

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

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

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

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

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

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1 calendar date change, do you have any feel for the
2 number and the kind of clinical experiences that
3 didn't met that threshold? Were these just
4 parenteral diuretics for a slight change in symptoms?

5 Was it a large number? Small number? Do you have
6 any feel for those that didn't reach that threshold?

7 DR. CARSON: We would -- because the data
8 that was collected was in terms of a calendar date
9 change from the sites, we would not have had events
10 that then we would have excluded.

11 I do have to say that, as I have thought
12 about this in multiple clinical trials, I would have
13 to say that these events would have to be exceedingly
14 rare in which a patient would be admitted to the
15 hospital, not treated in an outpatient setting, but
16 admitted to the hospital, and then discharged
17 sometime late at night after therapy.

18 It's not a practice I am familiar with as
19 a practicing clinical cardiologist for close to 20
20 years. And I think within the clinical trial milieu
21 you have to be exceedingly rare. This has been of
22 concern previously. This was brought up when VALHeFT

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1 presented its data in 2001, and at the time we did
2 not have data then either. No clinical trial has
3 really presented -- has really collected data that I
4 know of on these kind of events.

5 The VALHeFT question before the panel in
6 2001 did bring up the issue, and the Overture trial,
7 for example, went back and looked at their heart
8 failure hospitalizations and found a very small
9 number of them that were, in fact, less than a 24-
10 hour period or did not involve a calendar date
11 change. So I'm afraid I don't have any data beyond
12 that.

13 DR. YANCY: No, that's helpful. It seems
14 as if it was, then, largely operational. I just have
15 one short question for Dr. Saxon. It has to do with
16 the safety issue. The chart that is slide 99 shows
17 that the coronary venous trauma occurred in 3.7
18 percent of cases. And it appeared to be of no really
19 meaningful consequence.

20 I'd just like to understand if those were
21 episodes of tamponade that were just monitored or if
22 these really were inconsequential with just

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1 extravasation of dying. Can you just help us
2 understand that? At first glance, it seems like it
3 would be a fairly traumatic event. But it seems as
4 if the consequences were less so.

5 DR. SAXON: Great. I'm happy to answer
6 that. Let me just reflect back to your question to
7 Dr. Carson, which was what was sort of types of
8 things that occurred in this trial that might -- that
9 occurred in this trial that might not meet the
10 calendar date change.

11 And one thing we could look at would be,
12 for instance, lead revisions for any reason. Thirty-
13 six of the 50 lead revisions did trigger a calendar
14 date change, so a minority didn't, just to give you a
15 sense of those types of events.

16 Related to coronary sinus trauma, you're
17 right, the majority of coronary sinus venous traumas,
18 which were carefully classified in this trial as
19 either dissections, meaning that there was simply dye
20 in the lumen of the vessel, a perforation indicating
21 that the dye was free-flowing beyond the vessel but
22 did not require an intervention, required observation

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1 alone, and in some instances one even proceeded with
2 the implant, who had tamponade would be defined as
3 requiring an intervention or resulting in some type
4 of event.

5 So when you look at coronary venous
6 trauma, the majority of those events were staining or
7 required a non-invasive or just an observation period
8 for resolution. But some of them -- some of the
9 perforations as well as obviously the tamponades did
10 require some type of invasive procedure to correct.

11 DR. YANCY: Thank you.

12 ACTING CHAIR LASKEY: Dr. Somberg, and
13 then we'll take a break.

14 DR. SOMBERG: Dr. Bristow, you were
15 discussing the issue of the availability of devices
16 in the course of the trial, and that this was
17 considered a problem because people might want to
18 take their patient out of the study and give them the
19 benefit of something that was approved.

20 For that reason, it was introduced -- if
21 I'm paraphrasing you correctly, it was introduced --
22 the concept that to do that there would have to be a

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1 worsening of congestive heart failure, and that would
2 have to be an indexed hospitalization.

3 With that said, wouldn't that then be
4 sort of an admonition or a call to increase the
5 number of hospitalizations in the CRT-P group? And
6 if that be the case, or possibly the case, can you
7 show me a data breakdown of the number of
8 hospitalizations in CRT-P before that edict was
9 announced and after it?

10 DR. BRISTOW: Well, I can't pinpoint the
11 data. All I can say is that the primary event rate
12 was linearly consistent over time. That is, there
13 was no inflection of the primary event driven by
14 hospitalizations -- 90 percent of the primary events
15 hospitalizations. There was no change in the primary
16 event rate over time in the OPT group, and --

17 DR. SOMBERG: Am I right to assume that
18 was sort of like a midpoint decision in the trial?
19 Because looking at that peak of entry, and then a
20 decline rapidly --

21 DR. BRISTOW: Yes. So that obviously --
22 that decision had to be made after these devices were

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1 available. So it's -- you saw the enrollment per
2 month, a bell-shaped curve, and it was beyond the
3 peak of that bell-shaped curve and we began to
4 institute these measures. And it did not lead to an
5 increase in the number of primary endpoints.

6 And I can tell you that, you know, we
7 often rejected the data as not being adequate. They
8 had to provide an admission note if the patient was
9 in the hospital, clearly showing that there was
10 progression of heart failure. They had to provide
11 data on the treatment of heart failure, which had to
12 be substantive. That is, it had to be IV therapy
13 such as IV Lasix, for example. Backup slide 19.

14 So this was a very stringent process.
15 The Steering Committee was aware that this had the
16 potential to, as you paraphrase your thoughts, create
17 endpoints. But I don't believe this actually did
18 based on the stringency of the process.

19 And I will also say that the
20 investigators were strongly encouraged to maintain
21 their equipoise. So here are cumulative -- this is
22 cumulative by month. So that's not -- there's

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1 another -- yes, you don't see a turn up anywhere.
2 Log log plot would be good. There's no spike,
3 there's no up-tick in that curve, and there are
4 better curves to look at perhaps.

5 But what I was saying -- okay. Now, that
6 last little point is out there where there's maybe
7 one patient left in the OPT group out there at the
8 end. So that needs to be ignored. But --

9 DR. SOMBERG: Doesn't this need to be at
10 a flexion point of 5.5?

11 DR. BRISTOW: So there wasn't any change
12 in event rate over time. And, again, the
13 investigators really did a great job of maintaining
14 their equipoise. Our message to them was, we haven't
15 proven this therapy works in this kind of advanced
16 heart failure population.

17 And the data that you're seeing or that
18 led to the approval of these devices were based on
19 much less sick patients. These were not hard
20 endpoints. This wasn't true intention to treat from
21 the start of randomization -- none of these data.
22 And I would say that 95 percent of the investigators

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1 truly believe that and maintain their equipoise.

2 All right. Here we go. This is the best
3 slide for this purpose. This is the actual rate by
4 month, and you can see the OPT group is not up-
5 ticking anywhere.

6 ACTING CHAIR LASKEY: Well, it's a
7 notable finding, because this panel has seen
8 expansions in use of devices shortly following the
9 approval. So this would be certainly unique and an
10 exception. But -- do you have one more question?

11 DR. SOMBERG: Yes, I have one more. The
12 other thing was it was mentioned the duration of
13 hospitalizations might be different between the
14 initial implant and the CHF therapy. I wonder if you
15 have the data in terms of duration of hospitalization
16 for the CRT-D versus the CRT --

17 DR. BRISTOW: Yes. We showed earlier --
18 data we have to show you we had on earlier.

19 DR. FELDMAN: Here it is.

20 DR. BRISTOW: Here is what we have. And
21 so this is implant hospitalizations, elective implant
22 hospitalizations, in either group, drop-ins in the

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1 case of OPT, and then CRT-D upfront or reimplant
2 attempts versus medical hospitalization that were
3 part of the primary endpoint.

4 DR. SOMBERG: Yes. But I'm asking to see
5 the total hospitalizations of the two groups in terms
6 of duration.

7 DR. BRISTOW: Okay. We have -- that
8 would be in the morbidity data we showed. So just
9 give us a second; we'll pull that up.

10 Again, as has been alluded to a couple of
11 times, looking at hospitalization data in isolation
12 in a trial where there's a competing risk of death of
13 problematic. And so we always start with a
14 disclaimer. But if you go to the right, this cardiac
15 morbidity in hospitalized patients is how it was
16 done. So it's the duration of -- it's not purely
17 hospitalization. It's the duration of the event
18 driven by hospitalization.

19 And, obviously, there seems to be a
20 difference in favor of CRT-D. It's not exactly what
21 you're looking for, but it's driven by what you're
22 looking for.

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1 ACTING CHAIR LASKEY: Great. Thank you.

2 I have 11:15. Let's regroup at 11:30 and
3 have the FDA presentation.

4 Thank you very much.

5 (Whereupon, the proceedings in the
6 foregoing matter went off the record at
7 11:18 a.m. and went back on the record at
8 11:34 a.m.)

9 ACTING CHAIR LASKEY: We're doing well,
10 folks, if we can take our seats and resume. Thank
11 you. I promise that everyone gets where they need to
12 be this afternoon, so let's move forward.

13 DR. FARIS: Ready to get started.

14 ACTING CHAIR LASKEY: Thank you, sir.

15 DR. FARIS: Good morning. My name is
16 Owen Faris and I'm FDA's lead reviewer for this
17 submission in which the sponsor is seeking expanded
18 indications and claims for their CRT-D devices. The
19 physical reviewer for this submission was Dr. Barbara
20 Krasnicka. The clinical reviewers were Dr. Scott
21 Proestel and Dr. Ileana Pina and bioresearch
22 monitoring was directed by Rachel Solomon. The

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1 regulatory background for the COMPANION clinical
2 trial is extensive and includes the following
3 important events.

4 The COMPANION was approved under a
5 binding agreement between the sponsor and FDA
6 formalized September 8th, 1999. On January 20th,
7 2000 the first patient was enrolled. On May 2nd,
8 2002, the sponsors CONTAK CD device received FDA
9 approval. On November 30th, 2002, the COMPANION
10 trial was stopped for reasons previously discussed by
11 the sponsor. On January 26th, 2004, the sponsor's
12 CONTAK TR, Renewal TR devices received FDA approval.

13 Thus, at that point, both devices which had been
14 studied in the COMPANION trial were market approved.

15
16 On March 26th, 2004, the submission
17 currently under review was received by FDA. The
18 formal agreements between FDA and the sponsor
19 regarding the COMPANION clinical trial included
20 agreement on the inclusion and exclusion criteria,
21 the primary and secondary hypothesis and the
22 statistical analysis plan. It was agreed that the

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1 statistical plan would not support CRT-D versus CRT-P
2 comparison. In addition, to address the issue of
3 multiplicity, the statistical plan required
4 consistency across the primary and secondary end
5 points in order to evaluate the results from any one
6 end point.

7 The sponsor's proposed indication
8 requests the following changes based upon results
9 from the COMPANION clinical trial; an expanded
10 indication to include the entire population described
11 in COMPANION and new claims based on the primary
12 composite end point as well as the secondary end
13 point of mortality.

14 The proposed indication reads as follows;
15 Guidant Cardiac Resynchronization Therapy
16 Defibrillators are indicated for patients with
17 moderate to severe heart failure, NYHA III/IV, and
18 remain symptomatic despite stable optimal heart
19 failure drug therapy and have left ventricular
20 dysfunction, EF less than or equal to 35 percent and
21 QRS duration greater than or equal to 120
22 milliseconds. Guidant Cardiac Resynchronization

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1 Therapy Defibrillators have demonstrated the
2 following outcomes in the indicated patient
3 population specified above. Reduction in risk of
4 "all-cause" mortality or first "all-cause"
5 hospitalization, note hospitalization is defined as
6 administration of IV inotropes or vasoactive drugs
7 greater than four hours outpatient or inpatient or
8 admission to the hospital that includes or extends
9 beyond a counter date change, reduction in risk of
10 "all-cause" mortality, reduction of heart failure
11 symptoms.

