectiveness analyses, the sponsor
7 conducted a number of additional analyses.
8 This table presents the pre-specified alpha
9 allocated primary effectiveness endpoint on
10 the top row, and I have already gone through
11 those results, 0.18 heart failure event per
12 six month, reduction in the Chronicle group
13 with a p-value of .33.

14 The second row shows the results
15 of a pre-specified alternate analysis of the
16 primary effectiveness endpoint to which no
17 alpha was prospectively attached. This is the
18 relative risk reduction of heart failure
19 related hospital equivalents. You can see it
20 here.

21 The next three rows present
22 completely post hoc analyses, consisting of

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1 relative risk reduction of all-cause death or
2 heart failure related hospital equivalent,
3 relative risk of all-cause death or heart
4 failure related hospitalization, and relative
5 risk of heart failure related hospitalization.

6 The final one is the one that was presented
7 in the sponsor's presentation.

8 You can see the reported results
9 and the reported p-values. I am not going to
10 read them all to you, but again the p-values
11 of all except the top row are of unclear
12 significance.

13 The sponsor also assessed the
14 impact of Chronicle Guided Care beyond the
15 six-month randomization period when access to
16 the Chronicle data was enabled for all study
17 participants. This analysis was post hoc.

18 As you have heard, this analysis
19 included 240 patients for whom paired data was
20 available from both the six-month
21 randomization period and the subsequent six
22 months. Only heart failure hospitalizations,

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1 not all heart failure events, were included in
2 this analysis. All events in this analysis
3 are based on investigator adjudication.

4 As you can see in the graph,
5 events in the Chronicle group, represented by
6 the darker bars, were fairly consistent in
7 both time periods, .57 during the
8 randomization period and .60 during the
9 subsequent six months.

10 In the control arm, during the
11 randomization period heart failure
12 hospitalization events occurred at 0.81 and
13 dropped then down to 0.55 during the
14 subsequent six months. This is the period
15 when the investigators had access to the
16 Chronicle data.

17 These two findings suggest that,
18 whatever the effect of Chronicle Guided Care
19 has, it does appear to be consistent on heart
20 failure hospitalizations, at least over 12
21 months.

22 So to review the major findings of

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1 the COMPASS-HF trial: The pre-specified
2 safety endpoints were met. The pre-specified
3 primary effectiveness endpoint was not met.
4 The treatment effect, meaning the rate of
5 heart failure related hospital equivalents,
6 appears to be an absolute reduction of 0.18
7 heart failure related hospital equivalents per
8 patient per six months in the Chronicle group
9 compared to the control group.

10 Another way to think about this
11 might be to say that, if we treat 100
12 patients, we might save 18 heart failure
13 related hospital equivalents over six months.

14 Finally, FDA has some questions
15 raised by the apparent treatment difference
16 according to New York Heart Class. There is a
17 trend toward increased heart failure related
18 hospital equivalent events in the New York
19 Heart Class IV patients managed using the
20 Chronicle data compared to the control group.

21 Thank you. Now I would like to
22 introduce Nilsa Loyo-Berrios from our

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1 Epidemiology Branch just to discuss issues
2 about the post-approval study.

3 DR. LOYO-BERRIOS: Good morning,
4 distinguished members of the Panel and members
5 of the audience. I am Nilsa Loyo-Berrios. I
6 am one of the epidemiologists in the Division
7 for Postmarket Surveillance in the Office of
8 Surveillance and Biometrics.

9 As one of the epidemiologists in
10 this PMA review team, I have reviewed the -- I
11 was responsible for reviewing the PMA with the
12 purpose of identifying postmarket questions,
13 and I worked interactively with the sponsor in
14 developing the proposal for the post-approval
15 study.

16 So what you heard today the
17 sponsor describe was the result of that
18 interactive communication.

19 Before I start talking about the
20 post-approval study, I need to make this
21 disclaimer, that discussion of the post-
22 approval study prior to a formal

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1 recommendation on the approvability of this
2 PMA should not be interpreted to mean that FDA
3 is suggesting the Panel to find the device
4 approvable.

5 The plan to conduct a post-
6 approval study does not decrease the threshold
7 of evidence required to find the device
8 approvable, and the premarket data submitted
9 to the agency and discussed here today must
10 stand on its own in demonstrating a reasonable
11 assurance of safety and effectiveness in order
12 for the device to be found approval.

13 These are the topics that I am
14 going to cover in my presentation. First, I
15 am going to describe the general principles
16 and reasons for having the post-approval
17 study. I will follow that with some important
18 questions related to this device, and then I
19 will briefly describe the study proposed by
20 the sponsor, and I will conclude by presenting
21 to you some issues that we want the Panel
22 members to consider when assessing the post-

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1 approval question.

2 As we all know, premarket data are
3 collected from patients that are highly
4 selected and treated by best trained
5 physicians. In contrast, when a device is
6 permitted to be on the market, patients that
7 receive the device are less restricted and are
8 treated by physicians that are not limited to
9 the best trained.

10 Additionally, some rare events
11 that may not have been seen premarket could be
12 observed post-market due to an extended
13 observation period and as the population
14 broadens.

15 Therefore, the objective of having
16 a post-approval study is to evaluate the
17 device performance and potential device
18 related problems in a broader population over
19 an extended period of time after premarket
20 establishment of reasonable device safety and
21 effectiveness.

22 Post-approval studies should not

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1 be used to evaluate unresolved issues from the
2 premarket that are important to the initial
3 establishment of safety and effectiveness.

