

1 difference what that analysis shows.

2 Frankly, I'm looking for things
3 that would be a signal that, you know, the
4 safety and efficacy isn't shown. But this
5 looks like it ought to go off the table, and I
6 wonder what other people think about that.

7 DR. VASSILIADES: I'd like to make
8 a comment about that. Just in looking at that
9 data, some of the sites, not to mention any
10 sites, some of the sites have a reputation of
11 doing a tremendous volume of VADS and
12 transplants, yet some of those sites had the
13 worst performance or significantly lower than
14 the average for the entire study.

15 I think perhaps the sponsor can
16 provide us some additional insight into that.

17 But I would be troubled, as you are to some
18 degree, perhaps moreso, that certain sites
19 that I consider VAD specialty places didn't do
20 very well. I'm concerned about that.

21 DR. DOMANSKI: The concern I have
22 is small numbers, difficulty adjusting. I'm

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1 beginning to wonder how to use this at all.

2 DR. YAROSS: I'd also like to point
3 out that there seems to be a significant
4 difference on this issue between the data in
5 our panel pack, in the FDA summary and what
6 was just presented on the slides.

7 If you look at Slide 64 and then
8 contrast that with page 19 of the FDA summary,
9 and I think this gets to what the last speaker
10 just, last panel member just commented on,
11 there is one site, Site Code 6, that had 12
12 patients and shows a 16.7 percent success
13 rate.

14 Yet in the FDA presentation a
15 moment ago, the center with 12 patients had a
16 41.7 percent.

17 So you know, what I would ask is if
18 FDA can please clarify which of these is the
19 correct presentation. That might help on this
20 issue.

21 MR. CHEN: I can do that. The
22 information that's provided in the panel pack

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1 was data based on March 16th, for the primary
2 cohort. The data that's shown in the
3 presentation and in the slides is based on
4 September 14th, 2007.

5 So what's being shown on the slides
6 and what you have is the most up to date
7 success rates for each hospital.

8 DR. NORMAND: Can I just clarify
9 Dr. Domanski's, give you at least the
10 statistician's viewpoint of the need for
11 adjusting. The question about poolability is
12 whether or not in your analysis you need to
13 account for the fact that the observations
14 within each of these sites are independent or
15 not.

16 That's related to the poolability.

17 What we mean by poolability is whether or not
18 you need to account for the fact that the
19 patients are clustered within a site. So let
20 me finish. No, let me finish.

21 So the reason why that's important
22 is because the standard analyses do not do

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1 that, and in fact you're supposed to do it.
2 If you do do it, the confidence intervals are
3 wider.

4 So it's not -- I guess I would
5 argue strongly, it's not an issue that's off
6 the table. It's standard statistical practice
7 that you adjust for clustering within the
8 hospitals.

9 DR. DOMANSKI: Yes. My problem is
10 not that I don't know everything you just
11 said. The problem that I'm having is I think
12 that my concern -- well, I'm sorry, but you
13 know -- well let me finish now.

14 I think the issue that I'm having
15 is that I'm not sure that they have the data
16 to make the adjustment. That's the concern I
17 have. So I don't, you know, it's kind of
18 garbage-in garbage-out on an analysis.

19 You can do a very fine analysis,
20 but if the data that you have really are
21 insufficient to make it a valid analysis, and
22 that's the concern I have.

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1 Now I'm not -- I'm concerned that
2 that's the case, but not convinced. That's
3 why I'd like to hear the wisdom of the panel
4 about that.

5 DR. NORMAND: Well, I thought you
6 had asked for at least the statistician's
7 viewpoint. So hence my reaction. Clearly
8 other people can comment on it.

9 But I just -- I would suggest that
10 the way this data, I would interpret the
11 poolability of the analysis, is whether or not
12 -- we know if you adjust for the fact that
13 there's clustering, the confidence interval's
14 going to get wider, okay. So it's only going
15 to make it worse for the sponsor if you adjust
16 for the clustering.

17 So you are right, that even if they
18 go and adjust for the patient characteristics,
19 it's still going to be a wider interval by
20 definition than the interval presented by
21 ignoring the site effects.

22 So it's not going to change the

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1 assumption about -- it's not going to make the
2 confidence interval any shorter than it
3 currently is. So that's going to be the
4 outcome of this.

5 Whether it's 60 percent or 62
6 percent, it's not going to be 65 percent for
7 the lower limit.

8 So that's the outcome of what's
9 going to happen here, because when you add
10 variability, what this is doing is it's going
11 to make the confidence interval wider.

12 So that's a fact, and it doesn't
13 matter -- I'm not talking about adjusting even
14 for patient characteristics.

15 DR. DOMANSKI: Do you think we have
16 the ability to make this kind of adjustment?
17 I mean do we know enough to put into a model
18 the things you need to have to adjust? I
19 guess that's a more general question for the
20 panel, rather than just a statistical one.

21 DR. NORMAND: So he doesn't want
22 me to answer anymore, but I'll stay one more

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1 thing and then stop. That is that at the very
2 least, you need to adjust for site
3 characteristics, and the site characteristics
4 is actually the site identifier.

5 Whether you need to adjust for
6 patient care, that's clearly a clinical
7 question and not a statistical question.

8 DR. LINDENFELD: Yes. I'd like to
9 just make one comment on this issue. It seems
10 like while I understand that talking about
11 post-market approval is no confidence for
12 approval, that we'll need to suggest a post-
13 marketing approval study.

14 We have already seen this wide
15 variation in sites. In some way, I would like
16 to see the post-marketing approval study
17 address that. I'm not sure how. We may have
18 some suggestions.

19 But if there are truly these huge
20 differences in success, how do we evaluate it
21 and how do we address that? That seems to me
22 to be one thing that we may want to at least

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1 start to try to get at in a post-marketing
2 approval study.

3 CHAIRMAN LASKEY: And we will get
4 to that this afternoon. We'll incorporate
5 that. But there's much more to site to site
6 variability, as Tom's alluding to.

7 I mean it's a very complex
8 variable. It can't just be encoded by site
9 number one-two-three-four-five. Dr. Page?

10 DR. PAGE: Yes. Dr. Swain, you
11 alluded to the fact that the performance goal
12 was based on the actual transplantation
13 statistic, and in your presentation, you
14 implied that kind of yes, it was being
15 generous to allow the 180 day still listed in
16 that performance goal.

17 But just for my information, the
18 data on which the performance goal was based,
19 that was not limited to 180 days, was it?
20 That was longer-term eventual transplant; is
21 that right?

22 DR. SWAIN: Yes. Nothing to do

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1 with 180 days; survival to transplant only.

2 DR. PAGE: Okay. So realistically,
3 for us to have some sort of end point for the
4 study, that was the compromise, that you, the
5 FDA and the sponsor, felt was reasonable at
6 180 days, and I'd agree with that.

7 I'm actually troubled by the post-
8 approval study design, and I'd just like to
9 know whether there has been any discussion or
10 negotiation between sponsor and FDA to this
11 point, and if not, why not?

12 DR. TAVRIS: Yes, we have been
13 discussing certain issues, and the issues that
14 I brought up today were those that we wanted
15 input from the panel on before going further
16 with them, before going further with the
17 discussions with the sponsor.

18 DR. PAGE: The reason I ask because
19 it seems like that the proposed post-approval
20 study is fairly far off the mark of what I
21 would have expected, and what I imagine the
22 FDA would have expected. That's why I'm a bit

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1 puzzled by the difference.

2 DR. TAVRIS: Well, we did iron out
3 some things, and the other things that I think
4 are important to be ironed out are the issues
5 that I brought up today.

