

1 option in those who are randomized away from it, for
2 example.

3 DR. YOUNG: Well, those are extremely
4 important points and I think queasy about control is
5 what we're talking about here a little bit. And I
6 share your queasiness in many senses. All of the
7 warts of a database inquiry such as this are present
8 and the statisticians have done a great job of
9 pointing those out, and I certainly agree with many
10 of their points. This is, however, I think as I
11 indicated in my talk, an unusual and unique
12 database. It's a very large database containing
13 patients with a variety and spectrum of difficulties
14 prior to transplantation who were extraordinarily
15 ill, first of all.

16 And if you look at the unfortunately
17 small control group that is present, it is just
18 that: It's a control group. It's not a randomized
19 control group. It's not necessarily a concurrent
20 control group and it suffers from all of those
21 limitations. However, despite the improvements in
22 therapies that have occurred over the decade and the

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1 time period, this represents a group of patients
2 that I submit really don't have many more choices.
3 If you look at the trial entry criteria, having to
4 be on two inotropes or balloon plus an inotrope, the
5 proportion of patients that have had a cardiac
6 arrest being so high prior to that; there was
7 reasonable proportionality between the control group
8 and the LVAS treatment group. And I think the death
9 as early as it did, bespeaks the severity of illness
10 that these patients have.

11 Now, I'm not one to abandon clinical
12 trials easily. I look at myself as a clinical
13 trialist. But I am one to support the concept of
14 equipoise driving a randomized clinical trial. And
15 I don't have equipoise in this type of patients.

16 I want to do something, and I feel that
17 mandates. And so that is why I believe it's not
18 ethical to do a randomized prospective trial in this
19 type of patient population, and I believe we have
20 enough support to say that an expanded indication,
21 which is a hugely expanded indication to destination
22 therapy for sure and isn't intended to be a back

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1 door, I think is appropriate.

2 DR. BAILEY: Well, what is the average
3 number of contraindications in the patients you're
4 trying to extrapolate to?

5 DR. YOUNG: The average number? Well,
6 we had as I indicated, 18 that had two or more or
7 three that had more than that. So the average
8 number would be a little bit over one.

9 DR. BAILEY: In the current data. But
10 what I'm wondering is it equivalent in the people
11 that you're trying to label it for?

12 DR. YOUNG: I actually think there's
13 more contraindications that we're dealing with today
14 from my clinical perspective --

15 DR. BAILEY: More in the current dataset
16 or more in the patients you're trying to get the
17 label for?

18 DR. YOUNG: Yes. More than in the
19 current dataset is my impression.

20 DR. BAILEY: Well, see, that's the
21 problem. I mean, these patients are the fringe;
22 that was my argument. You're trying to extrapolate

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1 the people that have much worse problems.

2 DR. YOUNG: Well, I'm not sure I would
3 characterize it as being much worse problems, but
4 I'm seeing more combinations of renal insufficiency
5 and pulmonary hypertension, for example, that was
6 in this dataset. And I don't agree that that
7 diminishes the impact that ventricular assist device
8 therapy can have in this group. I actually think
9 that dropping pulmonary artery pressures and
10 increasing renal perfusion work together in many
11 senses to improve the patient.

12 So I'm comfortable with the concept that
13 this will in certain patients turn around
14 difficulties that make them a queasy candidate, if
15 you will. We talk about queasy controls, we can
16 talk about queasy candidates for transplantation.

17 DR. BAILEY: Just a small point here. I
18 guess in terms of adjusting, it's always very
19 difficult to find the right -- well, there probably
20 isn't any right adjustment model. But I guess I
21 would argue for including all of the covariates
22 rather than trimming them down just because you're

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1 trying to remove bias rather than variance. So in
2 other words, I'd rather see some of those variables
3 in there such as -- I guess prior cardiac arrest may
4 have been in the model, but prior stroke or TIA,
5 valve surgery, etcetera. These were things that
6 were not nominally significant as predictors or as
7 differences between the groups, but put it together
8 and I think there's bias there that's not in your
9 adjustment model.

10 BMI should be looked at not as a linear
11 covariate, and I didn't see anything to the affect
12 that you tried it as the two -- looking at it as a
13 U shaped curve. In other words, cachexy as one end
14 of it and then obesity as the other end. I just saw
15 it in there as a linear term.

16 Okay.

17 CHAIRPERSON LASKEY: Dr. Tracy?

18 DR. TRACY: Just a couple of points.

19 This whole thing strikes me as more about clinical
20 practice than a regulatory issue. Maybe I'm being
21 naive here, but it seems to me that although I don't
22 have the full package labeling here, there is

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1 nothing here that tells me that you cannot put in
2 this device in a patient who has a creatinine of
3 2.7. You cannot put this device in a patient has a
4 bilirubin of whatever. I don't see anything that
5 precludes the use of the device in these patients at
6 this time.

7 And, admittedly, different centers that
8 were involved in the baseline study, some patients
9 would have been considered noncandidates at one
10 center but were candidates at another, so that's the
11 variability in clinical practice that existed even
12 within the study.

13 So I'm kind of lost trying to figure out
14 why are you trying to regulate my clinical practice?
15 Not that I do transplants, but my point is, isn't
16 this about clinical practice and doing what's right
17 for the patient?

18 MR. BRYDEN: Well, it is exactly that.
19 And our intention, and if we can capture it
20 properly, I think what would be achieved by the
21 proposal is to facilitate that clinical practice not
22 to limit it.

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1 The discussion just before lunch is
2 somewhat related to your point, that is is it
3 contraindicated. It is our understanding, and it
4 seems to be shared by the commissions we've been
5 working with, that the first decision is whether in
6 this particular case whether the potential recipient
7 of the device is a transplant candidate. It is
8 approved for use by transplant candidates. It's not
9 approved for use by any person suffering from the
10 reverse left ventricular failure at risk of imminent
11 death, they have to also be a transplant candidate.
12 And the interpretation of what is meant by a
13 transplant candidate I think has been quite clear,
14 and that is that they are listed for transplant.
15 That's how you determine are they transplant
16 candidate or not.

17 So it is not a medical condition, it is
18 a listing on a list. And our point is the whole
19 basis of this analysis is that the listing on the
20 list is variable and is intentionally left variable
21 from center-to-center. And we're not making any
22 comment about the wisdom of that, I think it's

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1 probably a fine thing, it just is a fact that from
2 center-to-center who gets listed is not always the
3 same. And that the standards to which the centers
4 are held is, first, that they must establish
5 criteria which must not be patently unreasonable.
6 And as long as they're not unreasonable, within
7 quite broad limits, then they must consistently
8 apply their own standards to make the recipient a
9 candidate by putting them on the list.

10 What we're saying is that it is the need
11 to make that judgment in a situation where those
12 clinics also and the publications which were
13 referred to by Dr. Young and also referred to, I
14 believe, in some of the FDA staff's papers, make it
15 quite clear that the generally accepted practice is
16 that to be a candidate, the patient should be one in
17 whom the clinic would implant a donor heart if it
18 were available at that time. Not someone who if
19 certain things happen, which may or may not happen
20 at sometime in the future, they would be candidates
21 or appropriate recipients.

22 In order to allow those clinics to now

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1 deal with patients who present themselves with
2 contraindications, which the clinic decides they
3 expect will be recovered, recognizing they can never
4 be sure, but if the clinic decides they may be
5 recovered today they must put them on a list and
6 then give them a device in order to be within the
7 label. It's not so much contraindicated for this,
8 that or the other reason; they're either a candidate
9 or they're not.

10 And by requiring that they be put on the
11 list, it requires a judgment to be made which is
12 contrary to the other judgment that that same center
13 would normally make, and that is I put them on the
14 list if I had a donor heart I'd give it to them
15 today, but not so for a significant share of these
16 patients.

17 All we're saying is that process has the
18 effect of putting sand in the process, of making it
19 more difficult, a different decision for a clinician
20 than simply deciding I think that if I gave this
21 person a VAD, they would probably recover to be a
22 candidate and therefore I'm going to give them a VAD

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1 as a bridge to transplant. They can't do that.
2 They can put them on the list, which they otherwise
3 wouldn't have done in order to give them a VAD.
4 Some do, but many do not. And it is that
5 discrepancy that we're trying to address.

6 The other factor that I hope might be a
7 satisfactory monitor on protection against opening a
8 wide door is, first, it is the judgment of the
9 clinic that this person, this patient, is likely to
10 become candidate, is expected to become a candidate.
11 It's not that they have a contraindications. It's
12 that they're expected to become a candidate. They
13 have to make that judgment.