4 We also use post-approval studies
5 to gather information on long term
6 performance, also to get data on how the
7 device performs in a broader population who
8 are treated by the average physician.

9 Post-approval studies are also
10 used to evaluate the effectiveness of training
11 programs for device users and also to look at
12 how the device performs in subgroups of the
13 population. Clinical trials tend to have
14 limited numbers and, as such, may not include
15 all subgroups of the general population.

16 Additionally, post-approval
17 studies are needed to gather real life
18 experience and rare events that were not
19 observed in clinical trials may be observed
20 post-market.

21 Another reason is to account for
22 Panel recommendations. Panel members may have

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1 some issues or concerns based on their
2 experiences, and post-approval studies can be
3 used to address those.

4 These are some questions that we
5 consider are important related to this device.

6 The first one is related to survival. The
7 question is: Is the long term survival of
8 heart failure patients that receive the
9 Chronicle device different from the long term
10 survival of patients that receive the standard
11 of care for heart failure?

12 The second one relates to
13 morbidity. That is if the admissions to the
14 hospital are decreased in the Chronicle group
15 compared to the control group?

16 The last one is related to safety.
17 That is if the device will continue to be
18 safe postmarket, again as it is exposed to a
19 broader population over an extended period of
20 time?

21 To address these questions, the
22 sponsor proposed a multi-center, prospective,

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1 observational, two-arm study that will be
2 conducted in the United States. The study
3 participants will be followed for 24 months,
4 and these are the three main hypotheses.

5 The first one relates to the
6 survival. That is the 24-month all-cause
7 mortality in the Chronicle patients is no
8 worse than the all-cause mortality in the
9 control group.

10 The second one relates to the
11 safety. That is that the freedom from system-
12 related complications is at least 80 percent
13 24 months after implant.

14 The last hypothesis is that the
15 risk of all heart failure events among
16 Chronicle patients is reduced by 25 percent
17 compared to the control group.

18 This will be an observational
19 study and, as such, there are going to be
20 baseline differences, and the sponsor proposed
21 to use propensity scores to balance those
22 differences.

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1 In terms of statistical analysis
2 for hypothesis number 1, they will conduct a
3 Kaplan-Meier Survival Analysis. The safety
4 criteria will be that the lower one-sided 97.5
5 percent confidence limit is at least 80
6 percent 24 months after implant, and for the
7 effect on the admissions they will use the
8 Anderson-Hill method, and these considered to
9 be appropriate methods.

10 Now the Panel members received an
11 overview of the post-approval study that is
12 proposed, and we would like you -- when you
13 are addressing the post-market question, we
14 would like you to consider the following.

15 First, there is a question on what
16 is the most appropriate outcome to use for the
17 survival analysis. The sponsor proposed to
18 use all-cause mortality instead of heart
19 failure mortality, and to provide the heart
20 failure mortality as a secondary objective.
21 However, as the secondary objective, it will
22 not have a pre-defined hypothesis test or a

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1 pre-defined alpha attached to it.

2 Since this device is intended to
3 manage heart failure patients, FDA argues
4 heart failure mortality may be a more
5 appropriate outcome. We are working with the
6 sponsor, and we have requested a justification
7 for the use of all-cause mortality to be
8 included in the study protocol, but we would
9 like you Panel members to consider the
10 advantages and disadvantages of using each one
11 of these two endpoints, and to produce a
12 recommendation as to which one will be more
13 appropriate.

14 As I mentioned earlier, some rare
15 adverse events that are not observed premarket
16 could be observed postmarket, as the
17 observation period extends and the population
18 broadens.

19 Data on occurrences may be rare
20 but could result in patient harm if a
21 physician uses the data to make management
22 decisions. We would like you to discuss if

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1 this issue is addressed post-market -- is
2 possible to be addressed post-market, and to
3 make a recommendation.

4 This concludes the FDA
5 presentation, and now the floor is open now
6 for questions for the FDA.

7 CHAIRPERSON MAISEL: Thank you
8 very much for a concise presentation. I would
9 like to open up for questions from the Panel.

10 I have a question for Dr. Brockman
11 first, if I may.

12 Randy, we heard from the FDA that
13 post-hoc analyses were "exploratory" and "p-
14 values are not meaningful yet." In your
15 conclusions you state that there is a
16 treatment difference based on New York Heart
17 Association classification, despite fewer than
18 20 percent of the patients having New York
19 Heart Association Class IV and despite a
20 nonsignificant p-value.

21 So can you clarify that apparent
22 contradistinction?

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1 DR. BROCKMAN: Well, I have to
2 admit, for myself I would say that the New
3 York Heart class was not post-hoc. It was
4 pre-specified. It just wasn't alpha
5 prospectively attached to it.

6 So there were about five pre-
7 specified subgroup analyses. New York Heart
8 class was one of the five. The others were
9 ejection fraction, etiology of cardiomyopathy,
10 absence or presence of coronary disease,
11 etcetera.

12 So they were pre-specified. It
13 just wasn't alpha attached to them. I think
14 what I said was we have just some questions
15 about the New York Heart class subgroup
16 analyses.

17 CHAIRPERSON MAISEL: You concluded
18 there was a treatment difference based on New
19 York Heart Association class.

20 DR. BROCKMAN: They move in
21 opposite directions. So in the Class III
22 subgroup, it tracks more closely with the

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1 overall where we saw a trend toward a
2 reduction in heart failure hospital
3 equivalents. In the Class IV subgroup, the
4 treatment effect appears to go in the opposite
5 direction. So I wanted to just point that out
6 as, hopefully, a point for discussion.

