

1 patients, 651 implant attempts. There were
2 multiple reasons for inability to--there were 84
3 unsuccessful implant attempts in 81 patients. 555
4 were successfully implanted on the first attempt.
5 This partially gets back to your questions, Tony--
6 555 were successfully implanted on the first
7 attempt. Fifteen patients were brought back for a
8 second attempt, twelve of which were successful and
9 three of which were not.

10 There were 84 unsuccessful attempts in 81
11 patients. So, of those 81 patients, fifteen were
12 taken back. Twelve of them were ultimately made
13 successful.

14 DR. BRINKER: How many of them required
15 epicardial lead placement?

16 DR. WILKOFF: In this study, only one
17 patient was brought to an epicardial lead
18 placement. It is not part of the protocol. What
19 you have to do is have a successful implant, have
20 the lead work, have it dislodge and then bring them
21 off to epicardial placement. They were excluded
22 once you couldn't implant them.

23 DR. BRINKER: Of all these 80-some-odd
24 patients who failed at the first implant, did every
25 one of them at the first implant get a successful

1 defibrillator placement?

2 DR. WILKOFF: No; I think it was four
3 patients that refused--they said, "If I can't have
4 biventricular pacing, I don't want to have a
5 defibrillator either."

6 DR. BRINKER: So they woke up under their
7 conscious sedation and said, "If you can't--"

8 DR. WILKOFF: No; they told us that
9 beforehand. They said, "Either you get this in or
10 I want nothing."

11 DR. BRINKER: Okay. I mean, that is the
12 choice they made.

13 DR. BRINKER: No; that's fine. All the
14 others got a defibrillator?

15 DR. WILKOFF: Yes.

16 DR. BRINKER: And all the others got an
17 approved defibrillator or this defibrillator.

18 DR. WILKOFF: They couldn't put this in
19 unless--an approved defibrillator.

20 DR. BRINKER: Okay. Great.

21 DR. WILKOFF: It's possible they could
22 have gone to another clinical protocol, I suppose.
23 But I don't think so.

24 DR. BRINKER: Okay. Just some other
25 general questions. The entrance criteria is a

1 prolonged QRS greater than 130 milliseconds. What
2 if you get patients, and we will come to this, who
3 already have a pacemaker and their native rhythm is
4 normal QRS. But their pace rhythm is prolonged.
5 Would you consider that an indication for this?

6 DR. LEON: First of all, with respect to
7 this particular trial, you had to demonstrate that
8 the patient did not need to have ventricular pacing
9 to the point that you had to shut off ventricular
10 pacing for a period of 30 days, or effectively shut
11 it off--now, if you are referring to a population
12 of patients outside this study--is that what your
13 question is?

14 DR. BRINKER: This labeling that you are
15 going to send for this is not going to exclude
16 patients that have a pacemaker; right? When you
17 sell this device, you are not going to label it,
18 "Do not use this--"

19 DR. LEON: I am not.

20 DR. BRINKER: Well, Medtronic isn't. They
21 are not going to say that. So the question is, if
22 you have a patient that has had a pacemaker, even
23 if it is not pacing all the time, if it is
24 occasionally pacing, or your thought process is
25 that pacing-induced prolonged QRS is the same risk

1 factor.

2 DR. LEON: At our center, we have recently
3 submitted, and a manuscript has been accepted,
4 looking at 60 consecutive patients who had heart
5 failure who had a requirement for right ventricular
6 pacing who had pacing-induced ventricular
7 dysynchrony who underwent a procedure to upgrade
8 the pacemaker, not to a defibrillator but to a
9 biventricular unit approved by the Human
10 Investigations Committee at Emory University, and
11 we demonstrated a benefit in those patients and
12 that has been accepted.

13 I can't comment on the labeling or what
14 the sponsor would show.

15 DR. WILKOFF: I am going to give you
16 another half of that population.

17 DR. BRINKER: Just a second. Ventricular
18 dysynchrony defined only on the basis of the QRS
19 duration.

20 DR. WILKOFF: Because it was ventricularly
21 paced.

22 DR. BRINKER: That's fine. But not
23 echocardiographically.

24 DR. WILKOFF: Not that way. The other
25 half of that population is that we have a growing

1 number of patients. What I do when I consult,
2 patients are getting atrial synchronous pacing and
3 they are preexciting the right ventricle and they
4 are getting the same QRS prolongation and have
5 severe heart failure, the first thing I do is
6 prolong the PR interval. In over half the
7 patients, the patients remarkably improve.

8 DR. BRINKER: So that is the basis of my
9 last question, or semi-last question. Do you think
10 resynchronization therapy actually is effective--
11 and I believe it is effective--but as effective by
12 coordinating the actual contraction process or do
13 you think you are really realigning left atrial to
14 left ventricular?

15 DR. WILKOFF: We answer this by showing
16 that, in another twenty consecutive patients who
17 had chronic atrial fibrillation with no atrial
18 transport who had undergone HIS bundle ablation and
19 had complete heart block demonstrated for a mean
20 time of 24 months, we took those patients, upgraded
21 them to biventricular pacing and demonstrated an
22 increase in functional status ejection fraction.
23 That manuscript has been accepted by JAC and will
24 published in April of this year.

25 DR. BRINKER: Okay. That's it.

1 DR. LASKEY: Thank you. We are all
2 hypoglycemic and irritable. I am going to see how
3 many of us remember habits from internship. I
4 would like to break for thirty minutes and try and
5 regroup at 1:30 to resume and, hopefully, bring
6 this meeting to closure.

7 Thank you very much.

8 [Whereupon, at 1:05 p.m., the proceedings
9 were recessed to be resumed at 1:35 p.m.]

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

2 [1:45 p.m.]

3 DR. LASKEY: Thanks for trying to stay
4 with the program. We really did get off schedule
5 this morning. At this point, traditionally, we
6 have an Open Committee Discussion. We reread the
7 questions posed to us. I don't think we should do
8 that. There are far too many questions and we have
9 the list in front of us.

10 So if I can attempt--well, first of all, I
11 think I need to have the sponsors and the
12 presenters step back from the table at this point.
13 Thank you. We will call on you again, I'm sure.

14 What I would like to try and do here in
15 the next several minutes is, from one man's
16 perspective, to try and summarize the points of
17 consensus or striking differences among the panel
18 members as we go through the questions. I am
19 assuming everybody up here has a copy of the
20 questions.

21 Following that, I will ask the sponsor and
22 then the FDA if they have any comments or questions
23 before the vote. We will ask our industry
24 representative and our consumer rep for their input
25 at that point.

1 So let's start with the questions
2 pertaining to the study design and analysis. We
3 are asked to comment on the study design, the
4 adequacy of the sample size that contributed data
5 for the primary endpoints. There were repeated
6 concerns about 20 percent of the data being
7 missing. If I can paraphrase, the consensus of the
8 group was the decision to stop at the patient
9 enrollment rather than at another point certainly
10 was a repeated theme that we are all concerned
11 about.

12 So that answers the question, are there
13 concerns related to the "administrative censoring?"
14 Yes; we certainly are concerned and that is
15 reflected in our discomfort with the 224.

16 We were asked to discuss benefits and
17 limitations associated with six-month follow up
18 duration. I am not sure that we specifically honed
19 in on six months versus one year or the durability
20 or longevity of the endpoint. We certainly
21 discussed the robustness of the endpoint. I think
22 it is fair to say that there was a divided
23 sentiment on the panel about the level of
24 robustness.

25 At any point, if people want to chime in,

1 please do, to complete my summary. We were uneasy
2 with the propensity--we were uneasy with the
3 crossovers, period, and we are certainly uneasy
4 with the propensity for crossover and what lay
5 behind people crossing over, whether there was
6 unblinding and whether there was bias.

7 So I think that those issues were quite
8 loudly aired. The near Talmudic discussion about
9 these p-values and prespecified Hochberg criteria,
10 again, while, certainly of relevance from a
11 statistical standpoint, again need to be weighed
12 against the evidence in favor of the clinical
13 benefit.

14 I think we are all aware of the strengths
15 and limitations of doing combined endpoint analyses
16 and I am not sure we should engage in a further
17 discussion about the limitations of dual endpoints
18 or triple endpoints. Suffice it to say, the
19 committee dealt with that, discussed it but moved
20 beyond that to the relationship between what is
21 statistically significant and what is clinically
22 meaningful in this setting.

23 Is that fair?

24 DR. ZUCKERMAN: Dr. Laskey, if I could
25 just ask for some clarification. Question 1 refers

1 to some general questions regarding pertinent
2 points about CHF device trial design. You have
3 addressed them for this particular trial, but there
4 was another intent here for upcoming trials in the
5 field. What have we learned today with respect to
6 these four points that might be useful for new
7 trial?

8 DR. LASKEY: I didn't want to get vehement
9 so shortly after lunch, but to echo Mitch Krucoff's
10 concerns, none of us are happy with receiving what
11 is essentially an incomplete dataset. We would
12 turn that around and request the FDA to devote
13 additional consideration and discussion to bringing
14 things to panel when, in fact, there are fractions
15 of data approach 20, 25 percent or perhaps more,
16 depending on what we are looking at, that really
17 make it very difficult for us to provide an
18 unbiased and objective evaluation of the material.

19 I think it is fair to say we are all
20 unhappy with having to evaluate and interpret an
21 incomplete dataset even though it has been done.