14 If were to implement appropriate post-
15 PMA monitoring, one could easily determine over a
16 fairly short period of months and years whether the
17 share of those patients who moved on to transplant
18 was significantly different than the share of
19 patients who were listed before having had that,
20 which would suggest that there's, perhaps, something
21 wrong with the judgment or it's being used too
22 broadly. But I do not believe that what we are

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1 suggesting is interfering with medical practice,
2 rather it's allowing the medical practice not to
3 have to be done in the face of violating what is
4 quite clearly their own standards or the regulatory
5 requirement.

6 DR. TRACY: I appreciate that point.
7 But I'm wondering what the practical impact would
8 be? How often, for example, is a patient listed and
9 transplanted the same day? And alternatively, what
10 percentage of patients who are on a list at some
11 point are deactivated because of something that
12 happens, some reversible thing that happens?

13 MR. BRYDEN: Perhaps Dr. Young or Dr.
14 Edwards will speak to that.

15 DR. EDWARDS: Well, as a practical
16 matter, the waiting time varies from region to
17 region. There's some regions where patients if
18 they're listed status 1-A may get transplanted
19 within days or some regions where that could be
20 months.

21 Your other question was?

22 DR. TRACY: How often are patients

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1 temporarily deactivated from the list? If a heart
2 came along today and I happened to have a fever this
3 day, you would turn that heart down, obviously, and
4 give it to the next person. So I'm off my priority.

5 DR. EDWARDS: I don't know that that
6 data exists, because I think that often times
7 centers aren't always deactivating patients, but
8 they may pass on the offer for a variety of reasons
9 whether the patient has a fever, or it's a size
10 mismatch, or the donor hospital is so far away that
11 the ischemic time will be long; I don't think that
12 particular piece of data can be obtained very easy.

13 DR. TRACY: I don't think there's
14 anything else that I need to ask.

15 CHAIRPERSON LASKEY: Dr. Ferguson?

16 DR. FERGUSON: Well, first, I want to
17 thank the sponsors for a very lucid explanation of
18 the problems we have here.

19 I'm appalled a little bit at the dilemma
20 that we're in, "we," meaning medicine is in as
21 you've described it because we've had transplant
22 around for many, many years. It's a very

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1 sophisticated technical procedure done by a variety
2 of very experienced people. And I've watched the
3 UNOS and the way in which the transplant community
4 has worked together, and I think there's probably
5 give or take a few fall of the wagon, but there's
6 never a group of people that have worked more
7 closely together to work on the problem of donor
8 procurement. I mean recipient procurement.

9 Some of my question really sort of goes
10 with what Cynthia just has said because if I've
11 heard what I think is the truth, or what actually
12 goes on today, a patient who is fairly sick but for
13 one reason or another has a condition that will not
14 permit the group, the honest group, to put him down
15 for a transplant listing and then at the same time
16 he is not permitted to have at least a bridge to
17 transplant device put in, can have other devices put
18 in and so forth, but that truly to me is a -- that's
19 not a crack, that's a big gap in the way in which we
20 practice medicine. And I'm for doing something
21 about that.

22 I think I was taken a bit by the

1 comment, and I'd forgotten that that was in Les
2 Miller material that the group came up with, and
3 that is if you list a patient, you must a priori if
4 a donor heart comes up, you must put that heart in
5 that patient that day. I'd forgotten that that was
6 in the rules.

7 This long preamble gets to this
8 question: How often do we follow the rules, which
9 leaves this fairly large group of patients falling
10 through the cracks, as it were, and how many
11 transplant teams either circumvent the problem by
12 listing when they "shouldn't be listing," and how
13 many go ahead and put an LVAD in, one of your LVADs
14 in, when they are not certain that that patient is
15 going to be truly on a bridge to transplant course?
16 Because if everybody followed the rules, there is a
17 large group of patients that are not being served;
18 there's no question about that.

19 Dr. Edwards, you can answer my question.

20 DR. EDWARDS: Well, I think you've
21 identified the crux of the argument. And I don't
22 know that we know the number or really have a sense.

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1 I know that there are certainly many
2 patients, often time young patients, who don't fit
3 the criteria. And as I said earlier, one has to
4 from an ethical standpoint, say what's the best
5 interest of the patient. And if the treating
6 clinician believes that an LVAD is in the best
7 interest, I think that's where most centers would
8 go. But it can be an off-label indication and we do
9 off-label indications of drug therapy and devices.
10 But it's particularly difficult in devices where a
11 third party player looks at the labeled indications
12 and say this was an off-label indication.

13 But at the end of the day there are
14 patients when you put the device in they are not
15 device in they are not transplant candidates
16 strictly speaking and your goal is not destination
17 therapy. Your goal is bridge to transplant or
18 bridge to candidacy.

19 DR. YANCY: I wanted to focus my
20 comments just a bit with some observations and then
21 just raise one area of questioning.

22 I am very sensitive to the statement

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1 that Dr. Edwards especially made that we should be
2 patient centered, because I too am at the bedside.
3 And when people are within days to weeks of life,
4 it's very difficult to reconcile the need for
5 statistically purity with the need for clinical
6 immediacy. So I completely appreciate that.

7 In my judgment, the current indication
8 does in fact allow for this patient population to
9 have its needs met. I think that the current
10 statements that have given a certain degree primacy
11 and respect to our listing criteria as controlling
12 the behavior of transplantation in this country
13 would be by the admission of all involved in this
14 business much less clean than we've made it out to
15 be. That's not a statement that any of us are proud
16 to make, but it's a reality that we have a very
17 dynamic environment with regards to listing
18 criteria. It's very flexible. It's open to wide
19 interpretation on a regional and individual basis.
20 So I don't know that that is sufficient leverage
21 that we specifically need this in order to move
22 forward.

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1 So here is where I'm going with my
2 questioning. As has been pointed out, 65 percent of
3 the 75 patients who received VAS with relative
4 contraindications did go on to get transplanted. And
5 I have anxiety about that group, because I would
6 hate to think that that group's needs are not met if
7 they are denied transplantation. So to that extent
8 I think that there is something to be said about
9 embracing it. But I'm focusing right now on the 35
10 percent who did not make it to transplant but have
11 the VAS in.

12 We can quibble with the phraseology, but
13 these patients fall into a chronic LVAS support. I
14 don't want to use the word destination therapy, but
15 a chronic LVAS support mode. If that is the case,
16 then we need to raise the question along the lines
17 of efficacy and safety what are the outcomes for
18 that group?

19 Now, it could be that the relative
20 contraindications enrich this patient population to
21 the extent that they don't do as well as we'd like,
22 but looking at the numbers that are in our packet,

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1 four patients are alive the two years. And that
2 would suggest that of the 26 that did not get
3 transplanted, that's about a 15 percent survival,
4 which would appear to be below threshold. Please
5 correct me if those quick calculations are
6 incorrect.

7 So when I look at 15 percent survival to
8 two years, and then I reflect back on table 8-1 that
9 we haven't addressed today, which is a summary of
10 adverse events that are related to VAS implantation,
11 and I'm especially struck by the 41 percent
12 neurologic deficit rate and especially struck by the
13 infection rate, bleeding rate, etcetera.

14 so I guess what I need to have some
15 clarity on and the one area where I would like to
16 focus on is in those patients in whom the hypothesis
17 is not realized that they are not in fact stabilized
18 to the point that their relative contraindications
19 are improved and are reversed and they do in fact
20 end up with chronic LVAS support from the sponsor's
21 perspective, give me a sense of your interpretation
22 of their event rate, their survival, their quality

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1 of life. Help us to understand if this is in fact a
2 reasonable option. Because as we wrestle with the
3 question of wanting to do for the patient and we all
4 feel that yearning, we also are guided by a desire
5 to do no harm and to provide safe and reasonable
6 therapy even for people who are seriously ill. So I
7 need the sponsor to address the adverse issue, the
8 survivability and quality of life in those people
9 that do end up with chronic VAS support.

10 MR. BRYDEN: Thank you.

11 I'll just make a brief comment simply
12 from the stats and then one or more of the doctors
13 may wish to comment further.

14 With respect to adverse events effecting
15 the patients who remained on the VADs for longer
16 periods of time. The share of the total VAD
17 recipients that were within this contraindications
18 group was about 40 percent, 39 percent I believe.
19 We will give you the specific details, but they
20 can't be available in time for you to make up your
21 mind; so there you go.