7 CHAIRPERSON MAISEL: Okay. Thank
8 you. Dr. Teerlink.

9 DR. TEERLINK: Actually, this is
10 for you, too, Randy.

11 I notice in your presentation that
12 you mentioned that there are -- for example,
13 on Slide 53 -- 0.55 heart failure related
14 hospital equivalents per patient per six
15 months. I believe, actually, all the data was
16 presented as events per six months.

17 Actually, if you do it per patient
18 per six months, the event rate becomes .0013
19 heart failure equivalents per patient per six
20 months.

21 DR. BROCKMAN: I apologize. That
22 was a mistake.

1 DR. TEERLINK: And if you do a per
2 100 patients, it becomes reduction of 0.13
3 heart failure equivalents per patient per six
4 months.

5 DR. BROCKMAN: I think it should
6 have been per six months.

7 CHAIRPERSON MAISEL: Dr. Normand.

8 DR. NORMAND: I have three
9 questions. On Slide 54 you indicate, the last
10 row of the slide which I can hardly read right
11 now, but it is the relative risk of heart
12 failure related hospitalization using a Cox
13 proportional hazard regression.

14 Can you clarify? Is that time to
15 first hospitalization? Or somebody?

16 DR. BROCKMAN: I think I may defer
17 on that one.

18 DR. NORMAND: So that plot is
19 actually measuring time to first heart
20 failure hospitalization, not necessarily all
21 hospitalization? I just want to clarify that
22 for everybody, because I was confused.

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1 Doesn't mean everybody else was confused.

2 Slide 55, again another
3 clarification. We have outcomes measured in
4 the first six months and then again in the
5 last six months. I think I hear you say that
6 the assessment method was different. That is,
7 it was investigator adjudicated in the last
8 six months, but not in the first six months.
9 Is that true?

10 DR. BROCKMAN: My understanding of
11 this is that all of these were investigator
12 adjudicated as opposed to the CEC adjudicated.

13 DR. NORMAND: All of them?

14 DR. BROCKMAN: So this analysis
15 was performed with investigator adjudicated
16 events, heart failure hospitalization.

17 DR. NORMAND: So regardless of
18 time frame, it is always investigator
19 adjudicated endpoint?

20 DR. BROCKMAN: In this analysis.
21 That's my understanding. For this analysis,
22 yes.

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1 DR. NORMAND: Okay. I have one
2 last question. That is, certainly, along the
3 lines of what Dr. Maisel said.

4 You made a statement on Slide 56
5 about the 0.18 heart failure related
6 hospitalization. You interpreted it as -- You
7 may be regretting your interpretation, but
8 you interpret it as -- was it admissions
9 avoided or something like that?

10 Now I want to emphasize this.
11 That was not statistically significant. So I
12 want you to restate that now. Either take
13 back the statement or restate it by putting
14 the confidence intervals on it, and the
15 confidence intervals would say actually caused
16 some heart failure.

17 So can you clarify for the Panel,
18 and especially for me, the statement?

19 DR. BROCKMAN: Sure. The attempt
20 was to put that number into something that
21 might be a little bit more meaningful for
22 clinicians. There is a reason that it is not

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1 on my slide. So the attempt was simply,
2 rather than just say .18 heart failure related
3 hospital equivalents for six months, to try to
4 put it in terms that might be a little bit
5 more familiar. I didn't mean to imply any
6 statistical significance.

7 DR. NORMAND: But if you were
8 going to have that interpretation, the
9 interpretation really should be presented with
10 its interval, which actually would say it
11 increased heart failure admissions, because
12 that confidence intervals include zero and
13 goes to the negative side.

14 So although I appreciate --

15 DR. BROCKMAN: Certainly would
16 include -- Yes.

17 DR. NORMAND: Well, it's negative.
18 I mean, it goes on the other side as well,
19 just so everybody understands that your
20 interpretation, I guess I would argue, might
21 not be helpful, I would argue as a
22 statistician, because it covers both

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1 increasing heart failure related events as
2 well as decreasing them.

3 DR. BROCKMAN: Thank you.

4 CHAIRPERSON MAISEL: Dr.
5 Blackstone.

6 DR. BLACKSTONE: On Slides 43 and
7 44 I wish we could put to rest that the only
8 thing that is important to us is up to six
9 months, because as you say, beyond six months
10 there is a single arm crossover. So any
11 statistics beyond that in terms of mortality
12 is irrelevant to us, and there is no reason,
13 in fact, for presenting it beyond six months,
14 either in the Panel pack or in here.

15 So I think we should ignore all
16 that beyond six months.

17 The second idea is on Slide 47.
18 The only models you seem to have considered
19 are either the Poisson or the Negative
20 Binomial model, but just a simple ruler on the
21 events that you have says that this is not a
22 constant hazard and so on and so forth.

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1 I wonder, while the Cox
2 proportional hazard, so long as it is
3 incorporating all of the events, may get
4 around that, I wonder if some of the problems
5 are just that we are not using the right
6 distribution of events. The hazard function
7 isn't constant here.

8 DR. BROCKMAN: I'm not the right
9 person to respond to that.

10 DR. SPARKS: Brandon Sparks. I am
11 an employee of Medtronic, the statistician on
12 the study.

13 CHAIRPERSON MAISEL: Could I ask
14 you to take a seat, please, and we can give
15 Medtronic a chance to respond to the question
16 later. If the FDA doesn't have a response,
17 then we can move on. So if you could please
18 take a seat, and then if the FDA could give us
19 their best response.