22 DR. NISSEN: Let me just modify by saying
23 that I don't have any problem with that it is
24 prespecified. Yesterday, we had incomplete data.
25 Today, we have incomplete data. If, in fact, that

1 is the prespecified sample size and, when it is
2 reached, the database is locked, I don't think that
3 is a problem.

4 Do I think it is wise to do so on the part
5 of the company? Maybe not. In both days, I would
6 have loved to have had more data. But, if that is
7 the prespecified analysis, then it meets all the
8 legitimate rules that I have and, therefore, you
9 give them the endpoint if they make it--as long as
10 it is prespecified.

11 DR. PINA: I would like to make one
12 additional comment, sort of, hopefully, to help the
13 FDA in the future. The instruments that we use for
14 assessment of quality of life are not always 100
15 percent reliable. I think my colleagues may be
16 able to attest to this. This quality-of-life
17 assessment is not always consistently parallel
18 other things like mortality that we have seen in
19 drug trials.

20 I think there are some better instruments
21 around now that may hone in on the more sick
22 population and may, in fact, parallel the New York
23 Heart Class better and even provide some prognostic
24 input from the results of the questionnaire in
25 several different domains.

1 The Minnesota Living with Heart Failure
2 asks a lot of questions about does your heart
3 failure not allow you to work. Well, for a lot of
4 these patients who are already older, retired and
5 may be on disability, that is a question that
6 doesn't process. I think that Dr. Barold showing
7 the scattergram of the results really points to
8 that.

9 That has been the case with this
10 questionnaire, that a lot of the trials have shown
11 this scattergram of results. So I think that maybe
12 it is the tools, that we need to find better tools.
13 Is the six-minute hall walk a good tool? It is
14 probably a good tool in the sicker patients, not in
15 the less sick patients.

16 These guys know how I feel about VO2s. I
17 feel that that is a very objective test, if you are
18 doing it right, if you look at your parameters
19 appropriately. So maybe it is not as we are doing
20 them, but maybe it is the tools that we have are
21 not as exact to pick up these changes that we would
22 like to see, if that helps the FDA.

23 DR. LASKEY: I would just want to
24 elaborate on that. I think Steve mentioned
25 yesterday, we dealt with an incomplete dataset but

1 I think when you are dealing with mortality and a
2 harder endpoint, it is somewhat easier to swallow
3 than these softer endpoints.

4 I think what we are all grappling with
5 and, as Ileana just articulated better than I
6 could, I think we are grappling with issues, with
7 devices, that we haven't ordinarily thought about
8 in new areas. This is new terrain. We need better
9 tools and we need better endpoints.

10 We are dealing with what we have but that
11 doesn't mean that we are that precise in our scale.
12 That pertains to Question No. 2 so I won't belabor
13 that. Ileana just summarized the fact that there
14 is discordance in the industry, that is the
15 scientific end of this, between these three
16 measures.

17 We saw those same scattergrams with the
18 parent InSync trial when it was presented before
19 this panel, so it is not something that we like to
20 see but we are going to have to figure out how to
21 live with that, I guess, for a while until we come
22 up with more precise tools.

23 DR. WITTES: May I say something?

24 DR. LASKEY: Yes.

25 DR. WITTES: I think even precise tools

1 will show tremendous scatter in patients like this.

2 DR. LASKEY: That's true. To get to
3 Milt's point, the noise goes inversely as the
4 square root of N. So, as your sample size
5 increases, the noise will diminish generally and we
6 try and find the signal within that noise. So
7 larger studies are always desirable but we have to
8 be practical.

9 Question No. 3, the clinical relevance of
10 the choice of secondary endpoints. Again, a lot of
11 this was discussed during the last panel meeting on
12 these devices, is my recollection. I am not sure
13 that we can summarize the results of the discussion
14 today because we didn't dwell on it. I have been
15 particularly quiet throughout all of this but there
16 are things that I would have like to have seen
17 change that didn't.

18 The echocardiographic assessment of
19 cardiac output didn't budge. The assessment of
20 mitral regurgitation didn't budge. Filling plus,
21 minus. So there were things that you would like to
22 have seen change that didn't so I am not sure we
23 can hang our hat on any one of these endpoints. We
24 need to continue to look at them.

25 Mitch?

1 DR. KRUCOFF: Warren, I think at least for
2 both sponsors and for FDA and certainly for the
3 panel's purposes, I think one of the key features
4 is to remain clear, though, that, ultimately, a lot
5 of the dialogue about what is meaningful or not
6 needs to happen in the pre-IDE planning process,
7 that once you put down primary endpoints for a
8 clinical trial, those primary endpoints--and once
9 you put down a denominator for a clinical trial,
10 that that denominator is a live-or-die point.

11 Being on this side of the table, if
12 anything, it seems overly simplistic sometimes, but
13 the only way I can see to function is to recognize
14 that a prospective clinical-trial design, once it
15 is done, has to be evaluated based on the
16 prospective clinical-trial design.

17 There, for instance, to come to a
18 conclusion that this device includes functional
19 capacity or exercise tolerance in these patients
20 when the only primary endpoint that touches on that
21 area is the six-minute walk, you just can't
22 leapfrog over the fact that you don't have any
23 impact on your primary endpoint because you have
24 secondary endpoints that look good.

25 I think you really have to recognize that

1 the time for all this Talmudic discussion is before
2 you finalize the protocol and that, once you
3 finalize a protocol, your primary trial design has
4 got to be the fish-or-cut-bait point and that,
5 certainly, I think the mandate we have is that
6 safety and efficacy is or is not demonstrated based
7 on a prospective clinical-trial design. Primary
8 endpoints; period.

9 DR. NISSEN: Warren, I just wanted to
10 correct one small thing you said and that is that,
11 actually, the best echocardiographic parameter was
12 normalized LV filling time. LV filling time was
13 the single strongest p-value in the whole group of
14 echocardiographic endpoints.

15 DR. DOMANSKI: I actually want to take a
16 little bit of exception to that. That is not quite
17 true. They have to report their primary endpoints
18 but I can see a situation--and, again, this is the
19 regulatory process we are talking about where the
20 study was null for the primary endpoint but where
21 the secondary endpoints present a compelling data
22 that it, indeed, was effective or safe. So I don't
23 think it is quite true that they have to live or
24 die in terms of approval by their primary
25 endpoints.

1 DR. KONSTAM: Can I take issue with that?
2 Clinically, I would like to agree with you, Mike,
3 but the problem I have and I think we have
4 experienced situations like this. If your primary
5 endpoints are negative, I don't know how you are
6 supposed to statistically evaluate the significance
7 of your secondary endpoints and how you correct for
8 that problem.

9 I don't think there is a way to do it.
10 That is the problem. So, yes; secondary endpoints
11 might be interesting and they might have very low
12 nominal p-values associated with them, but if your
13 primary endpoint is neutral, I don't think we know
14 how to evaluate the p-value of your secondary
15 endpoint.

16 DR. DOMANSKI: I think we do. I think
17 that, for instance if you have--let me give you an
18 example, just a concrete example. I will do it
19 quickly and then move on. One could perceive a
20 trial in which you study atrial fibrillation. It
21 is powered for morality. You found out there is no
22 difference but, in fact, quality of life is
23 markedly different in one arm or the other.

24 There, I would think, you could make a
25 decision based on that.

1 DR. LASKEY: I think the FDA is getting
2 the message.

3 DR. ZUCKERMAN: Dr. Laskey, there was a
4 specific reason for asking Question 3. Maybe I can
5 go back to that reason. This was brought up by
6 panel and sponsor this morning. There are certain
7 secondary endpoints that, perhaps, we have learned
8 now that are better tools than what we thought were
9 primary endpoints such as peak VO2. Does the panel
10 have any comments right now as to whether this is,
11 of these limited CH endpoints, they are all limited
12 that we are using these device trials, perhaps a
13 more objective endpoint, given that it can have
14 core-lab review and is associated with other
15 parameters such that one can really look at the
16 quality of this type of exercise testing.

17 DR. KONSTAM: I am not sure about that. I
18 think that, certainly, VO2 can be viewed as a more
19 objective number. But you get to VO2 based on how
20 long you exercise, VO2 max. I don't think, and my
21 colleagues can disagree with me if they want, I
22 know, and maybe Ileana will, but I don't think that
23 there is universal agreement about which direction
24 the submaximal exercise versus maximal exercise is
25 the optimal way to evaluate particular populations

1 of patients.

2 I think the viewpoint in the heart-failure
3 community about this is extremely divergent. I can
4 easily imagine that, if everything was backwards
5 here--that is, they had chosen VO2 max as the
6 primary endpoint, it had been neutral but they
7 overwhelmingly saw a positive six-minute walk, we
8 would be having exactly the discussion in the
9 opposite way.

10 That is my view. I don't think that this
11 is the last word on this, that VO2 max is the way
12 to go here, personally.

13 DR. PINA: Marvin, I am going to correct
14 you because it is not VO2 max. It is just peak
15 VO2. It is not VO2 max unless it fits a very
16 strict criteria and I don't think that that is what
17 they were intending to do here. They wanted to do
18 sufficient exercise which I commend them on doing
19 that, finally seeing that in a protocol, where they
20 want to push the effort level to a level that you
21 can compare apples and oranges. That is what they
22 were trying to do.