12 FDA's review covered the following areas;
13 COMPANION primary and secondary end point results,
14 COMPANION hospitalizations and adverse events,
15 consistency with a pre-specified clinical and
16 statistical plans and presentation of data and device
17 labeling. At this time, I would like to introduce
18 Dr. Barbara Krasnicka to present FDA's statistical
19 review.

20 DR. KRASNICKA: In my presentation, I
21 will focus in on the problems connected with the
22 study design, data quality and study scholar

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1 analysis. As it was mentioned before, the objective
2 of this study was to demonstrate the safety and
3 effectiveness of the OPT plus CRT-D and OPT plus CRT-
4 P through the comparison with OPT alone. In this
5 statistical review, only a comparison of CRT-D versus
6 OPT will be presented. As mentioned before, the
7 COMPANION trial was a prospective multi-center
8 randomized study on patients suffering heart failure.

9
10 The clinical trial for all the group,
11 sequential design. The study was planned to stop
12 after 1,000 primary end point events would be
13 identified. It was expected that compared to the OPT
14 alone, the CRT-D could reduce combine "all-cause"
15 mortality and "all-cause" hospitalization which was
16 the primary effectiveness end point. And "all-cause"
17 mortality and cardiac morbidity which were the
18 secondary effectiveness end points. The safety end
19 point was not specified.

20 Quality of data is influenced by clear
21 definitions of response variables and methods used
22 towards data collection, editing and assessment. The

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1 primary effectiveness end point was modified three
2 times during the study. The end point was originally
3 defined as "all-cause" mortality and "all-cause"
4 hospitalization where "all-cause" hospitalization was
5 defined as admission to a hospital for any reason.
6 In addition, this end point would include emergency
7 room visits that resulted in IV therapy. "All cause"
8 hospitalization definition was finally revised as the
9 one for which the discharge date was different from
10 the admission date or as hospitalization longer than
11 four hours during which patients received IV therapy.

12 The collection of hospitalization events
13 was based only on admission and discharge dates, not
14 taking into account exact time. Therefore, the
15 capture of hospitalization event longer than four
16 hours during which patients receive IV therapy, was
17 based on the duration of the IV therapy as recorded
18 in the follow-up case report form.

19 However, some hospitalization events did
20 not have a case report form. Therefore, there are
21 some concerns that such events may not be captured.
22 The study stopped in December 2002. Some patients

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1 were followed up only for a few weeks or days. At
2 the moment of trial stopping 941 primary end point
3 events had been submitted. This means the target
4 number of primary events had been approximately
5 reached. However, there were many withdrawals from
6 the study. The withdrawal rate was especially high
7 in the OPT group. At 12 months, it was 21 percent in
8 the OPT group but only four percent in the CRT-D
9 group.

10 FDA is concerned that worsening of
11 patients health status was probably the reason for
12 many withdrawals. Due to many withdrawals and an
13 imbalance between the two treatment groups in the
14 number of withdrawn patients, the withdrawn patients
15 were asked to consent again to collect end points
16 data and status. FDA is concerned that post-
17 withdrawal information regarding hospitalization may
18 be unreliable.

19 The differences between groups with
20 respect to the primary effectiveness end point and
21 all "all-cause" mortality work is low grant
22 statistics. Kaplan-Meier method was applied to

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1 estimate the survivor functions for the two groups
2 and the Cox Model was used to estimate hazard ratio.

3 In the case of cardiac morbidity and adverse events,
4 mainly the exploratory analysis were performed.

5 Now, let us discuss the statistical
6 analysis of the primary effectiveness end point.
7 This means analysis related to combine "all-cause"
8 mortality and "all-cause" hospitalization. The data
9 set contained 202 and 386 primary events in the OPT
10 and CRT-D arms respectively. It is worth noting that
11 the primary end point was driven mainly by
12 hospitalization events which constitute over 92
13 percent of all primary end points.

14 This slide shows the class of estimates
15 of event free functions based on the Kaplan-Meier
16 method. The figure demonstrates some separation of
17 both curves over time but the curves are clearly
18 separated only in a period of time, about one year
19 after randomization. After 800 days, the estimations
20 are based on the relatively small number of
21 observations and may be unreliable.

22 To perform meaningful survivor analysis,

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1 for example, to apply the Kaplan-Meier method, some
2 assumption should be made, among other assumptions
3 are quality of data set was good, the primary
4 effectiveness and definition was not changed, and
5 censoring was non-informative. Censoring is non-
6 informative if it is independent of the occurrence of
7 an event. This means patients' withdrawals should be
8 at random and should not be caused by deterioration n
9 the health condition of a patient. It is essential
10 to notice that the fundamental for the survival
11 analysis assumption of non-informative censoring may
12 not be satisfied for this study. The even free time
13 of some patients was censored due to worsening of
14 their health status.

15 Therefore, the censoring may be
16 informative. This means it may not be independent of
17 the occurrence of an event. Now, let us assume that
18 the before mentioned assumptions are valid and we can
19 take a closer look at the event rate changes.
20 Changes over time of the event rate are given in this
21 table. The smallest differences, one to two percent,
22 is an event rate between the two groups occur during

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1 the first several days and around 200 days after
2 randomization, and the largest difference, 10
3 percent, took place about 400 days.

4 Under our temporary assumptions the
5 results of statistical analysis are as follows.
6 Survivor functions for the CRT-D and OPT groups are
7 different at significant level 0.025 based on the
8 Wilcoxin test which is more appropriate than log rank
9 test in this situation. The Cox proportional hazard
10 model supplies the hazard ratio equal 0.81, at
11 significant level 0.015. It is worth noting that
12 hazard functions clause and Schoenfeld residuals may
13 not support proportionality assumption which is
14 essential for the Cox model.

15 Therefore, the claim that CRT-D therapy
16 reduces the relative risk about 20 percent is
17 questionable. The results of the statistical
18 analysis for the primary effectiveness end point may
19 be problematic because the primary effectiveness end
20 point definition was changed during the study. The
21 assumptions on the line statistical models use may
22 not be satisfied. The censoring mechanics applied

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1 may not be independent on the occurrence of the end
2 point. The censoring was probably informative.

3 The hazard functions and the Schoenfeld
4 residuals suggest that the proportionality assumption
5 which is essential for the Cox model, may not be
6 valid in this case. Statistical analysis for "all-
7 cause" mortality secondary end point raises similar
8 statistical concerns as the primary effectiveness end
9 point analysis and will be discussed here shortly.
10 Let us now assume that the censoring is non-
11 informative. We can use the Kaplan-Meier method to
12 estimate the survival function for the two groups.
13 The effect of CRT-D therapy on the "all-cause"
14 mortality is presented in this figure. The plus show
15 that the estimated survival functions are different
16 and the survivor function for the CRT-D group is
17 almost always greater than or equal to the one for
18 the OPT group.

19 Please pay attention to the scale on the
20 vertical axis. In this figure, the scale is the same
21 as in the figures for the primary effectiveness end
22 point. In the next figure, the scale on the vertical

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1 axis was changed and confidence intervals for the
2 Kaplan-Meier survival functions were added. The
3 black curves are the survival functions shown in the
4 previous slide. The red lines are the upper and
5 lower confidence limits of the survivor functions for
6 the OPT group, while the blue ones are for the CRT-D
7 group. The confidence intervals for the survivor
8 functions are crossing each other and even crossing
9 the CRT-D survivor function itself.

10 Changes of the death rate over time by
11 treatment groups are shown in this table. During the
12 first 150 days after randomization, the differences
13 in death rates between the two groups are small,
14 maximum two percent, however, at 400 days, death
15 rates for the CRT-D and OPT groups were 12 and 22
16 percent respectively, so therefore there is a
17 difference in the survivor at 400 days is about nine
18 percent in favor of the CRT-D group.

19 In the case of "all-cause" mortality and
20 the tentative assumptions, survivor functions for
21 the CRT-D and OPT groups are different at significant
22 level 0.003. The Cox model supplied the hazard ratio

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1 0.64 at significant level 0.003. But for the "all-
2 cause" mortality, again, the statistical results may
3 be problematic because the assumptions underlying the
4 statistical methods used may not be satisfied.
5 Hazard functions and the Schoenfeld residuals do not
6 reasonably support the proportionality assumptions
7 that is essential for the Cox model.

8 Now let us discuss the cardiac morbidity.

9 Sponsor considered only cardiac morbidity events
10 which occurred in hospitals but some events could and
11 did take place outside hospitals. The hospital
12 cardiac deaths is only a part of the cardiac
13 morbidity. There were five cardiac deaths in the
14 CRT-D group and three cardiac deaths in the OPT group
15 during the first 30 days after randomization;
16 whereas, numbers of only hospital deaths was zero and
17 two respectively. This is shown in this table.
18 Therefore, cardiac morbidity based only on
19 hospitalization data that was used by the sponsor
20 does not supply the full information on all cardiac
21 morbidity events.

22 Adverse events were defined by the

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1 sponsor as undesirable clinical outcomes and included
2 device related events as well as events related to
3 the patient's general condition. This table presents
4 the over times summary of all adverse events through
5 six months. We can observe that over time the number
6 of events increases rapidly. During additional 120
7 days, the numbers are double in the two groups.
8 Assuming that each was to follow up patient before
9 the six months was free, the adverse event rates were
10 3.21 and 2.05 for CRT-D and OPT groups respectively.

11

12 Using the worst case scenario, the
13 adverse event rate through six months was 3.73 for
14 the CRT-D arm while the similar rate for the OPT
15 group was 2.80. According to both, the worst case
16 and best scenario analysis, the OPT patients
17 experienced fewer adverse events during six months
18 after randomization. It is worth noting that the
19 validity of sponsor statistical analysis is of
20 concern since correlation between multi-events within
21 a patient was ignored. Time of an adverse event
22 occurrence was not taken into account. Many follow-

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1 up patients were excluded. Therefore, all
2 exploratory analysis should be interpreted with
3 caution.

4 The statistical review conclusions are as
5 follows: treatment comparisons for the primary
6 effectiveness and mortality end points should be
7 interpreted with caution because of changes of "all-
8 cause" hospitalization definitions, withdrawals not
9 clearly independent of outcome, and open label and
10 design. All cardiac morbidity events that occurred
11 outside hospitals were not taken into account. Lost
12 follow-up patients, correlation within a patient and
13 times of the events occurrence were not included in
14 the sponsor's statistical analysis of cardiac
15 morbidity and averse events. Thank you for your
16 attention. Now, Dr. Proestel will present clinical
17 review of the study.

18 DR. PROESTEL: Hello, thank you. I am
19 Scott Proestel. I'm the Medical Officer at the US
20 Food and Drug Administration. For my presentation, I
21 will very briefly summarize COMPANION design, issues
22 surrounding the primary end point and secondary end

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1 points, some additional FDA efficacy analysis that
2 were performed as well as a safety analysis.

3 We've already reviewed the COMPANION
4 trial quite well, I believe, so I will skip through a
5 number of slides. And I think you're familiar with
6 this as well. This describes the primary and
7 secondary end points. As you know, the primary end
8 point was timed to "all-cause" mortality plus "all-
9 cause" hospitalization. The secondary end points for
10 the trial are listed as well. The results have been
11 quite well reviewed as well. Just briefly 1638
12 patients were enrolled, 93 percent were randomized.
13 Enrollment occurred between January 2000 and November
14 2002.