22 When we look at the total of all adverse

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1 events, which you had asked be a focus, the rate of
2 all adverse events declines to very low, that is
3 less than 5 percent, after about six months. It
4 drops very quickly after the first month, then again
5 within six and then it stays low. And that low
6 level, given that there was such a significant
7 percentage of that where the group with the
8 contraindications would be inconsistent with a
9 significant rate for such a large share of the
10 total. We will break that out for you. Our belief
11 is from recollection that the data shows not
12 material difference after that first short period of
13 time.

14 So for those who are chronic users,
15 which was your question, the data will show that
16 there is a relatively low in the sense of a fraction
17 of the first 90 day period continuing event rate.

18 DR. YANCY: So if that is the case, then
19 what is the reason for the detriment of 15 supported
20 on VAS at one year versus four at two years. If we
21 have not had a logarithmic decline in adverse
22 events, obviously we have lost people unless they

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1 are being transplanted late, but that would not be
2 consistent with what's been told. So what's
3 happened to the 15 that have decreased to four?

4 MR. BRYDEN: The answer is they were
5 primarily transplanted, although --

6 DR. YANCY: Well, that's what I need
7 clarity on. Because it looks as if, and I can only
8 go by what's here, it looks as if of the 75 patients
9 that had the VAS --

10 MR. BRYDEN: We do have that
11 specifically on a --

12 DR. YANCY: -- 65 percent transplant and
13 35 percent were not. I'm assuming were never
14 transplanted. If you're telling me now that that
15 group that was -- my presumption's never
16 transplanted was transplanted late, that's new
17 information. But I'd just like to understand that.

18 And just so we can be clear, I'm looking
19 at slide 43 that was in Dr. Pina's presentation and
20 it says 15 LVAS patient greater than one year, four
21 patients greater than two years. I'm assuming that
22 means that we lost patients from year one to two,

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1 from 15 to four and trying to understand that model

2 DR. PORTNER: Can I try and make some
3 comments?

4 Let me first introduce myself, since I
5 haven't been so far. My name is Peter Portner. I'm
6 a consulting professor of cardiothoracic surgery at
7 Stanford. I should also note that I was the founder
8 of Novacor and involved with Novacor in one capacity
9 or another for more than 30 years. I'm currently an
10 advisor to World Heart.

11 The specific data you're asking for is
12 available, but I mean we'd have to go back and
13 analyze it. But what I wanted to point out just
14 looking at some information that you have in your
15 panel pack, that the so called group one who are the
16 patients without contraindications form one group at
17 risk and the group two form another group at risk.
18 And if you look at page 11 of section 4, the
19 patients at risk out at 18 months to 36 months are
20 pretty comparable between those two groups.

21 Now, that doesn't answer the question
22 you asked, but I don't believe that there's any

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1 substantive difference in their outcomes, either in
2 terms of survival or in terms of adverse events out
3 at a distant period of time. And I think the time
4 where you would see the greatest impact, at least
5 from my recollection, is in the first month post-
6 transplant where we have the data and have presented
7 it to you.

8 CHAIRPERSON LASKEY: What page are we
9 on?

10 DR. PORTNER: This is attachment 5B of
11 the panel pack. I'm looking at page 11 in section
12 4.

13 DR. YOUNG: Clyde, if you look at that
14 and trace out the actuarial survivor, the Kaplan
15 Meyer, there were three late deaths that you can see
16 there in the LVAS group. But if you turn to page 31
17 and 32, that also addresses some of the complication
18 issues, particularly the late occurring
19 complication. And if you look at the linearized
20 adverse event rates on this table and then the
21 following table, you can see that the majority of
22 them occur early on. And it doesn't completely

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1 address, I think, the concern that you have raised
2 which I'm sensitive to, but I actually don't believe
3 that this indicates that these patients with
4 relative contraindications actually were set up to
5 have worse post-transplant events.

6 Now, I agree with you that the database
7 is, as I have characterized it, robust in some
8 arenas, it's poultry in other arenas. And the late
9 follow-up because patients were transplanted, that's
10 why they were censored out of this, is compromised
11 by the fact that this isn't a long term set
12 necessarily. I prefer to use the word "longer." If
13 we have trouble defining long, maybe longer is
14 easier to define in many senses.

15 The other issue is is I'm also sensitive
16 to your comments about perhaps the labeling as it
17 stands right now allows us to practice what we're
18 doing. And, you know, another solution would be for
19 the FDA to explicitly come out and say that and make
20 that point.

21 I think there's another issue why I'm
22 sensitive to it, and that comes from my inclinations

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1 to study data and databases and whatnot. And when
2 you go back and you look at status ETRD data,
3 whatever, we can't get at this information because
4 we don't know what the true intent was because, in
5 fact, there is not an indication for this. I'll
6 grant people that there's not a contraindications
7 necessary, but there's surely not an indication.

8 And then finally the concern about
9 branching into other patients who are even more ill
10 with a lot of other complications that then could
11 compromise the outcomes, I think that sometimes
12 hinges on common sense more than anything. And,
13 again, those of us that do this everyday, I don't
14 think that that's our intent at all.

15 So there's a little bit of data I think
16 that gets to the point and maybe sways you a little
17 bit about this particular issue.

18 DR. YANCY: Well, the only reason for
19 this topic of discussion is that if the request is
20 to add a longer term use to the indication and if
21 the request is to embrace patients who have a
22 potential for not going forward to transplantation,

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1 I think cord to the decision making is to have at
2 least a feel for what are the longer term
3 experiences and in those patients who don't becoming
4 a transplant candidate irrespective of time, what
5 are their expectations. Obviously, we're dealing
6 with a population that is prone to die, we
7 understand that. But we have to understand based on
8 what we've accepted before as thresholds for
9 outcomes in that group, and we have a few limited
10 databases to give us that.

11 I want to understand are we consistent
12 with or in variance from. And if we're in variance
13 from, is it because of adverse events or what are
14 the circumstances.

15 MR. BRYDEN: If I can make a very short
16 summary statement on those points?

17 The data, and in fact there is I believe
18 sufficient summary data in the materials that are in
19 the panel pack and certainly in the material that
20 was supplied as a part of that long PMA process that
21 we're going through to the FDA, to show that as
22 patients live a longer period -- if they have first

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1 survived six months, the percentage of those who are
2 successfully transplanted is higher than those who
3 are in the first six months. If they have survived
4 12 months, the percentage of those that have lived
5 for 12 months that are successfully transplanted is
6 higher. And so on until the last patient has been
7 followed to death or to transplant.

8 The last patient in this trial was an
9 American who lived 3.4 years on this device and he
10 then got a transplant just after New Year's in 2002
11 after 3.4 years. So while he's no longer in the
12 trial because he was transplanted.

13 And the percentage of success to
14 transplant increased at every significant advancing
15 period.

16 The percentage, whether it is a
17 linearized rate or on a percentage of people at risk
18 of adverse events has declined throughout that
19 period, and remained low although in one case when
20 it was down to only three -- I believe at three
21 years, in one case there was an infection which had
22 the infection rate go up and you see a little blip

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1 in the three year adverse event rate.

2 So I believe that the data shows very
3 consistently an improving success to transplant and
4 a declining adverse event rate as the patient is on
5 it for a longer period.

6 DR. YANCY: It's just my last statement
7 and then I'll yield to the next person.

8 There may be one of you who knows this
9 answer very quickly. Of that original cohort of 75
10 that had the VAS that had relative
11 contraindications, as we stand today how many of
12 those have been transplanted?

13 MR. BRYDEN: Just a moment, we'll give
14 you that data.

15 DR. YANCY: Because the number that I
16 thought was in one of the slides was 65 percent.

17 CHAIRPERSON LASKEY: And that was
18 effective '03. What you want is current. Okay. If
19 we can't produce the answer, let's --

20 DR. PORTNER: The answer is 49 of 75.

21 CHAIRPERSON LASKEY: Which is 65 -- yes.

22 DR. PORTNER: Sixty-five percent.

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1 CHAIRPERSON LASKEY: So nothing changed?

2 DR. PORTNER: And the rest are dead,
3 they will not be transplanted.

4 CHAIRPERSON LASKEY: Dr. Kato?

5 DR. KATO: My comments, many of which
6 have been echoed by the panel, just wanted to make a
7 couple of additional statements.

8 I would like to congratulate the sponsor
9 for bringing to light several issues which the
10 sponsor feels are important in order to expand their
11 current indications in labeling. However, after
12 reviewing the FDA presentation, I haven't really
13 heard much from the sponsor in terms of rebuttal to
14 the comments and criticisms posed by the FDA.