23 Trying to get people at least to an RER of
24 1.1 assures you that you have the most nonvariable
25 parameter of exercise which is still the

1 ventilatory threshold. If that changes, then you
2 have something very meaningful physiologically
3 changing. What calls on beyond that is called
4 endurance and it depends upon the efficiency of the
5 patient walking on the treadmill, what muscles they
6 are using and how rehabbed they are.

7 I can put a patient in a rehab program
8 and, in eight weeks, get an increase in VO2 by 25
9 percent. That is purely with exercise. And Marvin
10 is right. It depends upon who is doing it. If it
11 is done right and you have a core lab, that is a
12 plus. Having a core lab, something that a core lab
13 can go over, is a plus.

14 Training the investigators to do it right
15 and doing it in centers that are experienced at
16 doing this, I think is very critical to the test
17 which is a different than the six-minute hall walk
18 that anyone can do with very little training.

19 DR. NISSEN: You know, the big problem
20 here is that none of these is consistent across all
21 clinical trials. So, to some extent, you pay your
22 money and you take your chances. That is the agony
23 of trying to develop a drug or other therapy for
24 heart failure, that there is inconsistency in the
25 direction of endpoints. In this case, there is

1 inconsistency.

2 If they had chosen VO2, it would have
3 looked a lot better than if they had chosen six-
4 minute walk and the next trial, as somebody pointed
5 out, could go exactly the opposite direction. The
6 problem is there is still some imprecision. Heart
7 failure is becoming more of a science but it has
8 got a long way to go.

9 Who knows? Maybe BNT will ultimately turn
10 out to be useful.

11 DR. LASKEY: There is a universe of
12 experience out there from the pharmacologic end of
13 treating heart failure that has, perhaps, some
14 instructive information for us. So, maybe, off-
15 line, we need to look at this. But, certainly, the
16 metrics right now for the device use in heart
17 failure are just not there. It may be premature
18 to try and pick one.

19 DR. KRUCOFF: I think there is another
20 important message here that is there is no one
21 endpoint outside of mortality and clinical outcome.
22 So, apart from doing multiple thousand-patient
23 trials, what we are talking here are about other
24 nonmorality types of endpoints. No one is so
25 compelling, either from the literature or, frankly,

1 in clinical practice, that I think any of us would
2 want to approve a device on.

3 But I think that is where the Hochberg and
4 other multiple covariate, or coprimary endpoint
5 strategies, do provide us a platform to do
6 relatively rigorous clinical investigations. I
7 think it does oblige you to think long and hard in
8 putting a protocol together about what you are
9 going to pick as your endpoints and, ultimately, I
10 think it obliges you to go with what you pick.

11 If you pick three out of the 300
12 possibilities, hopefully based on the collective
13 wisdom of high-powered investigators, and,
14 ultimately, then, you have a statistical analysis
15 plan, then you show efficacy or you don't.

16 DR. LASKEY: The search goes on. Question
17 4, I think, again, this morning's discussion dealt
18 with the results, generally, within the constraints
19 of the Hochberg criteria, within the constraints of
20 the prespecified endpoints, that there was data to
21 support the efficacy of the device for the
22 treatment of these patients.

23 DR. KRUCOFF: Is the assumption, Warren,
24 that we saw all the data we were supposed to see,
25 that we have a whole denominator rather than 80

1 percent?

2 DR. LASKEY: From what we saw, we wanted
3 to see more and we will see more, apparently. But,
4 from what we saw, none of us felt that the results
5 were not statistically significant. Is that true?

6 DR. KRUCOFF: I think the issue to me
7 would be that this is the assumption that, assuming
8 that, in fact, the prospective plan was to go to
9 224 patients and not add patients. Then, the
10 numbers speak for themselves.

11 DR. KONSTAM: I am not sure how to
12 interpret this question. I don't find the efficacy
13 results robust in this study. There are a few
14 different reasons for that. I think the
15 multiplicity question is one but the other is the
16 blinding issue.

17 I can't separate that problem from this
18 question. If the results rest on the quality-of-
19 life score and there is serious concern about the
20 blinding, then I have trouble accepting that as a
21 robust demonstration of efficacy.

22 DR. LASKEY: I didn't see the word
23 "robust" in your question to us, so I was
24 interpreting it in the general way. But,
25 obviously, there were still concerns here, as there

1 should be, with an incomplete dataset. But the p-
2 values are what they are. I'm sure the sponsor
3 will have more to say with their opportunity at the
4 podium.

5 Question No. 5, safety. There are many
6 subcategories of the safety issue. Certainly,
7 worsening of the underlying disease has to be at
8 the top of the list. The interference with the
9 normal function of the ICD has to be up there in
10 the top five and, certainly, the complication rate
11 or the maldeployment rate, all concern the members
12 of the panel and I think were articulated.

13 Do we have consensus on the concerns
14 surrounding whether this treatment worsens
15 congestive failure? Which way are you nodding your
16 head, that we are concerned that this may worsen
17 failure or that--

18 DR. DOMANSKI: I think there is no
19 evidence that it does. I don't think that is an
20 issue. I didn't think it was an issue.

21 DR. KRUCOFF: I think the only period
22 there is out to six months. I think, beyond six
23 months, we don't have any data.

24 DR. LASKEY: Right; and we were told at
25 the outset that the sponsor has been requested to

1 provide data out to one year, should this be
2 approved.

3 DR. KRUCOFF: Although, isn't it true,
4 Warren, everybody is on after six months?

5 DR. LASKEY: Yes.

6 DR. KRUCOFF: So there is going to be no
7 data other than just the mortality rate of the
8 whole population.

9 DR. LASKEY: The observational experience.
10 The study was not powered to look at mortality. I
11 don't think we can address that. The data on
12 hospitalizations, my read of that was that it
13 trended in the right direction but didn't meet
14 rigorous statistical significance. We didn't see
15 anything here to indicate that it worsened the
16 underlying disease state.

17 Question No. 6, I think that is what the
18 last hour was about before the lunch break with
19 respect to interference of proper ICD functioning.
20 We haven't seen that data. I think the huge gap at
21 the outset of this presentation was presented by
22 Dr. Barold who was asking, correctly, for more data
23 on this particular area, the rates of inappropriate
24 shocking and so on and so forth. I think all of
25 that is written in black and white in terms of what

1 we need to see before we can truly feel comfortable
2 with this. Is that fair? You have now heard it in
3 three iterations.

4 Question 7, again, to summarize this, I
5 would have to defer to my electrophysiology
6 colleague. Recommendations regarding program
7 considerations, what was the distillation of your
8 concerns surrounding programming around the various
9 critical functions?

10 DR. SIMMONS: Actually, I am not the one
11 that brought up those concerns but I did bring up
12 concerns about the fact that there just isn't any
13 data. What Dr. Wilkoff started to present is a
14 good start as far as comparison of this platform to
15 the Gem-3 platform. I think it is a good start but
16 we only saw a couple of slides.

17 My suspicion--if you want my suspicion or
18 my gestalt--is that probably is it okay. It is the
19 Gem-3 platform. The Gem-3 platform has got a big
20 history and the sensing and pacing characteristics
21 are probably going to be okay. But there is no
22 data in this panel pack. The couple of slides that
23 Dr. Wilkoff showed us were very encouraging, but
24 that is all I can say.

25 DR. LASKEY: So our recommendation

1 regarding this issue is to provide data.

2 DR. SIMMONS: Right.

3 DR. HAIGNEY: I think this is one small
4 concern also that may be important to include in
5 the labeling that patients who have very slow
6 ventricular tachycardias that are going to
7 interfere with their ability to pace, that the
8 clinician needs to realize that if you have got
9 somebody who has a ventricular tachycardia that is
10 going to give you a rate cutoff of 120, then you
11 can't have the patient pacing at 120 and they are
12 going to lose the benefit of biventricular pacing.

13 But that is true with any device, that you
14 can't pace at the same rate that you are going to
15 detect a tachycardia. I think that that just
16 should be pointed out as either a relative
17 contraindication of something in the physician's
18 brochure that they need to consider.

19 DR. SIMMONS: In reality, that is probably
20 a lockout. You probably couldn't even program it
21 that way if you wanted to. I think what you might
22 run into more is that inexperienced physicians may
23 have anxieties about programming the device in a
24 certain way. There are probably going to be
25 lockouts. Actually, what we were just shown is

1 that, by shortening the AV delay and having
2 everybody pace, it actually gives you more
3 opportunity to get lower heart rates.

4 But with any new system like this, with
5 new things to turn, new buttons to push, I think
6 there is going to be a significant learning curve.
7 I have, unfortunately, brought this up a number of
8 times at these meetings. I would love to see the
9 panel have some power to put into the device
10 indications or restrict the device to people who
11 have been trained to actually use it.

12 That is obviously not going to happen,
13 unfortunately. So I am not going to beat that
14 horse again here. But I think that the more likely
15 thing that is going to happen is patients are not
16 going to get things turned on that they normally
17 would, not that things can't be turned on that
18 should be turned on. But, again, I don't know. I
19 would love to see some of the other things that
20 Bruce is going to present.

21 DR. LASKEY: I guess a corollary is that
22 one of the things I am most uncomfortable with is
23 the moving target aspect of this, that things are
24 always changing. I draw on my experience in the
25 catheter business where everything that was

1 modified needed to go through a 510(k). I am
2 trying to make analogies between that and tweaking
3 something because these devices will always be
4 tweaked and need to be tweaked.

5 We talk about different leads and
6 different configurations of getting into the CS and
7 getting into the lateral cardiac vein and that
8 requires a different catheter with a different
9 preshape. So much is a moving target here and what
10 are we evaluating here.