6 After we receive input from the
7 panel on those issues, then we'll discuss
8 further with the sponsor.

9 DR. ZUCKERMAN: Let me just say in
10 a generic context, Dr. Page, it's not unusual
11 for FDA and the sponsor to be wide apart on a
12 post-approval study.

13 That's why the input that an
14 independent advisory panel can give regarding
15 the key post-approval study questions is often
16 extremely important.

17 It's a key part of our questions
18 this afternoon, and I know this panel will pay
19 attention to that question.

20 DR. PAGE: Thank you, and the
21 reason I ask is that it is -- I recognize that
22 fact, Bram, but this just seems so far off the

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1 mark. It's further than I've seen before.

2 DR. ZUCKERMAN: I think, as the FDA
3 presentation has indicated, the way in which
4 data are being collected and analyzed in
5 general in this field is perhaps not
6 appropriate for the very serious problem that
7 these important devices are trying to address.

8 Hence, we hear about the important
9 NHLBI effort; we need to hear from an
10 independent advisory panel as to how the post-
11 approval study phase for any of these devices
12 can fully compliment our learning and improve
13 the total product life cycle development of
14 these devices.

15 CHAIRMAN LASKEY: Yes, Dr.
16 Blackstone.

17 DR. BLACKSTONE: I found the
18 discussion of performance goals and OPCs
19 rather confusing this morning. We were told
20 by the sponsor that the OPC was based on
21 Thoratec in-house data.

22 Then we were told by the FDA we

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1 should be talking about performance goals on
2 Slide 50. Yet on Slide 52, you use OPC.

3 You both come up with the same 65
4 percent. Let me just call it "performance
5 criterion," because I don't know whether you
6 want to call it a goal or an OPC. Could you
7 please unconfuse us?

8 DR. SWAIN: Well, in 2001, we
9 started working on a performance goal, and had
10 external, internal FDA experts deciding and
11 looking at the literature. Presented this to
12 HFSA; had a public airing of it, and that
13 became the FDA's stance as a performance goal
14 of 65 percent.

15 Then I believe two years later, two
16 years after that, this study came in with a
17 proposal using in-house, their own device
18 data, which happened to match ours,
19 fortuitous, whatever.

20 So we view that that was the
21 performance goal we were going to go with, and
22 it's nice -- if the company or any company

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1 would have proposed a performance goal of
2 let's say they had some data and it was
3 internal data and it was 20 percent, we
4 wouldn't have agreed to it. We would have
5 said 65.

6 So it's fortunate that those came
7 up to match the one that we had publicly
8 stated was our goal, and we don't have that
9 data to know that that's the case. I assume
10 that that's the case. So it's fortuitous.

11 MR. CHEN: And I'd also like to
12 just comment, in addition to that, the
13 literature articles that we use to develop our
14 performance goal included devices that were
15 approved by FDA.

16 A couple of the devices in the
17 literature reports are devices owned by the
18 company, as well as -- and owned by other
19 competitors. So it's fortunate, as Julie
20 said, that the performance goal came out to be
21 the same number.

22 CHAIRMAN LASKEY: It's also

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1 unsettling, but Dr. Massie.

2 DR. MASSIE: I'd like to follow on
3 this. I'm philosophically challenged here by
4 this goal or criteria as well largely, I
5 think, because I come from a background of
6 evaluating drugs, and we always have control
7 groups and we usually have bigger numbers.
8 We've faced some of the other challenges.

9 So I want to ask FDA to give some
10 feedback, philosophical feedback. It's nice
11 to quantify and nice to have quantifiable
12 standards. But every step of developing this
13 quantifiable standard is quicksand.

14 We've got historical controls which
15 change with time. We have changing
16 interpretations of what's a success or not,
17 although to the credit it's written in the
18 protocol and we should follow what the
19 protocol says. I do believe that that's a
20 very important thing to do.

21 But one failure in my thinking is
22 we're calling it a goal. It's not a

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1 criterion, maybe. I would like to interpret
2 this as a goal and even frankly coming from
3 drugs, where we have two controlled studies
4 and P values, sometimes we don't have enough
5 data.

6 I remember the first drug that we
7 evaluated for primary pulmonary hypertension,
8 prostacyclin, something that seems to work,
9 does seem to save lives. We had two studies,
10 well-enrolled. About the same, total of 200
11 patients, 100 each. Neither had a P value of
12 .05, and the committee voted unanimously to
13 approve it.

14 So do you see this really as a
15 fuzzy goal or an absolute target? Because
16 frankly, almost all the discussion and the
17 tilt of all the presentations was to try to
18 convince us one way or another on that.

19 DR. SWAIN: Well, my personal
20 opinion is a fuzzy goal between those two
21 options. You have to kind of look at -- I'm
22 kind of a student of history.

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1 We've got five approved devices,
2 and those devices were approved on comparison
3 to nothing, sort of like, you know, the Meets
4 playing a baseball game and at the end of the
5 game, they had four runs.

6 What does it mean? If they're
7 playing the Yankees and the Yankees had two,
8 they'd win. If they Yankees had six, they'd
9 lose.

10 So you have five previous devices
11 and when we go by this level playing field,
12 that's part of the statutory law. So any
13 company can propose a randomized control study
14 against an approved device. But business-plan
15 wise, that's probably not what you would
16 propose.

17 So we're stuck with either saying
18 let's have another study with no comparator at
19 all or a comparator that everyone realizes is
20 just not a comparator, or a randomized study,
21 and again we have a hard time requiring that.

22 Or, could we come up with our best

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1 effort in literature that the investigator,
2 the field has not stepped up to the plate to
3 have common reporting like for heart valves,
4 which was developed in the 90's, and all the
5 journals published.

6 So this was the best we can do, and
7 we're giving you all the limitations of that
8 data. So to say that again, you have a
9 statistician and a secretary. 65-65, win or
10 lose. That's probably not the way you want to
11 think of it.

12 And most importantly is things are
13 changing. You keep hearing about INTERMACS,
14 and do we anticipate in another five years
15 that we're going to have studies against a
16 performance goal that is derived from early
17 1990's literature? Most likely not.

18 What we now have is a relatively
19 well-collected registry that's going to give
20 us data, that you're going to have a
21 concurrent ability for comparisons. We're
22 working very hard to make things different.

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1 CHAIRMAN LASKEY: That's actually
2 the first that we've heard anything more about
3 INTERMACS than INTERMACS. So we're kind of in
4 a void at the moment, speaking collectively.

5 We keep hearing about this as
6 coming to the salvation. But I hope we hear
7 about INTERMACS this afternoon. Okay, Dr.
8 Somberg, Edmunds, and Tom and then we'll break
9 for lunch.

10 DR. SOMBERG: Well, I'm glad Dr.
11 Massie brought that up. I do come from the
12 drug; I'm a pharmacologist and been involved
13 with cardio-renal for a long time. So I know
14 where you're coming from, and it's very
15 different in devices. After being on this
16 panel a couple of years, I can tell you that
17 with surety.

18 The performance goal is another
19 approach to development, and it's one with
20 these quote-unquote "small populations," very
21 difficult studies. Whether that's justifiable
22 or not I think is way beyond the purview of

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1 this committee right now and this particular
2 sponsor's problem.

3 But what I would say is that once
4 you get into that, and once you buy that
5 system, you are sort of locked into meeting
6 the performance goal. Otherwise, you have
7 nothing.

8 So this idea, I must say, of fuzzy
9 or hard, is really, you know, a one choice.
10 We have to be hard, and we have to say you
11 have to meet that.

12 With that said, I think you have to
13 take clinical decisions into account. There
14 are a lot of nuances here and it's in the
15 details.

16 I think that the pivotal question
17 is is do you take the small study; do you
18 combine it with the additional patients who
19 have a small body surface area, and then you
20 combine it with the other additional patients,
21 who didn't meet the transplant listing
22 criteria, which is also arbitrary.