15 As you can see on the slide, those are
16 the numbers of patients that were ultimately enrolled
17 in each cohort. Here are the baseline
18 characteristics for the three cohorts. In
19 particular, I'd certainly like to focus on the CRT-D
20 and the OPT cohorts. Two things that I would like to
21 mention is that within the cohorts, there was a
22 modestly higher proportion of Class IV and ischemic

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1 patients in the OPT arm. Mortality in Class IV
2 patients was 2.9 times higher than in Class III
3 patients and 1.7 times higher in ischemic patients
4 than in non-ischemic. Therefore, both of these
5 imbalances favor the device arm.

6 This slide provides additional baseline
7 characteristics which appear to be well-matched. One
8 thing I'd like to say as well is that my presentation
9 will provide only descriptive statistics and should
10 be considered adjunctive to the statistical findings
11 discussed by Dr. Krasnicka. All events from
12 randomization until patient withdrawal or November
13 30th, 2002 are included. This is the primary end
14 point that was specified in the protocol which I
15 believe you're all familiar at this point.

16 However, the definition changed three
17 times during the trial. The definition initially was
18 changed in March 2001 to include only
19 hospitalizations lasting greater than 24 hours. This
20 definition changed again in February 2002 to include
21 only hospitalizations for which the discharge date
22 deferred from the admission date. Regarding the

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1 infusion requirement, there was no required duration
2 specified in the protocol, although a duration of
3 greater than four hours was ultimately used in the
4 analysis.

5 As the sponsor has provided case report
6 forms from the beginning of the trial that also
7 specified this greater than four-hour time
8 requirement, it appears that this last change to the
9 definition did not occur during the trial. A
10 compelling explanation for the change in definition
11 would have been that the new definition is inherent
12 to the old; meaning that to be hospitalized
13 necessarily means staying in the hospital overnight.

14 However, this is not the case.

15 First, if this were true, the revisions
16 would not have been necessary. Second, the trial
17 temporarily used a different definition, meaning
18 requiring that a hospitalization be greater than 24
19 hours in duration. Finally, I have only a decade of
20 experience in clinical medicine, but during that time
21 I have hospitalized patients for less than 24 hours
22 and for less than an overnight stay so can state with

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1 certainty that neither requirement is inherent to
2 being hospitalized. So far from adding clarity, the
3 requirement of a minimum duration makes the
4 definition more complicated. After all, to establish
5 the duration of hospitalization, one needs an
6 admission order and a discharge order. However, to
7 abide by the pre-specified definition of the primary
8 end point, one only needs the admission order.

9 If the intent was to require a
10 hospitalization of a certain duration, one would
11 argue that it should have been stated up front. So
12 what was the ultimate definition of the primary end
13 point? While this is a busy slide that is somewhat
14 the point, the definition was considerably more
15 narrow than the encompassing claim of "all-cause"
16 mortality plus "all-cause" hospitalization. So as
17 can be seen, the hospitalization had to be associated
18 with a date change, could not be a hospitalization
19 associated with an implant or a repeat attempt at
20 implant and could not be considered elective and
21 associated with the device. In addition, events that
22 were not hospitalizations were considered as such for

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1 the purpose of the primary end point.

2 Getting back to the issue of the changes
3 that occurred to the primary end point, the first
4 question one could ask is whether the new primary end
5 point is clinically important. I think that the
6 answer is, is yes and in fact, it is likely more
7 important than the original version due to the
8 requirement for a longer hospitalization. However,
9 the next question that must be asked is, do the
10 changes that occurred in the primary end point
11 undermine our belief in the observed effect?

12 This is a concern for FDA because if the
13 primary end point is modified in response to events
14 occurring during the trial, this would allow for the
15 possibility of modifying the end point in such a way
16 as to favor the device arm. This is one of the
17 issues that FDA will ask the panel to address.

18 This slide presents data related to "all-
19 cause" mortality which was a secondary end point. In
20 addition, all cardiac death and the sub-groups of
21 pump failure deaths and sudden cardiac death are
22 provided. This table presents all deaths during the

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1 trial, including those that may have occurred
2 following subject withdrawal if that data was
3 available and is presented in terms of death per 100
4 patient years of follow-up. The CRT-D arm is
5 associated with a reduction not only in sudden
6 cardiac death and pump failure death but in cardiac
7 death overall and "all-cause" mortality. There has
8 been some concern in the public that the CRT aspect
9 of the device, of the CRT-D device, might be
10 associated with an increase in sudden cardiac death.

11 However, as can be seen here, the improvement in
12 pump failure death overwhelms the modest increase in
13 sudden cardiac death leading to an improvement in
14 cardiac death and "all-cause" mortality associated
15 with the CRT intervention.

16 So solely for the purposes of
17 understanding the CRT aspect of the CRT-D device,
18 these point estimates might be considered reassuring.

19 Cardiac morbidity was another secondary end point.
20 It was defined as the occurrence of the following
21 events listed on this slide and I believe this has
22 been addressed before, so I won't read them to you.

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1 These events were also considered cardiac morbid
2 events.

3 However, the definition that was used did
4 not match the definition provided in the protocol.
5 The definition that was used for cardiac morbidity
6 was any hospitalization during which one of these
7 specified cardiac morbid events occurred. Therefore,
8 a single hospitalization that had multiple cardiac
9 morbid events would only count once towards the end
10 point. Using this definition, as you can see, there
11 was a mean of 0.5 events per year in the CRT-D arm
12 and 1.0 events per year on the OPT arm. The FDA does
13 not have the data to calculate the original cardiac
14 morbid end point as specified in the protocol.

15 I would like now to discuss some
16 additional analysis that were performed for the
17 purposes of device labeling which may help to clarify
18 the results of the study. These were not specified
19 end points for the trial. This may, in some way,
20 address a concern that Dr. Brinker had discussed. As
21 the primary end point only counted the time to first
22 event, any subsequent hospitalizations were not

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1 counted. Therefore, FDA felt it would be informative
2 to perform an additional calculation, the "all-cause"
3 hospitalization rate which was not specified in the
4 protocol. In this evaluation of hospitalizations for
5 any cause, which included implant attempt
6 hospitalization, there was a mean of two
7 hospitalizations per year in the CRT-D arm and 1.6
8 hospitalizations per year in the OPT arm.

9 In addition, the CRT-D patients were in
10 the hospital for a mean of 11 days during the year
11 and in the OPT arm 10.7 days per year. There have
12 been arguments made as to why it might not be
13 reasonable or appropriate to include the implant
14 attempt hospitalizations in an "all-cause"
15 hospitalization analysis which I would like to now
16 address.

17 It has been argued that the implant
18 hospitalization is a single non-recurring event. It
19 is not. Forty-nine of the patients had to undergo
20 two implant hospitalizations and two patients
21 underwent three. And in approximately four to six
22 years the device subjects would need to be

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1 hospitalized again to have the device replaced due to
2 battery depletion. Even if one believes that the
3 implant hospitalizations were recurring but at a
4 trivial rate, the rate was certainly greater than
5 that for say cholecystectomy which was included as a
6 hospitalization during the study and luckily occurs
7 no more than once in a lifetime.

8 The fact of the matter is that each of
9 the causes of hospitalization is occurring at a given
10 rate and the implant attempt hospitalization is not
11 even the one associated with the lowest rate, so why
12 exclude it. It has also been argued that the --
13 including the implant attempt does not characterize
14 the effect of the device. This is true and this is
15 the point. The encompassing claim of "all-cause"
16 hospitalization by its very nature includes events
17 that may not be tightly linked or linked at all to
18 the action of the device. Indeed elective
19 hospitalizations were included as events that counted
20 towards the primary end point, so once again, why
21 exclude implant attempts?

22 Finally, even if one decides to ignore

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1 implant hospitalizations, it may be worth noting that
2 the effect of the device on hospitalization was not
3 of sufficient magnitude during the trial to account
4 for the implant hospitalizations that were required
5 to get the device. I would like to emphasize that
6 FDA is not advocating a change in the primary end
7 point. We are merely attempting to make the case
8 that this additional analysis of "all-cause"
9 hospitalization is reasonable, clinically relevant
10 and may aid patients and physicians in their
11 understanding of what may be expected with this
12 device therapy.

13 This slide provides the FDA analysis of
14 the implant hospitalizations which was considered
15 important to characterize despite not being an end
16 point of the trial. As can be seen, 541 patients had
17 a successful implant, 47 has unsuccessful implant and
18 seven were randomized to CRT-D but never underwent a
19 procedure. The mean duration of hospitalization was
20 2.9 days.

21 With respect to safety, FDA reviewed all
22 adverse events during the trial. These were defined

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1 as undesirable clinical outcomes, including device
2 related events as well as events related to a
3 patient's general condition. The first set of
4 numbers provides the total number of adverse events,
5 not adjusting for the larger number of subjects in
6 the CRT-D arm and the moderately longer follow-up in
7 that arm. The rates adjust for these issues and you
8 can see that the device arm had a greater rate of
9 adverse events. However, the adverse events in the
10 device arm were not of a rate or severity beyond that
11 which might be expected for the intervention.

12 Indeed, as can be seen in this slide, the
13 proportion of adverse events that were complications
14 was actually lower in the device arm. An observation
15 was defined as a clinical adverse event that was
16 correctable by non-invasive measures and a
17 complication defined as a clinical adverse event which
18 required invasive measures to correct. Therefore,
19 complications on average are more likely to be
20 significant adverse events. And it is reassuring
21 that the proportion of adverse events that were
22 complications was, in fact, lower in the CRT-D

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1 cohort.

2 What I would like to do now is let Dr.
3 Owen Faris present conclusions for the FDA
4 presentation. Thank you.

5 DR. FARIS: In summary, FDA's review
6 covered the following areas; COMPANION primary and
7 secondary implant results, COMPANION hospitalizations
8 and adverse events, consistency with pre-specified
9 clinical and statistical plans and presentation of
10 the data on device labeling. With regards to the
11 primary end point, modifications were made to the
12 hospitalization definition, part of the primary end
13 point, during the course of the COMPANION trial.
14 Fundamental statistical assumptions underlying some
15 analyses may not have been met. Where the COMPANION
16 demonstrated a benefit, the primary end point as
17 originally defined is unknown. FDA requests guidance
18 from the panel in interpreting the modified primary
19 end point.

20 With regards to the secondary end point
21 of mortality, the CRT-D device was associated with a
22 decrease in "all-cause" mortality compared to OPT.

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1 However, fundamental statistical assumptions
2 underlying parts of the analysis may not have been
3 met. Since the pre-specified statistical plan
4 required consistency between the primary and
5 secondary end points, FDA requests guidance from the
6 panel in assessing the impact of modifications to the
7 primary end point on interpretation of the mortality
8 benefit.

9 With regards to additional concerns
10 raised by FDA's review, the sponsor's analyses
11 included data obtained from patients after
12 withdrawal. When implant hospitalizations were
13 included, the CRT-D device was associated with an
14 increase in "all-cause" hospitalizations compared to
15 OPT. The CRT-D device was associated with an
16 increase in adverse events compared to OPT. FDA
17 requests guidance from the panel in determining how
18 these considerations should impact the sponsor's CRT-
19 D labeling.

20 Thank you very much.

21 ACTING CHAIR LASKEY: Thank you. Panel
22 members? Dr. Normand.

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1 DR. NORMAND: I just want to beat a dead
2 horse again, but I need to get some clarification on
3 the definition of "all-cause" mortality. So just to
4 state it in my understanding of what's been
5 presented, it is my understanding that the initial
6 protocol stated "all-cause" mortality and didn't -- I
7 guess didn't give a time frame for it. Is that
8 correct?