15 The issue, I believe, of a bridge to
16 candidacy I think is a good one that has been
17 brought up by the sponsor. However, I would then
18 challenge the sponsor to do the right studies and
19 submit the right data.

20 I believe that World Heart is an
21 experienced company that's been doing device studies
22 for a long time. And so therefore, instead of having

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1 a lot of anecdotal reports and anecdotal data that's
2 been talked about, I believe that much of the data
3 that in order to convince the panel of expanded
4 indications or at least convincing the FDA for
5 expanded indications should come from data that has
6 been publicly presented as opposed to slides that we
7 could not review due to the fact that this data was
8 not submitted for this presentation.

9 As a comment to the issue of off-label
10 indications, I actually do a fair amount of
11 consulting work for insurance companies and
12 reinsurers and I can assure that at least most
13 insurance companies and reinsurance companies are
14 very familiar with off-label indications. In fact,
15 there's a very nice summary of off-label indications
16 on the FDA website. And from everything that I've
17 heard so far, and particularly from comments from
18 the FDA, there's been nothing to suggest that the
19 current labeling would preclude the current set of
20 patients -- would preclude the specific set of
21 patients that the sponsor is bringing to light today
22 from receiving an LVAD.

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1 So, those are some of my comments about
2 it. I don't know whether you'd like to comment back.

3 MR. BRYDEN: Some of my colleagues may
4 have more specific comments.

5 First, I'd like to observe that we
6 followed one of the two alternative methods of
7 presenting our data that was stated to us in the
8 letter informing us of this panel hearing, and we're
9 not aware that one of those two was less desirable
10 to the panel than the others.

11 There is nothing in our slides except
12 for the two which were commented on by the panel and
13 excluded from discussion. That is not simply
14 presenting in slide format the data which is
15 included in the panel pack.

16 The data on which we rely is not in any
17 sense anecdotal. It may not be satisfactory to you,
18 but it is the data arising out of a prospectively
19 done trial approved by the FDA resulting in the
20 bridge to transplantation label which until the
21 single approval of HeartMate for destination
22 therapy, that and a comparable label for HeartMate

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1 done also in a similarly structured trial, are the
2 only two significant approvals for this type of
3 therapy in the United States until the REMATCH
4 trial.

5 So we believe that the data that we've
6 provided is substantive. It was prospectively done.
7 It's data that was done under the guidance and
8 reviewed by the FDA. It was found sufficient and
9 satisfactory as a basis to provide a very meaningful
10 indication.

11 We do not in any sense dispute, that's
12 why there's no rebuttal in that sense of the view
13 that the controls are inadequate controls. But this
14 indication is not seeking to have approval. The
15 principle discussion today seems to be you don't
16 need the approval, we can get it anyway. That it is
17 already approved. We would be very pleased if the
18 FDA could confirm that a clinic is at liberty to
19 implant within our label that candidate for
20 transplantation means a person who is listed or is
21 expected to be listed; that is just fine. But it is
22 not our understand that that is what it means.

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1 And I think we should be clear that
2 we're not making this up. And the fact that many of
3 these patients are in fact treated today, and many
4 are, is because clinicians in spite of the rules put
5 the patients first. That is, however, a factor that
6 in our view does significantly limit the number of
7 patients who are both brought forward and are given
8 the device as compared to those that commissions may
9 be prepared to deal with if they were not having to
10 act contrary to the rules of their own organization
11 and the structure of the regulatory process.

12 But if in fact bridge to candidacy is
13 what's intended, then if that could be clarified
14 even at this meeting, then we would agree with you
15 we should all go for a drink.

16 CHAIRPERSON LASKEY: Several drinks.

17 Well then, lest we labor any longer in
18 confusion, may we have the FDA's position on this
19 issue? This should be simple enough to address. I
20 would hate to think we're wasting our day here.

21 DR. PINA: This will take just two
22 minutes. On behalf of myself and on behalf of FDA,

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1 we'd just like to reassure Dr. Edwards that we are
2 equally worried about the patients, and that that's
3 our very reason for being here. So I'm a little
4 sensitive about that comment.

5 And to address Dr. Tracy's comment about
6 regulating practice, I would love to know who
7 reverses and who doesn't. The dataset presented
8 here does not help me tell who will and who won't.
9 And it would be terrific to have prospective data, I
10 agree.

11 DR. ZUCKERMAN: Well, first thing is,
12 I've heard multiple panel members correctly
13 interrupt the position of the FDA, and that is that
14 the FDA does not regulate the practice of medicine.
15 If an individual physician believes there's a
16 candidate who needs this device, then it's within
17 the purview of that physician to utilize this
18 particular device.

19 On the other hand, the FDA does regulate
20 the approval of devices and the FDA does look very
21 closely at the indications for use of these devices.
22 that is why Dr. Berman at the beginning of the FDA

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1 presentation quite clearly tried to express the
2 underlying conditions that FDA would need for
3 changing an indications for use statement.

4 I think if one were to summarize those
5 conditions, it begins with the need for appropriate
6 data. And what we've asked the panel today is
7 whether the data are there to make an expanded
8 indications for use of this particular device. We
9 are not asking the panel to regulate the practice of
10 medicine.

11 DR. YOUNG: Could I ask one point of
12 clarification: Does a candidate as you referred to
13 for transplantation, mean the individual is listed
14 for heart transplant?

15 DR. ZUCKERMAN: I would look at the
16 particular indications for use of this particular
17 device. There is a sort of gray area that you are
18 trying to discuss today, but the bottom line is that
19 the agency, if it works within a legal construct to
20 expand its indication for use, needs to see
21 appropriate data. And it's your obligation today to
22 argue that that appropriate data is here in this

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1 panel pack.

2 CHAIRPERSON LASKEY: Thank you very
3 much.

4 I think we're done with the panel
5 questions. But before we move on, I understand that
6 you had some additional information in response to a
7 few of the queries this morning. So I'd like to
8 take five additional minutes, if I might, and afford
9 you the opportunity to respond to those. I forget
10 which questions we were looking --

11 MR. BRYDEN: Yes. Our notes suggested
12 that you had asked for the number of patients who
13 had died in each of the subgroups within the
14 contraindication. So we'll just pull that slide up.

15 And also, I believe you had asked
16 whether we had done a multivariate analysis, and if
17 so, whether that was available.

18 So those are the two items that --

19 DR. KRUCOFF: Unless you have a
20 particular point, the latter request which I think
21 was mine, I could step back from.

22 MR. BRYDEN: Okay.

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1 DR. KRUCOFF: I think we've addressed
2 most of the issues that would be intrinsic to that
3 conversation.

4 MR. BRYDEN: Thank you very much.

5 And the slides are just coming up on the
6 screen with respect to the other one, which will
7 take only a minute.

8 Jim, would you mind just dealing with
9 these?

10 DR. YOUNG: Yes. I think, again,
11 hampered by the numbers that are present, if we look
12 at the causes of death pre-transplant that are in
13 our identified groups, four were over age 66. And
14 you can see the listing there, multi-organ failure
15 and neurologic dysfunction.

16 The next one is total bilirubin. And,
17 again, remember that there were only three patients.
18 And again, multi-organ failure.

19 Next one BMI less than 19, four of 12.
20 Bleeding, neurologic dysfunction, embolism,
21 infection, sepsis, arrhythmia. And, again,
22 remembering that the controls, one of which would

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1 have fallen into this group, were dying primarily of
2 difficulties related to cardiovascular dysfunction
3 and heart failure.

4 The next one. You have BMI over 32, two
5 of three in the controls. Cardiac dysfunction.
6 Heart failure here. And then, again, multi-organ
7 failure, neurologic dysfunction, intracranial bleed.

8 Next one. Creatinine greater than 2½,
9 multi-organ failure being the most predominate.
10 Here, again, I'm not surprised about. I think
11 perhaps this also refocuses attention on the touchy
12 subject of renal insufficiency pre-transplant. Kind
13 of 22 patients dying who were felt not candidates
14 because of this.

15 And I think that would be the last one.
16 Oh, PA pressure, we might -- that's the controls.
17 Okay. So the problems being equally grave in the
18 control patients. Go ahead to the control patient.

19 Five of six, a vast majority there with
20 renal dysfunction.

21 Next one. PAS, again, heart failure in
22 the one control death and cardiovascular

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1 dysfunction, embolism, neurologic dysfunction,
2 intracranial bleeds, infection. And that should be
3 the last one.