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1 But at some point, we have to
2 figure out if the totality of the clinical
3 data meets the performance goal or it doesn't
4 meet the performance goal. We can't say it
5 didn't meet the performance goal, in my
6 opinion, but it should be approved anyway
7 because it looks good or it looks bad.

8 I mean we have to settle for a
9 goal. But I think our discussion should focus
10 on which group is appropriate for this
11 consideration of approval or non-approval for
12 this sponsor.

13 I see a lot to be said for
14 understanding that it's the total number of
15 patients that were entered here, and that
16 being listed or not being listed may be a
17 secondary issue that wasn't anticipated and
18 was put into the mix maybe inappropriately.

19 But I don't want to go back and
20 argue this performance concept here, because
21 gee whiz, that would take away about what, 25
22 percent of your potential work, Bram et al.,

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1 at the agency? You had a lot of performance
2 goals.

3 DR. ZUCKERMAN: At least. While I
4 can understand the disquiet of some of the
5 experts around the panel regarding this type
6 of trial design, I must agree with Dr.
7 Somberg, and remind everyone that this is a
8 Center for Devices advisory panel.

9 This is a very important panel
10 meeting, where we critically need your input,
11 with the appropriate caveat. You need to
12 operate under the rules of the Center for
13 Devices. If we operate under the rules for
14 the Center for Drugs, then you're important
15 input doesn't help us make a decision,
16 unfortunately, on this device, and just as
17 importantly, advance this field.

18 CHAIRMAN LASKEY: Thanks, Bram.
19 John, can I assume that those comments were
20 ordinarily reserved for the afternoon portion,
21 where we all speak to each other, or was that
22 a question to the agency?

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1 DR. SOMBERG: Well, it wasn't a
2 question. It was a comment to the agency,
3 because I sort of had gotten the drift that we
4 were not trying to -- it was both to the panel
5 members and the agency, that we should focus
6 in on our charge today, which is did this
7 study or did this not meet the criteria for
8 acceptance or rejection.

9 CHAIRMAN LASKEY: Okay. Well,
10 that's our job after lunch. Hank?

11 DR. EDMUNDS: I think we could use
12 a transfusion of common sense, and you know, I
13 think we need to settle, as soon as possible,
14 on which cohort we're going to evaluate, and
15 decide that.

16 Then we can give up disputing
17 whether 65 is different from 64, or whether or
18 not they're close enough for government work.

19 As I understand statistics, and I
20 know less statistics than any one person in
21 the room, what that 65 percent confidence
22 limit is is that the probability of the

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1 Kaplan-Meier curve at that end point, 180
2 days, has only a five percent chance of being
3 wrong instead of a six percent chance of being
4 wrong.

5 Well, if I'm going to invest money
6 and I have a 94 percent chance of earning a
7 higher return, I think that's probably a
8 pretty good risk. We're betting lives, not
9 money.

10 CHAIRMAN LASKEY: Okay. I'm going
11 to -- Mike, one more point, and then I think I
12 would like to leave us all with a note that
13 when we come back, we will quickly get our
14 arms around what it is that we're supposed to
15 get our arms around, because otherwise we will
16 continue to flail all afternoon.

17 So I agree with Hank, about
18 focusing in on -- and Dr. Somberg, focusing in
19 on the population we're discussing here.

20 DR. DOMANSKI: Yes, and I guess
21 this will be my last comment on that score.
22 But you know, I think in doing this, we don't

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1 have a major, you know, we don't have a
2 randomized trial. We have performance
3 criteria.

4 We have all sorts of data, and I
5 really think it's going to be important to
6 take into account the entirety of what we're
7 looking at, and not sort of try to develop a
8 formalism that makes things easier than, you
9 know, they reasonably are.

10 I really do think we need to look
11 at the totality of data, and not just hone in
12 on one piece of it.

13 CHAIRMAN LASKEY: Again, that's the
14 purview of our conversation this afternoon.
15 So are there any more questions for the
16 agency? For the agency? Tom, go ahead.

17 DR. VASSILIADES: This is a
18 question. Actually Eric, you might be the one
19 to field this question.

20 Given the Heartmate II is a low
21 pulsatility device, perhaps one of the first,
22 if not the first on the market, and there are

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1 no specific end points to which you've looked
2 at end organ responses to that sort of device,
3 help me to understand how the agency felt
4 assured to design a study like this with the
5 sponsor, given there was nothing to look at
6 that?

7 Was it -- is there compelling pre-
8 clinical data, or did you also amass and
9 review the OUS clinical data?

10 But on the one hand you've
11 mentioned that this is a fairly new,
12 theoretically approach to assist devices, and
13 yet we don't have specific criteria, looking
14 at the end organ effects of that. So please
15 help me to understand that.

16 MR. CHEN: I think when we were
17 approached by the sponsor in regards to this
18 trial, we did look at the OUS data and we're
19 not majorly concerned with the adverse events
20 that we saw.

21 There is ways that you can perform
22 flow visualization through a pump, to

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1 demonstrate, to look at the flow patterns
2 through the pump.

3 It only -- it doesn't provide you
4 with information in regards to end organ
5 function or reduced pulsatility, and you can
6 kind of see that from animal testing. But
7 animal testing only provides you with so much
8 information, based on the type of animal that
9 you have, if it's a heart failure animal and
10 so forth.

11 Animals are very expensive, you
12 know. It's difficult to keep an animal alive
13 for 30 days with a ventricular assist device.

14 So given the very lack of
15 information and difficulty in saying that --
16 in requiring the company to perform some type
17 of engineering test to demonstrate
18 pulsatility, we weren't able to say, you know,
19 we can't have you move forward.

20 With that caveat, however, patients
21 that do have these devices, they do have a
22 pulse and they do have differences in

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1 pressures. It's just that the pressure
2 difference is reduced. Depending on how you
3 operate on the patient and depending on pump
4 speed.

5 So if a patient is nominally
6 running at 8,000 RPM, you have a higher pulse
7 pressure than compared to a patient that's
8 running at 12,000 RPM.

9 So depending on how you adjust the
10 pump speed, based on the need for circulatory
11 support for the patient, in some ways there is
12 pulsatility. It's just a reduced effect. I'm
13 not sure if that answers your question or not.

14 DR. SWAIN: Let me just comment.
15 We do have end organ data. Neural data, liver
16 data, renal data. Again, it's a one-armed
17 study, and against literature. So there's no
18 obvious defects in end organ perfusion. But
19 we have data on virtually all of the important
20 end organs.

21 DR. EDMUNDS: I generated some of
22 that data in rhesus monkeys. Leonard Goldman

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1 at the Cleveland Clinic had calves on
2 pulseless circulation for I think five or six
3 months.

4 There are data, and nobody has ever
5 shown that you have to have a pulse to nourish
6 all the cells of the body. I don't think we
7 need to revisit that.

8 CHAIRMAN LASKEY: Okay, and we
9 won't.

10 (Laughter.)

11 CHAIRMAN LASKEY: I want to thank
12 the panel, thank the FDA, and let's break for
13 lunch. I have twelve o'clock.

14 I think really, realistically, if
15 we're going to get people out of here to the
16 airport, we ought to be back in this room at
17 12:45. So please, let's try and reconvene at
18 12:45. Thank you.

19 (Whereupon, at 12:04 p.m., a
20 luncheon recess was taken.)

21 CHAIRMAN LASKEY: I wish that my
22 colleagues were as punctual, but we should

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1 resume, and we'll proceed with a panel
2 discussion with a review of this morning's
3 reviews, and we'll start with Dr. Lindenfeld
4 as the primary reviewer.