20 MR. KOUSTENIS: I apologize. That
21 was my fault. I just thought the two of us
22 together --

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1 You know, these rates were
2 proposed a long time ago. I don't disagree
3 that it is not necessarily a constant, but
4 based on the earlier analyses and modeling
5 effects, they thought -- the sponsor felt that
6 was a reasonable way to approach this, and at
7 the time the FDA agreed.

8 CHAIRPERSON MAISEL: Dr.
9 Blackstone, if you want to ask later the same
10 question of Medtronic, you may do so. Dr.
11 Somberg.

12 DR. SOMBERG: Yes. I would like
13 to come back to the clinical review and, while
14 we just heard that someone wants to disregard
15 things after six months, I think my
16 interpretation was that some were presenting
17 data that that equalization when hemodynamic
18 monitoring was used in both groups is a
19 further affirmation of the utility of the
20 system.

21 I was concerned by the FDA's
22 raising the point -- I think it is an

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1 appropriate point, because it was a pre-
2 specified secondary endpoint -- of the Class
3 II versus Class -- or Class III versus Class
4 IV effect on hospitalizations.

5 Getting to the point, my question
6 is did you look further at what happens after
7 six months, six to 12 months, in the
8 difference between the Class III and Class IV?

9 Did that go away or is that still a
10 difference with more benefit in Class III and
11 less in Class IV?

12 DR. BROCKMAN: So are you asking
13 if the difference -- if the effect we saw in
14 the first six months in the Class III and
15 Class IV subgroups were analyzed out beyond
16 six months?

17 DR. SOMBERG: Yes.

18 DR. BROCKMAN: I don't believe so,
19 but then again the data had been unblinded to
20 the control group. So the control group was
21 at that point being managed, at least in part,
22 based on the Chronicle data.

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1 DR. SOMBERG: Yes, but it could be
2 that the -- and we don't know this, but there
3 is a small number of Class IV patients, but
4 the algorithm that was applied to the
5 therapies, etcetera, may actually do harm in
6 Class IV and benefit in Class III, and the
7 differences in data would still be maintained
8 after and carry over, or it could have been
9 just by happenstance, as you said, because it
10 was three patients that had 16 admissions.

11 So I'm curious to see what that
12 data is. Maybe the company can look to that
13 in the afternoon session, present that
14 material.

15 CHAIRPERSON MAISEL: Dr. Teerlink?

16 DR. TEERLINK: Just to follow up
17 on this Slide 55, my understanding is that
18 this slide does a completely independent
19 analysis of the pre-specified endpoint and
20 actually uses investigator adjudicated events.

21 My also understanding is the
22 investigators during the first part of the

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1 study knew who was being monitored with
2 Chronicle and knew who had access to the data,
3 and then in the second part of the study they
4 all knew that they had access to the Chronicle
5 data.

6 So while one hypothesis and one
7 explanation for this finding is, okay, now the
8 Chronicle device is what makes this fewer
9 investigator reported heart failure events.
10 The other possibility is that people who think
11 that they have hemodynamic data think that
12 they can determine who is being admitted for
13 heart failure better than if they don't have
14 that data, and will report it accordingly.

15 So I would really, really caution
16 any interpretation of this data whatsoever to
17 imply a durability of effect. I would be
18 interested in hearing what your interpretation
19 of that is.

20 DR. BROCKMAN: The only
21 clarification I would offer is that this was
22 not the primary effectiveness endpoint. It

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1 wasn't all heart failure related hospital
2 equivalents. This was heart failure
3 hospitalizations, which did account for the
4 majority of the events, but this is not the
5 same. This is heart failure hospitalizations
6 -- but as opposed to heart failure
7 hospitalizations, ER visits and urgent clinic
8 visits. This is just the heart failure
9 hospitalizations.

10 DR. TEERLINK: Maybe I'm not --
11 The point I'm making, though, is that in the
12 primary endpoint it is a blinded adjudication
13 committee that is determining whether it is a
14 heart failure event or not, as opposed to this
15 analysis where it is the investigator who is
16 unblinded entirely to whether they have access
17 to the data or not determining whether they
18 call it a heart failure related
19 hospitalization or not.

20 DR. BROCKMAN: Your point is well
21 taken. This is investigator adjudicated
22 hospitalization.

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1 CHAIRPERSON MAISEL: Dr. Hauptman.

2 DR. HAUPTMAN: Thanks. This to
3 some degree takes off on where John just
4 finished, and that is to what degree did the
5 FDA actually look at the non-heart failure
6 cardiovascular hospitalizations? You were
7 obviously very focused on heart failure
8 because of the primary endpoint here, but I
9 didn't get a feeling as to the number of,
10 let's say, crossovers to other device therapy
11 and the degree to which all the lead
12 displacements were accounted for as
13 hospitalizations. I just wanted to have a
14 clarification of that and understand if have
15 you critically looked at those data as well.

16 DR. BROCKMAN: I don't have a
17 slide to show you on that.

18 CHAIRPERSON MAISEL: Perhaps the
19 sponsor can prepare answers to those questions
20 for later in the day. Any other questions for
21 the FDA at this point?

22 Thank you very much for your

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1 presentation.

2 At this point we are going to move
3 on to the primary reviews, and I am going to
4 ask Dr. Borer to provide his primary review.
5 Thank you.