11 The application in front of us just talks
12 about one thing at one point in time and it makes
13 it most disconcerting to try and predict which way
14 it is going to go and it is also unfair to
15 necessarily stigmatize the product at the moment in
16 time we are asked to evaluate it.

17 So we need to think about how to deal with
18 this very rapidly moving technology.

19 DR. ZUCKERMAN: Right, Dr. Laskey. But,
20 at the same time, the agency requires a reasonable
21 threshold dataset. What I have heard for responses
22 to Questions 6 and 7, is it fair to characterize
23 that there are still some holes.

24 DR. LASKEY: Correct.

25 DR. SIMMONS: It is certainly not clear to

1 me. From reading some of things that were said, is
2 it a reluctance on the part of the sponsor to
3 provide the data or is it just they haven't
4 provided the data or where we're at. Maybe we
5 could ask them later on. But, certainly, the data
6 is not in the pack as far as how these things are
7 programmed.

8 DR. LASKEY: No. 8, 9 and 10, as they
9 relate to the event-free survival from complication
10 rates, if you will, I am not sure that I heard
11 discomfort with respect to the pulse generator but
12 what we were in need of was more information on the
13 complications at six months, the lead-related
14 complications. We just don't have that entirety of
15 data to comment on.

16 I would also wonder how the lower 95
17 percent confidence limits were derived against
18 which these results are being benchmarked.

19 DR. SIMMONS: The data may very well all
20 be there. It just needs to be put in a plainer
21 term that we can actually understand what it means
22 to the patient--I mean, the data may be in this
23 pack. I am certain there are people out there in
24 the audience who understand exactly what it means,
25 but, to me, I am not sure that I could really

1 accurate describe what the risks and how many
2 reoperations and what these patients can reasonably
3 expect in the hands of the average practitioner
4 going to put this device in.

5 DR. KRUCOFF: I think, also, just to
6 structure the data, recognizing that this is a
7 patient population who weren't ICD placement, where
8 are the safety benchmarks that would say what, in
9 addition, to that ICD--the ICD is not the issue.
10 It is what else do you need to do to establish
11 biventricular synchronous pacing that has any
12 degree of risk for the patient that I think needs
13 to be distilled out of the data available and/or
14 added to the data that is available.

15 DR. LASKEY: I agree, which segues right
16 into Question 11. Again, what we are concerned
17 about here is the numerator. I think the
18 denominator--argue as we will, the denominator does
19 indicate that there is a significant impact on the
20 status of heart failure. However, the magnitude of
21 the numerator still remains unclear.

22 This was the biggest problem for me and I
23 am not sure I can fairly and accurately summarize
24 everyone's concerns about this, but I view this as
25 two Ven diagrams. I just cannot come up with a way

1 to quantitate the area at which they intersect.
2 There is the universe of patients who qualify for
3 an ICD or need an ICD and there is the universe of
4 patients who will need resynchronization therapy.

5 Where they cross and how they cross is
6 certainly not clear from this application and I am
7 not sure it is clear at all. But that is just my
8 read of this application as well as this morning's
9 discussion.

10 DR. NISSEN: Warren, may I help a little
11 bit and suggest that one way to do this is to say
12 that this device is indicated for those patients
13 who would otherwise require both an AICD and a
14 biventricular pacemaker. If both are indicated,
15 then this device is indicated. I don't think we
16 have to make this more difficult than that because,
17 in that setting, it has the potential advantage of
18 having a single procedure rather than two.

19 I don't think the indications for either
20 are going to change as opposed to the use of two
21 separate devices. Somebody correct me if I am
22 wrong, but is it really any different?

23 DR. LASKEY: I guess if we take our head
24 out of the sand, I think the indications for ICD
25 may certainly change substantially in the next

1 several years.

2 DR. NISSEN: But I mean, in terms of the
3 indication for a combined device, isn't it
4 indicated in those patients in whom both devices
5 are indicated clinically?

6 DR. DOMANSKI: Yes. That is an easy way
7 to come around it.

8 DR. LASKEY: The devil is in the details.

9 DR. DOMANSKI: Yes, but the details are
10 going to change as the ICV trials come out and they
11 are going to change as the resynchronization trials
12 come out, too.

13 DR. SIMMONS: Simpler is better. It is.

14 DR. DOMANSKI: But if you have a device
15 that does both and you say it is in the people who
16 are indicated, then you have kind of gotten around
17 it.

18 DR. BRINKER: Just from a practical point,
19 it is nice to think what you are suggesting, Steve.
20 But I think the real issue is to put down exactly
21 what the indications for each are and for those
22 people that have that amalgamate of indications.
23 But it is not like--I don't like to use the term,
24 if you need an ICD and you need a
25 resynchronization therapy, then you should qualify

1 for this, you could qualify for this.

2 I would rather, here are the indications
3 for this. Here are the indications for that.
4 Specifically use those indications in writing the
5 labeling for this. It is almost like if you were
6 saying--if it was the other way around, if you only
7 needed resynchronization therapy, you could say,
8 well, all those who don't need a defibrillator-
9 resynchronous combination could just get the
10 pacemaker. It just doesn't make sense.

11 I think you have to take the step and look
12 at the indications.

13 DR. NISSEN: The problem with that is that
14 we all recognize we are dealing with a moving
15 target. So, as the indications for defibrillator
16 and the indications for pacing change, you don't
17 want to label a device in such a way that it
18 represents the state of the art today. I think it
19 is easy to do this, to say, if both devices are
20 clinically indicated, this is an alternative to
21 placing two separate devices.

22 That is really all you need to say to tell
23 clinicians what makes sense clinically.

24 DR. PINA: But, from this dataset, which
25 is what we are working on, I don't know who the

1 patients are that are going to benefit from CRT. I
2 know they all have a indication for an AICD but I
3 have a very hard time telling which patient would
4 benefit from resynchronization therapy. I think
5 this is the dataset that we are dealing with right
6 now.

7 In the heart-failure world, and Jim and I
8 have had this discussion many times on the phone,
9 we are still grappling with who are the patients
10 that you want to refer for biventricular pacing.
11 It has a lot to do with your philosophy of
12 medication, how high are you willing to push some
13 people's drugs. If you get into trouble, then
14 maybe you have to pace them in order to push your
15 beta blockers--so there are so many variables.
16 But, from this dataset, I can't tell.

17 DR. SIMMONS: I think you are just making
18 an argument for what he is saying is that you are
19 never going to be able to write anything down so
20 you are either going to disapprove the device--if
21 you approve it, then you should leave the
22 indications open for the clinician to make the
23 decision as the dataset becomes more clear.

24 DR. KONSTAM: I would just like to weigh
25 in on this. I think that Steve's construct is

1 extremely tempting and it actually mirrors the
2 argument that Milt made earlier. It is tempting
3 and I would like to do it. But there are some real
4 problems logically in doing it and datawise in
5 doing it.

6 For starters, and I will turn this back to
7 the agency, we were not asked that question. Maybe
8 that is the question we should have been asked. We
9 are not provided with, in my judgment, perhaps, the
10 right kind of information to answer that question.
11 For example, for starters, we don't have in front
12 of us the InSync data.

13 Milton asked us to compare those data to
14 these data. First of all, that is extremely
15 difficult to do in the best of circumstances. When
16 you have an active treatment control, it is
17 difficult to do to have enough patients to be able
18 to say it.

19 To be able to compare it retrospectively
20 to another dataset is much more difficult. What
21 makes it even more difficult here, and I think this
22 is what Ileana was getting to, is that it is a
23 different patient population, that we don't know
24 the impact of that.

25 On top of all of that, we don't have the

1 data in front of us to do it. As I read this
2 application, we are being asked to judge the safety
3 and efficacy of this device based on this trial.

4 Now, I will say that, if presented the
5 data differently, if presented the data in a manner
6 that could be easily compared with InSync data, for
7 example, and with safety and efficacy data of a
8 separate ICD, perhaps--I don't know how to do it.
9 It is possible that I could get to a comfort level
10 to say just what you are saying, Steve, and so I
11 think that gives me discomfort about the whole
12 situation. I can't get from here to there based on
13 the packet that is in front of us.

14 DR. NISSEN: Marv, I think you are right.
15 The truth here is that, in any situation where we
16 have a new therapy, the specific clinical
17 indications for that new therapy are something that
18 there is uncertainty about. When drug-eluting
19 stents come out, we are going to have a great big
20 debate about who should get a drug-eluting and who
21 shouldn't.

22 That is always true. This trial was not
23 designed to tell us that, only to determine whether
24 this particular combination device was safe and
25 effective. So what you have to have faith in, that

1 is a guidelines question. That is a question for
2 NASPE and clinical-practice guidelines kind of
3 question.

4 I think appropriate groups at the ACC and
5 NASPE and so on should address the question of what
6 subset of patients ought to be biventricular
7 pacing. But that is not the question--

8 DR. KONSTAM: You are losing me. I agreed
9 with what you said a moment ago and you lost me.
10 What we are asked to do is to determine the safety
11 and efficacy of this device in this population
12 based on these data.

13 DR. NISSEN: Right.

14 DR. KONSTAM: That is where I am at with
15 this.

16 DR. NISSEN: I'm with you.

17 DR. KONSTAM: I think I am sort of
18 echoing--a variety of people for a variety of
19 different reasons are uncomfortable with making
20 that judgment based on the data that we have in
21 front of us.