5 Panel Deliberations

6 DR. LINDENFELD: Thanks, Warren.
7 Let me just summarize. So we are asked to
8 review the Heartmate II for approval as bridge
9 to transplant, based on the primary end point
10 of patient survival to cardiac transplant, and
11 180 days of that support, while remaining
12 listed as 1A and 1B.

13 We're asked to do something a
14 little bit new we haven't before, this
15 performance criteria. Based on the 126
16 patients that we saw that formed the group, we
17 see that the study didn't really quite meet
18 that performance criteria with a lower
19 confidence interval of 64 percent.

20 Now we have also seen very wide
21 confidence intervals of that, and we've seen
22 that the variation in the results by site

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1 contribute somewhat to that broad confidence
2 intervals.

3 We also see that this matches the
4 Heartmate XVE data pretty closely. But I
5 think what we haven't seen yet that we hope to
6 see this afternoon would be some demographic
7 data, at least showing us that, helping us to
8 feel comfortable that the risks for this group
9 were very similar to the Heartmate XVE data.

10 Then again I think we've seen a 20
11 percent mortality in this study. I think we'd
12 like to just feel comfortable that, as I
13 mentioned earlier, that this is a little bit
14 higher than one might have expected, at least
15 from the destination therapy.

16 Not only is it a little bit higher,
17 but the destination therapy data were patients
18 ten years older, a little bit higher risk
19 group. So it's a little bit more concerning
20 about the mortality. We'd like to see
21 something about that.

22 Now I think we've seen some issues

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1 in terms of subgroups. So we understand that
2 women seem to have a particularly high
3 incidence of reoperation and bleeding, and
4 success rates are not as high.

5 One of the really important
6 features of this device is that it can be used
7 in smaller people, and I think won't be
8 restricted to people just under 1.5 obviously.

9 But I think women are more likely
10 to get this device. They will be smaller. So
11 we've seen some concerns about the outcomes in
12 women particularly.

13 I think we've seen data that look
14 as if this device improves exercise and
15 quality of life, and I believe that. I'm
16 concerned, though, about the neurocognitive
17 function that we've seen.

18 I mentioned earlier that in
19 general, just a surgical procedure on bypass
20 substantially decreases neurocognitive
21 function. So I'm concerned that although we
22 see -- in two of the domains we saw an

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1 improvement, in three domains we didn't see
2 any improvement at all, which suggests that
3 the decline that comes from surgery was not
4 improved in those three.

5 So I don't know that I can make
6 much of that, but I'm concerned that the
7 neurocognitive data definitely does not, in my
8 view, support an approval over what might just
9 be expected in any postoperative patient.

10 I think that gets to whether or not
11 what we do about neurocognitive testing in
12 these patients.

13 Another comment about
14 neurocognitive testing is that some of these
15 tests don't just have a question domain, but
16 they have a time domain. That is, part of the
17 result is based on how quickly you do them.

18 So the baseline may not depend on
19 just what your cognitive function, although
20 there are cognitive tests, but it may depend
21 on your physical functioning. Because if you
22 can't -- if you're shaky or weak and can't

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1 complete the time, in a reasonable time
2 period, that affects the test, not just the
3 cognitive part of it.

4 Furthermore, on the neurocognitive
5 testing, there is a learning parameter, so
6 that patients when they repeat the test,
7 particularly fairly bright patients, have a
8 very rapid learning situation. So that they
9 learn from the test to do better on the next
10 test.

11 That was seen in the coronary
12 bypass study, that there was a substantial
13 learning effect from six months, six weeks to
14 three months. I think again, when these
15 neurocognitive tests improve, they should
16 improve just being post-op. Then they will
17 also improve from a learning function.

18 So as we look at neurocognitive
19 tests, I think for this type of study and
20 hopefully I know we have a neurocognitive
21 expert -- I think Thoratec has one that can
22 comment on this.

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1 But in general, when you repeat
2 these measures, particularly in a pretty
3 bright group of patients, there are some
4 neurocognitive tests that account for the
5 repeated measures.

6 So that it tests the same things,
7 but there are different questions testing the
8 same things so that there isn't a learning
9 effect. I think if we're really going to
10 look, if we're really interested in looking at
11 neurocognitive functioning, then we need to
12 evaluate that as well.

13 Then I think the other concern that
14 I still would have is that again, talking
15 about post-marketing approval, does not imply
16 anything about approval.

17 But in a post-marketing study, I
18 think it's going to be important for us to
19 discuss these issues of particularly sex and
20 how women do and smaller people, and to make
21 sure that we can understand them.

22 And also, I still think it's

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1 important to understand differences in
2 centers. Are there differences in centers
3 because they pick different patients or
4 because there are differences?

5 As you've outlined in the training
6 manual, there needs to be training for this
7 device. Are there differences here because
8 there are actually surgical techniques or
9 misunderstanding of how to use the device, or
10 are we just enrolling patients?

11 I think that will be important to
12 discuss as well.

13 CHAIRMAN LASKEY: Thank you, Dr.
14 Lindenfeld. Does anyone on the panel have a
15 question or a follow-up to what JoAnn just
16 said? Tom?

17 DR. VASSILIADES: I just want to
18 clarify something, and I may be wrong. But I
19 thought that, at least during Dr. Pagani's
20 presentation, that he pointed out the
21 operative mortality or the 30-day mortality
22 for the Heartmate II was ten percent. That

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1 compared to 20 of the existing approved
2 device. I thought you said 20 percent.

3 DR. LINDENFELD: I believe 25
4 patients died in the study. That's at 180
5 days, and that was 20 percent.

6 DR. VASSILIADES: Oh, okay. You're
7 talking about 180 days. Okay.

8 DR. LINDENFELD: 180-day mortality
9 I think is 20 percent.

10 DR. VASSILIADES: Right. I was
11 talking more of operative mortality. Okay.

12 CHAIRMAN LASKEY: Good, okay.
13 We'll proceed with Dr. Blackstone's remarks.

14 DR. BLACKSTONE: My review will
15 focus primarily on effectiveness, but briefly
16 on safety and the post-market approval study.

17 Effectiveness. There's no doubt
18 this device was effective in saving the lives
19 of many patients in irreversible heart
20 failures we've heard about today.

21 However, the criterion for
22 effectiveness for this device was not couched

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1 in quite those terms. Effectiveness was pre-
2 specified in this single-arm multi-center
3 trial, on the basis of survival to transplant
4 or 180 days of LVAD support, with the caveat
5 of UNOS status 1A or B.

6 From at least some analyses, the
7 primary study did not quite meet the goal of a
8 lower 95 percent confidence limit of 65
9 percent. There is some dispute about this
10 between the sponsors and FDA, and it really
11 revolves around appropriateness of the
12 analysis, which I have chosen as my focus.

13 I submit that the form of analysis
14 apparently formulated to evaluate
15 effectiveness and presented in the panel pack
16 by sponsor and FDA, defies mathematical
17 reasoning, so much that the tables portraying
18 effectiveness are uninterpretable.

19 The sponsors comes close to a
20 reasonable analysis in the proposed
21 alternative approach, but even that has
22 problems.

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1 Here are the inescapable facts.
2 Support on this device was intended to be
3 short, bridge to transplantation. Therefore,
4 patients will be on this device a highly
5 variable amount of time, from a day or so to
6 perhaps many days and even years.

7 Patients will cross over to
8 transplantation as hearts become available. A
9 few recover and are removed from the device.
10 Some die on the device.

11 Actually sometimes, the device must
12 be discarded and another placed, and this was
13 a particularly pesky problem to which we must
14 return.

15 By 180 days, perhaps a third of the
16 patients will still be alive and maintained on
17 the device. A good number will have been
18 transplanted. Some have died, and a few will
19 be removed from the device as their heart
20 recovers.