6 DR. BORER: Thank you, Bill. This
7 was written before this meeting. So I am
8 going to try and cut out parts that you have
9 heard 17 times by now, and I am not going to
10 provide a firm opinion here, just a review of
11 what I think are key issues, irrespective of
12 the presentations and the data that we have
13 heard so far.

14 I won't re-describe the monitoring
15 system. You know what it is. I point out
16 only that it is fairly complicated, and Dr.
17 Page already raised some issues, technical
18 issues, and we may want to raise some others.

19 So even though the adverse event
20 rates were relatively low, we had small
21 exposure and short duration of follow-up,
22 relatively speaking. So we have to be a

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1 little concerned about it, very complicated
2 but very ingenious and innovative technical
3 tour de force.

4 The device measures RV pressure
5 pulse. It also measures an electrogram of
6 cardiac electrical activity and temperature,
7 and it processes these data. That is
8 important.

9 It processes the data to provide
10 several hemodynamic or cardiac functional
11 parameters that can be used to assess the
12 patient's fluid balance -- those aren't
13 primary data; they are process data -- and
14 specifically to predict imminent hemodynamic
15 and clinical deterioration that should enable
16 preemptive therapy to reduce the need for
17 hospitalization and/or emergent or urgent
18 attention, medical attention.

19 These goals, of course, are
20 laudable and potentially very useful. I am
21 going to restate, though, the mandate of this
22 committee as I see it, and ultimately the FDA.

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1 That is to determine whether the
2 available data support the effectiveness of
3 the device for this purpose and, if so,
4 whether the benefit derived from the
5 application of a system is of sufficient
6 magnitude -- not whether it is there or not,
7 but whether it is of sufficient magnitude so
8 that the risks associated with its use are
9 acceptable.

10 Now the sponsor provided us with
11 several sets of data for our review. The data
12 were very complete. I thought they provided
13 us with a wonderful package.

14 First there was a Phase I study in
15 which 32 patients underwent device
16 implantation, and then Swan-Ganz
17 catheterization several times, up to 12 months
18 after implantation, to enable assessment of
19 the comparability of device derived data
20 versus Swan-Ganz data as the standard for
21 comparison.

22 These comparisons showed

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1 relatively good equivalence between the two,
2 and I would point out here that the Swan-Ganz
3 catheter was the standard, but anyone who has
4 spent any time in the cath lab knows that
5 there is a variability in Swan-Ganz readings
6 as well. So that some of the lack of
7 concordance of the readings doesn't
8 necessarily mean inadequacy of the device.
9 Suffice it to say, the comparisons were pretty
10 good.

11 Then there was a Phase II study in
12 which 148 patients were followed for variable
13 times up to 73 months to enable assessment of
14 the durability and safety of the device. Some
15 failures were reported, but after some
16 manufacturing flaws were resolved, these were
17 within the limits pre-specified by the sponsor
18 as acceptable, and I'm sure in conjunction
19 with discussions with the FDA.

20 We need to determine whether these
21 adverse events are less important than the
22 benefits likely to be accrued by patients, and

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1 we will need to supplement this information
2 with knowledge of other predictable adverse
3 outcomes in any population with catheters
4 indwelling for prolonged periods. Again, Dr.
5 Page alluded to this earlier.

6 There weren't any infections here,
7 but you know, there are going to be
8 ultimately, if a lot of people get catheters
9 put in and they stay there for a while.

10 Finally, there was a single Phase
11 III trial in which 274 patients in New York
12 Heart Association functional classes III or IV
13 underwent device implantation and then were
14 randomized in single-blind fashion either to
15 have their recorded information transmitted to
16 their physician for use in their path or to
17 have their data stored but not transmitted to
18 their physicians so that their management was
19 by best standard care without continual
20 hemodynamic monitoring.

21 Now nonetheless, the single-
22 blindedness could have had some impact on the

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1 disposition of patients. I think this is what
2 John was suggesting a moment ago, and we have
3 to consider that.

4 This randomized phase continued
5 for six months after which the stored data
6 were remitted to the doctors of the control
7 group patients for whom all subsequently
8 collected IHM data also were available in real
9 time to be used for patient management
10 decisions.

11 The pre-specified primary
12 hypothesis was that significantly fewer
13 hospitalization equivalents, including heart
14 failure related hospitalizations, ER visits or
15 urgent care visits, would occur in the IHM
16 managed group during six months than in the
17 control group.

18 There were a number of secondary
19 outcomes to be assessed, and ultimately
20 several post-hoc exploratory analyses were
21 performed to help interpret the results of the
22 pre-specified analyses.

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1 The pre-specified primary
2 hypothesis was not statistically significantly
3 supported by the data. However, it is
4 possible that this failure was attributable,
5 at least in part, to a lower than expected
6 vent rate in the control group, and the latter
7 may have resulted from the very high rate of
8 interaction mandated by the protocol to avoid
9 unblinding between doctors and control
10 patients, as well as between the doctors and
11 the IHM patients.

12 Also, though, the failure may have
13 resulted in part because of the inherent
14 deficiencies in the approach, even if it is
15 better than other approaches. In this regard,
16 I allude to the question I raised before. It
17 is in the packet. We don't really have to see
18 the slide, I think.

19 The data were presented by the
20 sponsor. I thought it was appropriate for
21 them to do it. They did a nice analysis.
22 They monitored pressures in the control group,

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1 took the data from the patients that had been
2 collected.

3 They took the data that had been
4 collected and stored in the control group
5 patients during the six-month randomized
6 period, and then post-hoc looked to see
7 whether pressure rises that were thought to be
8 predictive of events indeed were predictive of
9 events, and these pressure spikes were
10 predictive in about three-quarters of the
11 patients. That's what the data showed. They
12 are in our packet.