4 PVR we do have data. Two of five with
5 high PVRs. Obviously, we don't have that in the
6 control group.

7 So those are the causes of death in the
8 pre-transplant group of patients that were
9 identified as having relative contraindications
10 compared to the controls.

11 MR. BRYDEN: Thank you.

12 And the last question that we had not
13 fully answered, the percentage of patients who
14 survived to transplant who were transplanted after
15 six months was 73 percent and those after 12 months
16 was 75 percent. So the overall was 65, a smaller
17 percentage of those who were done in the first six
18 months. Slightly more in each of the second two
19 periods.

20 CHAIRPERSON LASKEY: Thank you.

21 Colleagues, we're at that critical
22 point. Should we forge ahead with the possibility

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1 of getting people to their various destinations,
2 forgive the expression, on time. The schedule calls
3 for a break, but can we move ahead and do the
4 questions? Yes.

5 In that case, Geretta, if you would,
6 please.

7 MS. WOOD: Yes. We need the computer to
8 project the questions. Okay.

9 CHAIRPERSON LASKEY: As these scroll
10 through, I will do my best to summarize the
11 consensus of the panel discussion this morning, but
12 as always please feel free to add or detract.

13 MS. WOOD: Okay. If you can move it to
14 the next slide for me.

15 The sponsor makes outcome comparisons
16 between the selected subgroups of LVAS and control
17 patients, yet significant covariates of the two
18 groups are not matched. Are such comparisons
19 between groups with unmatched covariates valid?

20 CHAIRPERSON LASKEY: I think what we
21 heard this morning and the consensus of the panel is
22 that it can't be done.

1 Next.

2 MS. WOOD: Go to the next slide.

3 Seven variables with particular
4 thresholds were chosen as relative contraindications
5 to heart transplant. Comparisons were made between
6 transplant eligible LVAS and control patients
7 meeting the chosen criteria. All of the selected
8 patients were transplant eligible and were listed
9 for transplant. The majority were transplanted.
10 Are these patients comparable to patients with these
11 relative contraindications who are not transplant
12 eligible and would not be listed or transplanted?

13 CHAIRPERSON LASKEY: That, of course,
14 has been the crux of the debate all day long. I
15 think it's the feeling of the panel that it's very
16 difficult to establish comparability, certainly
17 going in and on the tail end coming out as well.

18 Comments?

19 DR. ZUCKERMAN: Would Dr. Lindenfeld or
20 Dr. Yancy with their personal experience expand upon
21 Dr. Laskey's comments?

22 DR. YANCY: I'll yield to Joanne.

1 DR. LINDENFELD: No, I agree with Dr.
2 Laskey. I think that right now it appears that
3 within these contraindications patients can still be
4 transplanted.

5 DR. YANCY: The only to add to that is
6 that it's obviously a very dynamic bucket of
7 patients that can change very easily, and I would be
8 very hard pressed to try to give any definitions or
9 make a proviso of any sort.

10 MS. WOOD: Okay. If we can have the
11 next slide.

12 Is there a sound scientific or clinical
13 rationale for choosing the particular seven relative
14 contraindications selected and not included the
15 others, for example, high PRA, history of cancer,
16 etcetera?

17 CHAIRPERSON LASKEY: Well, as has been
18 alluded to, it comes down to issues of clinical
19 judgment rather than even consensus or better yet,
20 what we would like to see are specific guidelines.
21 We realize that that's not likely to be the case. It
22 is a dynamic area and we can't even establish

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1 consensus within the profession when there's so much
2 site-to-site variability for what is a relative
3 contraindication. So we'd have to say,
4 unfortunately and it is unfortunate, there is no
5 sound scientific evidence. There may be a
6 consensus, but it's probably violated everyday with
7 the inter-site variability.

8 DR. YANCY: The only amendment to that
9 statement, Dr. Laskey, would be that to the extent
10 that the device improves the humandynamic profile,
11 with the exception of age, these are several
12 relative contraindications that could be modified by
13 a change in humandynamics.

14 DR. LINDENFELD: And the one other
15 comment that might fit in there is that the data has
16 been well presented and there is a small amount of
17 data, I understand, in small numbers. But within
18 this group of relative contraindications, I don't
19 feel as if I have enough data to know if perhaps we
20 should expand this with one, but perhaps not with
21 another. In other words, we saw that 45 percent of
22 patients with renal insufficiency didn't make it to

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1 transplant. That concerns me. And if the mortality
2 is higher after transplant, we got down to a number
3 of 10 out of 22 didn't make it transplant, it
4 concerns me that even within this group that's been
5 picked out we don't know that this is the right
6 group, that they should all be encouraged. So I'm
7 concerned about that.

8 MS. WOOD: Next slide, please.

9 Is there a sound scientific or clinical
10 rationale for choosing the threshold values of the
11 seven selected variables such that these variables
12 singly or in combination are relative
13 contraindications to transplant?

14 CHAIRPERSON LASKEY: Well, again, I
15 think there's probably even less discussion here.
16 The cut points were, admittedly, arbitrary from both
17 sides of the room today. It is the best that people
18 can come up with, but it is arbitrary. And, in
19 fact, we haven't seen any information to suggest the
20 incremental utility of combination of variables to
21 add to the predictive validity of this approach.
22 So, unfortunately, not enough information that's

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1 defended.

2 DR. YANCY: I hate to consistently be
3 the voice, but correct that we didn't see the linear
4 function of these risk factors, nor did we see any of
5 them in aggregate. But I will say that the
6 discipline of transplant medicine, either by
7 convention or by -- does in fact respect the
8 majority of these as reasonable thresholds.

9 DR. BAILEY: But I guess it concerns me
10 that we pick a cut point and we don't have data that
11 show that there are significant variation between
12 the two sides of the cut point. But we're not given
13 any other criteria for saying you have to have at
14 least this good a creatinine or this good a
15 pulmonary pressure. So, I mean, we're just
16 extrapolating to everybody on the other side of the
17 cut point. And I guess I don't see any data to
18 support that.

19 DR. YANCY: Well, the only way I can
20 modify that, Dr. Bailey, is that you don't see those
21 data in this data set, but in the broader context
22 and particularly with clinical experience, I think

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1 the numbers are reasonable.

2 CHAIRPERSON LASKEY: Does that mean
3 there's sound scientific evidence to support this?
4 To answer their question.

5 DR. YANCY: My vote would be yes based
6 on what we currently use as a threshold of practice
7 this medicine.

8 DR. FERGUSON: I'd like to add a
9 comment.

10 I think that -- I guess it's incumbent
11 upon the sponsor to validate these, but these cut
12 points come from clinical practice of medicine for
13 years. And I don't think that we can really impugn
14 the sponsor for selecting this particular group.

15 DR. YANCY: I couldn't agree more.

16 DR. KRUCOFF: I'd at least say that the
17 context and the practice that to me are two key
18 features that are missing from extracting these cut
19 points for this type of indication are issues of
20 reversibility and issues of multiple comorbidities,
21 which you know if you have two or three of these in
22 practice, that while I agree with Clyde entirely, I

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1 think empirically are these sorts of numbers, cut
2 points in our minds, yes. But how we use them
3 relative to their individual selection as criteria
4 for an indication, that's where I think the actual
5 practice with context and multiple comorbidities is
6 a departure, actually, from their clinical meaning.

7 DR. SOMBERG: I just would add that we
8 have to say they're arbitrary because they were
9 cited post-hoc and that there was clear knowledge of
10 the results so they were decided arbitrarily. If
11 they were set a priori in the BTT trial, they would
12 have considerably more weight.

13 DR. YANCY: The only final statement is
14 the sentence before it says is there a sound
15 scientific and clinical rationale, and whether it
16 was post-hoc or not, there was a sound clinical
17 rationale for these thresholds.

18 CHAIRPERSON LASKEY: I think that's fair
19 enough. But admittedly, each of these is an
20 arbitrary as to what to include and what to exclude.

21 MS. WOOD: Next slide, please.

22 Is the data sufficient to demonstrate

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1 the effect of the LVAS to normalize these seven
2 variables to justify expanding the label to include
3 patients who are expected to become transplant
4 candidates with mechanical circulatory support?

5 CHAIRPERSON LASKEY: Well, we wish it
6 were but it's not, and that's obviously a major part
7 of the challenge today. There is no data to suggest
8 normalization or even a change that we can evaluate.

9 Okay.

10 MS. WOOD: Next slide.

11 Does the retrospect subgroup analysis of
12 transplant eligible patients provide sufficient
13 evidence of safety and effectiveness to expand the
14 labeling to include patients not eligible for
15 transplantation?