21 This is a classic example of a
22 multi-state problem of competing risks of

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1 time-related events, with patients migrating
2 to one state or the other, and being censored
3 from the state of alive and on LVAD support.

4 Amidst this relatively rapid change
5 in state, I believe the fundamental question
6 must focus on the device that is the object of
7 this submission, and the question is how best
8 to assess effectiveness from the standpoint of
9 the time-relatedness of the end point.

10 The method presented in the panel
11 pack, a simple counting method, demonstrates
12 inadequacies when estimates of effectiveness
13 are shown to be exceeding volatile, rather
14 than progressively stabilizing as follow-up
15 continues. Even intra-institutional results
16 changed.

17 At the risk of appearing to be
18 condescending or offending both sponsor and
19 particularly the FDA, let me remind you why
20 all of this consternation about counting is
21 unnecessarily complex.

22 1662, John Graunt introduced the

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1 hazard function, based on the Bills of
2 Mortality in the City of London. 1693, Edmond
3 Halley introduced a modern non-parametric
4 method to estimate survival.

5 1766, ten years before this country
6 was founded, Daniel Bernoulli introduced
7 disease-specific analyses, which became known
8 in demography as multiple decrement analysis,
9 and in statistics as competing risk analysis.

10 In 1950, Berkson at the Mayo Clinic
11 realized the folly of cancer investigators
12 insisting on only assessing survival in so-
13 called evaluable subsets of patients, who had
14 reached certain follow-up milestones,
15 introducing them to the 1912 Society of
16 Actuaries pamphlet on censored data analysis.

17 1952, Edward Kaplan at Bell Labs
18 and Paul Meier at Hopkins published the most
19 cited paper in the medical literature on the
20 product limit method for estimating survival.

21 In 1972, and I'll quit with history
22 with that, Wayne Nelson of GE introduced a

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1 general method to estimate the cumulative
2 hazard of repeating events, which is very
3 important in the safety aspect of this device.

4 These methods, ranging from 35 to
5 345 years old, were devised to facilitate
6 accurate, stable counting methods for time-
7 related events, in the face of censoring.
8 They are essential for estimating in
9 quantities we are faced with today, not only
10 for evaluating effectiveness but safety as
11 well.

12 The material in our panel packs
13 demonstrate clearly why of necessity these
14 methods had to be developed. You have seen
15 some effort, of both sponsor and FDA, to
16 recast some of the data into this framework.

17 But this too has introduced
18 additional confusion that I'll attempt to
19 address. First, a time-related analysis of
20 some type is the appropriate way to answer the
21 question of effectiveness.

22 Second, this time-related analysis

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1 must of necessity be some form of competing
2 risk analysis, but the question is of what
3 type.

4 If we look at Figure 15 of Section
5 7.5 in the panel packet, you'll see a classic
6 example of competing risks, and this was
7 actually shown by the sponsor. It shows what
8 might be called the net results at any moment
9 of time, of the competing migration of
10 patients into one of several mutually
11 exclusive states, from the primary state of
12 being alive on the device, to transplant,
13 death or weaned.

14 If I can get this thing to go
15 another step. There we go. The graph will of
16 necessity be altered by the rate at which
17 transplantation is performed, for example.

18 Therefore, I believe the
19 appropriate form of competing risk assessments
20 is the marginal probability of survival on the
21 device. This may be approximated by the
22 Kaplan-Meier estimate, with migration to all

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1 other states serving as censoring mechanisms,
2 which is depicted on Figure 14 of Section 7.5.

3 It shows the estimate of 180 day
4 survival as if the device had been used for
5 destination therapy and transplantation was
6 not an option. Appropriately, a couple of
7 papers on which the performance criterion was
8 generated related to Dr. Rose's destination
9 therapy study.

10 95 percent lower confidence limits
11 seem barely to be above the 65 percent figure.

12 However, there are some important caveats.

13 One, unlike a cross-sectional
14 follow-up by which we can be reasonably
15 certain that censoring the patients is non-
16 informative, it is by no means certain that
17 the censoring mechanism of cardiac
18 transplantation is similarly non-informative,
19 as is implicit in the ordinary Kaplan-Meier
20 estimates.

21 Two, no account is taken of
22 poolability or patient factors that may play

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1 into this issue.

2 Three, the confidence limits would
3 narrow if the two studies were pooled
4 carefully, with attention to differences
5 between groups.

6 You suggest this for the labeling
7 cohort, but astonishingly you suggest using
8 only so-called evaluable subsets of patients,
9 rather than the entire combined cohort for no
10 defensible scientific reason.

11 Four, however I suggest that one
12 could argue that the cases of device failure
13 resulting in exchange should all be considered
14 a failure mode, and this could raise the total
15 failure, death of patient and device, to
16 perhaps 30 percent, with a 95 percent
17 confidence limit that may or may not reach the
18 target level.

19 Fifth, the question about small BSA
20 is not one that should be lightly dismissed.
21 It is possible there is no difference, but
22 remember that women are smaller than men, and

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1 the decreased safety profile on women is
2 confounded with BSA.

3 So briefly safety. How I long for
4 a cumulative incident graph of every repeated
5 safety event. We are told the hazard function
6 is highest early after implant, and therefore,
7 linearized rates are not applicable.

8 We know this is true of previous
9 devices. It's probably not simply because
10 transplantation is rapidly removing patients
11 from LVAD, but we don't know that. How I also
12 long for a context for these from past
13 experience with pulse devices, and especially
14 if it were concurrent.

15 We're giving the reassurance that
16 adverse events rates are similar to or better
17 than currently approved Thoratec devices, but
18 only a white paper is offered, a selected data
19 for the vented electric device.

20 Alas, we can only work from the
21 anecdotal counting and descriptive information
22 we are given. Bleeding and thrombosis of the

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1 device and anticoagulation management does
2 appear, however, to be a unique safety issue
3 of this device.

4 At least ten percent of the deaths
5 on the device were directly related to
6 failure. Thirty-one percent of the patients
7 experienced confirmed device malfunction, and
8 eight of the 39 were deemed serious.

9 There was considerable right heart
10 failure requiring either another device or
11 prolonged inotropic support. This seems
12 commensurate with other VAD experience. But
13 perhaps it is greater with this device.

14 We know patients supported on LVADS
15 experience many events, and it is unfortunate
16 we have no concurrent data to see if this
17 generation of device is really different from
18 the past.

19 Now briefly the post-market
20 approval study. The sponsors suggest a real
21 world study of 50 patients, now perhaps 78
22 patients, with no concurrent control group and

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1 follow-up for only six months. The INTERMACS
2 registry would be used.

3 What more will we learn from this
4 small number of patients? In the real world,
5 there will no doubt be a temptation to use
6 device in less sick patients, because of
7 perceived, advertised or claimed lower
8 incidence of adverse events.

9 Will there be an evidence base for
10 this? In the real world, it will likely be
11 used in some patients for destination therapy
12 and that has already happened. I suggest a
13 concurrent control group for adverse events,
14 and a focus on small habitus patients as just
15 a start.

16 In summary, I am certain of device
17 effectiveness, but am appalled at the archaic
18 fashion by which performance with respect to
19 other LVADS is being assessed. I suggest it
20 is likely within tolerance, given the weight
21 of all the evidence such as it is. I'm
22 concerned about unique safety issues of the

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1 device without an evidence base for lower risk
2 from the usual adverse events.

3 I am uncertain about the value of
4 the sponsor's proposed post-market approval
5 study. The claim that there is already in
6 excess of a thousand of these devices
7 implanted to date suggests that maybe it's
8 time for more meaningful surveillance of this
9 device. Thank you.

