

1 this appear more compelling than immediately meets the
2 eye to me. So I'm kind of being straight forward
3 about it and cutting to the chase.

4 So I'd like to go first to the primary
5 endpoint and, certainly, with respect to that and its
6 components. There appeared in the data to be no
7 suggestion of benefit.

8 I'm concerned, by the way, about the trial
9 design here. I want to say that also up front, that a
10 differently designed trial, perhaps with longer follow
11 up -- and there are a number of design issues about
12 this trial that might have demonstrated better.

13 But I'd like to -- but let's take the trial
14 that's before us, because it's the only one we can
15 consider in this venue.

16 And I'd like to go through first the primary
17 endpoint. I see nothing in the primary endpoint to
18 suggest benefit. Am I wrong about that? I'm not sure
19 who should respond to that from the company.

20 DR. SWAIN: Please identify yourself for our
21 transcriptionist. Thank you.

22 DR. JOHN BOEHMER: Yes, my name is John

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Boehmer. I'm from Penn State Hershey and I am a site
2 principal investigator and on the events committee and
3 was involved with the trial from the onset.

4 The trial did evolve, and I think a timeline
5 was included as to how it evolved. And the initial
6 portion of the trial, we were very clearly looking at
7 peak oxygen consumption, we were very clearly trying
8 to do an exercise trial, and we were doing it in the
9 most expeditious fashion we thought possible, in part
10 because of the need for thoracotomy. That trial was
11 actually enrolling even as we went on and included the
12 EasyTrak leads via non-thoracotomy approach.

13 But it was at the end of that enrollment
14 phase that discussions began to go on between the
15 sponsor and the FDA as to what would be appropriate as
16 an endpoint to demonstrate the safety longer term.

17 Six months was the timeframe discussed and
18 I did consult in terms of what that endpoint should be
19 and we tried to come up with some very objective, very
20 countable endpoints.

21 As it turned out, event rates were not
22 sufficient, although the trend, if we would have had

1 the event rate anticipated, would have clearly shown
2 the benefit. If that trend continued in exactly that
3 direction with the sample size that was calculated, it
4 would have shown benefit in the primary endpoint. It
5 did not show benefit in that endpoint.

6 However, I'd like to point out that that
7 endpoint is very different from the secondary
8 endpoints that look at functional capacity and
9 symptoms.

10 DR. DOMANSKI: I'll come to that. I'm going
11 to sort of track through them. And I think the -- I
12 would make the same comment though, and I think it's
13 important. I want to give you a chance to respond.

14 None of the components of that endpoint are
15 in any way significantly changed by this therapy. Do
16 you think that's incorrect?

17 DR. BOEHMER: Well, there was a strong trend
18 in terms of benefit and trends are trends. Interpret
19 them as you will. What it did show though was that
20 there was no suggestion of any harm. But, no, the
21 primary endpoint did not meet statistical
22 significance. But the magnitude is clinically

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 meaningful.

2 DR. DOMANSKI: Now in the -- so now let's
3 track through some of the secondary endpoints. With
4 respect to peak VO₂, can you comment on what you think
5 your data on peak VO₂ tell us in this study?

6 DR. HIGGINBOTHAM: Well, regarding the --

7 DR. SWAIN: I'd ask you to say your name.

8 DR. HIGGINBOTHAM: Michael Higginbotham.
9 I'm just trying to field that question regarding the
10 significance of the VO₂ measurements. I talked earlier
11 about the functional significance of a two cc change
12 in the higher risk group, the advance heart failure
13 group and the concordance with the rest of the
14 findings. I won't repeat that.

15 I think the change in the overall group,
16 although the sponsor's not applying for
17 acknowledgement that that group significantly changed,
18 achieved a measure that's normally associated with
19 clinical relevance.

20 It was concordant with the other factors. In
21 fact, in the total group, that is the other variables,
22 it achieved a P value of .08, I think.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 It's a matter of how you interpret the P
2 values, whether you -- when you look at multiple
3 endpoints that kind of describe the same thing,
4 whether you require a P value to be lower or higher,
5 though technically you have to acknowledge that at the
6 P value of .0 -- 95 percent confidence limit it didn't
7 achieve its goal.

8 Whether you just stop the conversation there
9 and say there's no suggestion or it doesn't seem to be
10 effective really goes to the question of the effect of
11 looking at a multitude of concordant endpoints, seeing
12 them move all the same direction, which to me
13 personally, just not being a statistician, requires a
14 lower P -- a higher P value, not a lower one, and
15 whether you think a 92 percent chance of an accidental
16 finding is that much more significant than a 95
17 percent chance.

18 DR. DOMANSKI: You know, I'm sort of taken -
19 - I'm not a statistician, but I'm taken with the
20 comment by the FDA statistician in the summary.

21 In his summary he says one of the five
22 secondary endpoints, peak VO₂, produced a P value of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 .03 at six months, which is not statistically
2 significant of any reasonable adjustment for
3 multiplicity is applied. Do you disagree with that?

4 DR. HIGGENBOTHAM: Well, I can't disagree
5 with that statement. I could disagree, I guess, as a
6 clinician, with the need to adjust for multiplicity.
7 I think that the Bonferoni type multiplicity
8 correction's appropriate.

9 When you're looking at a scatter of
10 unrelated endpoints, it's very likely that if you look
11 at ten different things you're going to get a fluke.

12 But if you look at the same thing from
13 different angles, and in my view all the functional
14 elements are either a primary feature of heart failure
15 or something that secondarily occurs through known
16 mechanisms, to me the onus is a little less to make
17 that adjustment, personally.

18 DR. DOMANSKI: Could we also have a comment
19 -- you know, one of the things that struck me about
20 this also is it seemed to be awfully difficult to show
21 any difference in anything that really affected the
22 patient.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Could you comment -- maybe -- am I wrong
2 about that with respect to either the six-minute hall
3 walk or the change in quality of life? I mean, it
4 looks like there's no difference, really, or no
5 substantial difference.

6 DR. HIGGENBOTHAM: In the total group?

7 DR. DOMANSKI: Yes.

8 DR. HIGGENBOTHAM: I mean, there's a huge
9 difference in the advanced --

10 DR. DOMANSKI: I'm going to come to that.

11 DR. HIGGENBOTHAM: To the extent that you
12 acknowledge --

13 DR. DOMANSKI: But I want to talk about the
14 whole group.

15 DR. HIGGENBOTHAM: In the whole group? No.
16 I mean, it was a marginal statistical significance,
17 and the overall magnitude of the difference wasn't
18 great. I agree. They were concordant and drifted in
19 the same direction, but certainly weren't compelling.
20 I agree.

21 DR. DOMANSKI: So at least in the group as
22 whole, I would conclude that there's no difference in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 primary or secondary endpoints of any significance,
2 and I guess what I'd like to do now is go to the
3 advanced heart failure group, because it's here that
4 there's -- you know, I'm going to have trouble
5 probably -- I may have trouble convincing myself that
6 there's a fire, but there certainly seems to be some
7 smoke.

8 Because in that group, there appear to be
9 some difference. The problem that I have in looking at
10 those analysis and trying to suggest that a device be
11 put on the market, is that it really is a post-hoc
12 analysis, potentially data driven.

13 And I guess -- it seems to me, and I may be
14 wrong, because other panel members may feel
15 differently and I'm just one person. But I suspect
16 that if one were going to climb the hill of getting
17 this group to be enthusiastic about approving this
18 particular application, one would have to somehow
19 convince them that it's reasonable to analyze the
20 advanced heart failure group and use that.

21 And I wonder if -- usually, one uses these
22 post hoc analyses as hypotheses generating, but not as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 the basis for drawing conclusions that relate to
2 treatment. That's true if you look at a clinical trial
3 and post hoc analyses of those.

4 Can you make the case that that's not the
5 case here, that that's not true here?

6 DR. BOEHMER: I think if you --

7 DR. SWAIN: Please say your name first for
8 our transcriptionist.

9 DR. BOEHMER: John Boehmer. I think if you
10 take these data in pure isolation you have a strong
11 point. But they're not in isolation. They're in light
12 of a number of other things that have come about in
13 emerging data while the trial was under way.

14 And additionally, that's where the clinical
15 need is greatest. We really need therapies for
16 patients with advanced heart failure. And those
17 therapies have a clinically meaningful magnitude of
18 benefit.

19 So that's where we have the clinical need
20 and that's where other studies have demonstrated there
21 is a meaning -- it wasn't anything pulled out of thin
22 air and it wasn't just data dredged out.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. HIGGENBOTHAM: Michael Higgenbotham.

2 While Leslie's getting ready to answer that, Dr. Gray
3 made the point that if the initial group that you look
4 at doesn't have any trend toward an improvement, then
5 it's kind over-inventive to go and look at subgroups.

6 However, if you look at the overall group
7 here, there was a trend. If you'd look at the total
8 group, I don't believe you'd look at that and say
9 well, there's nothing. Let's dredge around for some
10 subgroups.

11 I think that there is a strong trend toward
12 improvement in the functional measures that would
13 indeed, as he suggested, make you look closer to ask
14 yourself where is this change occurring?

15 DR. SAXON: Thank you, Leslie Saxon,
16 University of California, San Francisco. I'm an
17 electrophysiologist, a principal investigator in this
18 trial and a consultant to Guidant.

19 I'd like to just in general address your
20 general questions about -- for the indications that
21 the sponsor is seeking labelling, is there a potential
22 usefulness of this therapy that has not come out in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 the data that you've seen so far.

2 And I think if you consider the fact that
3 what they're looking at are an extremely high risk
4 group of patients, defined by not only their advanced
5 functional class of heart failure, but also the fact
6 that they've had a ventricular arrhythmia or at
7 significant risk for one.

8 And if you look at what the available
9 therapeutic options are at the current time for this
10 patient, if you accept the data that the addition of
11 this lead in a patient who has otherwise indicated for
12 a device is safe, I think it's difficult to make an
13 argument not to put the lead on, because you're giving
14 the patient a therapy that is well accepted to
15 improve, have marked effects on systolic function,
16 will improve blood pressure, DP/DT, by ten to 30
17 percent and the data in the trial show that there has
18 been marked upward titration of medical therapy in
19 patients treated in the trial.

20 So I think that you are -- what you're doing
21 is your giving patients the ability to perform longer
22 on an exercise test, potentially, in part, due to the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 therapy, but in part also due to the fact that you can
2 have more options with medical therapy.

3 DR. SWAIN: Let me stop you for a second.
4 We need to discuss data that's presented here in this
5 trial. And the DBDT and upward regulation of medical
6 therapy is not data that were presented here. So that
7 -- we cannot discuss that.

8 DR. SAXON: Right.

9 DR. SWAIN: We cannot discuss that.

10 DR. SAXON: Well, then let me just speak to
11 the fact that the use and dosages of drugs increased
12 during the trial and that that --

13 DR. SWAIN: Excuse me. That data is not
14 present in our panel package. The amount of drugs
15 used. Or am I wrong with that? I don't see that.

16 MR. DILLARD: Jim Dillard. I might just
17 clarify something here. I think that Dr. Domanski has
18 asked a question, I think, of the sponsor.

19 Some of the information, I think, that's
20 being discussed here is information that while it may
21 not be directly in the application, may be available
22 in the medical literature, and I think at this point

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 would be an interesting thing to hear.

2 DR. SAXON: Well, I understood the question
3 as am I missing something?

4 DR. SWAIN: No, that's fine to discuss
5 what's in the medical literature. But in relating to
6 this trial, I believe that the rule is that it's data
7 that is presented that the package has.