16 CHAIRPERSON LASKEY: Well again, the
17 high road is that retrospect subgroup analysis
18 doesn't really help us in too many respects, and in
19 particular this approach in the material at hand
20 does not help to expand the labeling.

21 DR. ZUCKERMAN: Are there --

22 CHAIRPERSON LASKEY: We've been over

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1 this. There is no safety data that we can fall back
2 on. I believe Dr. Lindenfeld has articulated that.
3 We're looking for meaningful data out to periods of
4 time that it is likely these patients will endure
5 the device for, and we've not seen that.

6 And in terms of effectiveness, we've not
7 seen that side of the coin either. With long term
8 data with so few patients it's very difficult to
9 make anything of those Kaplan Meyer curves.

10 DR. ZUCKERMAN: Are there any differing
11 opinions from other panel members on this critical
12 question?

13 DR. AZIZ: You know, Warren, I think for
14 the time periods that it has shown, I mean I don't
15 think -- I think I would be -- to say that that
16 device is not a safe device. Okay. It hasn't gone
17 for more than two years in a lot of patients. But
18 the time period that they have shown, and even the
19 bench stuff, that the device itself is quite safe.

20 In terms of being effective and it
21 functions as an LVAD in a number of the slides that
22 they've shown, the data, the creatinines do

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1 decrease, the PA pressures do come down. I mean, for
2 the time periods that they're projecting, I think it
3 seems that they have shown that it does do that.

4 CHAIRPERSON LASKEY: Let's not forget
5 the critical part of this question is that can we
6 extrapolate the data from this subgroup of patients
7 not eligible for transplant or from the group of
8 patients that were eligible. And the answer is no,
9 we can't. We've been struggling, and everyone's
10 been struggling to find comparability. But we can't
11 make any extrapolations from patients that are
12 originally eligible for transplant and then to take
13 that information and apply it to these patients that
14 are deemed not eligible.

15 DR. KRUCOFF: I think I read two
16 somewhat separate issues embedded in this question.
17 One is the issue of long term use or whatever that
18 is intended to mean, where the durability of the
19 device and the track record, etcetera, may give us
20 some insight.

21 To me the much murkier one is the
22 patients in the BTT study who were analyzed who had

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1 a relative contraindication who were analyzed for
2 one reason or another were listed for transplant.
3 And as we get into patients who for whatever reason,
4 be it systematic or be it good medical judgment,
5 have renal insufficiency or one of these criteria
6 who were not listed for transplanted in the BTT type
7 of environment, we really have absolutely no idea
8 how or what role, what the safety profile or
9 effectiveness of this device would be. And that to
10 me is the other part of this question.

11 So I think the long term durability is a
12 little bit separate question, and I guess I think
13 both of those may be wrapped up in this question a
14 little bit.

15 DR. YANCY: I agree with Mitch. I mean,
16 that was the context of my questioning. In this
17 patient population trying to understand the longer
18 term issues of safety, adverse events, durability,
19 that's the struggle.

20 DR. AZIZ: But you know in the patients
21 that where the creatinine came down, where the PA
22 pressures came down, they came down fairly quickly

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1 within a matter of months. I mean, you're not
2 talking about years. Isn't that what the data
3 showed? You're not looking to have this device in
4 for four years before the patient becomes transplant
5 eligible.

6 DR. YANCY: But you are dealing with by
7 their own admission 26 of 75 patients who got the
8 device and didn't go on to transplant. And we are
9 at that point talking about longer term questions of
10 safety and efficacy. And that's not an
11 insignificant percentage if you extrapolate out to
12 larger numbers of patients. And I think we have a
13 responsibility to know what it is we are subjecting
14 those patients to experience if they fall into that
15 category.

16 DR. KRUCOFF: That might even be an
17 optimistic percentage if we extrapolate out into a
18 little wilder field.

19 MS. WOOD: Next slide, please.

20 The sponsor wishes to add language
21 indicating "short" or "long term" use of the LVAS.
22 Of 190 LVAS patients from the BTT trial, 30 were on

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1 the device greater than or equal to six months. Of
2 those, 15 were on the device greater than or equal
3 to one year. Of those four were on the device
4 greater than or equal to two years. Is that
5 sufficient support to expand the labeling to include
6 long term use?

7 CHAIRPERSON LASKEY: Well, I think
8 there's two issues here. One, which was overt and
9 the other which was finally stated this afternoon.

10 The overt issue is that there aren't
11 enough patients that go out long enough, and long
12 term is in the eye of the beholder, but whatever the
13 definition is there's not enough patients out there
14 beyond the year to provide meaningful information.

15 And the subliminal concern here has been
16 it may not be an intention on your part, but many of
17 these patients may wind up with this device as
18 "destination therapy." We realize that no one is
19 back dooring any of this, but it's conceivable that
20 a significant fraction, and I would be loath to
21 guess that number but it's going to be in double
22 digits, would wind up with the device being

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1 ineligible for transplant even after the device, and
2 that troubles us.

3 Next.

4 MS. WOOD: Next slide.

5 Does the retrospective subgroup analysis
6 of transplant eligible LVAS patients provide
7 sufficient data to judge whether expanding the label
8 to include patients not eligible for transplant is
9 safe?

10 CHAIRPERSON LASKEY: Well, again, it's
11 just a corollary of what we've been saying.
12 Unfortunately, the curves don't go out far enough
13 and there's not enough patients out there to make
14 that claim.

15 Labeling.

16 MS. WOOD: Okay. Let's move to the next
17 slide, please.

18 Premarket review of an expanded
19 indication for use for an approved product includes
20 review of the modified labeling. The labeling must
21 include a description of the patients for whom the
22 expanded use is intended and an explanation of how

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1 the product is to be used for those patients to
2 maximize clinical benefit while minimizing adverse
3 events. Does the proposed expanded indication for
4 use meet the requirement?

5 CHAIRPERSON LASKEY: The consensus of
6 the panel seems that, no, it does not.

7 Would you care to elaborate primary or
8 secondary reviewers?

9 DR. KRUCOFF: I think that's accurate.

10 CHAIRPERSON LASKEY: Yes. We don't mean
11 to be this blunt, but I think this is fairly
12 straightforward. These questions are specific and
13 so are the answers.

14 Okay.

15 MS. MOORE: Mr. Chair, there's one point
16 that I as a consumer would like to make reference
17 to, is that possible?

18 CHAIRPERSON LASKEY: I will be coming
19 back to you in just a bit to ask for some input.
20 Thank you very much.

21 I am obligated by protocol to open the
22 public hearing portion of the afternoon.

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1 Is there anyone in the audience who
2 wishes to address the panel on today's topic? If
3 not, it's my pleasure to close this portion of the
4 open public hearing.

5 And I will be asking Dr. Zuckerman if
6 the agency has additional comments. I'll be coming
7 to the sponsor and then I'll be asking industry and
8 consumer for their comments.

9 So, Dr. Zuckerman?

10 DR. ZUCKERMAN: Yes. Today we've had a
11 very important panel discussion on an extremely
12 important topic. One of the issues facing this
13 panel for what is a nitch device is whether there is
14 enough data in the present application to justify an
15 expanded indications for use.

16 The panel will shortly need to decide
17 this question. However, I think there is a more
18 general problem that has been hinted at for the LVAD
19 industry today, and I do make my comments to the
20 whole LVAD industry since they're all seated here.

21 We have a situation where potentially in
22 the post-market arena or what the agency has tried

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1 to underline as the total product life cycle, a lot
2 of patients have gotten a particular device, and
3 with study could have provided additional supportive
4 data. Unfortunately, we don't have those data here,
5 but the agency is committed to continuing support of
6 these devices throughout the approval process, both
7 in the pre and post approval domains, especially
8 when it is difficult to recruit patients.

9 Thank you.

10 CHAIRPERSON LASKEY: I'd like to invite
11 the sponsor to provide any final or near final
12 comments before the vote.

13 MR. BRYDEN: Yes. I just want to thank
14 you for your time and attention. We're, obviously,
15 disappointed with your conclusions. We've learned
16 something, I at least and perhaps others in our
17 group perhaps have a broader understanding about the
18 scope that the agency intends clinicians to be able
19 to apply in determining who is and who is not a
20 candidate. That whole discussion may prove to be
21 helpful to the centers as they struggle with the
22 issue of matching patient requirements.