13 The pressure algorithm was correct
14 in predicting something three-quarters of the
15 time, incorrect about 25 percent of the time.

16 Nonetheless -- and Lynne Stevenson
17 pointed this out. I mean, this may be better
18 than other options. So maybe we are ahead of
19 the game using this, but it is not a perfect
20 algorithm.

21 Thus, we will need to determine
22 whether the benefits that may occur, which

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1 were not rigorously proven from the trial,
2 actually do occur and are of sufficient
3 magnitude to mandate the use of an implantable
4 device rather than, for example, more
5 intensive interaction between doctors and
6 patients, which may have worked pretty well in
7 the control group, and whether these benefits
8 outweigh the magnitude of risk that we can
9 know from the current data at a relatively
10 modest exposure level.

11 Now though the primary hypothesis
12 wasn't supported statistically significantly,
13 the results tended to support the hypothesis,
14 and several secondary analyses also tended to
15 support the hypothesis, though most results of
16 the secondary analyses weren't statistically
17 significant.

18 I was -- I won't say troubled --
19 but I noted that no effort was made to account
20 for multiple comparisons in defining the p-
21 values, and this was raised by the FDA as
22 well. So I'm not sure how to interpret those

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1 secondary analyses, even though they all tend
2 to go in the right direction.

3 Of possible importance, mortality
4 was not significantly affected by the device
5 use. Now that was not a -- It was not
6 hypothesized that it would, but it tended to
7 be slightly worse in the IHM group during the
8 randomization period. I think the numbers are
9 so small, I can't draw any conclusions from
10 that, but perhaps more importantly, the days
11 alive and out of hospital didn't differ
12 between IHM and control either. This, I
13 think, was the point that Dr. Brinker raised
14 earlier also.

15 In addition, patients in New York
16 Heart Association functional Class III tended
17 to do better with the device modulated
18 therapy, while patients in functional Class IV
19 tended to do worse. I don't know how to
20 interpret that.

21 The sponsors provided several
22 post-hoc exploratory analyses suggesting that

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1 imbalances of important risk factors mitigated
2 against the IHM success in functional Class IV
3 and account for the very small tendency toward
4 the increased IHM related mortality.

5 We need to determine whether we
6 agree that the statistical modeling performed
7 by the sponsor post-hoc is sufficiently
8 compelling to exclude other and more troubling
9 potential explanations for the findings.

10 In this regard, it needs to be
11 noted, I think, that continual hemodynamic
12 monitoring over many months in a heart failure
13 population like this one never has been
14 available before. It is an ingenious thing to
15 do. It has never been available.

16 Therefore, we really don't know
17 the optimal medical response to the data, and
18 what we are evaluating here is not just a
19 device but a system. We don't know whether
20 the medical response part of that system was
21 optimal, whether it was even appropriate. It
22 seemed to work.

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1 The sponsor and its consultant
2 investigator teams derived an algorithm for
3 management that seems reasonable, and it
4 tended to work. However, it is not really
5 known whether this algorithm is optimal or
6 appropriate, and we need to consider the
7 possibility that some of the apparent
8 adversity was due to excessively aggressive
9 use of diuretics in these patients based on
10 application of data with which no one ever has
11 had previous experience and which are
12 available only in a relatively small group of
13 study patients.

14 Now the sponsor presented data
15 that suggests that diuretics weren't overused
16 in IHM versus control, and that was very
17 helpful. But in a small population with few
18 events and possible marked individual
19 variation in response to drugs, etcetera, this
20 analysis isn't necessarily dispositive. I'm
21 not saying that it is wrong, but we have to
22 think about it.

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1 Finally, it is noteworthy that
2 after the blind was broken and control
3 patients could use IHM data, their event rate
4 fell to the value that continued in the IHM
5 patients. Though not a significant change,
6 this certainly is a result worthy of
7 consideration, but once again, the fact that
8 all of this was unblinded may temper our
9 evaluation of those data.

10 Finally, if we believe the device
11 is approvable, we will need to comment on the
12 proposed post-approval condition of approval
13 study, an unblinded, non-randomized
14 prospective observational study comparing
15 patients who accept IHM with those who don't
16 or who receive care in medical centers that do
17 accept IHM -- that don't accept IHM, rather,
18 and crossover is permitted.

19 The study is intended to provide
20 further information about long term safety and
21 feasibility. Although there are some specific
22 questions that Dr. Loyo-Berrios raised, I

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1 won't try to answer them now. I think you
2 meant it for the whole panel at a later time.

3 In closing, I would say there are
4 a number of unanswered questions here that I
5 have tried to raise. I don't think the
6 response to this application is immediately
7 apparent, though my intuition is that it
8 probably is a helpful thing.

9 It probably is. It certainly is a
10 great research tool. If this device were
11 implanted in more people and studied further,
12 I think we would learn a tremendous amount,
13 first about the pathophysiology of heart
14 failure, but in addition about the appropriate
15 therapeutic response to data of this sort.

16 So once again, I think we are left
17 with a lot of questions, and I will stop
18 there.

19 CHAIRPERSON MAISEL: Thank you,
20 Jeff. At this point Dr. Teerlink will provide
21 his review.

22 DR. TEERLINK: So the initial

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1 intent was not for me to have to come up here.

2 We were going to have a clicker back there,
3 but anyway -- So thanks for this opportunity
4 to be one of the primary reviewers on this
5 packet.