8 So it's fine to say it's in the medical
9 literature, but not that this particular trial showed
10 it, because we have no evidence of that and the data
11 have not been presented. Thank you.

12 MR. DILLARD: I guess what I was trying to do
13 is I was really trying to let them have a kind of a
14 full -- a little bit of a full discussion of the field
15 so that -- I know there's a process issue and in the
16 end the data that we use to make a final decision does
17 have to be resident.

18 But it's resident in a context of knowing
19 something about medicine and what's going on. So
20 actually I appreciate -- I sort of appreciate the
21 comments, because I don't want to leave something here
22 -- I don't want to not see something approved that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 ought to be out there on some very, very narrow
2 procedural ground.

3 We obviously have a box we have to operate
4 in and stuff. But I think those comments are actually
5 useful. I have a question for you that maybe really is
6 a question without a point of view.

7 I was impressed that at least a couple of
8 the coronary sinus perforations resulted in the
9 patients deaths -- you know, it's hard to adjudicate
10 those things, probably sometimes and other times not.

11 But I guess I'm -- I mean, I do a fair
12 amount of interventions cardiology, putting in devices
13 and things that I think are probably easier to put in
14 some ways than this thing.

15 But that strikes me as -- that's a really
16 lousy result in two, three, four people and I guess I
17 wonder if that's really the expected result. Because
18 if it's completely safe then, of course, the oar
19 should be less heavy to pull.

20 But this thing doesn't look completely safe.
21 It looks like you can have a misadventure of pretty
22 substantial proportions.

1 DR. SAXON: Leslie Saxon. I don't think
2 there's any question that you can have a misadventure
3 in a procedure in patients with advanced heart
4 failure.

5 And the majority though of coronary sinus
6 traumas were simply staining, such as you'd see in
7 routine arteriography or anything else. The incidences
8 -- and I've reviewed most of these cases in Contak and
9 the larger companion trial.

10 The cases of perforation where there was
11 cardiac tamponade, the deaths were typically the
12 result -- the perforation added to a heart failure
13 exacerbation and subsequent problems with caused the
14 death of the patient.

15 But it seems to me that compared to the
16 alternative of a thoracotomy, that the safety data for
17 a new lead in patients whose coronary sinus branch
18 veins anatomy varies greatly is strong data with only
19 two deaths out of 500 plus.

20 DR. DOMANSKI: I'm not sure the alternative
21 is a thoracotomy though. The alternative may be not
22 doing it. And I guess that's kind of -- you say it

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 contributed in an exacerbation. You know, those are
2 very few cases.

3 Can somebody tell us something about the two
4 that we know died as a result or seem to have died as
5 a result of it? Let's see if it's contributory or
6 primary.

7 DR. BOEHMER: Well, if you want --

8 DR. SWAIN: I hate to do this, again, but we
9 need name for transcription.

10 DR. BOEHMER: John Boehmer. Did you want a
11 description of one of those patients?

12 DR. DOMANSKI: Yes, let's start with one,
13 and if it doesn't take too long, maybe the other,
14 because I'm kind of curious about whether that
15 resulted in the downhill slide.

16 DR. BOEHMER: One of those patients was a
17 patient under my care, Class IV heart failure,
18 refractory symptoms, BUN running over a hundred,
19 significant renal insufficiency, refractory congestion
20 who we offered the companion trial, not this trial,
21 where I believe there were no deaths at all.

22 He was enrolled in the companion trial and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 during the procedure, when the sheath was placed we
2 found ourselves on the wrong side of the coronary
3 sinus in the pericardial space.

4 He was actually taken to the operating room,
5 sheath removed, nothing happened, no tamponade. He
6 developed a low SBR over the ensuing 24 hours,
7 progressive shock, renal insufficiency and then more
8 shock and death.

9 But his family was very happy about the fact
10 that we tried something because that patient really
11 had no options.

12 DR. DOMANSKI: Now, I think it also fits the
13 description of the advanced heart failure being
14 contributive, because that's somebody who might have
15 recovered if they hadn't been already pretty sick.

16 MR. DeVRIES: Could we have Dr. Mester also
17 talk on this topic?

18 DR. MESTER: Stephen Mester. I'm an
19 interventional cardiologist. I'm a site principal
20 investigator and consultant with Guidant.

21 Not giving these patients a procedure is,
22 unfortunately, not an option. I think I'd like to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 remind the panel that all of these patients will
2 receive implantable defibrillators.

3 They already have an indication to undergo
4 an implant procedure. They require two leads to be
5 placed and a post generator.

6 Out of over 1,300 patients, two deaths is
7 actually a quite reasonable number of patients who are
8 receiving it.

9 DR. DOMANSKI: Yes, I guess, but not a
10 coronary sinus lead. I mean that's the thing that
11 actually caused the death in these two, or it was a
12 major contributor to the death in these two people.

13 And if you hadn't -- if this device hadn't
14 been available, they wouldn't have died at least of
15 that cause. They might have died of something else,
16 but they wouldn't have died of this.

17 So I think it is a safety issue. It may be
18 an entirely acceptable one, but only if the device is
19 really proven.

20 Do you think -- let me ask you one -- I
21 have, I guess, one last question and one comment. If,
22 and I know this is a little bit unfair, but I do want

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to put it into the context, if this study -- if we
2 were just discussing the medical literature as you
3 feel it exists and your study were unavailable to that
4 discussion, do you think you could make a compelling
5 case for resynchronization in the literature and if
6 so, what -- can you give us a sense of the quality of
7 data that you feel that's based, or the type of data
8 those are based on?

9 DR. BOEHMER: Yes. I suppose this afternoon
10 you're going to be hearing some of that data -- John
11 Boehmer. You'll be hearing some of that data and
12 there was a controlled cross over trial in Europe, the
13 MUSTIC trial that also demonstrated benefit as well as
14 a series of uncontrolled trials, as well as a number
15 of mechanistic trials that have been shown as well
16 that have looked at changes in DP/DT, pulse pressure
17 stroke volume, ejection fraction.

18 Have looked at changes in energetics, where
19 there is actually an improvement in energetics with a
20 decrease in oxygen consumption, despite an increase in
21 inotropy, which is -- the only other therapy that's
22 comparable to that is beta blockers.

1 So I think given the overall literature, I
2 just haven't seen anything that has been negative in
3 that sense.

4 The other thing about this specific trial is
5 this was a challenging study. We were taking a group
6 of patients that almost by definition were unstable in
7 trying to do an exercise study. And that was a
8 challenge.

9 And I'm impressed at the magnitude of
10 changes, given the noise of background medication
11 changes and so forth that was significant within this
12 trial.

13 I think this was a tough trial and I think
14 the strength of the therapy actually is borne out to
15 some degree over the noise of the trial.

16 DR. DOMANSKI: Let me close then, at least
17 my part of this thing, with the following comment,
18 which is really intended, perhaps more for the panel.

19 I think that we may be dealing with a
20 therapy that -- we're dealing with a therapeutic
21 maneuver that is, in fact, useful and that's going to
22 find some real clinical application.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 I guess there are two things that bother me.
2 One is that if that were the case, that is, if we have
3 a -- let's suppose that we have a real fine therapy
4 here.

5 We're actually considering a very specific
6 device and that device, at least with the test that
7 was asked -- the hill it was asked to climb failed to
8 do it. Now, that may be that the hill wasn't well
9 designed or it may be that that device is not climbing
10 a hill that maybe another device would. I don't know.

11 But I guess I'm left -- I guess my concern
12 relative to this specific application isn't set aside.
13 So that's my thing as a primary reviewer and that's
14 the end of it, I suppose.

15 DR. SWAIN: Well, thank you very much. It's
16 ten after 10:00 and we'll reconvene at 25 after. Thank
17 you.

18 (Whereupon, the proceedings went off the
19 record at 10:10 a.m. and went back on the
20 record at 10:20 a.m.)

21 DR. SWAIN: Let's reconvene. And what we're
22 going to do is have the sponsors have a response to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 some of Dr. Domanski's questions for about five
2 minutes, then we will have the rest of the panel ask
3 their questions. And let's, actually, await until Dr.
4 Domanski gets back.

5 Okay. Dr. Domanski's back, so we're going to
6 have -- Mike, we're going to have a response to their
7 questions from the sponsor. Okay.

8 DR. DeVRIES: Yes, we'd like to have Dr.
9 Larntz comment on the statistical process we used in
10 evaluating and writing at the subgroup and the meaning
11 of the data that we have.

12 In addition to that, we'd like to have Dr.
13 Boehmer then follow up with some comments about the
14 clinical implications and relevance of that.

15 DR. LARNTZ: Dr. Kinley Larntz. I'm an
16 independent statistical consultant to the company. My
17 financial interest is I received payment as a
18 consultant and I have no equity interest in the
19 company, nor any other company for that matter.

20 Subgroup analysis is problematic. There's no
21 question, statistically. Okay. I'm there. I'm a
22 statistician. I understand that. They mentioned

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 independent statistician in their slide. Well, I'm it.

2 And I think it's very important to
3 understand that we prospectively wanted to try to see
4 if there were variables that could be clinically
5 identified that might divide the data to identify a
6 group that would benefit more from the therapy. So
7 that's actually what I asked for.

8 I said how many variables do you have? And
9 they said we've got a lot. I said give me no more
10 than five, at the most, to think about dividing the
11 data. No more than five.

12 They came up with the five that Pat Yong
13 showed you. Fair enough? That's what the committee
14 did.

15 Then what I wanted to do is I wanted to look
16 for significant interactions of any of those variables
17 with the primary endpoint. There were none. There
18 were none.

19 DR. DOMANSKI: Let me ask you a question
20 though, just about that specific point.

21 DR. LARNTZ: Oh, sure.

22 DR. DOMANSKI: You know, it's good to look

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 for interactions, and I'm out of my depth a little bit
2 statistically, but Janet Wittes is going to help me.

3 DR. LARNTZ: We have someone who can help
4 with that.

5 DR. DOMANSKI: My understanding is that if
6 you see an interaction, you've got an interaction. But
7 the power of the test for interaction is too low to
8 conclude much if you don't see it. So I don't buy the
9 negative conclusion, unless you can educate me.

10 DR. LARNTZ: Oh, I agree completely. If I
11 don't find an interaction, that doesn't mean there
12 isn't a powerful subgroup for which this device works.
13 That's true. Okay. I mean, if I don't find an
14 interaction, that doesn't mean that there isn't a
15 subgroup for which the device works really well.

16 DR. DOMANSKI: Yes, but that's not the
17 conclusion I'm drawing.

18 DR. LARNTZ: Okay.

19 DR. DOMANSKI: That's true, but unrelated to
20 at least the discussion I was having. What I mean is
21 that there could still be an interaction, that that is
22 with what you've tested. Your test for an interaction

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 is unlikely to find one, even if one's present.

2 But if it does, then you know there's an
3 interaction. That is it's low power. That's what
4 power is.

5 DR. LARNTZ: I agree with that. I'm not
6 disagreeing with that. I agree.

7 DR. DOMANSKI: So the fact that you didn't
8 find interaction is not that exciting.

9 DR. LARNTZ: Well, if I had found one it
10 might have been exciting.

11 DR. DOMANSKI: Yes, it would have been. And
12 that's the point I'm making, it would have been very
13 exciting, but you didn't.