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1 I do think it's important to observe
2 that in the current indication the implant of our
3 device or any device as a bridge to transplantation
4 cannot be assured that the patient will receive a
5 heart or that they will remain eligible throughout
6 the period of time it takes to wait to obtain one.
7 So the issue with respect to longer term use is one
8 which is not unique to the group with relative
9 contraindications. Nonetheless, that decision is
10 past and as the Chairman observed, I think it's
11 clear to the panel that our intention was exactly
12 what the proposal suggested and that our view is
13 this would have opened the door to destination
14 therapy. If it were, we wouldn't be carrying on the
15 relatively large trial that we're now engaged in to
16 achieve that indication.

17 So, again, thank you very much for your
18 attention.

19 CHAIRPERSON LASKEY: Thank you.

20 And, again, we acknowledge the integrity
21 of the sponsor and in no way meant to impugn the
22 purpose of this. It's clear, though, that what

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1 we've learned -- what I've learned is that in order
2 to change a label, some very specific requirements
3 need to be met. And I don't think they were met
4 today.

5 Ms. Moore?

6 MS. MOORE: The point that I wanted to
7 speak to was the one having to do with the values of
8 the seven selected variables. That's 2C. And if I
9 understand the discussion that I've heard today,
10 then this is my comment regarding that particular
11 point.

12 As a consumer, I think that one of the
13 questions that one of us would ask would be how do
14 you determine patient A as opposed to patient B. So
15 I'm thinking that as something that's definitive to
16 present to patients would help to answer that
17 question.

18 I'm inclined to believe that despite all
19 of the problems regarding statistical significance
20 and the like, we do need consistency in defining the
21 characteristics which will qualify one for being on
22 that list for transplantation, even though I

1 recognize that that list is not exhaustive. And I
2 think there should be the caveat that the physician
3 has the leeway then to make some judgment or a
4 decision that may be contrary to that list if the
5 need indicates such. And I think that -- I know
6 you've made your decision on that item, but somehow
7 or the other it seems to me that from the consumer's
8 point of view more attention needs to be given to
9 that particular item.

10 The other items, I think -- oh, I can
11 say this. Can you not do whatever procedures you
12 want to do without specifying whether it's short
13 term or long term and just keep the statement as it
14 is, that intended for use as a bridge to
15 transplantation in cardia transplant candidates?
16 Can't you do still do whatever you want to do
17 without specifying whether it's long term or short
18 term since we don't know what the definition of long
19 term is or what short term is? That's a question
20 that just went through my mind as you were
21 discussing.

22 But I think those are the points that I

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1 had an interest in.

2 There was another minor point. I
3 noticed your population consisted primarily of white
4 males and a few females. I was wondering if there
5 were any ethnic groups in some of these studies that
6 you have done? And if there were, then what your
7 findings?

8 Thank you.

9 CHAIRPERSON LASKEY: Michael?

10 MR. MORTON: Just a couple of notes to
11 also acknowledge what's been stated several times
12 today; that the sponsor did a good job of
13 presentation of data. And also to recognize the
14 commitment that the sponsor came here with a
15 commitment to do what was best for the patient, and
16 that was not exclusively stated by the sponsor, but
17 also echoed by the FDA and by the panel. And that
18 was made very clear today and made me proud to be
19 part of this.

20 All parties also recognize the
21 requirement that we have to limit discussion to the
22 data at hand. And I think the sponsor and the FDA

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1 and the panel showed good restraint and in balance
2 in that today, and I'd like to recognize that.

3 Thanks.

4 CHAIRPERSON LASKEY: All right.
5 Geretta, you can read the voting options, please.

6 MS. WOOD: The medical device amendments
7 to the Federal Food, Drug and Cosmetic Act as
8 amended by the Safe Medical Devices Act of 1990
9 allows the Food and Drug Administration to obtain a
10 recommendation from an expert advisory panel on
11 designated medical device pre-market approval
12 applications, PMAs, that are filed with the agency.

13 The PMA must stand on its own merits and
14 your recommendation must be supported by safety and
15 effectiveness data in the application or by
16 applicable publicly available information.

17 Safety is defined in the Act as
18 reasonable assurance based on valid scientific
19 evidence that the probable benefits to health under
20 conditions on intended use outweigh any probably
21 risk.

22 Effectiveness is defined as reasonable

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1 assurance that in a significant portion of the
2 population the use of the device for its intended
3 uses and conditions of use when labeled will provide
4 clinically significant results.

5 Your recommendation options for the vote
6 are as follows:

7 Approval, if there are no conditions
8 attached;

9 Approvable with conditions. The panel
10 may recommend that the PMA be found approvable
11 subject to specified conditions such as physician or
12 patient education, labeling changes or a further
13 analysis of existing data. Prior to voting all of
14 the conditions should be discussed by the panel; and

15 The third option, not approvable. The
16 panel may recommend that the PMA is not approvable
17 if the data do not provide a reasonable assurance
18 that the device is safe or if a reasonable assurance
19 has not been given that the device is effective
20 under the conditions of use prescribed, recommended
21 or suggested in the proposed labeling.

22 Following the voting the Chair will ask

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1 each panel member to present a brief statement
2 outlining the reasons for their vote,

3 CHAIRPERSON LASKEY: I'd now like to ask
4 for a motion on the PMA. Dr. Krucoff?

5 DR. KRUCOFF: Move to recommend that
6 this application is not approvable.

7 CHAIRPERSON LASKEY: And is there a
8 second? Dr. Somberg seconds.

9 Can we have some discussion? Are we all
10 of a like mind? Okay. We have to have some
11 discussion.

12 DR. BAILEY: Do we have to have
13 discussion on it?

14 CHAIRPERSON LASKEY: We must. Well, you
15 looked like you were ready to --

16 DR. BAILEY: Oh, no, no. I was trying
17 to look expectant.

18 CHAIRPERSON LASKEY: I see. Well, I'll
19 alleviate that expectancy.

20 If there is no discussion, then I'd like
21 to proceed with the vote.

22 All in favor of the motion put forth by

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1 Dr. Krucoff that the PMA is not approvable, please
2 raise your hands. Ten in favor.

3 Opposed? And one opposed, Dr. Aziz.

4 The motion that it is not approvable
5 passes ten to one.

6 And we need to go around the table and
7 just defend the voting situation.

8 Salim?

9 DR. AZIZ: I think there are a group of
10 patients, as we've discussed, who fall in between
11 absolute contraindications and actual indications
12 for being transplanted. I think the boundaries are
13 obviously are quite blurred and it's a moving
14 target.

15 Having seen and looked after patients
16 who could be transplanted but there are certain
17 contraindications, I feel that a device such as this
18 which clearly has not shown any evidence of device
19 malfunction, and although our comments are related
20 to the information presented today, I'm aware
21 obviously of data from other trials and other
22 centers where the device has been in for a long time

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1 where it's really been shown to be effective over a
2 long period of time.

3 So I think that devices like this are
4 needed, and even though this was, obviously, not an
5 ideal trial, I feel that there are patients who
6 would benefit and that the term bridge to candidacy
7 will, I think, take an increasingly important role.

8 CHAIRPERSON LASKEY: Dr. Krucoff?

9 DR. KRUCOFF: I think we have to
10 recognize the reality of our health care system.
11 That pre-market evaluation, study and approval is
12 certainly not identical to what physicians face in
13 real work post-market use. And that in fact
14 relative to their specific indications, probably
15 more than the majority of devices in real world care
16 are used on the basis of the practice of medicine
17 off-label than specifically on label. And I think
18 Dr. Zuckerman's suggestion to sponsors that they
19 could be of important help in bridging that gap by
20 gathering systematic post-market information would
21 be one way for the sponsor in this case to think
22 about a way of gathering data that might in fact

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1 come to a different conclusion on review.

2 I think the major social and health care
3 issue that everyone has spoken to today, that the
4 management and extended support decisions for
5 patients who are dying who might be transplant
6 candidates if they could be stabilized or improved
7 in some way is a huge current and very difficult
8 issue. In fact, a proportion that one might again
9 suggest to the sponsor is to think about whether
10 professional societies or the National Institutes of
11 Health might be a more appropriate approach to
12 understanding really where these devices might play
13 an important role beyond what they already do in
14 current practice.

15 I think the phrase "bridge to candidacy"
16 is the critical phrase. It's obviously a component
17 of the real world of bridging to transplant. But
18 largely the way I see it and what I heard in the
19 discussion today is that bridge to candidacy is
20 defined by reversibility and multi-factorial
21 complexities that simply were not a part of the data
22 set that we had at hand today.