22 DR. DOMANSKI: I think you guys are
23 saying--I think you are both saying something that
24 has nothing to do with what the other one is. What
25 you are saying is do we have enough to approve this

1 based on what we have got. That is a question we
2 are going to have to answer.

3 He is saying that, once you do approve it,
4 understand that the indications may change and make
5 it a little more general. So I think neither of
6 you are necessarily--I don't think the two ideas
7 are in conflict. I don't even think they are
8 related.

9 DR. KRUCOFF: The one thing I do think we
10 should dispel with, though, is the straw man that
11 somehow putting two devices in these people is the
12 bar that we are measuring against because, from a
13 technical point of view and from a reality-based
14 point of view, everything I understand is that
15 putting two devices in is not an option in this
16 population and it not what is being measured
17 against--or not a tested option in these patients
18 and not what we are measuring this against.

19 DR. SIMMONS: It's an option.

20 DR. DOMANSKI: It is clearly an option.

21 DR. KRUCOFF: It is not what is in these
22 data. It is not what I think we are measuring
23 against in this patient population.

24 DR. BRINKER: I agree. I think the
25 substrate of the patient population has been

1 suggested by both the presenters and people on the
2 panel is different than the typical patient
3 population who has heart failure of YQRS and no
4 indication for an ICD and that the benefit may not
5 be the same.

6 So we have had ways around this in the
7 past. The simple thing to do would be putting
8 something in the labeling that basically summarizes
9 the results of this trial, in patients who have
10 heart failure YQRS, low ejection fraction and
11 ventricular ectope that would otherwise be treated
12 with an ICD, one might expect the following from
13 biventricular pacing.

14 DR. ZUCKERMAN: If I can underline Dr.
15 Brinker's point, that is usually the way that we
16 handle these types of problematic labeling
17 questions. So, perhaps, it will be easier for the
18 panel to give us some input if we put the proposed
19 sponsor's indication statement and see if it hits
20 that benchmark.

21 DR. BAROLD: It is Slide 11, if that
22 helps.

23 [Slide.]

24 DR. ZUCKERMAN: Dr. Brinker, can you
25 comment on the indications as they now read?

1 DR. BRINKER: I think that there is
2 evidence based on the statistically significant
3 changes in the patient's quality-of-life
4 questionnaire and New York Heart Association
5 Function class that would validate this first
6 bullet. You could do it--in the past, we have done
7 it a little bit differently--and basically
8 summarize the kind of data that are in the clinical
9 trial.

10 But I think that this does it in a more
11 general way so I would agree with the first bullet.
12 I agree with the second bullet. I don't have a
13 major problem. I would put, then, in a footnote
14 the actual statistical results, the quality of life
15 changed X and the New York Heart Association class
16 changed Y in X number of patients treated for six
17 months so that they understand that this isn't a
18 blanket endorsement of a prolonged effect of a
19 significant--you are not going to have patients
20 coming in after a month of this saying, "I'm normal
21 now," or you are not going to have many.

22 So I think that the reduction of symptoms
23 should be put in some context to an individual who
24 hasn't read the paper which will soon, I assume, be
25 published, and that is that it is a significant

1 reduction but not an overwhelming reduction.

2 DR. LASKEY: Isn't the recitation of the
3 trial data supporting the application a given?
4 Isn't that in there?

5 DR. ZUCKERMAN: Yes. The indications for
6 use are traditionally quite short in order to cut
7 to the chase in terms of the intended use and
8 benefit. There is a separate clinical-trials
9 section which should, in sufficient detail, address
10 what happened during the trial and then, after that
11 section, the agency usually likes to see if the
12 sponsor and agency can construct some sort of
13 guidelines for tailoring therapy to individual
14 patients, individualization of patient care, et
15 cetera.

16 But the main issue that we ask for panel
17 input is the actual indications for use because, as
18 alluded to, it has significant implications for how
19 the device is used and advertised.

20 DR. NISSEN: What is actually missing from
21 this indication for use is it doesn't really state
22 explicitly that it is indicated in patients in whom
23 an ICD is required and meet these--and that is what
24 I was asking for in my description of what the
25 indications--I think it is almost like the ICD part

1 is kind of an afterthought here and I would make in
2 integral that the ICD is clinically indicated and
3 they meet those above criteria. Maybe that would
4 help some of the folks who are a little bit on the
5 defensive.

6 DR. KRUCOFF: I actually agree with that
7 one. I think the first bullet point would be, this
8 device is for people who need an ICD based on the
9 data from this study. The second bullet point,
10 based on the data from this study, is that, in
11 addition, in the setting of heart failure, that
12 this device has been shown to improve quality of
13 life which is actually the statistically important
14 efficacy endpoint that meets the Hochberg criteria
15 in the, at least, intention-to-treat analysis and
16 that it may also positively impact heart-failure
17 class symptoms.

18 But I think my trouble with these
19 indications for use is, number one, the bullet
20 points are backwards and, number two, that, based
21 on the data, what the IFU should support is that
22 adding biventricular synchronous pacing in these
23 patients will improve their quality of life and may
24 improve their heart-failure class.

25 DR. LASKEY: I am not sure you are going

1 to get any more fine tuning on the nature of the
2 patient population.

3 DR. ZUCKERMAN: I think you have given us
4 the general construct, though.

5 DR. BRINKER: Are we privy to see the
6 Warnings Section or something along those lines
7 because I think that part of this should include
8 that this carries some additional risk compared to
9 just and ICP input, in terms of success and lead
10 stability.

11 DR. ZUCKERMAN: The intent of this
12 question really is to comment on the entire
13 labeling package, warnings, precautions, et cetera.

14 DR. KRUCOFF: I think, in addition to what
15 Jeff is saying about added risk that it would also
16 be quite reasonable, based on the data, to say that
17 the benefits of this device are known to extend to
18 six months.

19 DR. LASKEY: You have answered your own--
20 if we go to Question 13, you have answered the
21 large majority of this with approval of this
22 device, FDA and sponsor agree to the collection of
23 post-approval data, 12-month mortality, three-year
24 evaluation of morality and lead performance, and so
25 on and so forth. Please comment on whether

1 additional clinical follow up or postmarketing
2 studies are necessary. I would rather defer to the
3 voting to see if there are conditions which are
4 applicable because I am not sure that we actually
5 discussed that level of specificity this morning.

6 So may we await? I've been reminded of an
7 important oversight here. Within the labeling in
8 the IFUs, and so forth, are we happy with the level
9 of information on the training and experience
10 requirements to place this device? Has that been
11 adequately stated? I know we didn't really discuss
12 that. We talked about the learning curve and
13 increased operator experience. I am not sure we
14 actually touched on whether there are specifics put
15 down.

16 DR. PINA: I read the manual about the
17 training. It seems like there is a didactic
18 program and then I believe there is training--is it
19 in an animal model? There is other kind of
20 training added in here and then there is something
21 about the Medtronic rep will refer the individual
22 to a center where they will get trained.

23 I think that should be mandated, not just
24 suggested, because it is obvious that you had
25 centers here who put in leads all the time and

1 there was one center, for example, that had six
2 failures even though they were one of your highest
3 enrollers. It has been very inconsistent. Every
4 center has had a least three or four that they have
5 not been able to implant.

6 So I think that should not be an option.
7 I think that that should be mandated if this gets
8 approved.

9 DR. SIMMONS: Actually, I think the way
10 the manual reads is these are options. So one of
11 the options is that if you are a physician in a
12 somewhere hospital, you can have the Medtronic rep
13 come in and give you a slide show and bring a
14 little model in and then you are free to go.

15 Another option is you could go to
16 Medtronic where you could get a didactic program,
17 do some hands-on stuff with a model and then maybe
18 or maybe not do an animal. Then a third option
19 would be that you could go to a center and get this
20 training done.

21 The way it is written, it is kind of up to
22 the physician and the Medtronic rep what kind of
23 level of training the physician gets before he is
24 free to start--

25 DR. PINA: But I would like to see it a

1 little bit tighter than that.

2 DR. SIMMONS: I would love to see it a lot
3 tighter than this. I would like to see the NASPE
4 guidelines followed before these devices were sold
5 to anyone.

6 DR. PINA: My recommendation would be that
7 it has to be tighter than that.

8 DR. LASKEY: Isn't this a spill-over from
9 InSync?

10 DR. PINA: Yes.

11 DR. LASKEY: I think the horse is out of
12 the barn on this one.

13 DR. PINA: We requested something very
14 similar

15 DR. LASKEY: Yes; we did. But I wasn't
16 aware of the fact that there were three, a
17 tripartite approach to this.

18 DR. KRUCOFF: In fact, it is a little bit
19 of a question in my mind of why wouldn't the
20 already-in-place training for the original InSync
21 device be what is in this packet as a
22 recommendation for training for operators? Why
23 would that change?

24 DR. LASKEY: I don't think it should.

25 DR. SIMMONS: What were the

1 recommendations for training for the InSync device?
2 Does anybody remember?

3 DR. PINA: I know we had talked about
4 didactic training and we had also talked about
5 heart-failure training, too, so that patients are
6 not necessarily referred to this who are not
7 medicated appropriately. We had specified all
8 those things with the InSync and we had talked
9 about hands-on training in experienced centers.

10 I have not seen the revision of the manual
11 after the InSync trial. I don't know if the agency
12 has gotten it yet or not.