14 DR. LARNTZ: With respect to the primary
15 endpoint. That's true.

16 DR. DOMANSKI: Well, that's what we're
17 discussing right now and then we can move on.

18 DR. LARNTZ: Well, I think the -- you asked
19 about the choice of subgroup.

20 DR. DOMANSKI: What I'm trying to do is
21 point out that you said that there's no interaction.
22 And I'm saying that if you'd found one, of course,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 that would have been important.

2 The fact that you didn't is not particularly
3 important, because of the low power of the test to
4 find the interaction. That's all.

5 DR. LARNTZ: Fair enough. Fair enough. And
6 if I can proceed with how we chose the subgroup.
7 Because the subgroup choice did involve the secondary
8 endpoints. So if I could go ahead and talk about that.

9 Now, with respect to the secondary
10 endpoints, and particularly the two endpoints that are
11 peak VO₂ and quality of life, if you want to call
12 them, in the presentation -- how do I say this?

13 The primary secondary endpoints and
14 additional other endpoints, there were three variables
15 that did have significant interactions, and I think
16 that was stated a little bit differently in one of the
17 presentations earlier.

18 But there were three variables that did have
19 significant interactions for those secondary
20 endpoints. And those three variables were New York
21 Heart Class and QRS and LVF.

22 So those three of the five that were

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 prospectively chosen, three of those five did have
2 significant interactions with respect to --

3 DR. WITTES: With what? Significant
4 interaction with what?

5 DR. LARNTZ: With respect to peak VO₂ and --

6 DR. WITTES: And treatment?

7 DR. LARNTZ: And treatment. Yes. Oh, no,
8 no. I'm sorry. I'm sorry. I'm sorry, Dr. Wittes. It's
9 interaction with treatment. So there was a different
10 effect of treatment based on those groups.

11 DR. KRUCOFF: And New York Heart Class at
12 the time of implantation or New York Heart Class at
13 the time of randomization, or did you test both?

14 DR. LARNTZ: Well, both were actually
15 significant. Right. For one or the other variables.
16 Okay. The only one that was significantly --

17 DR. KRUCOFF: So you tested both.

18 DR. LARNTZ: The two both were tested.
19 Sure. They were both tested. In fact, that was on our
20 slide.

21 DR. KRUCOFF: So it's really more than five
22 variables.

1 DR. LARNTZ: Well, six, if you want to look
2 at the other one, yes. I don't disagree. Okay. The
3 only one that had a significant reaction with the two
4 that we were looking at, that is peak VO₂ and quality
5 of life was the three/four class at randomization.

6 Now in point of fact -- now I'm going to
7 step back and look at this as a statistician looking
8 at the holistic picture if I can. And I'm sorry if I
9 used that word incorrectly.

10 All the effects that we saw were such that
11 quote -- and I use quotes because I'm a statistician -
12 - "sicker patients showed bigger effects." That's
13 what we saw. Sicker patients. The group -- however
14 you define it. So the III/IV Heart Class or high QRS,
15 or low LVEF. Those were the directions. They were all
16 in the direction of sicker patients showing bigger
17 effects. Fair enough?

18 And they demonstrated bigger effects for the
19 functional variables and, actually, if we look, they
20 actually show bigger, but not statically significantly
21 effects or interactions for the primary endpoint. They
22 show bigger effects, but not significant effects for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 the primary endpoints.

2 DR. LASKEY: May I ask one question about
3 the NYHA variable?

4 DR. LARNTZ: Sure.

5 DR. LASKEY: At this point, this is a dummy
6 variable with four things in it. One, two, three,
7 four. Or is this an NYHA variable of three, four
8 versus non-three/four?

9 DR. LARNTZ: It was used as class dummy
10 variables. There was --

11 DR. LASKEY: So you had everybody in there,
12 one, two, three, four.

13 DR. LARNTZ: Well, actually, what it was two
14 -- there was an indicator for two or less. There was
15 an indicator for four. So there were two indicators
16 for Class IV and then II or less. Do you understand
17 what I'm saying?

18 DR. WITTES: So it's three categories. One
19 and two.

20 DR. LARNTZ: Yes, three categories. Two
21 degrees of freedom test. That's the way it was. I
22 didn't treat it ordered or continuous in this context.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Okay.

2 Now as I said, all of these three that
3 showed a significant -- showed that sicker patients
4 seemed to have -- at least the group that would be
5 defined as sicker patients had a greater benefit with
6 respect to the primary endpoint, but not statistically
7 significant, but with respect to the functional
8 endpoints, peak VO₂, quality of life, and some of the
9 other endpoints.

10 Now how do you decide with that information
11 -- see, in a sense, again, I'm trying to show you or
12 tell you what I think is going on here, is it looks to
13 me like sicker patients -- there's a group, if you can
14 define it, as sicker patients, that benefit from the
15 device. That's what seems to point from the
16 statistical analysis.

17 Now how do I decide which of those variables
18 to use? Which of those to do? Well, if I were and if
19 I were a truly exploratory statistician, I could go
20 find cut points that would make your eyes bulge out,
21 with respect to significance. I could.

22 What we did though, however, is we then said

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 well, what clinically will be able to be used to
2 define a group? What clinically will we be able to
3 define our group?

4 And this is where I dance out of the
5 picture because there's the information and now a
6 group has to be chosen to work from that does -- that
7 clinically describes that phenomenon. If I can.

8 That's as complete a picture and a complete
9 a story as I can with respect to the choice of the
10 subject.

11 DR. BOEHMER: John Boehmer. And, clearly,
12 Class III/IV was not pulled out of the air. That was
13 present in a number of studies. And as pointed out,
14 this study started as an exercise study and still was
15 in large part an exercise study at the end, looking at
16 Peak VO₂. And we wanted to maintain some of that.

17 So the real time to try to assess New York
18 Heart Class, to separate out the sicker patients from
19 the less sick patients is at the time of
20 randomization.

21 The time of enrollment is an interesting
22 point, but as mentioned, there's a lot happening

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 between time of enrollment in the study and time of
2 randomization.

3 So it will look for, in effect, of this
4 therapy -- the time of randomization appeared to be
5 the appropriate time and the Class III/IV patients was
6 quite rational in a clinical basis, based on what was
7 known from a number of studies that wasn't really
8 available at the time we had initiated this study.

9 DR. SWAIN: Thank you. Dr. Laskey.

10 DR. LASKEY: Well, I just want to open by
11 echoing the sentiments of people that have preceded
12 me. Congratulations to the sponsor and the
13 investigators. This was a heroic study, clearly.

14 To the FDA and, in particular, to the
15 statistician who, speaking on my behalf, took us to
16 school with respect to methods of statistical rigor.

17 And as an interventional cardiologist who
18 has watched this field basically explode, I found this
19 just fascinating, and learned a great deal along the
20 way of reviewing the data.

21 Now I have a couple of opening questions
22 that are a bit more general in nature, but I think

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 talk to the indications -- the patients in whom this
2 procedure is likely to benefit.

3 You're really dealing with, as you've said,
4 a patient population that have received an ICD.
5 They're at high risk for sudden cardiac death.

6 And I would expect then for the composite
7 risk of death in these patients, this thing could now
8 be eliminated, or mitigated. You don't have to worry
9 about sudden death in this group. They've received an
10 ICD and they're likely to die from other causes. Those
11 causes are well described in the heart failure
12 literature.

13 And as a general rule of thumb, as the
14 statistician was alluding to, the sicker the patients
15 are, in general, in clinical trials, the greater the
16 relative risk reduction that you see.

17 That dramatic effects are seen in the sicker
18 patients, albeit with higher event rates, but the
19 relative changes are quite meaningful.

20 So to that end I found -- is it Pat? I
21 found two of your slides most interesting, and I
22 wonder if you could go back and pull them out.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 The first one was when you showed the
2 relative changes in the component endpoints in the
3 whole group of patients in this trial. Not the
4 subgroup?

5 Even though we shouldn't be doing this, if
6 your trial is negative overall, you really shouldn't
7 be doing this, but let's do this to look for signals
8 and what they mean and what happens when you do
9 subgroup analysis.

10 So there is an impressive, as you said, risk
11 reduction in mortality. It may not be statistically
12 significant, but we go 36 percent relative risk or
13 relative reduction in mortality and the VT/VF is not
14 what I would have expected, but those are the numbers.

15 Now show us this same slide in the
16 three/four subgroup.

17 DR. YONG: Okay.

18 DR. LASKEY: Now, in this subgroup, at
19 highest risk, why is the relative reduction in
20 mortality somewhat less? It's underwhelming. Is this
21 what happens when you do divide and conquer or look at
22 subgroups? I don't understand the clinical

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 implications of this?

2 DR. BOEHMER: John Boehmer. One of the
3 things that happened in subgroup analyses is you end
4 up with smaller numbers, and that's why a composite
5 endpoint was used.

6 And the magnitude end of the reduction in
7 the composite endpoint was very similar, and also I
8 think you'd agree clinically meaningful, although it
9 did not reach statistical significance.

10 If you want the exact numbers, it was 11
11 versus ten mortalities and in terms of pump failure in
12 the treated group there were four. In the no-CRT group
13 it was six. So that's a 33 percent reduction in pump
14 failure deaths.

15 But, again, those numbers are small and
16 hence the reason that a composite endpoint was used
17 and not the individual ones.

18 And, again, as therapy changed in the course
19 of this trial, beta blockers became much more commonly
20 used, spironolactone was introduced and even using
21 some fairly good trials as guidelines we ended up with
22 a lower event rate than we would have otherwise

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 anticipated.

2 But that is a strong trend in the right
3 direction of a magnitude that's clinically meaningful.

4 DR. LASKEY: Well, I guess we've heard those
5 terms before, clinically meaningful. There's
6 statistical significance and clinical significance,
7 and I'd like to come back to that, particularly with
8 respect to the primary endpoint and I'm not sure it
9 even approaches discussion for the secondary
10 endpoints, which are physiologic endpoints and how one
11 translates those to clinical significance is a subject
12 of huge literature in your business, I know. We're not
13 going to settle that today.

14 But another perplexing feature of the
15 subgroup analysis is in the Kaplan-Meier plot, another
16 thing I don't understand. I still don't understand
17 this.

18 I really would like to see the sickest
19 patients derive the best benefit from this device, and
20 that data does not support that, trends or not.

21 If you go to the K-M plot, time to death by
22 study group, figure A2 and A3, that's overall death.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 In the sicker group, three/four, the log rank here is
2 not statistically significant. These two curves are
3 dead on.

4 But in the "healthier group," I see a
5 benefit here. This is discordant with your take home
6 message. Can you resolve this for me?

7 DR. BOEHMER: Remember, the therapy was
8 turned on in six months and this is a plot that goes
9 out to 24 months. There was no separation of the
10 curves and it just happened to be a quirk of the
11 advanced heard failure group that eight of the 21
12 deaths in both groups were defined as either non-
13 cardiac or unknown.

14 So there were deaths there that were not
15 necessarily cardiovascular. In fact, they were
16 adjudicated into those two categories by a blinded
17 independent events committee.

18 So we just did not have large numbers to be
19 able to separate those out. But if you look at
20 strictly pump failure deaths, you know, if you want to
21 look at the early trend in small numbers, that's four
22 versus six, or a 33 percent relative reduction.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. SWAIN: Warren, do you have any
2 questions and follow up to that? Otherwise, we'll just
3 kind of keep going around and get your other questions
4 afterwards.