9 DR. PROESTEL: The definition for death
10 remained constant throughout the trial.

11 DR. NORMAND: Okay, but it was just -- it
12 said, I'm sorry, "all-cause" hospitalization was just
13 "all-cause" hospitalization. There was no timeframe
14 of the "all-cause" hospitalization.

15 DR. PROESTEL: Not in the protocol.

16 DR. NORMAND: Not in the protocol. So
17 that -- no one pushed for a definition. One just
18 said, okay, "all-cause" hospitalization.

19 DR. PROESTEL: With the caveats of the
20 greater than four hours of IV infusion and that the
21 implant attempt would not be counted. Beyond that,
22 it was "all-cause" hospitalization including elective

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1 hospitalizations.

2 DR. NORMAND: Okay, and another point of
3 clarification. It's indicated that the definition
4 changed three times. Hospitalizations greater than
5 24 hours and then the next one was a hospital in
6 which a calendar date it was apparent. It seems to
7 me for the first to be true, the second has to be
8 true. Anything greater than 24 hours by definition
9 the calendar date has to change.

10 DR. PROESTEL: Right, correct.

11 DR. NORMAND: So if my understanding is
12 correct and I may be wrong about this, if you're
13 going with the greater than 24 hours, then indeed,
14 using the second definition, hospitalizations for
15 which there was a calendar date change, you could
16 actually include patients that were hospitalized for
17 less than 24 hours, correct?

18 DR. PROESTEL: Correct.

19 DR. NORMAND: Okay, and then my last just
20 clarification, help me think through some things. It
21 is, I think you indicated that there was -- there
22 were revisions but I heard a little bit earlier that

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1 there was never a revision of the data collection
2 form. Did you mean revisions to the numbers that
3 reported to FDA or did you mean revisions to the data
4 collection instrument?

5 DR. PROESTEL: Revisions to the primary
6 end point, I mean, you can collect data on a case
7 report form that is not necessarily -- in fact, most
8 of the data on the case report form is not related to
9 the primary end point. So the fact that that data is
10 on the case report form, certainly does not mean that
11 the primary end point was, in fact, a date change or
12 24 hours. It should have been what was stated in
13 the protocol.

14 DR. NORMAND: Thank you very much.

15 ACTING CHAIR LASKEY: All right, next?
16 Yeah.

17 DR. KRUCOFF: Dr. Krasnicka, I'm going to
18 ask you for help because -- and I want to talk just
19 about mortality, okay, death. Your contention that
20 I'm just going to need some education on, I guess,
21 about the underlying assumptions for the Cox model.

22 DR. KRASNICKA: Yes.

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1 DR. KRUCOFF: Does that effect the
2 mortality reports and effect of the device on
3 mortality in this model?

4 DR. KRASNICKA: Yes. This means -- the
5 second part, the sponsor plan is that there is 66
6 percent of reduction in related risk if the
7 assumption is not -- we don't know exactly, again,
8 because it's really this estimation is biased.

9 DR. KRUCOFF: So to the relative lay
10 person, can you help me understand what's bad about
11 this?

12 DR. KRASNICKA: I can show you Schoenfeld
13 residuals and you can see how this estimation is
14 change over time. It's from the plus to minus and
15 this is mortality -- slide. The next one. And you
16 can --

17 DR. KRUCOFF: Would you mind getting
18 closer to the mike, I can barely hear you.

19 DR. KRASNICKA: You can see that the
20 coefficients at treatment in Cox model is changing
21 from the plus to minus and then to plus. This means
22 that the proportionality assumption is not true of

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1 the Cox model and we cannot claim, for example, that
2 there is 66 percent of the reduction in related risk.

3 DR. NORMAND: Perhaps if I could -- if I
4 could maybe just ask a question to perhaps clarify
5 the answer. I guess part of the panel members are
6 wondering if the Cox -- if you use a Cox model to
7 analyze the data, and you reported an estimate based
8 on a Cox model in which the proportionality
9 assumption is violated, I think that's what you're
10 suggesting.

11 DR. KRASNICKA: Yes.

12 DR. NORMAND: The Cox model, that the
13 proportionality assumption was violated, in which
14 case it says that they cross and you wouldn't want to
15 say that it, indeed, was a -- you know, one way or
16 the other. They crossed and so sometimes it's good
17 and sometimes it's bad. Is that a fair
18 characterization of what you're --

19 DR. KRASNICKA: Yes, yes.

20 DR. KRUCOFF: Okay, so to my mind, when I
21 look at this, what I see is that, in fact, the
22 relative benefit to death rate over time in a

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1 population treated and not treated with the device,
2 may be different at different times --

3 DR. KRASNICKA: Yes, yes.

4 DR. KRUCOFF: -- along the time.

5 DR. KRASNICKA: Yes.

6 DR. KRUCOFF: It's not uniformly
7 beneficial.

8 DR. KRASNICKA: Yes.

9 DR. KRUCOFF: But how much impact does
10 that then have on the end conclusion or inability to
11 reach a conclusion that at the end of 300 days or a
12 fixed time period that ultimately in a population who
13 has some heterogeneity through a range of mechanisms
14 that may behave differently at different times, that
15 at the end of a prolonged observation, you could make
16 a wrong claim.

17 DR. KRASNICKA: The best way it would be
18 adjusted for the baseline providers and to check if,
19 for example, the models are correct, are good for
20 this case, and to check for example, how centers have
21 impact on the result because in the case of the
22 survival analysis, really you have to adjust for the

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1 covariance to get not bias estimation of the
2 treatment. It's completely different. For example,
3 in the case of binary outcome, at one year, you don't
4 need, really to adjust for the covariance. That --

5 DR. KRUCOFF: So has anybody done that?
6 Have you guys done that? Can anybody show us any
7 adjustments?

8 DR. KRASNICKA: No, I got that set only
9 for really two, three weeks and I didn't have time.

10 DR. KRUCOFF: All right, one other
11 clarification question and I'm done. We've obviously
12 heard clearly that there's a concern about whether
13 the censoring process was informative.

14 DR. KRASNICKA: Yes.

15 DR. KRUCOFF: But as I understand it, at
16 least, if it is, if basically patients who in the OPT
17 arm, were getting sicker so they got pulled so they
18 could not be a violation, go and get their device
19 through other means, if the presumption is those
20 patients were getting sicker and they are withdrawn,
21 doesn't that -- isn't that actually unfavorable for
22 the device?

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1 DR. KRASNICKA: Yes, but when you look at
2 the "all-cause" hospitalization definition,
3 definition was changed and really all hospitalization
4 for any reason was dropped and when I was thinking
5 that maybe the patients from the CRT-D group got
6 problem with device, and for example, went to
7 hospital for one, two hours, so we don't know really,
8 what's happened with the primary effectiveness end
9 point.

10 DR. KRUCOFF: Okay, I understand the
11 definition got changed, but I think this is going to
12 be really important. To me, are you saying that
13 there's some relationship in your mind? Are you guys
14 thinking that the change in the definition of "all-
15 cause" hospitalization somehow relates to an informed
16 or biased censoring or withdrawal of patients from
17 the OPT group? Or are these separate issues?

18 DR. KRASNICKA: Separate issue.

19 DR. KRUCOFF: They're separate issues.
20 So all I was asking is, on the informed -- on the
21 concern about informative censor. That's all I was
22 asking --

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1 DR. KRASNICKA: Yes, okay.

2 DR. KRUCOFF: -- is if I understand the
3 concern, which is a real concern, at least the way I
4 see that one issue, it's actually unfavorable to the
5 device if patients who are getting sick are in the
6 control -- the in OPT arm, are getting dropped out --

7 DR. KRASNICKA: Yes.

8 DR. KRUCOFF: -- that would be
9 unfavorable for the device. Is that not true --

10 DR. KRASNICKA: Yes, could be.

11 DR. KRUCOFF: -- in terms of claiming a
12 benefit for the device?

13 DR. NORMAND: I think you could make
14 arguments along a number of different directions on
15 that. I just feel I have to say this.

16 DR. KRUCOFF: I'm just asking a question.

17 DR. NORMAND: No, and I'll give you at
18 least my opinion on that. And that is if --
19 certainly one could argue that they could be
20 healthier, there's no doubt about that, but one
21 sicker -- but only may say they're healthy enough to
22 receive the device, so there is some selection. So

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1 you could in some ways argue about them, yes, maybe
2 they were sick enough to get the device, but yet,
3 they had to be healthy enough to actually receive the
4 device in the absence of this. So there is a
5 selection process in there that does raise a concern
6 -- not raise a concern but --

7 DR. KRUCOFF: But assignment to the
8 device was randomized.

9 DR. NORMAND: Well, no, you're saying
10 there are a group of people -- I'm asking a
11 hypothetical question, so there's a hypothetical
12 question where someone was randomized to treatment
13 one or treatment two. I'm saying it hypothetically
14 because I don't want to -- I don't know the answer to
15 this in this particular situation but if they were
16 randomized to treatment one or treatment two and
17 another therapy becomes available and someone says,
18 "Gee, I want to get it, I want to pull out of this
19 and get this", there are considerations that say,
20 "Yeah, I recommend you actually do that".

21 And, yes, they may be sick enough to need
22 the new device but often there are patients that get

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1 devices that are healthier, because they're robust
2 enough to actually get the device rather than the
3 physician saying, "No, stay on the current
4 treatment". So you could argue both ways.

5 DR. SOMBERG: But the trouble with that
6 is it sort of addresses the question that Dr.
7 Proestel showed me that there was really no major
8 inflection point in the -- in the data because that
9 would occurred during the course of the trial when
10 these devices became available and there wasn't a
11 change in the number of patients who were in the
12 pharmacologic therapy were then being censored from
13 the study. Am I correct in that?

14 DR. NORMAND: I'm not sure about the
15 answer to that question but I am sure about the
16 answer to the question that it's not necessarily true
17 that it would have favored the therapy arm if some
18 people left. I can't conjecture on why there wasn't
19 because normally you see a big jump.

20 DR. KRUCOFF: I'm sorry, I lied. I have
21 one other quick clarification, Scott, at least
22 because it's on the record. In your slide, showing

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1 the baseline characteristics, I just want to make
2 sure that I heard what you said versus what I see.
3 The Class III, Class IV ischemic population, Class IV
4 population slightly higher incidents in the CRT-D
5 arm, than in the --

6 DR. PROESTEL: The ischemic and the Class
7 IVS were --

8 DR. KRUCOFF: Were higher in the OPT than
9 in the CRT --

10 DR. PROESTEL: Right.

11 DR. KRUCOFF: Okay.

12 DR. PROESTEL: Did I say that the other
13 way?

14 DR. KRUCOFF: I'm not sure what I heard
15 or what you said.

16 DR. PROESTEL: Okay.

17 ACTING CHAIR LASKEY: All right, this is
18 not a rhetorical question. For this statistician
19 again, my -- when I look at the data presented by the
20 sponsor in these figures, these blocks, the survival
21 curves. There are two pieces of data reported here.
22 The first is the log rank statistic that compares

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1 the two survival curves which is the standard way to
2 do product limit survival analysis. And then there's
3 this hazard ratio which comes out of another
4 analysis. Is that correct?