13 DR. DOMANSKI: Maybe it would make sense
14 just to say that--to guide the FDA by saying that
15 we expect they will have similar training
16 requirements to the InSync study and let it go at
17 that.

18 DR. LASKEY: Fair enough. I think we have
19 successfully summarized points of consensus and
20 differences among us. I would like to ask the
21 sponsor to approach the table one more time for,
22 perhaps, a five- to ten-minute rebuttal, wrap-up,
23 oversight.

24 I realize a great deal has been discussed
25 here in terms of our response to the FDA, to their

1 questions to us, but is there a cogent unified
2 message that you would like to send to us before
3 we vote?

4 MR. MANDA: Dr. Lasky, My name is Ven
5 Manda. I am a Medtronic employee. First off, on
6 behalf of Medtronic and the study investigators, I
7 would like to thank the panel for the deliberations
8 today. This is certainly a learning experience for
9 us, as well.

10 I wanted to respond to two points that
11 were raised during the discussion. First off, I
12 just wanted to clarify that, as it relates to the
13 data on the interaction of the devices, between
14 biventricular pacing and InSync ICD, I just wanted
15 to assure the panel that there was no reluctance on
16 our part to share the data. It was really a
17 question of timing between when we were aware of
18 the questions and the panel packs being ready, and
19 so forth. So we have no doubt that we will be able
20 to provide all the data to the FDA.

21 The same is true for the patients who are
22 still in double-blind follow up, should we not be
23 able to produce the documentation to demonstrate
24 that such a commitment was made before.

25 Thank you.

1 DR. PACKER: Just one parenthetical
2 comment. As often happens in the interpretation of
3 clinical trials, those who review them occasionally
4 have to distinguish between looking at the
5 magnitude of effect and looking at the statistical
6 significance of effect, that they are not identical
7 concepts.

8 One can have large effects that may be
9 borderline significant. One can have small effects
10 that are highly statistically significant. These
11 are readily distinguishable concepts that are
12 important to distinguish, very important to
13 distinguish.

14 So I just want to emphasize that the
15 magnitude of the effect that is seen here is very
16 meaningful. This is as good as we get in heart-
17 failure trials. I am sympathetic to the issues
18 that have been raised about statistical
19 significance but I just wanted to clarify, in terms
20 of magnitude of effect, this is not a small effect.

21 DR. YOUNG: I would like to just make one
22 quick comment about the issue perhaps tingeing on
23 labeling and patient selection because that is a
24 very important thing. This is a unique trial as
25 was InSync because of the collaboration between

1 heart failure and electrophysiology and focussing
2 on using a procedure and a device to try to
3 ameliorate our severely symptomatic heart-failure
4 patients and perhaps that is where the patients
5 really are going to be coming from is the heart-
6 failure world, and it is going to be an attempt to
7 look at individuals who have an indication for one
8 device, the ICD, who are symptomatic despite
9 aggressive therapy.

10 I like Ileana's suggestion about training
11 everybody to be heart-failure doctors. I wish.
12 And then, if they have other appropriate
13 indications, and you believe you can
14 symptomatically improve them, that seems to be the
15 appropriate patient.

16 So it is two Ven diagrams that are
17 overlapping. Personally, I do agree with Steve's
18 commentary and approach on that.

19 Thank you very much.

20 DR. LASKEY: Thank you, gentlemen.

21 Does the FDA have any additional comments
22 before we vote?

23 DR. ZUCKERMAN: No; we don't.

24 DR. LASKEY: Mr. Dacey, you have been so
25 patient. Do you have any input before we proceed?

1 MR. DACEY: No. Ileana addressed the core
2 issue I had around the quality of life. As soon as
3 I saw that as a primary efficacy endpoint, it
4 occurred to me that this is an issue, quality of
5 life, that we keep dealing with. But it certainly
6 has a bigger burden of proof when it is a primary
7 endpoint.

8 There is really not any hard science to
9 apply to it as you would to other primary
10 endpoints. Obviously, a lot of work is being done
11 in this area and I was hoping to find out if there
12 was real comfort with instrument that was used, the
13 Living with Heart Failure instrument, which is not
14 the only one out there right now.

15 I can only assume that a lot of work is
16 being done to maybe not make it hard science but to
17 strengthen and to define this subject better for
18 when future panels meet, they have something they
19 can really grab onto. I know it is a validated
20 study and there are other validated studies.

21 The only other comment I had was on the
22 patient manual, and Lord knows I spend enough time
23 producing these kind of things, the last one I saw
24 around this general subject was 40 pages long and
25 now it is 102 pages. I realize that patients are

1 highly motivated when it comes to having these
2 types of interventions, but there is also a
3 substantial population who are not as literate as
4 the manual, itself, is presented.

5 I can't help but wonder if we are really
6 looking at several documents. The guideline used
7 to be fifth-grade level. That is fine if you are
8 doing an eight-page brochure. But when you get to
9 102 pages, that is a lot of information for a
10 patient and a family, because families are
11 obviously involved.

12 So those are my two issues.

13 DR. LASKEY: Mr. Morton?

14 MR. MORTON: Thank you. No comments.

15 **Open Public Hearing**

16 DR. LASKEY: I would like to just,
17 hopefully briefly, open this to public hearing. Is
18 there anyone in the audience who wishes to address
19 the panel on the topic before we vote?

20 If not, we will close the open public
21 hearing session.

22 **Committee Voting**

23 DR. LASKEY: I would like to have Leslie
24 read the voting options.

25 DR. EWING: Thank you. The Medical Device

1 Amendments to the Federal Food, Drug and Cosmetic
2 Act, as amended by the Safe Medical Devices Act of
3 1990, allows the Food and Drug Administration to
4 obtain a recommendation from an expert advisory
5 panel on designated medical-device premarket
6 approval applications that are filed with the
7 agency.

8 The PMA must stand on its own merits and
9 your recommendation must be supported by safety and
10 effectiveness data in the application or by
11 applicable publicly available information. Safety
12 is defined in the Act as reasonable assurance based
13 on valid scientific evidence that the probable
14 benefits to health under conditions on intended us
15 outweigh any probable risk.

16 Effectiveness is defined as reasonable
17 assurance that, in a significant portion of the
18 population, the use of the device for its intended
19 uses and conditions of use will provide clinically
20 significant results.

21 Your recommendation options for the vote
22 are as follows. Approval if there are no
23 conditions attached. Approvable with conditions.
24 The panel may be found that the PMA be found
25 approvable subject to specified conditions such as

1 physician or patient education, labeling changes or
2 a further analysis of preexisting data. Prior to
3 voting, all of the conditions should be discussed
4 by the panel.

5 Not approvable. The panel may recommend
6 that the PMA is not approvable if the data do not
7 provide a reasonable assurance that the device is
8 safe or if a reasonable assurance has not been
9 given that the device is effective under the
10 conditions of use prescribed, recommended or
11 suggested in the proposed labeling.

12 Following the voting, the chair will ask
13 each panel member to present a brief statement
14 outlining the reasons for their vote.

15 DR. LASKEY: Panel members, may I have a
16 motion?

17 DR. PINA: I actually have a motion to not
18 approve. I will specify my reasons why. We are
19 dealing with the dataset that we are dealing with.
20 Based on this particular dataset, I am not
21 comfortable with the benefits in patients who need
22 an AICD and there is no question about it, the
23 benefits of this therapy on heart failure symptoms.
24 I don't see concordance of data and I have some
25 real concerns about the crossover including the

1 effect of crossover on the quality of life.

2 I think that there is a huge scatter
3 quality-of-life results and that these positive
4 results which keep getting quoted this number 10
5 may be, in fact, driven by a few patients who had a
6 marked improvement. But most of the others are
7 sort of in the middle.

8 So those are my reasons.

9 DR. LASKEY: I need a second.

10 DR. KONSTAM: Second.

11 DR. LASKEY: With the seconding, we should
12 proceed to voting, then, starting on my right.

13 DR. WITTES: I approve the motion.

14 DR. LASKEY: We are voting on the motion
15 to not approve.

16 DR. WITTES: Right; not approve.

17 DR. DOMANSKI: I say no. I would prefer
18 to see the thing approved and so I am voting no to
19 the motion as it sits.

20 DR. HAIGNEY: I vote no.

21 DR. KONSTAM: Yes.

22 DR. OSSORIO: Yes.

23 DR. NISSEN: I vote no.

24 DR. AZIZ: I vote that the device should
25 be approved.

1 DR. PINA: I made the motion, so.

2 DR. KRUCOFF: I vote yes on the motion.

3 DR. BRINKER: I vote no on the motion.

4 DR. LASKEY: May we have that tally, Dr.

5 Ewing?

6 DR. EWING: That is five yes, five no.

7 DR. LASKEY: Was it five yes?

8 DR. EWING: The chairman votes in the case

9 of the tie.

10 DR. LASKEY: Let's count again. No; I see

11 the tally. Besides asking for benign intervention,

12 I would cast my lot with the motion to approve;

13 that is, I vote no to the motion to not approve.

14 DR. EWING: So the motion to not approve

15 has not been passed.

16 DR. NISSEN: I would like to make a second

17 motion.

18 DR. LASKEY: Dr. Nissen, please.

19 DR. NISSEN: I would like to move a

20 conditional approval with the condition that the

21 postmarketing study that is described here by the

22 agency must be conducted following approval.