5 DR. LASKEY: On the next go around? No.

6 DR. SWAIN: Okay. Dr. Pina?

7 DR. PINA: Thank you, I want to say, again,
8 that this is a very tough group of patients to take
9 care of and I think the fact that the mortality was
10 what it is was is a tribute to the centers that have
11 been taking care of these patients.

12 I want to back up into the entry criteria.
13 You had 28 percent of your patients had dilated
14 cardiomyopathy's, non-ischemic. I'll leave the
15 ischemics out of this momentarily.

16 What were considered the indications for ICD
17 therapy in that group. Had they all had sudden death?
18 Had they all had V-tach that was poorly tolerated?
19 Because I always have trouble with that group, as to
20 who needs and AICD and who doesn't.

21 DR. YONG: This is Patrick Yong.
22 Approximately, half the patients had monomorphic V-

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 tach. Approximately 30 percent of the patients fit the
2 criteria where they had non-sustained V-tach, but with
3 inducible MVT.

4 DR. PINA: Let me back you up. Is that
5 ischemic or non-ischemic?

6 DR. YONG: This would be ischemic.

7 DR. PINA: I'm asking about the non-ischemic,
8 which are the ones that I always have trouble with
9 knowing what to do. Leslie?

10 DR. SAXON: Hi. Leslie Saxon. Yes. So the
11 non-ischemic would have had to have sustained VT or VF
12 to get in. Because the screening -- the two groups of
13 patients in the study were non-ischemic and ischemics.
14 Ischemics had to have sustained VT or VF or screening
15 tests that identified them at high risk.

16 Non-ischemic had to have sustained VT or VF.
17 So they had traditional ICD indications.

18 DR. PINA: Okay. My next set of questions,
19 and I'll make this brief. I'd like to know how many
20 patients were really placed on beta blockers before
21 randomization?

22 Because I'm thinking that this change from

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Class III to Class II has got to have a beta blocker
2 background, and I'm trying to see where this therapy's
3 going to fit in my total armamentarium when we've got
4 beautiful Copernicus data out there of class 3 and 4,
5 sick advanced heart failure patients.

6 DR. BOEHMER: Certainly. Approximately half
7 of the patients were treated at the time of
8 randomization. However, many of those were instituted
9 on therapy around the time of enrollment. I don't
10 think we have exact data on patients who were
11 initiated prior to enrollment within a very short
12 period of time. But remember, that's only a one-month
13 titration and stabilization period.

14 And it was a necessary component of this
15 study because of the urgent need for AICD therapy and
16 then trying to get the exercise component in after
17 some period of stabilization. Clearly, ideally, you'd
18 like to put patients on beta blockers and allow at
19 least three months prior to randomization.

20 It adds noise to the study, but the control
21 group was evenly divided in terms of who received beta
22 blockers and who didn't. And all that could do is add

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 noise to the study. It wouldn't enhance one therapy
2 over the other.

3 DR. PINA: But you don't think that that may
4 have influenced the number of patients that went from
5 class 3 over to class 2, which was balanced in both
6 groups.

7 DR. BOEHMER: It may have, but it would have
8 been a short duration of treatment. And beta blocker
9 effects, as you know, are little time dependent. And
10 one month is a little short to see big improvement.

11 DR. PINA: Dr. Swain, my next set of
12 question has to do with the VO_2 's. I can either ask
13 them now or wait for the next one.

14 Dr. Higgenbotham, as you know, I am a big
15 believer in VO_2 's, but I'd like to see more than that.
16 Since there was so much variability when we saw the
17 line diagram, what was your mean RER and when the VO_2
18 changed did the ventilatory threshold go with it?

19 DR. HIGGENBOTHAM: Ileana, I haven't looked
20 at all of the data. I have looked at the RER data, at
21 the anaerobic threshold data and the anaerobic
22 threshold data were not significant in the study. The

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 mean RER during maximal exercise you mean?

2 DR. PINA: Yes, during maximal exercise.

3 DR. HIGGENBOTHAM: I would have to ask Pat
4 if he knows the data. I do not know. Sorry. We'd have
5 to get it for you.

6 DR. PINA: The comment, as you know, is that
7 if the peak VO_2 improves, and this is a true
8 improvement in functional capacity, it should be with
9 a VT going with it, with the ventilatory threshold
10 going with it.

11 I mean, I'm not surprised about the V_E/VCO_2 ,
12 but I'd like to see some concordance which would make
13 me really believe that --

14 DR. HIGGENBOTHAM: It would -- I mean, we
15 saw concordance with V_E/VCO_2 slope, which is a little
16 more objective, a little easier for multiple sites to
17 get together and produce reliable data.

18 There were multiple sites, not all of whom
19 were professional CPX testers in this study. It's one
20 of the problems where we get some noise creeping in
21 and we got some consistency with VO_2 , the trends seem
22 to be concordant with the changes in V_E/VCO_2 and they

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 were the primary things looked at.

2 I can attest to the maximal nature of the
3 tests attended to. I've read each of the studies, and
4 we actually excluded those tests that were obviously
5 submaximum.

6 There were some that were clearly either
7 indicated by the maximal Borg scale or by the maximal
8 symptoms, or by the ventilatory pattern that were
9 obviously excludable, and we excluded those.

10 Pat may know or we may have to find out what
11 proportion of those studies were not included.

12 DR. PINA: It would be interesting to know
13 how much --

14 DR. BOEHMER: There weren't a lot of them.
15 I really was -- I only assigned studies submaximal
16 when they were obviously so. So they would be
17 guaranteed less than ten percent of them.

18 DR. PINA: My other comment with VO_2 has to
19 do with the fact that in a population of a lot of 60
20 year olds, 14 is not terrible, as they're probably
21 over 50 percent predicted. Do you have the percent
22 predicted?

1 DR. BOEHMER: I don't think we do have the
2 percent predicted, but the mean baseline VO₂ in the
3 advanced heart failure group was 12.

4 I agree, they were not -- these were
5 ambulatory heart failure patients who stood to benefit
6 from an intervention to improve functional capacity
7 and everything that trickles down from it.

8 If you look at the Weber classes, the zero
9 to ten, ten to 15, 15 to 20 classification, about 80
10 percent of these people -- about 70 percent were in
11 Weber class C and 15 percent in B and whatever else a
12 hundred leaves in Weber class D.

13 So not a great number of people were
14 anything but Weber class C. They fit in really well
15 with the concept of a moderately impaired population
16 with heart failure.

17 DR. PINA: I think your six-minute walk kind
18 of shows that too, because it's less than that 300 --

19 DR. BOEHMER: Yes, it was consistent.

20 DR. PINA: Okay. I'll wait for my next
21 round.

22 DR. SWAIN: Dr. Haigney.

1 DR. HAIGNEY: I want to yet again echo the
2 comments that have been made before. It's an honor to
3 review this application. I think the investigators
4 have done a terrific job.

5 And I want to say that my major
6 qualification for being here is that I'm the only
7 electrophysiologist in the country, maybe the world,
8 that hasn't implanted one of these leads or devices.

9 And I have some questions about the leads
10 that directly result from my ignorance or innocence
11 with regard to using them.

12 There were some perforations. And these
13 would not be expected with a normal right ventricular
14 pacing lead.

15 And these were in the hands of -- well, one
16 would anticipate to be really elite
17 electrophysiologists, at the leading centers in some
18 of the most active private practice sites.

19 What was the training that Guidant gave to
20 these investigators, and what sort of training do you
21 envision, if this were approved for the less elite
22 electrophysiologists who, presumably, some day are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 going to be putting these in?

2 DR. YONG: This is Patrick Yong. When we
3 brought physicians in for training, we required that
4 at least one implanting physician be brought in from
5 every investigational center.

6 It was a day-long course, we bring
7 physicians in the morning, go through the mechanisms
8 of cardiac resynchronization therapy, talk about the
9 lead, its properties, how it was developed. Then we
10 spent the remainder of the afternoon in the animal lab
11 with hands-on training. We do plan to have a similar
12 program for market release situation.

13 DR. HAIGNEY: So this was in a canine model?

14 DR. YONG: Yes.

15 DR. HAIGNEY: And so then they went directly
16 from there to implanting in a human.

17 DR. YONG: Yes.

18 DR. HAIGNEY: And was there supervision
19 there by some other -- an electrophysiologist who is
20 experienced in the procedure?

21 DR. YONG: We started initially supervised
22 by other individuals who were experienced in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 implanting in an animal lab. We've since expanded it
2 to include field training as well.

3 MR. DeVRIES: We'd like to have Dr. Higgins
4 make a few comments related to this and then we may
5 make, if we could, a general presentation about
6 training, because we actually have market released
7 this in Europe and we've already implemented a
8 training program.

9 DR. HIGGINS: I'm Steven Higgins. I'm a
10 clinical cardiac electrophysiologist at Scripps
11 Hospital in San Diego. I'm a consultant to Guidant
12 without other financial interest. I won't describe
13 myself as an elite cardiologist or
14 electrophysiologist, but with the largest implanting
15 center.

16 It's hard when you're the first to do
17 something to be supervised by somebody else. So
18 learning to do this was likely more difficult for us than
19 it would be for you or others who were coming along at
20 this juncture.

21 The tools have also changed as well. We're
22 here, primarily, to review the lead and the generator,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 but a key part of implantation not only is the
2 technique, which has progressed over the implantation
3 experience, but also the guiding sheaths and tools.

4 In our particular experience, complication
5 rates were exceedingly low and non-existent for the
6 last 50 implants, as experience has progressed.

7 I entered this with similar trepidation,
8 recognizing that we were sticking catheters in a vein
9 that was not easily accessible, recognizing that veins
10 potentially had less resiliency than arteries, and
11 that this was uncharted territory, and was
12 pleasantly surprised to see that the number of
13 complications were exceedingly low.

14 I personally think that dissection is
15 probably more a function of looking for it with
16 contrast. When we stick other EP catheters in the
17 coronary sinus, we may very well have minor disruption
18 of the vein that we don't recognize because we don't
19 inject contrast with an inflatable, and to look for
20 that -- and although we focused on tamponade, you must
21 recognize that this study itself has absolutely no
22 cases of tamponade. And you also must remember that RV

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 leads alone are associated with a small incident of
2 tamponade.

3 So when you take three combined studies
4 resulting in a 0.1 percent incidence of tamponade, to
5 me that's a very acceptable risk and comparable to
6 what you likely would achieve even without this third
7 lead.

8 In terms of training of others as well, I'll
9 defer to the presentation here, but will point out
10 that as our experience progressed, utilizing improved
11 guiding catheters and other techniques, that will be
12 shared with the first-time implanter.

13 So I would expect implantation time, as well
14 as safety, to be better than what was achieved in the
15 study.

16 MR. MILLERHAGEN: My name is Jay
17 Millerhagen. I'm the director of heart failure therapy
18 development at Guidant and I'm an employee
19 stockholder.

20 In early 1999, we developed a physician
21 training program in preparation for the market
22 introduction of the Contak CD and EasyTrak implant

1 systems.

2 The physician training included cardiac
3 resynchronization therapy, Contak CD, EasyTrak and the
4 lead delivery system itself.

5 It has been used for over 600 implanters
6 from 300 medical centers across Europe. The experience
7 gained from this training program has been quite
8 positive and is summarized in the European registry of
9 the first 1,000 patients implanted with the Contak CD,
10 Contak TR and EasyTrak systems.

11 It's this program that's provided the basis
12 for the training that was employed for investigators
13 in the U.S. clinical trials and is planned for the
14 U.S. commercial availability.