5 DR. KRASNICKA: Yes, yes, correct.

6 ACTING CHAIR LASKEY: That comes out of a
7 Cox proportional hazards regression.

8 DR. KRASNICKA: Yes.

9 ACTING CHAIR LASKEY: And that's a
10 different set of statistics than the standard product
11 limit Kaplan-Meier set of statistics. And that's I
12 think, part of the confusion up here, is that on one
13 plot both of these, quote "results" are being
14 reported and yet, the problem you're having with the
15 Cox proportional hazards has been well articulated
16 but it's -- I guess the other issue is how we
17 interpret the Kaplan-Meier curves and I guess we'll
18 come back to that this afternoon, but there's two
19 separate analyses going on here.

20 DR. KRASNICKA: Yes. Completely
21 separate.

22 ACTING CHAIR LASKEY: Yeah. Thank you.

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1 Dr. Somberg, are you not hungry?

2 DR. SOMBERG: No, not really. I'm on
3 Central Time, remember that. It's not lunch time
4 yet. I'll make it very quick. Number one, I'm going
5 to play devil's advocate for a moment here and the --
6 while there's debate whether the four-hour infusion
7 was to be counted or not between what we heard of the
8 sponsor's presentation or the academic
9 investigator's, I should say, presentation, and the
10 FDA. Let me ask you, does it really matter, because
11 it only contributed, I think we said four percent?

12 DR. PROESTEL: Well, basically, we are
13 cataloging the changes to the end point. In fact,
14 the case report form originally was designed to
15 capture greater than four hours from the beginning of
16 the trial, so I don't see that as a problem. I do
17 think that the other two changes to the primary end
18 point are concerning because they occurred during the
19 trial.

20 DR. SOMBERG: Okay, I hear you, and my
21 other next question is the study withdrawals, that
22 was a very high number, 20, 25 percent and that's

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1 what really got the investigators to decide to go
2 back and to re consent and to go through it. I was
3 very impressed how thorough that was but I understand
4 that comment was made that there's a question of the
5 reliability, that it may be unreliable and may have
6 added a bias into a blind. I mean, isn't that to be
7 commended, to go back and to look at it. If we left
8 that 25 percent and we found that 20 percent
9 difference, then we would have said, "Hey, look, that
10 could have contributed, but now we've gone back. It
11 was reduced to next to nothing and why is there a
12 bias, why is it unreliable?

13 DR. PROESTEL: Well, there's a number of
14 issues. One is there is an -- if you allow -- that
15 would be, I guess, the fifth change or well, maybe
16 the fourth change. You know, there should be some
17 limit on the number of ways one can reinterpret the
18 design of the trial. And while I certainly agree
19 that this additional information is valuable, I think
20 it's worth considering that the original specified
21 plan should also be presented with that data and this
22 would be adjunctive data that could be included.

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1 Another issue, as far as the reliability,
2 I'm going to try and find a piece of paper. It
3 provides the description the sponsor provided for
4 what was done. You can chat amongst yourselves.

5 ACTING CHAIR LASKEY: While we're doing
6 that, is Dr. Waldo still with us?

7 DR. WALDO: Yes, I am.

8 ACTING CHAIR LASKEY: Great. Did you
9 have any queries for the FDA?

10 DR. WALDO: I mean, I think this whole
11 discussion of the statistics is critical. I share
12 with my colleagues, I'm not a statistician and I
13 think I have to tell you honestly, when I first read
14 this, I -- my tilt button went off because of all the
15 numerous changes. I mean, the first change was well
16 over a year after into the trial. The second change
17 was still a year later. I mean, that just bothered
18 me but again, I have to rely on my statistical
19 colleagues to say if that's -- something which is
20 intuitive has merit in terms of my being upset. I
21 just think that was really bad.

22 Of course, I mean, you -- and this -- and

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1 we kept hearing that this was -- all previous trials
2 had done it this way. Why didn't they design it that
3 way from the beginning? I think that was a problem.

4 And I think I need some more statistical help.

5 The other thing that bothered me was that
6 some of the adverse -- some of the things with the
7 implantation of the pacemakers were considered as
8 adverse events because of the way that they were --
9 with the revised definition. So in other words, if
10 you had a revised lead or something like that and you
11 didn't have to stay overnight in the hospital, that
12 was just an adverse event and it didn't require
13 hospitalization, the reason that really bothers me,
14 again, I notice, I think I heard there weren't that
15 many revisions but I don't know how many other things
16 there were, but what bothers me about that, is that
17 really we've heard over and over again from both the
18 presenters and from the FDA analysis that this whole
19 thing was driven by hospitalizations, I thought 90
20 percent roughly I think is right, of the events, so
21 hospitalization, I think, is really critical.

22 And I share a lot of the concerns about

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1 how you consider hospitalization because the
2 hospitalization is the reason that you reach the end
3 point in this trial and you make conclusions. So if
4 you just give devices a buy as they seem to have
5 done, I don't think that's valid. It just doesn't
6 make any sense to me. It doesn't make economic
7 sense. I think when you consider all things with
8 patients, they have to understand that you know, that
9 the hospitalization is part of this. So that bothers
10 me also because it's hospitalization driven.

11 In fact, I'd be honest with you. I was
12 thinking that if I were designing this trial and I'm
13 an electrician and not a plumber, but I would have
14 thought that mortality was a critical part of this
15 and it's not the major driver of the primary end
16 point. And I was even asking -- well, so I'm saying
17 a lot of things. I have two other points. I'm
18 saying too many things before lunch, I think, but I
19 have read many, many times the approved indication
20 and the request for change that Guidant is asking for
21 and I have difficulty sorting out the difference.
22 So, I mean, that's even a more fundamental question

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1 for me. What are we here to talk about, because I
2 haven't appreciated the difference between the
3 approval that I understand they have and the change
4 that they're asking for. So that many -- and I have
5 a few other things listed by maybe that's enough to
6 start for now.

7 ACTING CHAIR LASKEY: Right, we'll come
8 around to general critique comments this afternoon,
9 but I just wondered whether you had any questions for
10 the three FDA presenters but --

11 DR. WALDO: Well, I only worry about that
12 my relative unsophistication in understanding
13 statistics and I respect the statisticians and I know
14 Dr. DeMets, too, and I think he's a well-respected
15 person, so I wish that the two groups of
16 statisticians could maybe come to some understanding
17 or do we understand there are disagreements between
18 them because I'm not sophisticated enough to
19 challenge one or the other. I do very much worry
20 about all of these hospitalization changes and in a
21 the study driven by hospitalization where that's
22 really what has driven all -- virtually all the

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1 conclusions in this trial, that this seems very messy
2 and very worrisome to me.

3 ACTING CHAIR LASKEY: All right, well,
4 rest assured we'll try and get some consensus for you
5 this afternoon. Thank you, Dr. Waldo. We'll get --

6 DR. WALDO: Sorry, I couldn't be there.
7 I got to Baltimore, but the plane wouldn't land.

8 DR. PROESTEL: I'm sorry, just to follow
9 up, we had discussed this issue with Guidant and they
10 provided a response. It's a withdrawn patient
11 consent process and I'd like to just read a portion
12 of this so that you might understand our concern.
13 "Guidant determined that if patients did not withdraw
14 their consent at the time of discontinuation in the
15 trial, they would not require re-consent. Rather they
16 would be covered by the original study consent if the
17 coordinator was aware of the patient's status and did
18 not require consulting the family or medical records.
19 A second letter was sent to the principal
20 investigators on March 6th, 2003 clarifying this
21 information. A copy of this letter is attached for
22 reference".

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1 This letter cites, "to review their
2 patient's consent status from the patient device
3 status form attached, if the withdrawal reason
4 selected was either 13, patient refused follow-up or
5 possibly 88 other if explanation given indicates
6 consent was withdrawn. The situation would require
7 reconsent with the additional informed consent as
8 outlined in the February 20th, 2003 letter". This is
9 the important part. "All other reasons for
10 withdrawal would allow the research coordinator to
11 fill out required CRFs including withdrawal contact
12 and treatment modification if patient received his
13 device if data was known without contacting the
14 patient, family or medical records".

15 So to me this indicated that data was
16 being filled in to CRFs based on memory which I think
17 is unreliable.

18 DR. SOMBERG: I mean, I hear what you're
19 saying but I'm not sure that states that. It says
20 that they would fill out the CRFs if they didn't feel
21 that it required a secondary consent form filling
22 because of those two issues. If a data coordinator

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1 fills out a CRF, and we can ask the group here that
2 monitored the studies, they would have to go back to
3 the source records. I mean, I do investigations all
4 the time and my brain is zilch for remembering what
5 happened yesterday in terms of all sorts of things
6 because you hear a constant in-flow of data so you go
7 back to the source records. So I don't think there's
8 that implication there because I think that goes to
9 the heart of the matter is the changes and, you know,
10 I grant you there may be, and we can have a debate
11 on this and all that but if there were changes, does
12 it increase the unreliability and I thought going
13 back and reconstituting and going down to only about
14 four patients that were not in the data base was a
15 remarkable success from a potential failure of having
16 20, 25 percent not filled in. So I think we should
17 go back after maybe lunch and see if it was just on
18 guesstimates on what the data was or the data
19 coordinators were actually instructed at each site to
20 use source records and did they not get monitored and
21 have the source records checked.

22 ACTING CHAIR LASKEY: I don't. So do we

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1 have access to that, what you just read? Maybe you
2 could make some copies for us. It's somewhat at odds
3 with what Dr. Bristow described the process as being,
4 so it would just be helpful. I'm really suggesting
5 that we break for lunch at this point. I have 12:40.

6 Let us regroup at 1:40 and we'll resume. Thank you
7 very much.

8 (Whereupon at 12:40 p.m. a luncheon
9 recess was taken.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (1:45 p.m.)

3 ACTING CHAIR LASKEY: All right, people,
4 thank you for coming back on schedule. It being
5 1:45, I'd like to resume and before we have our lead
6 reviewer give his review, the FDA had one more point
7 to clarify something that came up during our
8 conversation with Dr. Waldo.

9 DR. FARIS: FDA would just like to offer
10 clarification on one important point that was raised.

11 Dr. Waldo asked a question about the significance of
12 the population change in the indication statement.
13 The sponsor's current indication requires that a
14 patient meet the specified heart failure criteria and
15 also have a conventional indications for and ICD.
16 The sponsor is seeking removal of the ICD indication
17 requirement based on the COMPANION results.

18 DR. WALDO: Thank you.

19 ACTING CHAIR LASKEY: Welcome back, Dr.
20 Waldo.

21 DR. WALDO: Thank you.

22 ACTING CHAIR LASKEY: All right, we'll

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1 start out with Dr. Maisel giving his review. Bill?

2 DR. MAISEL: Thank you. Good afternoon.

3 I will not review in detail any of the data that has
4 been eloquently presented by both the sponsor and the
5 FDA and I think many of the important issues have
6 already been touched on. I would like to focus on a
7 few of the contentious issues which, in my mind,
8 include a few things. One is the hospitalizations.
9 Second are the withdrawals. Third is the mortality
10 end points and then finally I'd like to talk about
11 some of the safety issues. So I will start with the
12 hospitalization issue.

13 Just as a point of clarification from the
14 sponsor, I'm interested in understanding exactly what
15 it was that prompted the changed in definition of the
16 hospitalization end point. One quote I heard this
17 morning was to make verifiable data possible. So is
18 it your position that the reason the hospitalization
19 end point was changed was so that the data could be
20 interpreted correctly that you were receiving in the
21 case report forms? It's a yes or no question.