23 DR. DOMANSKI: Second.

24 DR. LASKEY: Is there discussion on that?

25 DR. DOMANSKI: I would call the question.

1 DR. KRUCOFF: I think we ought to have
2 some discussion. I guess I have sort of a process
3 question. Is it within our purview as a condition
4 of approval to actually request that these data be
5 reorganized, completed and represented?

6 DR. EWING: That would be a second
7 condition.

8 DR. LASKEY: That is a condition.

9 DR. DOMANSKI: I don't understand. Are
10 you moving something. I don't understand what you
11 are asking them to do.

12 DR. LASKEY: I think we are asking
13 clarification from the FDA more than anything else?

14 DR. KRUCOFF: What are our options here on
15 approval with conditions?

16 DR. ZUCKERMAN: There are many potentials
17 for conditions once we get to that part of the
18 decision tree, among them being the ones that you
19 suggested allowing FDA to see the complete dataset
20 doing postmarket type surveillance as outlined in
21 Question 13. But we need to first concentrate on
22 the main motion of approval with conditions, has
23 that passed, and then we can go to--

24 DR. LASKEY: He wants to add another
25 condition.

1 DR. EWING: We vote on the conditions
2 first, and then vote on the motion.

3 DR. KRUCOFF: The question I am trying to
4 ask--because, to me, the vote to not approve was
5 simply based on the data available to us today. It
6 is not that I don't particularly believe the device
7 does or does not work. I don't feel like I have
8 the information in a fashion that helps me make
9 that decision.

10 So, to me, a very narrow swing would be to
11 simply say, to vote approval with the condition
12 that we have an opportunity to review the data when
13 they are complete, when FDA has been able to review
14 them and when they can be organized based on the
15 comments today. But it is a tautology because that
16 would be really asking for an opportunity to not
17 approve it if that did not--so that is my question,
18 Bram, is how do we--

19 DR. ZUCKERMAN: Right; and I think if you
20 vote approvable with conditions, that means that
21 you feel comfortable with data at hand, that there
22 is reasonable assurance of safety and effectiveness
23 and that these are additional things that will put
24 icing on the cake.

25 But if you believe that there are still

1 showstoppers here in the package as now
2 constituted, then that is a problem. We don't have
3 a conditional approval as you have just outlined.

4 DR. SIMMONS: What he is actually
5 describing is more like what you have discouraged,
6 is to table the motion until data is coming forth;
7 is that right?

8 DR. KRUCOFF: That would be what I would
9 think of as the normal--

10 DR. DOMANSKI: That sounds like a
11 functional disapproval. We just voted that down.

12 DR. BRINKER: To me, the real issue would
13 be whether we are comfortable enough to let FDA
14 staff make a final decision after they get the rest
15 of the data without us doing it. I think that is
16 an important differentiation. I, for one, would
17 be.

18 DR. DOMANSKI: That's fine. That's
19 different, though.

20 MR. MORTON: Dr. Laskey, that would not be
21 a precedent. That has happened many times.

22 DR. DOMANSKI: Yes, sure. In fact, it is
23 true all the time because FDA does the final
24 approval. We are only making a recommendation. So
25 that is easy.

1 DR. KRUCOFF: Yes, but it certainly feels
2 different to feel like we have a dataset that needs
3 some icing on the cake and we obviously can turn
4 that over to capable hands. To me, that is very
5 different than to feel like I have a dataset where
6 I don't know whether I have issues in it or not and
7 be asked to vote to approve or disapprove, or to
8 just turn it back over to your hands.

9 You could have skipped this whole panel
10 session altogether and made the decision if that
11 were the case.

12 DR. ZUCKERMAN: I don't think that is the
13 intent of our advisory panel process. We rely
14 heavily on our advisory panel input, have gotten
15 excellent input today. There is a close vote here
16 but I think, as pointed out by several other
17 people, there is a main motion of approvable with
18 conditions. Perhaps, we should just go around the
19 table again to make sure that that vote is 6 to 5.

20 DR. EWING: We need to discuss and vote on
21 the conditions first.

22 DR. ZUCKERMAN: Okay.

23 DR. LASKEY: Specifically, those
24 conditions are--

25 DR. NISSEN: The condition that I spoke to

1 you was that the postmarketing study defined in the
2 questions be performed.

3 DR. DOMANSKI: I will second that.

4 DR. KONSTAM: I have another condition I
5 wanted to add. So is now the right time, or do we
6 vote on that one?

7 DR. LASKEY: Why don't we vote on them one
8 at a time. I think that would be the way to do
9 this. So can we at least, by a show of hands, vote
10 on the first condition to Dr. Nissen's motion to
11 approve, and that condition is that the
12 circumstances outlined in Question 13 alluding to
13 12-month morality data and three-year evaluation of
14 mortality--just verbatim?

15 DR. NISSEN: Verbatim.

16 DR. PINA: But, in fact, we are voting for
17 approval.

18 DR. WITTES: I have a question. Does
19 voting yes for the condition mean voting for
20 approval?

21 DR. LASKEY: No. First we need to agree--

22 DR. PINA: We are voting on the condition
23 but not on approval.

24 DR. NISSEN: Janet, you can vote the
25 condition up and then vote against the motion if

1 you want.

2 DR. LASKEY: By a show of hands, all in
3 favor of this condition to be applied?

4 [Show of hands.]

5 DR. EWING: Unanimous.

6 DR. LASKEY: Good.

7 Is there another condition, Dr. Nissen,
8 that you wish to--

9 DR. NISSEN: No.

10 DR. BRINKER: I have another condition. I
11 mean, there was discussion before about getting the
12 data concerning interaction that was available but
13 apparently not part of the presentation that would
14 be important. So completing the dataset,
15 basically.

16 DR. LASKEY: We have heard that theme
17 throughout the day. It is most disconcerting to
18 hear it again in the final hour. Which interaction
19 do you want to see?

20 DR. BRINKER: The ICD pacing interaction.

21 DR. EWING: Complete the dataset and bring
22 back to panel?

23 DR. BRINKER: No, unless the FDA feels
24 uncomfortable.

25 DR. EWING: So not approve until the

1 dataset is final?

2 DR. DOMANSKI: That is another
3 disapproval. The condition is bringing it back
4 there, but we have already voted against the
5 disapproval. You can't put that in the condition
6 now.

7 DR. KRUCOFF: Isn't it implicit that if
8 the conditions are not met that the FDA still has
9 purview to act relative--

10 DR. DOMANSKI: They do without any motion
11 by this panel.

12 DR. KONSTAM: I think the sense of what
13 people are asking for, and I may ask for something
14 like that, is specifically articulating some of the
15 discomfort in terms of missing information that we
16 particularly want to see the agency pay attention
17 to before it makes its final decision.

18 I think that is the best we can do if we
19 are going to approve it. So is that appropriate?

20 DR. ZUCKERMAN: Yes. The general
21 condition of approval would be to vote on that the
22 sponsor has to complete the dataset as outlined by
23 the panel recommendations. Once that would be
24 done, the agency would evaluate the dataset and if
25 there are still problems could potentially bring it

1 back to panel. It is not an infrequent occurrence.

2 DR. LASKEY: But it would be helpful to
3 you to know exactly what it is that we want you to
4 see.

5 DR. ZUCKERMAN: If you could better
6 specify some of the questions.

7 DR. LASKEY: If we could hash that out.
8 We have one line item which is the data on the
9 interaction or lack thereof between the ICD
10 function and the synchronized pacing function. So
11 what other data?

12 DR. KONSTAM: We have talked about the
13 lead risk, the risk of the lead, specifically.

14 DR. LASKEY: Safety.

15 DR. KONSTAM: Safety, yes. So I think
16 what I would call for us a clearly aggregated risk,
17 combined risk, of lead placement failure,
18 implantation complications and subsequent
19 complications aggregated, that that really be
20 carefully looked at by the FDA and probably
21 expressed in the packet insert.

22 DR. WITTES: I think also an explicit
23 intent of the framers in terms of the sample size.

24 DR. LASKEY: Explicit intent--

25 DR. WITTES: Intent of the framers, the

1 protocol.

2 DR. NISSEN: Janet wants to make sure that
3 there was prespecified the sample size that we saw
4 here today.

5 DR. WITTES: Not only the sample size,
6 because I think the sample size was prespecified,
7 but the intent to stop at this point.

8 DR. NISSEN: Stop at this point was
9 prespecified.

10 DR. LASKEY: We heard repeatedly that that
11 was in writing somewhere, that there were
12 discussions and minutes of discussions. Do we need
13 to apply that again?

14 DR. NISSEN: Yes; we need to see it. They
15 need to see it.

16 DR. PINA: Can we ask for the rest of the
17 six-month data that are still missing with all the
18 primary endpoints that were specified including the
19 quality of life, the six-minute walk and see an
20 actual distribution?

21 DR. NISSEN: You could request that but I
22 would point out something to you that we have to be
23 very careful about. If that was not the
24 prespecified approach, then we are replacing valid
25 data within valid data. I think that would be a

1 very slippery slope and not a good precedent.

2 I always like more data.

3 DR. PINA: We haven't seen that.

4 DR. NISSEN: If an analysis plan called
5 for us to look at this point in time, then looking
6 at another point in time actually is the wrong
7 thing to do statistically.

8 DR. PINA: But we don't know that. That
9 is exactly what Janet is asking for.

10 DR. NISSEN: If she is asking for that.
11 If that is not the case, I assume the agency will
12 disapprove. If they come back and say, "Look; this
13 was not the prespecified ending point of the
14 trial," then it is all over.