15 Training will be provided for current ICD
16 implanting physicians. The content includes mechanisms
17 of heart failure, the concepts of cardiac
18 resynchronization therapy, patient selection and
19 indications, the design of the EasyTrak lead and lead
20 delivery system, the anatomy of the failing heart and
21 its impact on the coronary venous system, step-by-step
22 training on the EasyTrak implant procedure and left

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 ventricular lead placement, hands on use of the lead
2 delivery system and accessories and risks and
3 potential complications of implanting of coronary
4 venous left ventricular lead.

5 Physician training is required prior to the
6 implant of EasyTrak for the first time. We have
7 trained over 300 investigators from 170 medical
8 centers in the U.S. clinical trials, Contak CD and
9 companion. Guidant personnel will support implants of
10 Contak EasyTrak products only by physicians who have
11 been trained.

12 Training requirements may be satisfied by
13 attending a Guidant-sponsored physician program.
14 Several are planned across the United States. Or
15 participating in a one-on-one session with trained
16 Guidant personnel.

17 Depending on the physician's previous
18 invasive experience, they may be mentored by an
19 experienced EasyTrak implanter. Any questions?

20 MR. DeVRIES: We might also have Dr. Mester
21 make a few comments. Dr. Mester was involved in
22 developing a lot of the materials used to help

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 facilitate the training.

2 DR. MESTER: Thank you. Stephen Mester.
3 The data that we present here today indicates how much
4 of a learning process occurred. We have trained quite
5 a number of investigators since that time. The
6 training program has shown us worth statistically by
7 decreasing implant times from well over three hours to
8 approximately two hours.

9 Just to give you a frame of reference, two
10 hours, or 120 minutes, is approximately the implant
11 time that was seen with the initial single lead
12 endocardial defibrillators when they were all first
13 released.

14 As recently as 1997 the Emory University
15 experience was published with an average implant time
16 of 117 minutes. With this training program, we have
17 been able to provide comparable implantation to what
18 was found with initial ICD implantation.

19 DR. HAIGNEY: Okay. Well, I think I've got
20 some other questions for later. I'll just pass it
21 along.

22 DR. SWAIN: Okay. Dr. Krucoff.

1 DR. KRUCOFF: I'm an interventional
2 cardiologist. I'm going to ask just some simplistic
3 questions. Can somebody help me as to whether any of
4 the other data sets that have been pointed to, MUSTIC
5 or InSync involve patients who had a primary
6 indication for an AICD the way this study cohort did,
7 or are all of these heart failure?

8 MR. YONG: This is Patrick Yong. None of
9 those studies you mentioned look at a patient
10 population indicated for ICD.

11 DR. KRUCOFF: Okay. So clearly relevant
12 then to your cohort and I'm happy to echo what
13 everyone here has said.

14 I actually think this therapy probably
15 represents an important contribution to a very
16 vulnerable patient population and that this clinical
17 trial and the panel pack and its organization and the
18 data presented have certainly made my job easier,
19 which I greatly appreciate, including the FDA
20 contribution. I think we are ultimately down to the
21 data and the questions about safety and efficacy in
22 our focus.

1 Another simplistic question, a "lead
2 revision." Is that another procedure? Is that a
3 patient who has left the cath lab and who is brought
4 back for another procedure?

5 MR. YONG: This is Patrick Yong. Yes.

6 DR. KRUCOFF: Okay. Because to me there is
7 a very fundamental issue here about how we are talking
8 about EasyTrak Lead safety and whether it's comparable
9 to other coronary sinus procedures to me is a non-
10 question relative to the reality here that in these
11 patients who are clearly ill who have a primary
12 indication for AICD so the generator and the basic
13 lead sets associated with the defibrillator are
14 indicated.

15 Those are not a morbidity or even mortality
16 issue. The placement of the coronary sinus lead is
17 completely and uniquely related to the CRT
18 application. In my mind every single delay,
19 additional procedure, complication, revision,
20 reprocedure, is entirely incumbent on a balance as a
21 risk against the proposed benefit. That is a
22 simplistic way of looking at it but, to me, that is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 what's on the table here today.

2 The other issue that I'll just say out
3 right, to me is a very significant one, is if a third
4 of these patients are in a different heart failure
5 class from the time you implant the device to the time
6 that was randomized which was prospective study design
7 and I think a lot of descriptions as to how that might
8 occur, beta-blockers or added attention once they have
9 a device, follow up, etc.

10 To me the huge implication there is that as
11 we examine an indication for this device, you don't
12 have patients whose implants are 30 days old. You are
13 talking about making the decision when you first
14 implant the device.

15 To me the identification of the patient's
16 functional status by the American Heart Association
17 class at the time they were enrolled is a real dilemma
18 as to how you would propose indications.

19 From the way I look at your data, implanting
20 33 percent of these devices in the patients who need
21 defibrillators, but with the added coronary sinus
22 instrumentation time and risks, and a third of them

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 who won't need it 30 days later. I would love to know
2 if there are any additional comments on that.

3 I hear you but I'm just saying to me that's
4 a dilemma that this is such a profound difference and
5 it's an important decision you have to make up front.
6 You can't go back and slip this thing in or slip the
7 coronary sinus lead in 30 days later unless you're
8 going to tell me you can.

9 DR. BOEHMER: John Boehmer. In terms of the
10 types of patients you're looking at, they do come in
11 a couple of different varieties. Some of them have
12 had long-standing Class III for heart failures and the
13 odds of them suddenly getting better from the time of
14 implant to some time in the future without a
15 significant intervention is going to be low. There
16 are patients --

17 DR. KRUCOFF: Let me just ask you there
18 because unless I missed it either on the panel pack or
19 any of these presentations, I have not heard one
20 systematic way of understanding who those people are
21 at the beginning when you go to implant this device.
22 Am I wrong?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. BOEHMER: We did not provide data about
2 their class sometime prior to enrollment. That is
3 correct.

4 DR. KRUCOFF: Or any sort of predictive
5 approach that would identify which of these patients
6 are still Class III/IV 30 days after implantation?

7 DR. BOEHMER: The predictive approach would
8 be clinical. In other words, patients with long-
9 standing Class III/IV heart failure likely will
10 continue. Patients who have had an acute event or
11 present for the first time with heart failure or
12 recently with heart failure stand a reasonable chance
13 of improving.

14 We treat a lot of heart failure patients
15 and we develop an ability to get some idea of who you
16 can treat and who you can't. It's imperfect but we
17 would use clinical judgement.

18 I would also like to point out that in terms
19 of the amount of harm, if you look at all the
20 different events and all the functional capacities,
21 there is no evidence of harm in the group that is
22 Class II but, you know, the risk is with getting the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 lead and the additional procedures associated with
2 that.

3 But if you look at the magnitude of benefit
4 compared to that, if I'm sending a patient for a
5 defibrillator from a clinician standpoint and the
6 patient is very systematic and you are looking at do
7 I send them for two wires or three wires, from my
8 perspective, that's a small leap.

9 DR. KRUCOFF: Okay. Again, I'm -- sorry.

10 MR. DeVRIES: I was going to say maybe we
11 would have a couple of the other implanting physicians
12 come on that question.

13 DR. HIGGINS: This is Steven Higgins. Let
14 me address the first half of your question which I
15 think referred to dissection more. I think this
16 latter issue is something I can briefly address as
17 well.

18 DR. KRUCOFF: If you don't mind, I would
19 actually like to -- I'm not arguing about the data you
20 have presented on dissection. I'm just saying that
21 every single instance of provision or added instrument
22 time or whatever is something versus not putting the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 lead in. That is my only point.

2 My only other point is that the fact that
3 there are no guidelines evident to me or any analyses
4 that show that anyone is able to accurately identify
5 on the day of implantation which of the Class III and
6 IV heart failure patients are still going to be Class
7 III and IV 30 days later is part of my risk benefit
8 equation.

9 DR. HIGGINS: Sure.

10 DR. KRUCOFF: And that is a dilemma to me.

11 DR. HIGGINS: Obviously when the patients
12 were enrolled we did not know that we had to predict
13 who was still going to be in Class III 30 days from
14 now. Patients who had been stable heart failure
15 perhaps had a recent exacerbation.

16 As you well know, people whose heart failure
17 is out of control are more likely to have ventricular
18 arrhythmias may have presented with a cardiac arrest
19 and were enrolled in the study, today we would
20 recognize that those patients may not benefit from
21 this device as early as those who are sicker.

22 Patients who, as John mentioned, had a long-

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 standing history of heart failure present with an
2 indication for defibrillator may be more appropriate
3 in that setting.

4 DR. KRUCOFF: I hear you conceptually. I'm
5 just saying that ultimately we're going to have to
6 look at these.

7 DR. HIGGINS: In terms of the dislodgement,
8 when this lead was designed, obviously it was designed
9 with safety in mind with two tines extraction, steroid
10 elution over the wire concept so that there would not
11 be any issues until we were in uncharted territory.

12 Of the 29 dislodgements 25 of them were
13 repositioned. It is important to remember that 98
14 percent of the patients left the hospital with a
15 functioning biventricular cardiac resynchronization
16 system so I think the current system is very usable.

17 DR. KRUCOFF: I hear you. Extra procedure
18 and potentially a cohort patient who may or may not
19 either need it or benefitted from it. That's my only
20 point.

21 DR. MESTER: Stephen Mester. To try and
22 answer that, clearly there are going to be some

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 patients who would receive this therapy and not
2 receive a benefit from that additional lead. But the
3 data indicates that the majority of them will.

4 When we place defibrillators today, we know
5 that a sizable number of those patients will never
6 receive a counter shock. We cannot predict that with
7 certainty, but with physicians clinical judgement, we
8 can look at patients who we think are at high risk or
9 at high likelihood of benefit for this implantation.
10 I think that is a big component of it.

11 Clearly not every device -- when we stent
12 somebody, we don't always resolve their angina. In
13 this case I think with clinical judgement we can look
14 at patients who will have Class III/IV angina -- Class
15 IV CHF, excuse me, and have the potential for
16 improvement from the device.

17 DR. KRUCOFF: Point taken. Again, that is
18 presuming that there is a measurable benefit on the
19 efficacy side.

20 I wonder if maybe you guys could help me.
21 I could not find any data that actually associated
22 some of the functional measures like VO_2 and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 improvements and VO₂ with outcomes of survival or
2 reduced heart failure.

3 Mike or somebody, did anybody actually see
4 that the patients whose VO₂s got better live longer or
5 die less frequently? Is there any sort of analysis?

6 DR. BOEHMER: John Boehmer. We did not
7 divide the patients in terms of their net improvement
8 and then analyze them long term. The anticipated
9 result if you were to do such a thing is that patients
10 who get better do better than patients who don't get
11 better. I'm not quite sure that would be terribly
12 helpful to us.

13 DR. KRUCOFF: I think it would be very
14 helpful to you because the reality is we are sitting
15 here talking about a group of patients who are very
16 sick and very frail, and yet one of the things that
17 damaged this study most profoundly in its prospective
18 design.

19 You show a 23 percent reduction in your
20 primary endpoints and it's not statistically
21 significant because in your control arm, the outcomes
22 are not as bad as had been anticipated. There is a

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 dilemma here again that these are very sick patients
2 by description, and yet by outcomes they did a whole
3 lot better than your original trial was powered as a
4 basic assumption.

5 DR. BOEHMER: Right. I believe Dr. Larntz
6 had led you to believe that if anything there was
7 greater improvement in the sicker patients in terms of
8 reduction of primary endpoint.