22 DR. CARSON: The answer to that then is,

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1 yes. The -- once again, to reiterate and maybe I can
2 just amplify this because it keeps coming up, maybe
3 amplify a little bit more what was said this morning,
4 the -- for every trial in which hospitalization has
5 been used in heart failure as a primary or secondary
6 end point there's been a duration criteria. The
7 duration criteria has not always been stated in the
8 protocol. It wasn't stated in the VALHeFT. It was
9 stated in the MERIT Heart Failure protocol but then
10 the committee went to a calendar date change from a
11 24-hour. I'm sorry.

12 DR. MAISEL: I understand -- you can stay
13 there. I understand a lot of those issues and I
14 don't want to rehash them. What I'm trying to
15 understand is, you also said that you felt that
16 events that were less than 24 hours in duration were,
17 "exceedingly rare". So I'm trying to understand if
18 you felt that those less than 24-hour hospitalization
19 events were exceedingly rare, why you felt so
20 strongly about changing the primary end point which
21 obviously has led us to a great deal of --

22 DR. CARSON: Discussion.

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1 DR. MAISEL: -- discussion.

2 DR. CARSON: First of all, I would say
3 from my standpoint, the standpoint of the morbidity
4 and mortality committee, on the steering committee,
5 the end point did not change. The end point
6 committee, in a sense, finalized the criteria for
7 "all-cause" hospitalization by presenting a 24-hour
8 barrier. That was, in part, because it had been done
9 in previous clinical trials to that time and also it
10 represented a day in the hospital and I think as
11 everyone is pretty well aware, many hospitalization
12 systems define a hospitalization as being something
13 over 23 hours.

14 Now, what I said this morning was that a
15 calendar date change, hospitalizations that did not
16 involve a calendar date change, I believe, are rare
17 and a little difficult to figure out what they would
18 be. So 24-hour -- less than 24-hour hospitalizations
19 are not necessarily rare. In fact, in this trial,
20 and we have a backup slide on this, I think about 16
21 percent of the patients in CRT-D had a
22 hospitalization for less than one -- than a 24-hour

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1 period. About 20 percent in CRT did. So there --

2 DR. MAISEL: And what about OPT?

3 DR. CARSON: I'm sorry, 20 percent in OPT
4 and 16 percent in CRT.

5 DR. MAISEL: Okay. I guess, my point
6 simply is that while it seems that your intention was
7 to make it easier to interpret the end point, I think
8 you added a great deal of confusion and I think the
9 simple was the patient hospitalized or not, while I
10 understand the issues regarding whether that was the
11 appropriate end point to pick, it was picked and I
12 don't agree with the position that you clarified
13 things by changing it. I think it obviously, in my
14 view would have been a lot easier just to count how
15 many people were hospitalized as was initially
16 intended. And I'll give you a chance in a minute to
17 respond to that.

18 DR. CARSON: Okay.

19 DR. MAISEL: The other issue I had was
20 I'm trying to understand exactly when it was that
21 hospitalizations were first adjudicated. There's a
22 statement in Section 6-1 on page 4 that says, quote,

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1 "No hospitalizations were adjudicated until the
2 6/23/01 meeting". Is that accurate?

3 DR. CARSON: That's incorrect. That's
4 not correct.

5 DR. MAISEL: Okay, so were they first
6 adjudicated in March 2001?

7 DR. CARSON: The first adjudication
8 meeting was March 16th, 2001.

9 DR. MAISEL: So is it fair to say that
10 the data was not analyzed or looked at until those
11 events were adjudicated? What I'm trying to
12 understand as well is that in Section 5-4 on page 14,
13 there is a graph of the DSMB analysis. And the first
14 point where there is an analysis is dated November
15 10th, 2000 and it says, "combined mortality and
16 hospitalization end point", and it has a Z statistic.

17 So I'm trying to understand how they were able to
18 analyze the end point prior to any end point
19 adjudication, if you could clarify that for me.

20 DR. CARSON: I think that would probably
21 be a question for -- one would say then that what
22 they were looking at was unadjudicated data for the

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1 primary outcome. That would have been the only way
2 that could have been done because we did not meet
3 until March 16th of `01. That was the first time --
4 the first meeting we had and prior to the start of
5 that meeting and let me emphasize again, prior to any
6 end point ever being adjudicated, the 24-hour
7 duration hospitalization was in place.

8 DR. MAISEL: So the earlier discussion we
9 had this morning where it was stated that the data
10 went to the M & M committee and then back to the
11 clinical research organization and then to the
12 statistician and then to the DMSB was not necessarily
13 always the case.

14 DR. CARSON: Well, the adjudicated forms,
15 the adjudication data, would have gone to the M & M
16 committee. The adjudication data would have been
17 adjudicated by us. Whether there was another
18 communication of unadjudicated data, maybe Dr. DeMets
19 could tell.

20 DR. DeMETS: Yeah, the thing is quite
21 common in monitoring trials and groups like mine. It
22 would be reports for monitoring, that is you take

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1 what you have, the best most up to date data you
2 have, so at that point in time, you're correct M & M
3 committee would not have met but we clearly had data
4 on unadjudicated events, mortality and so you
5 typically present the best data you have, which is a
6 mixture along the way of adjudicated, unadjudicated,
7 at that point in time was all unadjudicated, and as
8 they move along, you have a mixture of adjudicated
9 events and plus the non-adjudicated and then you'll
10 probably -- we always do, at least at our place,
11 provide a table which has got the adjudicated, but
12 that's always behind.

13 So while it's adjudicated, it's old news.

14 So -- but we were looking at what the team was
15 looking at which we reported to them at that point in
16 time would have been unadjudicated, but they would
17 have seen that or known that.

18 DR. MAISEL: Right, but my obvious point
19 is that I'm concerned that there was statistical
20 analysis that was performed prior to the changing of
21 the definition of hospitalization and if you look at
22 the Z statistic, it's in favor of the OPT group. The

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1 Z statistic is minus 2.057. If you go to Section 5-
2 3, page 42, you show the DSMB same analysis for "all-
3 cause" mortality and the Z statistic favors the
4 device. And so what that says to me is that the
5 negative Z statistic was strongly because of a large
6 number of hospitalizations in the device group. And
7 so this was known as of November 2000 and so it just
8 begs the question of you know, five, four months
9 later now, there's a meeting to discuss changing the
10 definition and while I certainly understand and
11 respect the statements that have been made that
12 there's no communication, et cetera, you know, on
13 paper it seems that the fact that there were a lot of
14 hospitalizations in the CRT-D group early on, was
15 clear at the time of that, that the definition was
16 changed.

17 DR. CARSON: Could I just maybe help with
18 one comment here? Recall that what the sites were
19 being requested to send were events that from the
20 original CRF that had a date change. So, in fact,
21 all of those hospitalizations then would have come to
22 the external CRO. There would not have been an

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1 additional group of hospitalizations. Those
2 hospitalizations all then eventually came to us after
3 they assembled with all the clinical materials that
4 would make it possible for us to have an opinion on
5 each case.

6 So Dave, I think that would be --

7 MS. WOOD: If I could interrupt for just
8 a minute, just a procedural issue, the tables should
9 be left free. If you have a question to answer,
10 please come to the podium. That allows the advisory
11 committee to interface with both the FDA and the
12 sponsor. Thank you.

13 DR. DeMETS: I apologize for my lack of
14 protocol. Yes, there was no communication. In fact,
15 we followed almost to the letter the current
16 independent monitoring committee charter, draft
17 charter, that was issued in November 2001 to
18 alleviate just the kind of concerns that you are
19 pondering. That is by having an independent
20 statistical center, an independent monitoring
21 committee, an independent M & M committee which did
22 not communicate those kind of concerns are to be

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1 addressed in that way. So that's why the FDA charter
2 was written that way. That's why it's been
3 conventional practice for the past 30 years, I
4 suppose. So there was the communication to prevent
5 those kind of issues being an issue.

6 DR. MAISEL: Okay, thank you. It was
7 also -- it was stated in the FDA review but I'm not
8 sure I saw it in the sponsor review, that it was not
9 possible to go back and analyze the data based on the
10 initial definition of all hospitalizations,
11 recognizing that the implant hospitalization was not
12 going to be included. Is that an accurate statement,
13 that you do not have the data on "all-cause"
14 hospitalization putting aside the device implants?
15 In other words, hospitalizations that were -- any
16 hospitalization, the original definition in the
17 protocol.

18 DR. CARSON: Well, there would be -- what
19 we don't have particularly from my standpoint, Dr.
20 Bristow may have something to add, but there is not
21 data in which there was not -- the sites were asked
22 to report according to the case report form and that

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1 involved a calendar date change. So there is --
2 there's not data then on hospitalizations who did not
3 meet any sort of duration criteria.

4 DR. MAISEL: Because it was stated this
5 morning that -- and I believe it's on one of the
6 forms that it says, quote, "You must use this form
7 for each hospitalization". So was that -- were you --
8 - I mean, if I were doing it, I would have tried to
9 collect as much hospitalization data as possible and
10 then if you were going to narrow the scope, I
11 understand that, but it was stated this morning that
12 the participants were asked to submit a form for
13 every hospitalization. Is that not true? They were
14 asked to adjudicate the event themselves and only
15 submit the form if there was a hospital date change
16 or they submitted a form for every hospitalization?

17 DR. BRISTOW: Only if there was a
18 hospital date change did they submit a form. Let me
19 provide a little background here in terms of the
20 "all-cause" hospitalization notion so -- on June
21 17th, 1999, we met with the FDA about the thoughts
22 for this protocol and the concept was that we would

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1 be running a clinical end point that would include
2 hospitalization and death was a competing risk. And
3 some discussion took place with the FDA regarding
4 what that hospitalization would be.

5 Our notion, and I'll give you some direct
6 quotes here, I brought the wrong thing to the podium,
7 unfortunately. My direct quote though was something
8 like a real hospitalization in fact, DRG 127 for
9 heart failure and so our original notion was that we
10 were going to run a competing risk, primary end point
11 of death and heart failure hospitalization or at the
12 least, cardiovascular hospitalization because this is
13 the hospitalization component that can be benefitted
14 by an effective heart failure treatment.

15 So the idea was that we have a real
16 hospitalization, not something where somebody's blood
17 pressure is found to be 120, not 60 or his INR is
18 found to be two, not seven and then gets discharged
19 right away. This study would count real
20 hospitalizations, DRG 127 including heart failure.
21 So right from the beginning, the idea was to
22 eliminate these trivial things that could happen, use

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1 of hospitalization for short stay, for example, real
2 hospitalization and then the notion of "all-cause"
3 actually came from the FDA.

4 They said, "Well, fine, you know,
5 measuring heart failure, cardiovascular
6 hospitalization is okay, but we want you to measure
7 all real hospitalizations. We want you to capture
8 the stuff that might be a fallout from device use and
9 implantation. Okay, if you have a complication of a
10 device requiring a hospitalization, subsequent
11 hospitalization, we want that captured".

12 And so we agreed, "Okay, we'll do this".
13 Now, this is not ordinarily done in a heart failure
14 clinical trial because you're dragging along a lot of
15 noise. In our case, about a third of the total
16 hospitalizations were non-cardiovascular and were not
17 going to impact favorably on that with a heart
18 failure treatment, but because this was the mandate
19 from the FDA, this is where "all-cause" comes from.
20 Spreading out the mode of hospitalization, the cause
21 specific aspect beyond cardiovascular or heart
22 failure into non-cardiovascular, it never met stuff

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1 that really isn't a hospitalization. It doesn't
2 really require a hospitalization and we can track
3 this back historically.

4 So of course, what happened in COMPANION
5 is we had a much greater treatment effect on
6 cardiovascular hospitalization. In fact, the hazard
7 ratio is something like --

8 ACTING CHAIR LASKEY: Thirty-six percent.

9 DR. BRISTOW: No, it's not quite that.
10 It's .72 and for heart failure hospitalization, the
11 hazard ratio is .6. So the total comes from
12 measuring non-cardiovascular hospitalizations.