15 DR. ZUCKERMAN: I think you can assume
16 there will be a problem.

17 DR. LASKEY: We have four conditions.

18 DR. KONSTAM: I just have something else I
19 wanted to come back to and Mark originally brought
20 this up. I think that there is an opportunity to
21 mine the dataset both here and, I suppose, in
22 InSync to see at least if the hypothesis can be
23 generated about patient characteristics that are
24 particularly prone to benefit and not benefit.

25 I understand that the sponsor says they

1 project that has nothing to do with approval of
2 this product.

3 DR. NISSEN: I would also add that I am
4 quite certain that the investigators will be mining
5 this data for years to come. I think you ought to
6 let them do that. It is really not an approvable
7 issue. It is an issue, I think, of research. I
8 agree with Mike completely. I encourage the
9 principle investigators here to get as much as you
10 can out of these data. I don't need to encourage
11 you because I know exactly what you are going to
12 do.

13 DR. LASKEY: This is helpful. I think we
14 finally have some consensus and resolution here on
15 a motion to approve with four conditions, the first
16 being the adherence to those delineated in Item 13,
17 the second being to provide the FDA data on the
18 interaction between the two functions of the
19 device, the third condition being to provide in-
20 depth and up-to-date data on the safety of the
21 device in toto, and condition No. 4 to see in
22 writing the agreement between the agency and the
23 sponsor alluding to the stopping point.

24 DR. EWING: Do you want to vote on those
25 separately, then?

1 DR. LASKEY: I think we should vote on the
2 whole thing.

3 DR. EWING: If there are separate
4 conditions, then we need--it sounds like acquiring
5 more data is one condition and then a third could
6 be the agreement in writing, unless I am wrong.

7 DR. ZUCKERMAN: I would suggest that we
8 vote on each condition separately, just to make
9 sure.

10 DR. LASKEY: Okay. We have strived to get
11 consensus for you, but we will break them up.

12 DR. KRUCOFF: Warren, for me, my head is
13 spinning. This is still the issue, what are we
14 creating a consensus on, on conditions or on
15 approval.

16 DR. ZUCKERMAN: On conditions.

17 DR. KRUCOFF: We are still talking just
18 about conditions.

19 DR. LASKEY: Yes.

20 DR. KRUCOFF: We are not voting on
21 approval.

22 DR. LASKEY: No. So, by a show of hands,
23 can we vote on the condition to adhere to the
24 circumstances outlined in Question 13 alluding to--

25 DR. NISSEN: We already did that.

1 DR. LASKEY: Done. Show of hands yea or
2 nay on providing data to the FDA on the interaction
3 between the two functions of the device. Yea?

4 [Show of hands.]

5 DR. EWING: It is unanimous.

6 DR. LASKEY: The third condition being to
7 provide up-to-date safety data. Yea, all in favor?

8 [Show of hands.]

9 DR. EWING: Dr. Nissen?

10 DR. NISSEN: I am voting no.

11 DR. EWING: Four no's. Hands up until I
12 count.

13 DR. LASKEY: We are voting additional
14 safety data.

15 DR. OSSORIO: Can I ask for clarification
16 here? We are not talking about data beyond the 224
17 patients. We are talking about the data that
18 exists right now, representing it in a way that it
19 addresses some of the questions that were raised
20 today in the panel; right?

21 DR. NISSEN: That actually changes my
22 vote.

23 DR. OSSORIO: With that clarification, I
24 am in favor. You are also?

25 DR. NISSEN: I am also in favor with that

1 clarification.

2 DR. OSSORIO: So then it was unanimous.

3 DR. NISSEN: It was unanimous.

4 DR. EWING: Okay. A unanimous vote to
5 that condition.

6 DR. LASKEY: The fourth circumstance was
7 the provision in writing as to the agreement
8 between the sponsor and the FDA on the stopping
9 point.

10 [Show of hands.]

11 DR. EWING: That condition is passed
12 unanimously.

13 DR. LASKEY: I am informed that we are now
14 ready to vote on this motion with these conditions.

15 DR. EWING: I think this would be more
16 clear if we go around the room.

17 DR. LASKEY: So, one at a time. Janet?

18 DR. WITTES: No.

19 DR. DOMANSKI: Yes.

20 DR. HAIGNEY: Yes.

21 DR. KONSTAM: No.

22 DR. OSSORIO: No.

23 DR. NISSEN: Yes.

24 DR. AZIZ: Yes.

25 DR. PINA: No.

1 DR. EWING: Dr. Aziz; I'm sorry. I didn't
2 hear you.

3 DR. AZIZ: Approve.

4 DR. EWING: Dr. Pina?

5 DR. PINA: No.

6 DR. KRUCOFF: No.

7 DR. BRINKER: Yes; approve.

8 DR. EWING: That is five yes, five no.

9 DR. LASKEY: I voted earlier to move to
10 approve, so I would vote to approve with those
11 conditions.

12 In 60 seconds or less, can we have the
13 sentiments of each panel member as to why they
14 voted that way?

15 DR. WITTES: I voted this way because I
16 think we were asked to look at the safety and
17 efficacy data in the application. My guess is that
18 when all the data come through, everything is going
19 to be fine but I can't vote yes on a guess.

20 DR. DOMANSKI: Adequate demonstration of
21 safety and efficacy.

22 DR. HAIGNEY: I thought there was adequate
23 demonstration of safety and efficacy also.

24 DR. KONSTAM: I believe that the device
25 probably works. I don't think that the application

1 proves it to me definitively and I cite the
2 multiplicity issue, the subjective nature of the
3 one endpoint that was positive and, importantly,
4 the blinding question. That doesn't get me to a
5 clear evidence of efficacy, particularly in
6 relation to the uncertainty about the risk.

7 DR. OSSORIO: I think we are not asked to
8 vote on whether something sounds like a good idea
9 or would probably work, but whether the data before
10 us indicate that there is safety and efficacy to a
11 reasonable level, or a level at which we can be
12 reasonably convinced. I didn't see that before me.
13 A lot of really good ideas don't pan out.

14 I think the fact that we are dealing with
15 a patient population for whom other therapies have
16 failed doesn't mean that we should approve without
17 data showing that benefits outweigh the harm. It
18 might mean that we accept some higher degree of
19 risk, for instance. But just because the patient
20 population is in trouble doesn't mean that we
21 should impose on them something that actually
22 doesn't benefit them, or that we should even make
23 it available and it will be used on them.

24 DR. NISSEN: I really didn't have much
25 trouble here with the efficacy question. Frankly,

1 I thought they met the prespecified endpoint. That
2 is the first thing. That is the first question you
3 ask about a trial. That was further reinforced by
4 a slew of secondary efficacy parameters that all
5 went in the right direction.

6 So I ask myself the question, is it
7 conceivable that the device doesn't work and my
8 answer was that I don't think that it is likely,
9 even possible, that the device actually doesn't
10 improve symptoms and other secondary efficacy
11 parameters.

12 Secondly, I do think that providing
13 patients with the opportunity to get a single
14 device rather than two separate devices confers
15 substantial patient benefit and, ultimately, that
16 is the thing that has to come first.

17 DR. AZIZ: I think I like the concept of
18 one device providing two forms of therapy because I
19 think that is the way these patients are heading.
20 I think this device does provide that.

21 DR. PINA: My thoughts are very similar to
22 Dr. Konstam. I have to deal with the data that I
23 have in front of me and the data that I have in
24 front of me does not persuade me to think that
25 there is significant benefit. So if I had seen the

1 functional capacity going in the same direction,
2 and I do question the VO2 results, they do not
3 convince me and neither does the six-minute walk.

4 DR. KRUCOFF: On a very similar theme, I
5 think as much as my heart may lean toward this
6 being a great idea to have two in one, and a very
7 novel and important mechanism toward the treatment
8 of heart failure, ultimately, what I understand the
9 mandate of this panel to be is to assess safety and
10 efficacy based on the data that we are presented.
11 I just felt I could not say that was where these
12 data ended up in this presentation.

13 I think those last comments on the
14 magnitude of therapy being separate from
15 statistical power are important. The magnitude of
16 therapy is what I take to be the threshold of
17 clinical relevance. But the statistical certainty
18 is how likely is it that the benefit we are seeing
19 is related to the therapy that we are testing.

20 So I think both of these belong right in
21 the middle of the question of safety and efficacy
22 evaluation. I just felt, out of this panel pack
23 and discussion today, I didn't actually end up
24 comfortable knowing what the answer is.

25 DR. BRINKER: I think that we can't take

1 this study out of context of all the other studies
2 that have looked at ventricular resynchronization.
3 I think that, while this panel pack is not the
4 best, and it focuses the need for the FDA as well
5 as the sponsors to reach an acceptable idea of what
6 is necessary from the git-go and have that renewed
7 during the whole process of evaluation, I don't
8 feel uncomfortable with the data and I feel that
9 the FDA staff--I feel comfortable enough with the
10 data to entrust the FDA staff with making sure the
11 i's are dotted and the t's are crossed because the
12 general context of what I see is it is almost
13 assuredly safe and it is almost assuredly
14 efficacious in the appropriate patient population.

15 DR. LASKEY: Thank you, all. Thank you,
16 sponsor, audience, panel members. This meeting is
17 now adjourned.

18 [Whereupon, at 3:25 p.m., the meeting was
19 adjourned.]

C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a horizontal line.

ALICE TOIGO