6 I would share Dr. Borer's
7 congratulations to the investigators and
8 Medtronic for really doing a phenomenal job,
9 and in trying to look at how this device might
10 or might not help patients.

11 When I looked at the risk versus -
12 - and I should also say that I am not going to
13 go into nearly as comprehensive review as Dr.
14 Borer did, given that he has already provided
15 phenomenal background.

16 I would like to say that in my
17 approach to this packet, the main concern for
18 me was, obviously, in evaluating the risk
19 versus the benefit, and the benefit as a heart
20 failure clinician is so tantalizing. I so
21 want this to work.

22 The increased availability of

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1 information to the physician about hemodynamic
2 status of the patients -- you know, we
3 believe we will be able to reduce
4 hospitalizations, but this has to be balanced
5 by the risk that has been clearly mentioned by
6 the folks, by Dr. Bourge and the
7 representative for medtronic in terms of
8 saying it may actually result in appropriate
9 or even harmful changes in therapy.

10 In addition, there is the risk of
11 device related complications. We have to
12 remember that we are asking all patients to
13 undergo a procedure that otherwise they
14 wouldn't have to undergo in order to get this
15 particular benefit.

16 In addition, there is the
17 opportunity cost to the patient, which I will
18 discuss at the end. In other words, you are
19 using specific real estate on the chest for
20 this device, and that real estate, you know,
21 is gone or it needs to be replaced. There are
22 only so many times you can use that real

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1 estate.

2 In addition, they won't be able to
3 undergo MRIs where previously they could.
4 These are small issues but, nonetheless, need
5 to come into the possibility when we look at
6 this agent.

7 I won't go into details about the
8 criteria for pressure monitoring of the
9 effectiveness endpoints. They chose right
10 ventricle systolic pressure. I think that
11 makes imminent sense when you are using a
12 device that is based on a pressure tracing.

13 I would point out and suggest to
14 future companies when they are looking at
15 these issues that it is probably more
16 appropriate to choose a more clinically
17 relevant effectiveness endpoint in terms of
18 the pressure monitoring.

19 As you see throughout the packet,
20 end-diastolic, the estimated artery pulmonary
21 diastolic pressure is used throughout the
22 packet as being the main driver of these

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1 decisions, and when they looked at saying,
2 well, how well do these pressure changes
3 correlate with events, they pulled out the
4 estimated PAD as the measure.

5 In fact, if you apply -- and this
6 is also a slide to point out, that this is an
7 estimated and derived function. It is
8 estimated from the peak pulmonary -- the peak
9 RV dp/dt , which by a unique kind of
10 correlative physiology, tends to correlate
11 with the PA diastolic pressure.

12 I should note that in some early
13 studies in the presence of dobutamine, that
14 relationship actually spread and was not
15 consistent between -- the relationship between
16 the dp/dt estimated PAD and the actual
17 measured PAD. But nonetheless, it seemed to
18 correlate well.

19 If they had used the PAD pressure
20 as their pressure monitoring effectiveness
21 variable, one can see that, by and large, it
22 would have met most of the criteria.

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1 Interestingly, the correlation coefficient
2 would not have met their pre-defined criteria
3 for actually being effective, and the drift
4 rate of 4 millimeters of mercury per year in
5 this estimated PAD-P is not inconsequential,
6 though certainly within the parameters that
7 they defined as being acceptable, though a 10
8 millimeter mercury drift per year, I find not
9 to be acceptable clinically.

10 So the labeling that we have here
11 is similar to an efficacy claim, saying that
12 there is -- the real goal is to reduce
13 hospitalizations for worsening heart failure
14 in these patients, and one can look at the
15 COMPASS trial design to point out this -- to
16 examine this potential difference.

17 The demographics have already been
18 discussed. I think I would point out, as with
19 many heart failure trials, it's a relatively
20 small trial. The age of the patients is
21 markedly different than the average age of
22 heart failure patients who are admitted to

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1 hospital, which is in the seventies, and
2 markedly more male than in the general
3 population, which is usually about 50 percent
4 presenting with heart failure.

5 Nonetheless, this is typical of
6 heart failure trials, for better or for worse.

7 This is the primary effectiveness
8 endpoint, and I would like to point out here
9 that -- and this hasn't been discussed yet,
10 but -- So everybody has been mentioning this
11 21 percent reduction, but we haven't mentioned
12 the 95 percent confidence intervals of this.

13 Actually, the 95 percent
14 confidence intervals of this measurement,
15 which is the .18 reduction in events per six
16 months, includes an increase of 25 percent in
17 hospitalizations.

18 So we have not been able to
19 exclude a 25 percent increase in
20 hospitalizations due to the device with these
21 analyses.

22 So, therefore, I think, based on

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1 this, we can't say that there is a reasonable
2 assurance of safety and effectiveness based on
3 this primary endpoint.

4 In addition, while it has been
5 mentioned -- I brought this out, actually,
6 during the questioning in the FDA section --
7 the difference of 0.18 heart failure
8 equivalent events per six months occurs in 134
9 patients. And if one looks at what that is in
10 terms of a clinically meaningful number for a
11 heart failure physician, you can say that it
12 results in the reduction of 0.13 heart failure
13 equivalent events per 100 patients treated for
14 six months.

15 We can debate whether that is
16 clinically significant or relevant or not
17 later.

18 We also had a lot of presentations
19 of the secondary effectiveness endpoints. I
20 won't go through all of them, but I would like
21 to point out that, as has been pointed out
22 already, there was no pre-specified plan for

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1 the analysis of these secondary endpoints, and
2 in general one doesn't look at secondary
3 endpoints, certainly not as a affirming for
4 approval type approach, when the primary
5 endpoint is not met.