13 DR. MAISEL: I don't debate the well-
14 meaning or potentially even the appropriateness of
15 the definition that you ultimately ended up with. I
16 think there are a couple of important points. Number
17 one is a device trial is not the same as a heart
18 failure pharmacologic trial obviously. Number 2 is,
19 I'm still a little unclear as to why this
20 conversation that took place in March 2001 didn't
21 take place in 1999 when the protocol was written and
22 maybe you can shed some light on that.

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1 DR. BRISTOW: Frankly, I guess I can take
2 some of the credit for this. The steering committee
3 and myself specifically, never thought this was a
4 substantive change. This is the technical way the
5 end points committee does its business and this is
6 the way that I have handled it as a steering
7 committee member previously. We let the end points
8 committee decide how they're going to do things.
9 They do state of the art things. They tend to be the
10 same people from trial to trial and to me, this
11 really never made any difference. They had to use a
12 system that would allow them to have a verifiable
13 real hospitalization in the spirit of the protocol.

14 To me this was technical detail as
15 opposed to a substantive change in the primary end
16 point. That is the reason why we didn't basically
17 say, you know, "Sponsor, you've got to tell the FDA
18 blah, blah, blah". We just never thought that this
19 was anything substantive.

20 DR. MAISEL: Okay, I'd like to shift
21 gears a little bit and talk a little bit about the
22 withdrawals.

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1 DR. CARSON: Can I just answer one more
2 thing because you brought it up at the beginning of
3 this question and that was the fact that the end
4 point duration was 24 hours and then it was a
5 calendar date change. I just wanted to re-emphasize
6 that this was done because the data that was being
7 collected on the case report form was a calendar date
8 change. When the committee looked to try and pull
9 out to verify that these were 24-hour admissions when
10 it was a single calendar date change, we could not
11 verifiably do that. And that's why we made that
12 switch.

13 DR. MAISEL: Okay, thank you. It's been
14 well-documented that the withdrawal rate was much
15 higher in the pharmacologic, the OPT group compared
16 to the CRT groups and I think we all recognize the
17 reasons for those withdrawals regarding implantation
18 of CRT devices. I guess I have a couple comments and
19 then you can respond. Number one is, it seems
20 obvious to me from reading the instructions to
21 investigators that that was going to result in a
22 large number of withdrawals, I think, forcing

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1 physicians to get approval to do what is a medically
2 indicated procedure in a patient, I think would
3 automatically result in withdrawal.

4 So did you consider -- I mean, to be what
5 I probably would have done was simply given them very
6 specific instructions about who could get a CRT
7 device. Essentially, it seems to me that they were -
8 - physicians were forced to withdraw their patients
9 if they wanted to do what was right for their
10 patient.

11 DR. BRISTOW: Well, you have to
12 understand that the withdrawal rate began to go up
13 when these devices became on the market and then we
14 sort of reacted to this emerging problem that we had.

15 And you know, the truth of the fact is that we had
16 not proven that either of these devices works in this
17 patient population. And our position was that if
18 you're an investigator, you ought to have that report
19 about the treatment in your trial and this is
20 unproven therapy and you really shouldn't be doing
21 this.

22 But, yes, there comes a time and just for

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1 patient care, if you have an approved something but
2 there is what has to happen. There really has to be
3 deterioration and it has to be documented. We felt
4 that was a reasonable way to do things. So, what
5 would happen, of course, as has been mentioned
6 earlier, you know, the patients that were withdrawn
7 probably were the ones getting sick. And, of course,
8 if they're withdrawn and we never find out the end
9 point, that's going to work against the device. On
10 the other hand, we don't know -- as someone else
11 mentioned, we actually don't know how this is going
12 to work out. So the ethical mandate is to go get all
13 that data.

14 DR. MAISEL: Yeah, I think you should be
15 commended for an extremely thorough and difficult job
16 of filling in the blanks for all those withdrawn
17 patients and certainly had you not done that, I'm
18 sure we would have spent a lot of time discussing
19 that today. I'm a little bit concerned about how the
20 missing data, particularly in the hospitalizations,
21 what's filled in. There's some patient scenarios
22 given in Section 6-2 on page 4 and one example is

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1 that, you know, a patient is contacted by phone and
2 reports that they had not been hospitalized in the
3 last whatever it is, 18 or 19 months and that was
4 accepted as, you know, data and an end point, and I
5 think we can all recognize the inherent unreliability
6 in data like that.

7 I'm concerned about that, more for the
8 hospitalization data than for the mortality data.
9 What efforts -- I think if a patient -- well, maybe
10 you can clarify for me. If a patient denied being
11 hospitalized, they got marked down as not
12 hospitalized and if they said they were hospitalized,
13 the data was tracked down; is that --

14 DR. BRISTOW: Oh, yes, absolutely. I
15 mean, the only risk from this, I believe -- I mean,
16 the same procedures were undertaken as for non-
17 withdrawn patients and the only risk here is that you
18 would have under-reporting. You just wouldn't be
19 able to get all the events, in which case, that would
20 lead to a lower event rate in the disproportionate
21 withdrawal group, which would be the OPT group.
22 Again, the bias would be against the device.

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1 But we -- I mean, the coordinators,
2 investigators were instructed to go get these data.
3 They had to have source documentation. This had to
4 be adjudicated, had to have the dossiers filled with
5 all the source documentation and so forth. So it was
6 handled exactly the same.

7 DR. MAISEL: So, I guess to summarize my
8 position on the hospitalization, I would say I'm
9 quite concerned about a number of these issues,
10 perhaps any one of which may have been possible to
11 overlook but the data analysis prior to the initial
12 adjudication, the large number of withdrawals, the
13 unreliability of the data makes me concerned about
14 interpreting that end point as well as if you step
15 back and ask the clinical question, you have a
16 patient in front of you. You know, in my mind the
17 initial hospitalization, while I certainly recognize
18 the goal to demonstrate efficacy of the device,
19 taking a step back, you know, if I have a patient in
20 front of me and tell them that they're going to be
21 hospitalized, I think there's no conclusive evidence
22 that that's the case here.

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1 DR. BRISTOW: Well, another point is,
2 it's not just hospitalization that you're effecting,
3 heart failure hospitalizations primarily, but some
4 other cardiovascular perhaps. With that goes
5 improved quality of life, improved exercise
6 tolerance, all the stuff that relates to interrupting
7 the cycle of progressive heart failure. We haven't
8 presented any of that data because that was used for
9 previous approval of the device. But it's not just
10 the hospitalization, it's everything that goes with
11 progressive heart failure is benefited.

12 DR. MAISEL: I completely agree with what
13 you just said. With regard to the mortality end
14 point, I'm comforted by the statistical analyses that
15 have been presented today. I think in the log rank
16 or Wilcoxin statistical evaluation whichever you
17 prefer, both demonstrated in an unadjusted analysis
18 that mortality was improved in the CRT-D group. I
19 recognize the shortcomings of the Cox proportional
20 hazards analysis but that also showed a benefit.

21 I'm more comforted by the withdrawal
22 analysis of mortality simply because I think it's

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1 much easier to identify vital status. So I do
2 believe that these devices do result in improved
3 survival and decreased mortality.

4 DR. BRISTOW: In regard to that, I
5 certainly agree with that comment. The original
6 protocol actually gave some guidance for going after
7 patient's mortality data, vital status data, who had
8 withdrawn. It was in the protocol and what we added,
9 really to that was to go after the primary end point
10 data as well, and we totally agree that the mortality
11 date is undoubtedly more reliable in the sense of
12 getting the data out on a withdrawn basis.

13 DR. MAISEL: One of the questions that
14 we've been asked to consider is whether we can
15 consider the mortality data in isolation or whether
16 it should be part of a further analysis and I agree
17 with your comments that the sub-study certainly
18 suggests that the New York Heart Association class
19 improves, 6-Minute Walk improves, Minnesota Living
20 with Heart Failure, Quality of Life improves. I
21 think there is evidence that the device is improving
22 heart failure symptoms. I'm just not convinced about

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1 the hospitalization piece.

2 Finally, I'd just like to touch on safety
3 and I'll stop in a couple of minutes. I do not agree
4 with what was listed as the primary safety outcome,
5 which is complication in patients that were
6 successfully implanted. I think for obvious reasons,
7 this leaves out attempted device implants which have
8 relevance to device safety. If we consider an
9 extreme example. If 90 percent of patients die
10 getting a device implant and the 10 percent who got
11 it had not complications, your report would list 100
12 percent, you know, safety and zero complications. So
13 do we have data on the patients in whom events were -
14 - devices were attempted but not implanted regarding
15 their complications, and perhaps data on that quote
16 "Primary safety outcome" but for complications in
17 patients who had an attempted --

18 DR. SAXON: Right, so you're right, the
19 systems safety definition is -- it's an FDA
20 convention established in 2000 is the narrowest
21 definition because it only includes complications and
22 serious things in patients that were actually

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1 implanted. The system safety shown on the right here
2 is the issue that you're interested in. This is more
3 encompassing. This is all randomized patients
4 including unsuccessful attempts. This not only
5 counts those more serious complications, but also
6 includes any observation. So I believe that's the
7 answer to your question.

8 DR. MAISEL: So if I read that correctly,
9 there was a very small number -- the rate was
10 essentially the same in the -- of the complications
11 of the attempted patients.

12 DR. SAXON: Correct.

13 DR. MAISEL: Okay. And then finally in
14 the tables that are presented both in the labeling
15 and in our submission, there are times when the
16 numbers don't add up such as there might be a certain
17 number of complications, a certain number of
18 observations and then the total number is not the
19 same. I can give you an example, the phrenic
20 nerve/diaphragmatic stimulation, there were eight
21 listed complications and 52 observations but it says
22 the total is 58 and those sorts of discrepancies

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1 appear in multiple places. Can you explain why that
2 is?

3 DR. SAXON: Right, so some of the things
4 that you think of as being consistently related to
5 the LV lead actually aren't. Some of them are
6 related to the RV lead for instance, so that would
7 lead to a miscount. Some can be counted in both bins
8 because you can have phrenic nerve stimulation that
9 can either to away or need or not need a programming
10 change or an intervention to correct. Or you can
11 have new phrenic nerve stimulation that wasn't
12 initially counted.

13 DR. MAISEL: So there can be the same
14 event in multiple patients, I understand. Well, why
15 don't I stop there. I'll let some of my colleagues
16 fill in some of the blanks?

17 DR. BOEHMER: Could I possibly interject
18 something about hospitalizations? Your concern was
19 the total hospital burden to the patient, not
20 necessarily being represented by "all-cause"
21 hospitalization.

22 DR. MAISEL: I would say that is a --

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1 stepping back from the trial, that is a clinical -- a
2 question I have as a clinician analyzing the data or
3 looking at the data.

4 DR. BOEHMER: All right, well, as a
5 clinician that takes care of a great number of heart
6 failure patients -- by the way John Boehmer, Penn
7 State College of Medicine. My conflicts are as a
8 consultant for Guidant Corporation and investigator
9 and some reimbursement for travel here.