10 CHAIRMAN LASKEY: Thank you, Gene.

11 Anyone on the panel want to elaborate or ask
12 Gene a question?

13 DR. ZUCKERMAN: Sure. I'd like to
14 respond for the FDA. First of all, I'd like
15 to thank Dr. Blackstone for a very extensive
16 review, and in one respect, I agree with him.

17 In 1997, I believe Doctors Blackstone and
18 Naftel and others published a very important
19 paper on use of the methodology that he was
20 just referring to, competing risks, to
21 describe pediatric heart transplantation.

22 Certainly, the same methodology

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1 could and perhaps should be applied to this
2 area, if the agency had the data and the
3 literature to cull it from. But as Dr. Swain
4 indicated, this is a field that needs
5 tremendous development, in terms of clinical
6 trial design methodology.

7 In 2002, we went with the best that
8 we had. Frankly, other than Dr. Blackstone et
9 al.'s paper on pediatric heart transplantation
10 competing risk methodology, this is a
11 methodology that's been more applied to heart
12 valves, et cetera.

13 So the panel today has a critical
14 issue before it. The data are what they are.
15 We're asking you to use your best clinical
16 judgment to evaluate the data within this
17 construct.

18 Certainly, we look to move forward
19 from this construct. But the data are what
20 they are today, and to proceed, we really need
21 you to evaluate what you have before you.

22 CHAIRMAN LASKEY: Ordinarily, we

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1 would open the floor to other panel members
2 for questions, to either the sponsor or the
3 FDA as we dialogue amongst ourselves.

4 I think it not inappropriate to
5 have the open public hearing portion of the
6 meeting today occur now, because there is a
7 very important piece of our deliberations,
8 namely the INTERMACS registry.

9 So I'd like to just take a few
10 minutes and reshuffle our agenda, and open the
11 floor for the open public hearing portion.
12 Dr. Naftel is on the docket.

13 2nd Open Public Hearing

14 DR. NAFTEL: Good afternoon. My
15 name's David Naftel. I'm a professor of
16 Surgery and Biostatistics at the University of
17 Alabama in Birmingham, and I'm the Director of
18 the Data Coordinating Center for INTERMACS.

19 I'm speaking, in fact, I'm going to
20 read a letter from Dr. Jim Kirklin, who is the
21 Director of Cardiothoracic Surgery at UAB, and
22 he's the PI for INTERMACS. Both of us receive

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1 no compensation from Thoratec and no money for
2 travel.

3 Dr. Kirklin is at the European VAD
4 meeting, so I'm speaking in his stead. So
5 first of all, I'd like to read a letter from
6 him, and it's in your panel pack, in your
7 folder.

8 "My name is Jim Kirklin." You see
9 that's not true. This is a quote.

10 (Laughter.)

11 DR. NAFTTEL: "My name is Jim
12 Kirklin. I serve as the principal
13 investigator of the Interagency Registry for
14 Mechanically Assisted Circulatory Support,
15 known as INTERMACS. It's a national registry
16 for patients who are receiving mechanical
17 circulatory support therapy to treat advanced
18 heart failure.

19 "I'd like to thank the Food and
20 Drug Administration for providing the
21 opportunity to make a statement regarding the
22 approval of the next generation of mechanical

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1 circulatory devices, and specifically I'd like
2 to discuss the utilization of INTERMACS in
3 meeting the FDA post-market requirements for
4 such devices.

5 "INTERMACS was devised as a joint
6 effort of the National Heart, Lung and Blood
7 Institute, the Centers for Medicare and
8 Medicaid Services, the Food and Drug
9 Administration, clinicians, scientists and
10 industry representatives, in conjunction with
11 the University of Alabama at Birmingham and
12 the United Network for Organ Sharing, UNOS.

13 "Analysis of the data collected is
14 expected to facilitate improved patient
15 evaluation and management, while aiding in
16 better device development. Registry results
17 are also expected to influence future
18 research, and facilitate appropriate
19 regulation and reimbursement of MCSD
20 implantations.

21 "Over the last two decades,
22 mechanical circulatory support devices have

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1 been developed to augment or supplant failing
2 myocardial performance. This therapy has been
3 used successfully as a bridge to heart
4 transplantation, a bridge to recovery, and as
5 a permanent implantation or destination
6 therapy for intractable heart failure.

7 "Although cardiac transplantation
8 offers life-saving therapy for selected
9 patients, its use is limited by a supply of
10 donor organs which currently meets less than
11 one-tenth of the need.

12 "As a consequence, the number of
13 MCSD implantations has increased in recent
14 years. Despite favorable survival in quality
15 of life outcomes, MCSDs have severe and
16 sometimes life-threatening complications,
17 which include infections, thrombosis and
18 device failure.

19 "INTERMACS contains data elements
20 that have been established by clinical experts
21 in the field and manufacturers of the devices,
22 in collaboration with FDA, CMS and NHLBI.

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1 "These data elements represent the
2 collective best thinking on what is needed to
3 characterize the safety and effectiveness of
4 VADS in the post-market setting, where their
5 established data collection protocols and
6 accepted definitions of adverse events in
7 INTERMACS is uniquely positioned to meet the
8 requirements of post-market surveillance.

9 "There are numerous advantages of
10 INTERMACS serving as the post-market
11 surveillance for axial flow devices such as
12 the Heartmate II.

13 "These advantages include (1),
14 there would be one national registry which
15 would provide more consistent data definitions
16 and requirements, allowing for better analysis
17 for reporting and establishing best practice
18 guidelines.

19 "(2), FDA would receive accurate
20 data more often than the current post-market
21 registries, allowing for a prompter
22 recognition of device safety and effectiveness

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1 issues.

2 "(3), INTERMACS would provide the
3 least burdensome approach by establishing one
4 data collection protocol, eliminating the need
5 to review each manufacturer's post-market
6 registry definitions and standards.

7 "(4), FDA, CMS and NHLBI, hospitals
8 and manufacturers would benefit from one
9 registry, not only from a resource allocation
10 perspective, but also through the opportunity
11 to review and compare analyses, and therefore
12 identify and address potential concerns.

13 "(5), manufacturers would maintain
14 their role in the post-market surveillance
15 studies, by assuring compliance of INTERMACS.

16 "With the approval of continuous
17 flow devices and their potential for improved
18 device durability and reduction in adverse
19 events, it is even more imperative that
20 INTERMACS be recognized as the registry to
21 meet the FDA post-market requirements.

22 "As the field moves forward in its

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1 consideration of treating heart failure
2 patients before the terminal phases, it is
3 imperative that data refining patient
4 selection and documenting adverse events,
5 quality of life and cost could be available to
6 confirm the population to be studied, and
7 document the required outcomes.

8 "The care, commitment and the
9 accuracy of the data collected by each
10 participating institution will determine the
11 safety and efficacy of chronic MCS as a new
12 treatment option for one of the most difficult
13 and costly medical problems, that is the
14 malignant syndrome of advanced heart failure.

15 "My colleagues and I would like to
16 thank you for this opportunity to discuss how
17 the INTERMACS registry could be utilized as a
18 vehicle to satisfy post-market surveillance
19 study requirements.

20 "Sincerely, James Kirklin,
21 INTERMACS."

22 So now the quotes are turned off.

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1 Now it's me talking. A couple of things I
2 would like to address.

3 The INTERMACS study is a unique
4 collaboration of a lot of different entities
5 interested in VADS that we've read to you.
6 But it's also unique in that it's not your
7 typical registry.

8 I want to make sure that's clear.
9 We all deal with registries. We run two heart
10 transplant registries at UAB. So we all deal
11 with registries. But this one truly is
12 different. If you'll look at the slide behind
13 you, and I wonder which thing. Yes.