9 DR. LARNTZ: This is Kinley Larntz. When we
10 divided, as I talked about dividing the subgroups, the
11 benefit was greater on the composite; that is, the
12 overall composite endpoint. Obviously the number of
13 events we are talking about is relatively small.

14 I mean, there are a small number of deaths.
15 That was pointed out that there aren't that many
16 deaths in this population. In fact, our endpoint is
17 a composite endpoint. It's weighted to give death
18 more weight and then give hospitalizations second most
19 weight and then VT/VF events least weight. It was
20 weighted to allow for death if there was an imbalance.
21 It turned out the number of events is small. There's
22 no question.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 DR. KRUCOFF: Again, that's my point. It
2 would help me a lot to understand that if the
3 functional measures, which in the advanced heart
4 failure group start to look most profound, if those
5 functional measures correlated to our -- unfortunately
6 very rare in the control arm they had clinical
7 outcomes, it would help me to have more confidence.

8 DR. HIGGINBOTHAM: Michael Higginbotham.
9 Mitch, I think the problem, of course, is how you deal
10 with functional data which you've actually got to
11 collect in live people and patients who don't survive.
12 It's a big problem how to deal with dropouts as a
13 practical problem. It's a statistical problem. Of
14 course, there can be no absolute consensus on it.

15 There has been sort of a ground swell of
16 argument around the heart failure people whether you
17 should just have one endpoint that deals with all
18 undesirable events and that deals with the patient who
19 dies almost certainly, or very often, let's say,
20 subsequent to deteriorating and can't participate in
21 the exercise test.

22 They get kind of the worst score. We are

1 trending toward counting all bad events in one big pot
2 as an endpoint that deals both with events and bad
3 functional capacity.

4 I might note here that there were four more
5 deaths in the not CRT group than in the CRT group. If
6 those people -- if you assigned maximal oxygen uptake
7 of, let's give them the benefit of the doubt and say,
8 3.5 ml per kilogram per minute rather than the zero
9 that they actually had at the time they couldn't
10 participate in their exercise test, it would have
11 magnified the functional benefit.

12 I just don't think it's possible to look at
13 the correlation with a test you have to do with
14 somebody that drops out half way through the protocol
15 stuff.

16 DR. SWAIN: Mitch, do you have a follow-up
17 on that?

18 DR. KRUCOFF: This is my last comment. I'll
19 just say not only do I think there are strategies to
20 approach this, there is a dilemma no question but the
21 strategies to approach, I mean, what I'm really trying
22 to do is to try and find a way to connect the data

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 that has emerged from your trial to the impression
2 that it really leaves that there is potential 23
3 percent reduction by any new therapy and a
4 prospectively defined primary clinical endpoint
5 usually we would log as a terrific advance. I'm not
6 sure that's not true here. It's just that the data
7 construct doesn't allow it.

8 The one thing that you do have accessible to
9 you is the ability to turn half of these things off.
10 That is actually what I'm probably going to suggest to
11 make sure that this post-talk subgroup characteristic
12 is true.

13 I would take the cohort that you already
14 have these things implanted in, put a prospective
15 question to it, and on a randomized basis turn half of
16 them off because I think turning everybody on at six
17 months has left you with -- has certainly left me from
18 this side of the panel with a real problem.

19 DR. SWAIN: Dr. Wittes.

20 DR. WITTES: I'm going to have three
21 questions this round. One will be a comment because
22 it's my job to mention something about the subgroups

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 obviously.

2 My own feeling about the subgroup post-hoc
3 subgroup analysis of this type is that while it is of
4 interest, it is hardly -- I can't find it as a -- the
5 fact that it's retrospective, the fact that it's
6 exploratory, even though it's a controlled
7 exploratory, it's not willy nilly exploratory, leaves
8 it to me, as Mike says, the hypothesis generating
9 mode.

10 Usually when I see data like this, if I'm
11 consulting I'll turn back to the company and say,
12 "You've got to do the study again." Do you believe
13 this subgroup enough to take the risk? That is
14 actually one of the questions that I have here. Let
15 me tell you why.

16 One is, of course, my reflective attitude
17 that when you take a group with a non-statistically
18 significant result overall and you split it in several
19 different ways, in half, because basically this is a
20 split in half, one of those halves is highly likely to
21 be a little bit significant and that's what you have
22 here.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 But I'm curious about the ejection
2 fractions. I'm looking at Table 2 on page 28 at the
3 NYHA III and IV at randomizations and at all patients.
4 I'm looking at the means, especially ejection
5 fraction, but everything else.

6 The only thing that seems different between
7 the all patients and the III/IV's is the proportion of
8 II's suggesting that these Class II's are very similar
9 to the Class III/IV's. The mean ejection fraction,
10 for example, is roughly 20 in the whole group and in
11 the III/IV's.

12 These are Class II heart failure patients
13 with a mean ejection fraction of about 20. The lowest
14 ejection fraction of all which was 5 was in a Class II
15 patient. Basically they have the same QRS duration,
16 the same heart rate. To me these are funny Class II's
17 and you need to tell me about that.

18 DR. BOEHMER: John Boehmer. Again, the
19 determination of ejection fraction was done at the
20 time of enrollment and the determination of functional
21 class was done at the time of randomization. There
22 are a number of factors that could go into that as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 well.

2 Again, there were multiple medications added
3 in the course of this clinical trial that was
4 necessary because of the population of interest in
5 this study that we could not withhold appropriate
6 medical therapy from them. We had to study them
7 within a reasonable period of time from implant. We
8 tried to do the best compromise we could.

9 I agree they are in flux from the time of
10 enrollment from randomization. There is some change
11 there, but I believe the functional measures and other
12 measures suggest that they are a healthier population
13 if you look at them from a number of other measures.

14 DR. SAXON: Leslie Saxon. I understand what
15 you're saying but it's simply hard to imagine how you
16 could do this better in an ICD indicated patient, a
17 patient who arrives at your door after having had a VT
18 or VR fluorescent whom you can't really say, "I need
19 to optimize beta-blocker therapy for three months," or
20 optimize ACE inhibitor therapy, for that matter,
21 because there really is a pressing need to proceed
22 with the procedure.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 I can't envision a way to accomplish optimal
2 medical therapy with the need to place the device to
3 reconcile those.

4 DR. WITTES: I guess my question is are
5 these really Class II's. I hear that we can't really
6 tell that because of the measurements being done at
7 two different times.

8 Let me get to the issue that Dr.
9 Higginbotham just brought up, and I think that the one
10 that has been really troubling me a lot. Let's make
11 the assumption that we can buy into the subgroup. I
12 don't think I can but let's make that assumption.
13 Then where we are faced is do we accept that the data
14 on the functional measures show a benefit for therapy.

15 First, I want to point out that in
16 pharmacologic studies that the point was made that the
17 functional measures don't improve and here they do.
18 I would like to point out in a lot of pharmacologic
19 studies the difference is that there is a strong --
20 you save lives and presumably the people whose lives
21 you're saving are those who are sicker.

22 It's hardly surprising that at the end of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the day you don't see better functional measures in
2 either the treated group because they are presumably
3 the ones that wouldn't otherwise have died.

4 But I'm looking at these measures and I see
5 in a six-minute walk a third of the patients seemed to
6 be missing their six-minute walk data and that is many
7 more than the number who have died.

8 Twenty percent seem to be missing the
9 quality of life measure at the end of six months. And
10 20 percent seem to be missing the New York Heart
11 Association. I couldn't figure out what proportion
12 was missing the VO₂ measurements.

13 I think my numbers are right. I think what
14 I've done, it's hard for me to figure them out, is to
15 take the subgroup of people who were in Phase II and
16 ask what proportion of those people were missing.

17 There are two questions. One is do I have
18 my number of missing right, two, if so, how did you
19 handle the analysis because that is a big chunk of
20 missing data independent of the deaths.

21 DR. HIGGINBOTHAM: Michael Higginbotham. To
22 my knowledge, and I'm sure if they didn't have a max

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 test they won't drop out so that the -- excuse me.
2 They were removed. The only data that you see are
3 those patients who had successful testing at baseline
4 at three months and six months. There were no people
5 who contributed to earlier data who then dropped out.
6 Oh, not true?

7 DR. LARNTZ: This is Kinley Larntz. The
8 functional status variables were analyzed using a
9 longitudinal model. Every patient who had data at any
10 time point was included in the analysis.

11 What was done was we -- I assumed a multi-
12 variate response and used the data from everybody to
13 predict what would be the mean of the population at
14 baseline if they had advanced.

15 Those measurements from baseline to three
16 months to six months for patients that existed during
17 all this time, they were part of the study for all
18 this time, those patients were -- their responses were
19 highly correlated. Okay? .6 and .8 That's the range
20 of correlation so highly correlated.

21 If patients were low at baseline and then
22 later had no measurements, they contributed to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 lowering the expectation for the group they were in.
2 Okay? In fact, missing data were included in the
3 analysis using a multi-variate model.

4 I guess I have to admit I used the VMBP5E
5 program for longitudinal analysis to include all
6 patients for whom we have data on to project what
7 would happen based on the full patient cohort.

8 Do you want to follow up?

9 DR. WITTES: Yeah, can I follow up?

10 DR. LARNTZ: Please.

11 DR. WITTES: This is very helpful but I'm
12 going to ask a question and then make a statement.
13 The first question is related to the difference
14 between the Phase I and Phase II. I assume the Phase
15 I's are in the study.

16 DR. LARNTZ: The Phase I's are certainly in
17 there. They contribute to baseline at three months.

18 DR. WITTES: Okay. It seems to me that the
19 question is in general for these analyses are the
20 Phase I and Phase II data stratified into different
21 strata? The reason I ask is that I would assume that
22 they must be different in some sense. There must have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 been a different informed consent.

2 One group was coming in for a three-month
3 study. One group was coming in for six-month study.
4 One group was coming for functional measures. The
5 other group was coming for mortality. Presumably the
6 very process of entering people must have lead to some
7 subtle differences. I wonder whether that was
8 reflected in the analysis.

9 DR. LARNTZ: I didn't do it prospective
10 stratification. What I did was check afterwards with
11 the covariant to see if there was a difference and see
12 how they were different and there was no indication of
13 difference for those Phase I and Phase II for any of
14 the functional measures. No difference in effect of
15 the treatment. I did that one post-hoc.

16 DR. WITTES: Okay.

17 DR. LARNTZ: But I did check it.

18 DR. WITTES: For those of you who don't
19 understand what we were talking about, let me
20 summarize it briefly so I think it will be clear.

21 Basically, as I understand it, the analysis
22 was done. Each patient came in and had at most three

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 measures, baseline, three months, and six months. All
2 those measures were used for the analysis.

3 Now, the problem -- and I think that is the
4 right thing to do. However, when we looking at these
5 secondary measures, obviously the same would happen
6 but also I'll give you my opinion.

7 When you are looking at these secondary
8 measures as really the reason for approval, you are
9 saying these are the variable that we care about, it's
10 really important to realize that much of the
11 information here is coming from the three-month data,
12 not the six-month data because half of the patients
13 never were eligible for six months.

14 Among those who could have had six-month
15 data, at my calculation, 20 to 30 percent of them were
16 missing. This is what we call in statistics, and
17 correct me if I'm wrong, a highly modeled appended
18 analysis where you assume a model, you fit the model
19 as best you can, but what it means to me is we don't
20 have nearly as much six-month data as the graphs and
21 the presentations would suggest. Is that fair?