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1 So while I think there are some critical
2 issues here, and I would hope some ways that the
3 sponsor and the clinicians associated with the
4 presentation today might think about clarifying the
5 extension of where and when we decide to use an LVAD
6 in patients who are at imminent death, I think that
7 ultimately in terms of supporting a change in
8 indication, they simply don't based on the data
9 available. And that was the basis of my vote.

10 DR. SOMBERG: Well, I think it would
11 have been very helpful if we had the information
12 that could answer the critical questions of whether
13 this was an appropriate device for long term therapy
14 and whether it's appropriate for people who had a
15 relative contraindication to receive this device
16 because they had a higher likelihood of then being
17 appropriately transplanted. We didn't have
18 sufficient data on either of these points. But I
19 would like the sponsor and the other companies that
20 are present to hear that my objections were not that
21 we needed a randomized perspective controlled study
22 to prove this point, but there could have been a

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1 substantiation of the control groups, there could
2 have been data presented to show for instance group
3 one versus group two fared similarly or not
4 similarly. And these data sets were just not
5 presented, and that prevented us from when we wanted
6 to -- or at least where I wanted to see some
7 progress made in identifying patients who benefit
8 from long term device or patients who would be able
9 to be better decided as candidates. We just don't
10 have that data. So to approve a PMA without data is
11 to probably do more harm than good, and that's why I
12 voted yes on this negative proposition.

13 CHAIRPERSON LASKEY: Dr. Hirshfeld?

14 DR. HIRSHFELD: I think most of the
15 issues have already been articulated stated.

16 I came away from this discussion
17 convinced that patients in whom the efficacy of this
18 device has been demonstrated by the data that are
19 available to date are currently eligible for this
20 device under its existing labeling. And so I saw no
21 reason to expand the labeling at this point.

22 I think we'll eagerly await the results

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1 of the destination trial, because I think that will
2 -- if that trial shows efficacy, then that will
3 constitute a valid rationale for all of the
4 indications that the sponsor seeks.

5 CHAIRPERSON LASKEY: Dr. Weinberger?

6 DR. WEINBERGER: I think that the
7 sponsor probably didn't intend to create a new
8 concept, which is bridge to candidacy, but that's in
9 fact what you ended up doing. And that's a concept
10 which is a worthwhile concept to flush out with
11 clinical trials with evidence gathering at
12 scientific meetings. But in a forum to try to use
13 that new concept to define the change in labeling is
14 a very, very high threshold which frankly was not
15 sustainable by the data. And that's the reason why
16 it could not support the proposition.

17 CHAIRPERSON LASKEY: Dr. Lindenfeld?

18 DR. LINDENFELD: I, too, as Dr. Somberg
19 am not so concerned about the lack of a comparable
20 control group, although we spent time discussing
21 that. My decision was based on two things.

22 First, I believe right now the

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1 appropriate patients are not limited from getting
2 this device and being transplanted. But more than
3 that, if we're going to expand the indications, I
4 would like to see enough data to know that those
5 expansions are appropriate and that the outcomes,
6 even though the numbers are small, give us some
7 reassurance that when we expand those indications
8 that down the line these patients are actually
9 surviving a year or two post-transplant somewhere
10 near with the same results as patients who don't
11 have the contraindications. And we just didn't see
12 any data at all like that today. The only data we
13 saw is that they get transplant. And within that as
14 well, we don't know that these specific relative
15 contraindications would have the same outcome, that
16 is that a creatinine of 2.5 is just as safe to do as
17 somebody with a pulmonary pressure of greater than
18 60.

19 So I'm hesitant when we're not limiting
20 any of these patients, I'm hesitant to expand those
21 indications without some more data that it's the
22 right thing to do.

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1 CHAIRPERSON LASKEY: Dr. Bailey?

2 DR. BAILEY: Not very much to add.

3 I think I sort of agree that the
4 comparison control, though it might differ, is
5 really not the issue. And it's an issue of belief
6 and fact, and I think I believe that there is some
7 efficacy clearly in transplant eligible patients. I
8 think it's probably overestimated by the current
9 control treatment comparison, but it's there.

10 I also believe that you can extrapolate
11 it to some extent beyond the confines of the BTT
12 study. The question is where to draw the line. And
13 I think these data provide further information for
14 physicians as they make their decisions, but I don't
15 see how we can say that it's good evidence when it
16 just isn't.

17 It's terrible, because it's such an
18 important device and I'm sure it's very important to
19 be used, and for the indications to be as broad as
20 possible. But we have to make our decision based on
21 the data.

22 So that basically, for me it comes down

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1 to how good are the data within the BTT study for
2 extrapolating the performance of the device to
3 patients who were not eligible for the study. And,
4 you know, fortuitously there was a subset that had
5 some of these contraindications, but it could be
6 that these aren't a very unrepresentative subset of
7 all patients who would have been not eligible for
8 the study. So on scientific basis from a
9 conservative point of view, you just can't use the
10 data to extrapolate.

11 And that's the basis for my vote.

12 DR. TRACY: I think the sponsor's raised
13 a very important issue of the bridge to candidacy,
14 and I hope that the data that are here serve for
15 additional studies that can be done.

16 I think within the current indications
17 that the device is approved for there is room for
18 clinical studies that may not be solely sponsored by
19 industry. But I think that the data as presented and
20 trying to extract retrospectively information from
21 relatively small group without really overlap with
22 what might be clinical relevant, just doesn't quite

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1 meet the standards that I need to see, and that's
2 why I voted the way I did.

3 DR. FERGUSON: But I think it's
4 important for the record to indicate that the World
5 Heart device is not on trial here today. It's the
6 labeling change that's on trial. And I, like the
7 others at the table here, found it difficult to
8 justify changing the labeling either in anyway for
9 one of the two reasons, although my gut reaction
10 tells me that that's the thing to do, the data
11 simply is not there.

12 DR. YANCY: I supported the
13 recommendation, which was a vote against not the
14 paradigm, but rather the pre-market application
15 because I not only support the paradigm in clinical
16 practice, but I have respect for the sponsor for
17 making this and other platforms available for a very
18 difficult patient population when there is an
19 incredible need for mechanical support. And I have
20 tremendous respect for the consultants today, who I
21 think did an admirable job with the database that
22 was compromised for the way in which it was used.

1 So I respect both the presenter and the
2 sponsor for coming forward and making this effort
3 and raising new questions. And I hope that today's
4 vote does not work against any momentum to answer
5 these important questions and to believe that a
6 registry or some other clinical experiential format
7 will be the kind of way that we can go about doing
8 this. As a clinician I understand it is incredibly
9 difficult to do an evidence based
10 scientific/rigorous trial in this patient population
11 But as we all know, there are other ways to get the
12 same sort of data.

13 So, I hope that this has been a valuable
14 experience for all involved and we can move forward.

15 DR. KATO: I would also like to
16 congratulate the sponsor for bringing to light this
17 issue of bridges to candidacy. I have to agree with
18 Dr. Ferguson that my vote of not approvable was for
19 the labeling and not for the device itself.

20 I would like to echo Dr. Yancy's
21 comments though that it is vitally important that on
22 a going forward basis that the sponsor does try to

1 establish a database for all of their patients and
2 try to glean as much data that is potentially
3 possible from these very, very critically ill
4 patients so that we can learn something for the
5 future. Because it very well may be that a strict
6 randomized prospective study may or may not be
7 possible, but if you can at least give us a very
8 granular presentation of the data that you do have
9 from the entire experience of your company, I
10 believe that that would be a valuable asset for
11 future presentations.

12 CHAIRPERSON LASKEY: And for my part, it
13 just was begging for some evidence to support what
14 the LVAS does in these patients, the delta. And
15 something as simple as a multivariable analysis with
16 the delta improvement in variable X, Y, Z would have
17 been nice to see. But that is what you were trying
18 to sell, it's just that you didn't have any data to
19 support changes with the device.

20 With that, I'd like to thank my
21 colleagues on the panel, thank the sponsor, thank
22 the agency for a superb job.

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1 And I'd like to close today's session,
2 concluding the report and recommendations of the
3 panel on PMA P980012 supplement 4 from World Heart
4 for the Novacor N100PC and N100PC(q). Thank you
5 all.

6 (Whereupon, at 3:16 p.m. the panel was
7 adjourned.)

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CERTIFICATE

This is to certify that the foregoing transcript in the
matter of: Circulatory System

 Devices Panel

Before: DHHS/PHS/FDA/CDRH

Date: June 8, 2004

Place: Gaithersburg, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.