14 So if you just think on the Y axis,
15 that's some measure of how good a clinical
16 trial should be, however you define "good."

17 Usually, a typical study like this
18 Heartmate II, jumps through all the necessary
19 hoops and usually has a quite good measure of
20 being good.

21 A typical registry is usually down
22 there in the dirt. Well, we wanted to change

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1 that. Next slide.

2 This is a slide that we showed at
3 the very beginning of INTERMACS, when we were
4 comparing clinical trials in general, and now
5 we've specifically said Heartmate II.

6 But with INTERMACS, we wanted to do
7 everything we could to meet the quality of a
8 clinical trial. So we went through all the
9 clinical trial things that you need to have.

10 So let me start at the top.
11 INTERMACS has planned thoughtful analyses and
12 we'll be working with Thoratec on these. We
13 have not a data safety monitoring board but an
14 observational study monitoring board in place
15 that oversees everything we do.

16 There's an adjudication committee
17 that adjudicates the main events, death,
18 bleeding, neurodysfunction, infection. The
19 local PIs are totally involved in everything
20 that goes on that we're doing.

21 We have data freezes as you would
22 expect a good clinical trial to have, and when

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1 we work especially hard at data quality.
2 Auditing is performed by UNOS. That's taking
3 place.

4 As far as complete data and
5 complete follow-up in all cases, those things
6 are huge. We'll come back to those in just a
7 second, but let me move on to say that we have
8 very specific adverse event definitions for
9 about 15 of the major adverse events, and we
10 have very specific inclusion and exclusion
11 criteria.

12 The main thing is just it's
13 supposed to be all approved devices. The only
14 exclusion criteria is if you're in prison.

15 So we think we've done all we can
16 to raise this to a higher level. So let me
17 talk a little bit about capturing all
18 patients.

19 You certainly can call this a
20 voluntary registry, and I said that to one of
21 the institutions last week and they laughed at
22 me. They said there's nothing volunteer about

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1 this, and there's a key reason for that.

2 CMS last spring made the
3 requirement that if you implant destination
4 VADS and if you want to be reimbursed by CMS,
5 you have to enter your data into INTERMACS for
6 destination VADS.

7 But you also have to be an
8 institution in good standing with INTERMACS.
9 We define good standing as extremely good
10 follow-up, and we've said if you're using us
11 for your destination devices, you must use us
12 for your bridge to transplant devices, in
13 order to be a member in good standing. So you
14 can see where the voluntary aspect is starting
15 to melt away.

16 We're also working with industry.
17 Currently two companies, and I think the other
18 ones are starting to come around, also to help
19 us to look at the implants according to
20 industry and institution, and we match them to
21 the site. So we're getting a very good idea
22 if we're getting all the patients.

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1 Part of the auditing process is
2 also to check to make sure we're getting all
3 the patients. We think that our only
4 limitation, as near as we can tell, is lack of
5 informed consent.

6 All these patients must have
7 informed consent. So if you don't have
8 informed consent, you're not in the database.

9 But that's relatively few, and it's none of
10 the destination.

11 So INTERMACS, to raise up the whole
12 level of the study, we go through each local
13 IRB and must have approval. There's a
14 training process to enter the data. I said
15 informed consent.

16 We have a Hospital Standards
17 Committee that looks over compliance for
18 follow-up forms, for complete data, and we
19 have rules where we kick you out. We
20 deactivate you if you're not following the
21 rules.

22 I said auditing, adjudication,

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1 OSMB. All these things that you're used to
2 hearing in the clinical trial we are trying to
3 do, and we are doing them.

4 Now if you would like, I'd be happy
5 -- either questions, or do you want me to go
6 through those post-market questions that were
7 asked?

8 CHAIRMAN LASKEY: Not at the
9 moment, but you have one more -- we'll give
10 you one more minute here on your overage,
11 because we do have another speaker.

12 DR. NAFTEL: Well actually, I don't
13 need that minute. I'm finished.

14 CHAIRMAN LASKEY: Okay. Thank you
15 very much, Dr. Naftel.

16 DR. EDMUNDS: How is this funded?

17 DR. NAFTEL: It's funded totally by
18 NHLBI for this five-year cycle. We're
19 investigating -- we fully expect, we hope very
20 dearly that NIH will go a second five years.

21 I think they will. If not, we're
22 already putting in business plans to get money

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1 from industry, and even possibly talk to FDA,
2 to help fund it, and CMS.

3 DR. NAFTEL: Okay.

4 CHAIRMAN LASKEY: Thank you, sir.
5 We Have one more speaker on our schedule for
6 the open public hearing session. That's Dr.
7 Robert Bogaev. Did I pronounce that
8 correctly?

9 DR. BOGAEV: Yes. Thank you, Dr.
10 Laskey and members of the FDA panel. My name
11 is Roberta Bogaev. I currently serve as the
12 Medical Director of Heart Failure and Cardiac
13 Transplant at Texas Heart Institute, which was
14 one of the highest-enrolling centers in the
15 bridge to transplant trial.

16 I am here on behalf of my surgical
17 colleague, Dr. Red Frazier, who's currently in
18 Turkey and unable to be here, and on behalf of
19 the 72 patients who've been implanted at our
20 center with the Heartmate II device.

21 I also want to add that Thoratec
22 did not fund my travel nor my lodging for this

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1 meeting today.

2 To start with, I did want to
3 mention that I do have a B.S. in Mechanical
4 Engineering, but I do not profess to practice
5 engineering. I've been a clinical
6 cardiologist for the last ten years, caring
7 firsthand for many of the patients that you've
8 heard about today.

9 I also have the great honor of
10 caring for Salina Gonzales, the first speaker
11 that you heard today. I can tell you I stood
12 at the foot of her bed as she was literally
13 dying, and it was gratifying to be able to
14 offer her this device.

15 I want to remind you that without
16 this device, she would not be standing here
17 today.

18 Before we had small axial pumps, we
19 had only very large pulsatile pumps that were
20 too large to be implanted in small patients
21 without great difficulty. Many times, it was
22 logistically impossible to implant into

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1 patients such as Salina, many of whom are
2 women.

3 You heard Dr. Ileana Pina tell you
4 that women have been woefully underrepresented
5 in clinical trials. If you look even at our
6 medical trials for heart failure, they have
7 represented less than 25 percent of the
8 patients, and even less so in most of the
9 device trials.

10 The Heartmate II enrolled 23
11 percent women, which is one of the highest-
12 enrolling trials in all of the devices. I was
13 the first author of an AHA abstract breaking
14 down women versus men in this Heartmate II
15 bridge to transplant trial.

16 If you look at the outcomes, at 30
17 days, six months and one year, the outcomes
18 were equal and there was no statistically
19 significant difference between men and women.

20 The adverse events were also equal,
21 with the exception of late strokes, both
22 ischemic and hemorrhagic, which lends itself

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1 toward the need for gender-specific research
2 to investigate the differences in vascular
3 biology and the differences in platelet
4 function.

5 I think Dr. Ileana Pina mentioned
6 that that should be investigated in a post-
7 market analysis and study. I agree, that that
8 should be further investigated.

9 But I want to leave you with this
10 thought. Without this device, many of these
11 women and smaller patients would not survive.

12 So I urge you, please allow this technology
13 to go forth, because I can tell you as a
14 clinician, it is devastating not to be able to
15 offer these patients a chance to live. Thank
16 you.

17 CHAIRMAN LASKEY: Thank you. Does
18 anyone else wish to address the panel?

19 (No response.)

20 CHAIRMAN LASKEY: If not, I close
21 this open public hearing session, and return
22 us to the job at hand, which is to ultimately

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1 come up with recommendations to the agency on
2 this PMA. So I'd like to open the floor to
3 panel members for their discussion of what are
4 perceived to be the salient issues right now.