6 That being said, here we have
7 their pre-specified secondary endpoints in
8 terms of what they looked at, and nothing is
9 significant except for perhaps cumulative
10 hospital days, with the caveats that there has
11 been no adjustment for multiple comparisons.
12 Days alive out of hospital have a difference
13 of two days.

14 Remember that number for later on.

15 No difference in the composite response
16 endpoint, no difference in the quality of
17 life. "Where p-values" -- and I put it in
18 quotes -- "were available, this is what they
19 were."

20 We are not talking about
21 borderline effects here in terms of
22 significance. None of these were significant

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1 in any basis.

2 There were a number of post-hoc
3 analyses proposed. First of all, I would
4 remind that the pre-specified primary endpoint
5 was not. The subgroup analyses, which were
6 not pre-specified, out of at least five
7 analyses, all the interaction effects analyses
8 were non-significant.

9 There was a continued move to look
10 at the NYHA Class III and IV subgroups. the
11 interaction effect of that was non-
12 significant. The NYHA Class III was non-
13 significant.

14 While I don't want to be a slave
15 to statistics, I think we also need to be
16 confident in what recommendations we are
17 making, and based on these, we cannot use our
18 usual standard for confidence and saying that
19 there are any real differences here,
20 especially when there is no overall effect
21 difference and the interaction effect is not
22 different.

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1 In addition, the durability
2 analysis, as I have mentioned already, was
3 markedly confounded by investigator bias and
4 unblinding, and I find it impossible to
5 actually interpret in any meaningful manner.

6 So the other analyses that we saw
7 is the Chronicle use resulted in much more
8 frequent adjustments in diuretics, and we
9 presumed that this increase change in
10 medication would result in improvements in
11 outcomes.

12 There is no doubt that we are
13 asking patients to do a lot of work. We are
14 asking them to change their medicines
15 frequently, adjust their medication regiments,
16 and with the presumption that we are actually
17 going to provide a benefit.

18 Unfortunately, by the pre-
19 specified primary endpoint, there is no
20 evidence of reduction in hospitalization. So
21 we are asking patients to do a lot more
22 without any real evidence of benefit at this

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1 time.

2 In addition, there was no
3 difference in over-diureses related events.
4 They were very low in both groups, suggesting
5 that even without the Chronicle device
6 physicians were pretty good at avoiding over-
7 diureses in these patients.

8 Another part that wasn't mentioned
9 at all during this presentation so far is the
10 device related rehospitalizations within six
11 months. Once again, I emphasize that we are
12 asking patients to put in and have a device
13 implanted that they otherwise wouldn't need,
14 and you can see that there are 11 system
15 related complications that resulted in
16 rehospitalizations and four unique procedure
17 related complications that resulted in
18 rehospitalization.

19 This resulted in a total of 15
20 unique rehospitalizations in the 257.8 six
21 month period, which gives a rate of .058
22 rehospitalizations per six months. If we add

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1 that to the Chronicle group, which was not
2 included in the primary endpoint but is
3 certainly a heart failure related equivalent,
4 one can see that this purported difference
5 between Chronicle and control gets even
6 smaller.

7 Then if we look at that we are
8 asking patients to undergo a procedure that
9 they otherwise wouldn't need to undergo -- I
10 asked what was the process for the initial
11 hospitalization, and information was available
12 for the 86 patients, 31 percent of the 277
13 total patients in the study.

14 The average length of stay for
15 this initial implant was 2.1 days, which is
16 about the difference in the length of stay,
17 which was non-significant before.

18 All patients with the device can
19 be considered to have a heart failure related
20 event. This is how the distribution of the
21 devices went and, as Dr. Borer has pointed
22 out, most of these were resolved within one

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1 day, but if you add the initial
2 hospitalization to the potential patient
3 benefit from Chronicle versus control in the
4 events during six months, I don't think one
5 can really suggest that there is a benefit to
6 the patients.

7 In addition, as I mentioned, there
8 are other patient considerations. There's
9 limitations on the use of other diagnostic
10 tests, such as MRI, which they otherwise
11 wouldn't have. And then the impact on future
12 use of implantable devices. This is for the
13 limited real estate argument.

14 So in conclusion, from my review
15 of the data and the packet, I think
16 hemodynamic guided therapy remains a really
17 tantalizing goal for physicians. The big
18 question is does it help patients.

19 The device did not result in a
20 statistically significant or clinically
21 meaningful change in heart failure
22 hospitalizations or heart failure equivalents.

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1 The device requires implantation, occasional
2 rehospitalizations, and frequent medication
3 changes and, I don't believe, presents a
4 reasonable assurance of safety and
5 effectiveness at this time. Thanks very much.

6 CHAIRPERSON MAISEL: Thank you,
7 Dr. Teerlink. At this point I would like to
8 open up Panel discussion and give Panel
9 members an opportunity to make comments or to
10 question either the sponsor or the FDA. Dr.
11 Domanski.

12 DR. DOMANSKI: You know, Dr.
13 Stevenson's discussion of the primacy of
14 volume and fluid management in treating heart
15 failure patients was a very nice presentation
16 of it, and certainly clear.

17 The device itself is a tour de
18 force in elegant and sophisticated
19 engineering. It really is a remarkable
20 device.

21 The thing that intrigues me is
22 that the -- you know, just the management of

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