10 This is hospitalization rate by months.
11 Now, when I talk to a patient about getting a device,
12 they understand that they're going to get a device.
13 And I will need to explain to them that they're going
14 to get the device in a hospital, but what happens --
15 but if I'm going to tell them that it's going to
16 decrease their risk of hospitalization, they're not
17 going to be confused about the fact that they're
18 going to go in the hospital and get a device. What
19 they want to know is, "What happens after I get the
20 device", and this is all hospitalizations. This is
21 nothing held back and the skill doesn't help it a
22 great deal because they have to show the initial

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1 hospitalization for all the patients randomized to
2 CRT-D but immediately thereafter there's a drop in
3 the rate of hospitalization. That's maintained until
4 you get laid out in the trial when you start getting
5 into issues of who's left in the trial because there
6 is a survival differential.

7 And I think just the quality of these
8 data are reassuring to me when I would be talking to
9 a patient. I would never suggest to them that
10 they're going to magically get this device without
11 going in the hospital. That would be unreasonable.
12 Additionally, as things evolve, maybe they won't have
13 to go in the hospital as much. Maybe the techniques
14 will get better, maybe the care of them will get
15 better. In fact, this is already a moving target.
16 So I think this way of looking at the data and the
17 way we actually did it in the trial to give us a pass
18 on the initial hospitalization which was in the
19 protocol, I think this is the way a patient can
20 understand it. Thank you.

21 ACTING CHAIR LASKEY: Now that you've put
22 up that confusing graph to me, there were twice as

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1 many patients in the CRT-D as in the OPT so could you
2 go over the Y axis on this, please?

3 DR. BOEHMER: I'd be happy to. Those are
4 rates of hospitalizations; hospitalization rates,
5 number of hospitalizations over number of patients at
6 risk in any given time point. So the denominator
7 levels it out.

8 ACTING CHAIR LASKEY: So it is divided by
9 two.

10 DR. BOEHMER: Uh-huh, it's divided by the
11 number of patients at risk at any given time.

12 ACTING CHAIR LASKEY: Thank you. Okay,
13 let's attempt to confine our comments to 15 minutes
14 each, if possible, and we'll start with Dr. Kato,
15 comments or questions.

16 DR. KATO: Well, a question for the
17 sponsor; you mentioned that a number of patients had
18 in the CRT-D cohort, dysetinaria (phonetic)sepsis. I
19 guess there were 10 deaths there and five in the CRT-
20 P cohort. Can you explain a little bit more about
21 the sepsis? Was this related to the device?

22 DR. SAXON: You're correct, there were a

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1 number of septic deaths and I can just -- there are
2 enough that I can go through them with you. They're
3 not clearly related to the device implant either
4 temporally or looking at the clinical history. For
5 instance, there's a leg cellulitis that was thought
6 to have a history pre-operatively. There was an
7 acute appendicitis, a PIC line dialysis issue, septic
8 shock in a dialysis patient, not an uncommon event,
9 cellulitis proceeding to an osteomyelitis, substance
10 and setting of renal failure.

11 One issue that may have temporally been
12 related to the device, although there was proceeding
13 phlebitis or potential prostatitis, colitis. So the
14 vast majority of these events were not clearly
15 related to the implant and could be attributed to
16 another morbid event.

17 DR. KATO: Thank you. One other question
18 is, you know, in the final assessment looking at a
19 CRT-D versus CRT-P, do you -- you know, what do you
20 actually think is the final reason, if you can
21 summarize in a couple sentences why the CRT-D does
22 better. I mean, is it just that they are being paced

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1 and then they're defibrillated or whenever they go
2 into that rhythm and that's their final safety net or
3 do you have some other hypothesis or actual data
4 behind that?

5 DR. BRISTOW: I think what we can stand
6 behind is there is a reduction in sudden death in the
7 CRT-D group compared to OPT. There's not in the CRT-
8 P group and that might be expected, obviously, from
9 the ICD component. So the ICD component is adding a
10 reduction of sudden death. Both devices are reducing
11 pump failure deaths and then additional reduction in
12 mortality by sudden deaths. So if you look at
13 mortality or a composite, including mortality,
14 although it's washed out by hospitalizations for the
15 primary end point, the CRT-D is obviously doing
16 better for mortality.

17 DR. KATO: Is there any data that you
18 could obtain from the interrogation of these devices
19 after the patient dies or certainly in the CRT-D
20 group, is there any interrogation data?

21 DR. BRISTOW: We have no interrogation
22 data to share with you today. We're in the process

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1 of rounding that up but we don't have any. We do
2 have appropriate device firing data which Dr. Saxon
3 could review with you, if you'd like which is
4 consistent with this device in other settings, other
5 trials, and so forth.

6 DR. KATO: Well, then in the CRT-D group,
7 I mean, how often did the device fire?

8 DR. BRISTOW: I think it was 11 percent
9 of patients at one year and 19 or 20 at two. We can
10 give you the exact data.

11 DR. SAXON: Now, while we don't have the
12 deaths, we have the interrogations that we think are
13 relatively reliable from the centers for appropriate
14 chucks and that certainly looks like 11 percent a
15 year and around 20 months at 19 percent for VT or VF
16 therapy.

17 ACTING CHAIR LASKEY: One question, I
18 hate to keep bringing up this hospitalization issue
19 but I guess one of my question is, if you couldn't
20 identify the time of the admission and discharge and
21 you have to resort to the change in calendar date,
22 which is actually a typical method for hospitals,

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1 even hospitals to determine whether somebody is
2 hospitalized or not, how could you determine whether
3 the patient was on intravenous pressor support for
4 four hours?

5 DR. BRISTOW: I'll actually ask Dr.
6 Carson who reviewed these data as the adjudicated.
7 There obviously, was a special form that was filled
8 out, the IV infusion form. He'll give more color on
9 that.

10 DR. CARSON: Yeah, I think that's
11 correct, there was a separate form that we tried --
12 it was a follow-up case report form. This was what I
13 showed on the -- on my formal remarks, presentation
14 this morning. It was that form that was filled out
15 by a site that would give the exact times of
16 intravenous infusion of an inotrope or vasoactive
17 agents. As I said, the sites were not asked to
18 provide the information on discharge times or
19 admission times. We could find admission times
20 pretty clearly in charts, but we could not really
21 find discharge times in most patients and I think the
22 discharge time, as you know, is subject to some

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1 variability relating to social issues as well as
2 medical issues.

3 DR. KATO: Right, but I mean, so that
4 when you're doing an infusion time, there's no -- you
5 didn't record the start and stop time. You just said
6 the --

7 DR. CARSON: We asked the sites to
8 provide that information on this form. We did ask
9 them to do that.

10 DR. KATO: And so they could do that but
11 they couldn't do the other --

12 DR. CARSON: Well, they were not asked to
13 provide that data.

14 DR. KATO: Okay. Thank you.

15 ACTING CHAIR LASKEY: Dr. Yancy.

16 DR. YANCY: Thank you, Warren. One
17 question briefly and then a few comments. And it
18 pertains to one particular graphic shown in the FDA
19 analysis and it's specifically the FDA analysis when
20 we tally the secondary end point and it shows sudden
21 cardiac death event rate per 100 patient years and
22 numerically, at least the CRT-P group has a higher

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1 sudden cardiac death rate. The question is, is that
2 a statistical blip or do we think that that's an
3 issue that needs further thought?

4 DR. BRISTOW: Is that addressed to FDA?

5 DR. YANCY: Whoever can answer that, if
6 it's FDA or if the sponsor can --

7 DR. BRISTOW: Well, since you're
8 referring to the FDA analysis, why don't we allow
9 them to comment, then we'll respond?

10 DR. PROESTEL: Well, it was a concern
11 that had been brought up actually to us through
12 public presentation. So we were curious to know in
13 the CRT group what was going on with sudden cardiac
14 death. I think for the purposes of the CRT-D device,
15 the FDA can say that we were reassured that in fact,
16 pump failure death overwhelmed that increase in
17 sudden cardiac death. I mean, there's a number of
18 reasons why we should be skeptical about that sudden
19 cardiac death blip. It's obviously, a sub-group
20 analysis. It was not pre-specified. There is the
21 issue of competing risk. You know, so what I would
22 say is that for the purposes of the CRT-D device, we

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1 were reassured that in fact, "all-cause" cardiac
2 death as well as "all-cause" mortality was improved
3 in the CRT arm. And you know, it was -- as far as
4 statistical significance, I wouldn't calculate P
5 values for those.

6 DR. YANCY: Well, that's my reason for
7 bringing it up because I think that right now the
8 record from this morning's discussion states it was
9 increased and I don't know that we can say that
10 comfortably and I would not want that to stand as a
11 matter of fact.

12 DR. PROESTEL: That's correct. These
13 were really point estimates.

14 DR. BRISTOW: We agree with that and, in
15 fact, if we can just show the Kaplan-Meier curves and
16 so this is sudden death Kaplan-Meier curves and
17 basically there's no statistically significant
18 difference between A and B, which is CRT-P and OPT,
19 the P value of .495.

20 DR. YANCY: Thank you. Warren, my
21 comments are more along the line of my perspective as
22 a clinician who does this kind of activity on a day

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1 to day basis. And I don't know if this is where you
2 want me to speak to that or not but I think it's
3 germane to the discussion we've been having. And the
4 first thing I would say is with regard to the
5 implication of hospitalization, not all
6 hospitalizations carry the same weight and in the
7 context of a heart failure patient, a heart failure
8 hospitalization carries with it an extraordinarily
9 high incidence of rehospitalization and a 12 months
10 very high rate of mortality and so I think that if
11 there is even a signal that the hospitalization is
12 impacted as a practitioner who takes care of
13 desperately ill patients with this condition, I think
14 that signal needs to be respected.

15 But I think even beyond that, as someone
16 who actually helps participate in the writing of
17 guidelines that govern how heart failure medicine is
18 practiced across the country, there is pressing need
19 to have clarity on where this technology resides and
20 I think for whatever worts we may have uncovered,
21 this is the best data base we have right now for
22 patients with advanced disease who are at very high

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1 risk for serious events hospitalization and death and
2 so in my judgment, I would want to go on record
3 publicly for commending the investigators for working
4 with a difficult patient population and bringing
5 together important data and I think that even though
6 we may quibble with some of the definitions, and may
7 have to wrestle with how this was dealt with
8 statistically, I honestly believe what I've heard so
9 far is gymnastics and not substantive and I would
10 rather accept the implications as they are. So I
11 have no further questions.

12 ACTING CHAIR LASKEY: Dr. Brinker?

13 DR. CARSON: Pardon me for a moment. Dr.
14 Laskey, could I just make one clarification on the
15 response to Dr. Kato? I just didn't want to confuse
16 the issue of what you were asking because I think
17 there was some confusion in the morning between the
18 four-hour inotrope infusion and the hospitalization
19 criteria. In terms of events that were in the
20 primary end point, hospitalizations were "all-cause"
21 with a duration criteria. They did not require four-
22 hour inotropic use of anything. That was an

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1 outpatient end point to be considered part of the
2 primary end point.

3 And in the response I gave to you
4 earlier, we actually did not attempt to necessarily
5 capture whether an infusion was four hours or later
6 during the hospitalization except as part of the
7 morbid end point but it was -- except to count as one
8 of the morbidity criteria. The form that we used
9 particularly was for the intravenous therapy as part
10 of the CRF for the morbid end point but it was the
11 outpatient end point that was particularly at issue.

12 ACTING CHAIR LASKEY: Jeff?

13 DR. BRINKER: I just have a few
14 questions. Have you tracked changes in medications
15 level between the two groups and in fact, whether --

16 DR. BRISTOW: Yeah, we have and we'll
17 show you some data there.

18 DR. BRINKER: While you're getting that
19 up, one of the concerns I have is that there's an
20 implication in somebody's reviewed this packet, I
21 don't know who I can attribute it to, that the device
22 group had a higher incidence of hypotension

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