22 DR. LARNTZ: Fair? Do I have to define

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 fair?

2 DR. WITTES: Is it reasonably accurate?

3 DR. LARNTZ: I mean, sure, we do the best we
4 can. What we do is we have these data and I have an
5 opinion, a strong opinion, too. I use all the data.
6 I don't want to just use the completed data or the
7 pair-wise data. I want to use all of the data. I did
8 build a model. I think the model reflects what is
9 going on to the best of my ability to make it reflect
10 so.

11 It is true the amount of six-month data.
12 Obviously all the patients in Phase I didn't have it.
13 In point of fact, we did as much model checking,
14 residual checking, and so on. We did all the standard
15 kinds of things to justify what we're doing and it's
16 the best model I think we can come up with. I feel
17 very comfortable with that model as reflecting what we
18 have.

19 Would I like to have data? Well, if they
20 hadn't changed the half we would have more data. Fair
21 enough? If the design hadn't changed.

22 DR. HIGGINS: Let me comment. This is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Steven Higgins. Let me comment from a clinician's
2 standpoint, too. Put yourself in the perspective for
3 a minute of being a patient who has had a life-
4 threatening arrhythmia who is scheduled for an
5 implantable defibrillator and you are offered the
6 opportunity of entering the study.

7 Phase I where you have three months
8 randomization between two different program arms. You
9 get the cardiac resynchronization therapy device and
10 then you get activated at six months, versus Phase II
11 where you get the same surgery exactly and there is a
12 50/50 chance of having it on for the first six months
13 and then you get it on after that.

14 It's a pretty subtle difference for people
15 to appreciate. Even in relatively intelligent
16 population that lives in La Jolla who were my patients
17 and 70 some were enrolled in the study, there wasn't
18 a single patient who expressed concern with the
19 differences between Phase II and Phase I that resulted
20 in a change in enrollment. I would think those groups
21 are identical from a practical standpoint from signing
22 the informed consent and then entering the study.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 DR. WITTES: Well, of my two points, the one
2 that was less important was the stratification by
3 Phase I, Phase II. I think it's a nicety. I am more
4 concerned with how much actual six-month data there
5 are. That is really what my concern is. And how much
6 of the modeling makes the assumption of a smoothness
7 of progression from month three to month six.

8 DR. HIGGINS: I mean, I didn't model it as
9 a smooth as -- I didn't model it as a regression.
10 Okay? I modeled them as having a separate three-month
11 effect and six-month effect. That will allow us for
12 a different slope between zero and three and three and
13 six.

14 DR. WITTES: Thanks. That helps.

15 DR. SWAIN: Thank you. Dr. Aziz.

16 DR. AZIZ: I think I will just echo some of
17 the other comments that the other panel members have
18 made. I enjoyed reading it and I think it's an
19 important advancement in heart failure management.

20 My question, I think, will come from a
21 surgical perspective. We surgeons have been
22 cannulating the coronary sinus for myocardial

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 protection for some time. Unfortunately, sometimes
2 you do perforate it and if you don't know how to
3 manage it, it can sometimes be a problem.

4 Was an autopsy done on the patient who did
5 die?

6 DR. BOEHMER: My patient? No, it was not.
7 He did undergo echocardiography at least three times
8 during the course of what was going on and there was
9 no accumulation of pericardial fluid.

10 DR. AZIZ: I'll come to that in a second.
11 What percentage of patients in the study groups had
12 previous cardiac surgery whether it be CABG or a
13 valve?

14 DR. BOEHMER: We'll have somebody look for
15 that but I don't have those data readily available for
16 CABG.

17 DR. AZIZ: Patients who have had -- first,
18 the coronary system obviously is the low pressure
19 system. When you look at it as a circular tube, half
20 of it is already stuck onto the AV groove and then the
21 entry wall if you perforate it, you know, depending on
22 the size of the perforation obviously would give you

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 tamponade. If you have it to the sides, it go into
2 the LV or RV depending on how far out you are.

3 A few cases when one is taken to the OR in
4 the early days of RF ablation there are some that had
5 rather big holes. I was interested in seeing that you
6 had mentioned some had a dissection where you saw
7 staining but you didn't really see blood in the
8 pericardium.

9 In the OR sometimes when you get a
10 perforation in the coronary sinus, depending on the
11 type of catheter that you use, you might get hematoma
12 but nothing further happens. You may get a hematoma
13 that at the end of the case ruptures and, you know,
14 you get into problems.

15 But if a patient had previous cardiac
16 surgery, obviously you have adhesions and it is less
17 likely that you would end up with those patients
18 giving you a problem.

19 Were you able to find the data?

20 DR. BOEHMER: Yes, we were. Out of the
21 total there were 39 percent that had prior coronary
22 bypass surgery.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. AZIZ: Would you put this catheter in
2 somebody who had a tricuspid valve replacement or
3 would that be contraindication?

4 DR. BOEHMER: I'll defer to my physiologist.

5 DR. SAXON: Leslie Saxon. In general for
6 mechanical in those rare instances where there is not
7 a repair but a mechanical valve, our concern is
8 generally in advancing an RV lead across the valve.
9 We generally don't put RV leads. In fact,
10 interestingly enough, that's how coronary sinus leads
11 were first developed for LV pacing so I think we would
12 have more concern about the RV lead than the CS lead.

13 DR. AZIZ: Going back to the coronary sinus,
14 I think people's impressions vary. People who are on
15 steroids, I think, those sort of patients, adrenal
16 failure in my experience. Those coronary sinuses
17 rupture quite easily. Again, that may be a group you
18 may want to be leery of.

19 DR. SAXON: Leslie Saxon. Other cases of
20 tamponade you can perforate or dissect the coronary
21 sinus from either something as small as a guide wire
22 to the lead to something as serious as the guide which

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 is obviously a bigger hole.

2 In the other cases of tamponade, those were
3 successfully drained much like any kind of catheter
4 perforation. They didn't appear to continue to bleed.

5 DR. AZIZ: So the hole must have been quite
6 small.

7 DR. SAXON: It must have closed off.

8 DR. AZIZ: A number of patients in advanced
9 heart failure usually on Coumadin or anti-coagulation
10 are presumed before these devices were placed, the
11 anti-coagulation was stopped. When do you recommend
12 restarting the anti-coagulation in these patients?

13 DR. SAXON: Leslie Saxon. That's been
14 discretionary from center to center. In patients with
15 mechanical valves, we will generally start Innoxaperin
16 or something prior to Coumadin but, again, we have to
17 balance that against device site hematomas, etc.

18 DR. AZIZ: That's fine. Go ahead.

19 DR. SWAIN: At the risk of sounding like
20 George Bush, there are these big orange signs about no
21 cell phones. After the fifth one has gone off, maybe
22 everyone could kind of reach down and either put it on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 vibrate or turn it off, please.

2 Dr. Kaptchuk.

3 DR. KAPTCHUK: Most of my questions and
4 concerns have been raised already. I just had one
5 more question concerning the time between the implant
6 and the randomization.

7 As I understood it, the reason that you had
8 what I assume is like a kind of run-in is to reduce
9 the amount of noise and have stability of the patient.
10 Drugs would be tailored appropriately. By doing that
11 you have increased internal validity of the trial.

12 The question when you have a run-in like
13 that is always you have to balance the internal
14 validity with the external validity and the fact that
15 you won't be able to have this kind of one-month
16 period with real patients.

17 The way the question was asked was how would
18 you know who would need it given that you have this
19 large downward drift in terms of the class of the
20 severity. What was mentioned specifically was that
21 you would make that judgement based on clinical
22 severity of a previous duration.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 I wanted to know what percentage of the
2 patients in this trial were you able -- have you
3 looked at that question on the original data of the
4 trial.

5 What percentage of those people would have
6 had that longer duration? Was that something that was
7 looked at? And to what extent that change in
8 severity, how would you make that judgement in terms
9 of the external validity of the trial and if you were
10 able to with this patient population?

11 DR. BOEHMER: John Boehmer. That was not
12 prospective so I can't state that clearly. There are
13 going to be those that you are incorrect.
14 Predominately the change was from Class III to Class
15 II over that period of time.

16 I think a large number of those you can
17 estimate clinically because you begin treating the
18 heart failure. They diuresed readily. They have
19 adequate blood pressure. They look well-profused.
20 All the things we tend to do clinically to get some
21 ideas as to whether or not we can tread them.

22 In addition, you have their whole history in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 front of you instead of the data collected in the
2 context of a clinical trial and you can put that into
3 context and make an estimation as to whether you are
4 dealing with advanced heart failure or mild to
5 moderate heart failure. Will it be perfect? No, it
6 won't, but I think you can do a good job clinically in
7 doing that.

8 Additionally, I want to emphasize that in
9 those patients that get implanted, in terms of their
10 clinical outcomes there was no evidence of any
11 deterioration in their regard. I think I can do this
12 comfortably with patients presenting to me who are
13 going for this.

14 As a matter of fact, from my perspective as
15 a heart failure cardiologist, the statistics aside,
16 the magnitude of benefit that I'm seeing and the
17 relative human cost of putting in the third wire is
18 very small. I would clearly have a great deal of
19 interest in using this in advanced heart failure
20 patients.

21 DR. SAXON: Leslie Saxon. I think as an
22 electrophysiologist we make this decision everyday.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 We have a lot of very good -- we know the drugs have
2 advanced and are better. I think the chances of us,
3 if anything, we will probably err on the side of, my
4 guess would be, a patient who would regress to a Class
5 II.

6 I would just simply counter that by saying
7 even if we make that error, this is a progressive
8 disease and one would -- the error to me doesn't seem
9 too egregious in the percent of patients it would
10 occur in.

11 DR. KAPTCHUK: That's all for me.

12 DR. SWAIN: Okay. Mr. Morton, the industry
13 representative.

14 MR. MORTON: Just a quick comment. I would
15 also like to thank the FDA for a very thorough and
16 well-presented review and ask for a point of
17 clarification.

18 Some of the panel discussion has talked
19 about both safety and efficacy endpoints but, as I
20 understand, the agency did conclude that the safety
21 endpoints were madison. Is that a safe assumption?

22 DR. BAROLD: We concluded that they met the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 predefined end criteria for endpoints. The sponsor
2 had defined they met those criteria.

3 MR. MORTON: Okay. All right. That answers
4 my question.

5 DR. SWAIN: Okay. Mr. Dacey, the consumer
6 representative.

7 MR. DACEY: I have no questions at this
8 point. I may have an observation or two a little bit
9 later.

10 DR. SWAIN: Okay. Thank you. I have a
11 couple of questions before we go back to Dr. Domanski.

12 I think that really the study illustrates
13 the importance of study design. As a scuba driver the
14 golden rule is plan your dive and dive your plan. I
15 think our statisticians have kind of illustrated the
16 importance of that.

17 A couple questions. One is, as cardiac
18 surgeons, Dr. Aziz and I have a great deal of respect
19 for the coronary scientists and this is really not a
20 case of no harm no fowl due to the deaths that were
21 directly attributed or possibly attributed. I think
22 we have to kind of keep that in mind.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 You made a good point that the Phase I was
2 blinded both for patients and treating heart failure
3 physicians. What about the Phase II or the non-Phase
4 I ones?

5 DR. BOEHMER: John Boehmer. That was
6 blinded as well.

7 DR. SWAIN: Okay. So everything is blinded.
8 Excellent. The operative mortality was listed as 30
9 days. This is a comment really for the FDA also, that
10 we can keep almost anybody alive 30 days. Some of the
11 databases is an incentive to do that, let's say.

12 I really think it should be in-hospital
13 mortality or in-facility mortality. If they came from
14 home and they don't go home, that's a mortality. Were
15 there other deaths here that were in-hospital or in-
16 facility?

17 MR. YONG: These were deaths of all causes
18 in 30 days. Are you looking for --

19 DR. SWAIN: Yes, after 30 days, people that
20 had horrendous complication, let's say, and died at 31
21 days or 91 days. We can keep almost anybody alive 30
22 days.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 DR. HIGGINS: This is Steven Higgins. The
2 events committee defined mortality as death within 30
3 days or never leaving the hospital. You could be in
4 the hospital for 120 days and the 120th day that it
5 was related to that operation on day one you would
6 still be included in the first 30 days.

7 DR. SWAIN: Excellent because two or three
8 times that's not stated in the panel package and I
9 really think the FDA should make that a requirement.
10 That's excellent.

11 You say there are 48 centers but in
12 practicality, if you can, people that have done over
13 15 implants, this is a three-year study, five a year,
14 there's really only six studies and that may reflect
15 the 81 percent of the patients that have protocol
16 breaks.

17 I think that is also FDA wise a problem in
18 a number of institutions to say there are 48 and
19 somebody did one or two implants or less than 15 is a
20 problem. You have six highly experienced centers.
21 Did you stratify complications according to learning
22 curve? I think you said the last 50 were excellent.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Is that a significant difference in complications?

2 MR. YONG: This is Patrick Yong. We did not
3 do analysis like that.

4 DR. SWAIN: Okay.

5 Dr. Domanski.

6 DR. DOMANSKI: I really don't have anymore
7 questions.

8 DR. SWAIN: Dr. Laskey.

9 DR. LASKEY: Just two quickie comments to
10 the last question. The statement is made repeatedly
11 that the magnitude of benefit is greater in the III/IV
12 group than overall.

13 I'm looking at 25 percent in the III/IV
14 group for the composite endpoint versus 19 percent for
15 an endpoint which is not a continuous variable but a
16 bunch of stuff, some of which is soft and fuzzy and
17 some of it obviously includes death. This is a non-
18 parametric endpoint, if you will. Is a six-point
19 difference really that dramatic?

20 DR. BOEHMER: John Boehmer. In terms of the
21 events, I don't think there is a dramatic difference
22 between the two groups. If anything, a little more

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 benefit in the advanced heart failure groups. Neither
2 one reached statistical significance but clearly a
3 strong trend and clearly a clinically meaningful
4 magnitude of relative risk reduction.

5 It's more in terms of the functional data
6 and advanced heart failure patients if you gave them
7 a choice between feeling better or living longer, most
8 would choose feeling better. Those are very important
9 data. They are very distinct from the composite
10 endpoint. In treating patients on a day-to-day basis,
11 those are the areas that we really focus on.

12 DR. LASKEY: Okay. But the hospitalization
13 data doesn't support that either.

14 DR. BOEHMER: John Boehmer. The
15 hospitalization data, if you're looking at the total
16 hospitalization there isn't a trend in terms of
17 benefit but at the time to first event there were more
18 patients that did not require a hospitalization in the
19 treated group in both the advanced heart failure in
20 the total group.

21 The time to first hospitalization was longer
22 in the treated group. The time-to-first-event

1 analysis, which is typically what we do in event
2 counting trials, was improved by the CRT in a trend
3 again, but if you count all events they were highly
4 influenced by a handful of patients who had multiple
5 hospitalizations.

6 DR. HIGGINS: This is Steven Higgins.
7 Another way to look at that, one of the numbers that
8 jumps out more than any other to me is New York Heart
9 Class. John made an excellent point about these
10 patients dramatically wanting to feel better.

11 The advanced heart failure group none of
12 them were in Class I or II by definition at
13 randomization, yet by six months 72 percent of them
14 were in Class I and II.

15 These patients feel better and many of them
16 are extremely appreciative of the contribution this
17 therapy has given to them. I think that number speaks
18 for itself.

19 DR. LASKEY: Well, but 20 percent of that
20 you see in the placebo group as well.

21 Two quick points. On your percentages, the
22 comparison of the percentages, these are events or

1 patients? I ask this all the time and it's never
2 clear when you talk about the composite endpoint 25 or
3 19 or 29. Is this unit of analysis per patient or per
4 event?

5 DR. SWAIN: We'll appreciate succinct
6 answers.

7 DR. BOEHMER: Exactly. This is a risk
8 reduction per patient. It's risk reduction. It's
9 proportional hazards composite risk reduction on a per
10 patient basis.

11 DR. LASKEY: Okay. Two quickies. And the
12 definition of NYHA III/IV was made at the time of
13 implantation or enrollment? Where are we starting to
14 count from?

15 DR. BOEHMER: John Boehmer. It was made at
16 the time of randomization right before they went into
17 the exercise portion of the study.

18 DR. LASKEY: And did you look at it if you
19 did it from the time of enrollment? Did anything
20 change?

21 DR. BOEHMER: Did we look at New York Heart?

22 DR. LASKEY: Because something is going on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 with NYHA three to two.

2 DR. BOEHMER: Right.

3 DR. LASKEY: The patients are different at
4 different times so --

5 DR. BOEHMER: It was assessed as an entry
6 criteria at the time of enrollment and it was assessed
7 as a measure of what their functional status was at
8 the time of randomization.

9 DR. LASKEY: Although you did look at them
10 another time and --

11 DR. BOEHMER: Three months and six months as
12 well.

13 DR. LASKEY: Okay. And finally, just a
14 point for all of us to consider. Is six-month follow-
15 up for heart failure trial sufficient to look at these
16 particular endpoints given the variability in this
17 disease as well versus one year, for example?

18 I mean, if you look at the heart failure
19 literature, it's replete with one and greater years of
20 follow-up but six months unless you're geared towards,
21 which I suspect is the case here, the physiologic
22 endpoints, the exercise uptake, and so forth. It may

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 bias the results that way.

2 DR. BOEHMER: John Boehmer again. Again, as
3 originally designed as an exercise trial, this was
4 looking at six months and three to six months are very
5 common intervals to look at exercise capacity as well
6 as symptoms.

7 You get into trouble if you go longer with
8 more dropouts and other confounding variables that
9 occur in the trial. If you go too short, you may not
10 see the full evolution of the treatment effect. Three
11 to six months is a very common time interval for
12 exercise studies.

13 In terms of morbidity and mortality, which
14 is what you were discussing, clearly longer follow-up
15 would be advisable. That is underway. In the context
16 of functional improvement, this is a fairly good time
17 frame.

18 DR. SWAIN: Dr. Pina.

19 MS. PINA: Coming back to the mortality
20 issue, I think we must remind ourselves in the drugs
21 studies functional capacity hasn't always correlated
22 with survival. Based on that, and I know if you have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Dr. Foster here you must have some echo parameters, do
2 you have any supporting evidence of improvements in
3 left ventricular diastolic diameter, etc., or systolic
4 diameter?

5 DR. FOSTER: Thank you. Dr. Elyse Foster.
6 I have served as investigator directing the core
7 echocardiographic laboratory for the study. I have no
8 other financial interest.

9 I need to begin by saying that the
10 echocardiographic results are preliminary and the data
11 is still being analyzed. But, in answer to your
12 question, Ileana, we do have some key measurements in
13 approximately half of the patients.

14 We perform both two dimensional and MO
15 analysis. We were able to show by two dimensional
16 analysis that there was approximately a five
17 percentage point increase in ejection fraction in the
18 treatment group, about a three percent increase in the
19 control group at six months such that the difference
20 from baseline was statistically significant but no
21 between group difference.

22 Systolic volumes decreased also by about

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 nine percent. The decrease was seen early in the
2 treatment group at three months but then there was a
3 catch up by six months in the untreated group.

4 Measurements were very similar for dimensions as well.

5 The magnitude of change was similar for the
6 advanced heart failure group as it was for the total
7 group so they were analyzed separately.

8 The one parameter that I would say increased
9 only in the treatment group and only in advanced heart
10 failure group in terms of comparison to no treatment
11 was mitral deceleration time which increased by six
12 months significantly.

13 As you know, that is a parameter that
14 reflects left ventricular filling pressures and has
15 actually strongly been associated with prognosis in
16 advanced heart failure. This was improved only in the
17 treatment group at six months in the advanced heart
18 failure group, not in the untreated group.

19 I think that we encouragingly in this group
20 at six months we're not seeing progressive remodeling
21 of the left ventricle. In both the treated and
22 untreated groups there is an overall improvement both

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 in function as measured by echocardiography and
2 dimensions.

3 MS. PINA: Thank you. I think as you go on
4 and do your analysis, I would love to see it broken
5 down into those who are on beta-blockers and those who
6 are not.

7 DR. FOSTER: Right. We began to do some of
8 that analysis but I think at this point given the
9 preliminary data, we probably should not comment on
10 that analysis separately but we will look at that.

11 MS. PINA: I think in light of trying to
12 place this within our armamentarium, I just have one
13 more question for clarification. On figure 7 in the
14 sponsor handout, page 30, there are two models of
15 pulse generators listed here, Model 1822 and Model
16 1823. I'm assuming that the 58 patients initially,
17 were those the open procedures?

18 Okay. And then we go down to initial device
19 and we see 33 of those inactive and 22 deaths. Is
20 that death of the patient or death of the device?

21 MR. YONG: This is Patrick Yong. That's
22 death of the patient.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 MS. PINA: Doesn't that seem a bit high? I
2 realize that these patients were probably not put into
3 the randomization group.

4 MR. YONG: Well, these represent the very
5 first patients implanted. We started off doing
6 thoracotomy so these represent the very first 58 that
7 we had implanted.

8 MS. PINA: I would love to hear from our
9 surgeons if they think that is high. I think that's
10 high.

11 DR. SWAIN: That's a 40 percent mortality?

12 DR. BOEHMER: John Boehmer. That is total
13 mortality from time of implant to the time that this
14 was submitted. That's about three years of follow-up
15 roughly. For a heart failure population three-year
16 follow-up less than half mortality over three years
17 isn't too far off.

18 DR. SWAIN: You'd probably want to ask what
19 the in-hospital or 30-day mortality was.

20 MS. PINA: It's high if they aren't Class
21 III or IV.

22 MR. YONG: There were two deaths total in-

1 hospital after the thoracotomy.

2 MS. PINA: Then on the other side we have
3 for the initial device active 357 inactive 92 and 68
4 deaths. That's over how long a period?

5 DR. BOEHMER: The total follow-up varies
6 depending on time of enrollment.

7 MR. YONG: This is Patrick Yong. For
8 patients of the Model 1823 the mean follow-up time was
9 about 13 months. Maximum follow-up in that patient
10 group out to about 27 months.

11 MS. PINA: And these patients are, in fact,
12 randomized?

13 MR. YONG: Yes.

14 MS. PINA: I've heard the safety issue from
15 the part of the FDA but this graph kind of concerns me
16 a little bit. I have no other questions.

17 DR. SWAIN: Dr. Haigney.

18 DR. HAIGNEY: Quick question. What can you
19 tell me, and maybe it's in the application. If it is,
20 I apologize. Did you look at the QRS duration? Did
21 patients with greater QRS duration show a greater
22 improvement in any of the functional variables or echo

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701