5 At least on my list, the salient
6 issues are can we decide about the patient
7 population that we're going to decide on,
8 particularly with respect to the label? Can
9 we decide on the metric of efficacy that
10 should be used from henceforth, and can we
11 decide on the specifics of a post-approval
12 study that will address many, probably not
13 all, of the concerns raised here today.

14 The top of my list would be Dr.
15 Blackstone's concerns. Sharon?

16 DR. NORMAND: Because you said that
17 was the top of your list, I'm going to respond
18 to that, in regard to Dr. Blackstone's
19 concerns.

20 I guess I'm not so concerned with
21 the issues that were raised, and I guess the
22 reason why I'm saying that is I'm trying to

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1 see -- you know, obviously if we had a
2 concurrent control group, this wouldn't be
3 such an issue.

4 This is the real issue, because we
5 don't have a concurrent control group. So
6 that's the crux of the matter.

7 So I guess the issue would be if we
8 thought that the hazard rate were really
9 changing over time. Otherwise, it's perfectly
10 fine to look at counting. So I just wanted to
11 -- if we -- that's more of a detail, so I'm
12 surprised that's at the top of your list, Dr.
13 Laskey.

14 But I think we would have to have a
15 discussion about that, to determine whether or
16 not the information that was presented to us
17 was useful or not.

18 CHAIRMAN LASKEY: Maybe I should
19 just qualify that. I meant the measure of
20 efficacy, not necessarily the level of
21 sophistication.

22 DR. NORMAND: Okay, because his --

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1 well anyhow, the concern was the level of
2 efficacy, the methods to measure the level of
3 efficacy. So anyhow, I should --

4 CHAIRMAN LASKEY: Yes, Marcia.

5 DR. YAROSS: Regarding the second
6 and the third items on your list, you talked
7 about, you know, what should be the measure of
8 efficacy? There was discussion this morning
9 about whether or not it was a fuzzy goal
10 versus something else.

11 What I would put forth is that's a
12 pre-specified hypothesis. It's not a fuzzy
13 goal. There was a hypothesis. Now whether or
14 not that leads -- you know, if the assessment
15 wants the patient population as agreed upon,
16 is that it did or did not meet the hypothesis.

17 Then we're back to that issue of clinical
18 judgment.

19 On the third point, in terms of
20 post-approval study, there's been a lot of
21 discussion back and forth about what is the
22 proper population and study design. What I

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1 would ask the panel to consider is first, what
2 is the question to be answered.

3 I think in the FDA presentation,
4 they listed a number of possible areas, in
5 terms of questions to be asked and answered in
6 a post-approval study.

7 I would hope that if the panel can
8 first identify which areas require post-
9 approval study should an approval be
10 recommended; then use that to drive study
11 design.

12 CHAIRMAN LASKEY: Cindy.

13 DR. TRACY: Warren, it strikes me
14 that a lot of times we're sitting in this
15 room, and we're stuck with the same problem.
16 When we launch into a study, you have to come
17 up with some hypothesis. There has to be some
18 goal that's arbitrarily set.

19 Then you get halfway through or
20 three-quarters of the way through or worse
21 yet, all the way through, and you realize gee,
22 if my hypothesis had been slightly different,

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1 the answer would be different.

2 But I think this competing outcomes
3 is very important, because of any of the
4 things that we've looked at here, there are so
5 many competing outcomes, and who's to say that
6 this original hypothesis perfectly reflects
7 all the different outcomes that are possible
8 to come up with.

9 I think this, of all the studies
10 I've heard, this is one where we must really
11 look at the clinical implications and the
12 clinical outcomes, and put, as has been said,
13 put our clinical judgment into this.

14 So I'm not sure parsing, moving
15 people from the left to the right, I don't
16 intuitively think that that makes a whole lot
17 of sense to me.

18 It probably does from the
19 statistical standpoint, but as a clinical
20 tool, I think we have to look at it this way
21 in an extraordinarily complex patient
22 population.

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1 CHAIRMAN LASKEY: Barrie.

2 DR. MASSIE: Yes. I mean I think
3 there are two issues in what Cynthia just sort
4 of said. I do believe that there was a trial
5 design; there was a pre-specified way of
6 determining an end point and a pre-specified
7 goal. I think either way, we're left with a
8 little bit of a problem, because all of us see
9 there's some problems with the way it was pre-
10 specified.

11 But I don't think you can look
12 backwards and decide which way to switch
13 patients. So I think that is sort of out of
14 bounds, honestly, this so-called revised way
15 of looking at the outcome.

16 On the other hand, looking at the
17 totality of the clinical evidence, and its
18 relationship to the pre-specified goal, is I
19 think an area where we -- there are
20 discussions. There are more data, even though
21 there's one goal and only one statistical plan
22 for one end point.

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1 So I feel, whether it's
2 contamination or whatever from a drug
3 evaluation background, that we need to draw a
4 certain line, which is you can't look how it
5 didn't work and then decide how you can make
6 it work.

7 On the other hand, you can look at
8 what happened and draw some conclusions, and
9 that would be the way I would look at that
10 efficacy question.

11 CHAIRMAN LASKEY: I would agree. I
12 don't hear anybody advocating the former. I
13 think it's the latter we're grappling with,
14 and can I assume then that for the rest of the
15 discussion, what we're really talking about is
16 the entirety of the patient database that we
17 have?

18 DR. MASSIE: Well, it was the
19 sponsor proposal, that there be another
20 analysis, an alternate analysis that we should
21 consider. I guess what I was saying is I
22 don't think we want to open it up to consider

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1 that. That would be my point.

2 CHAIRMAN LASKEY: That was an
3 analysis with a revised end point. But can we
4 apply the larger, the continued access patient
5 population, the small-sized patient population
6 and the pivotal, and look at that in aggregate
7 as clinicians and move forward from there?
8 Bram?

9 DR. ZUCKERMAN: Yes. I just want
10 to emphasize that Dr. Massie now can sit on
11 the devices panel. He understands what is our
12 mission or what would be most helpful comment
13 to the FDA.

14 Number one, we had a pre-specified
15 hypothesis and protocol, analyzed the data
16 according to that hypothesis and protocol,
17 which really I believe the record shows is N
18 equals 126.

19 However, there are important
20 supplementary datasets. They are the
21 continued access protocol and the small BSA
22 protocol.

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1 However, where we, meaning FDA,
2 disagrees with the sponsor is that the agency
3 would recommend that you still look at those
4 three datasets as three separate trials,
5 rather than adding them all together, since
6 again, that was not a pre-specified
7 hypothesis.

8 DR. SOMBERG: I seem to enjoy
9 taking a minority position, because I do favor
10 looking not, as you said Bram, but to look at
11 them combined, because I don't know how to
12 apply my clinical judgment to a device that
13 I've never implanted, that until today I never
14 saw a patient with that particular device
15 implant, and seen these three lovely patients
16 here today, who are functioning well.

17 That doesn't give me the totality
18 of the clinical experience. So I would like
19 to take, and I hope the other panel members
20 would permit me and would come along, with
21 looking at the combined analysis, and seeing
22 if that met performance goal or aspiration.

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1 Because I was sort of very
2 reassured that, looking at either the
3 literature or internal company documents, and
4 having people working independent of each
5 other, they sort of came up to where this
6 device should perform.

7 So if you take everybody who's been
8 put on a device to certain cutoff point at a
9 certain point in history, and you see what
10 worked and what didn't work, and if it met
11 that performance goal, I think that would be
12 very important.

13 To say that well, it works in small
14 people; small people are important.
15 Certainly, they are. But we have no control
16 groups and I understand the call for other
17 analyses. But we're not going to have that in
18 time for a decision.

19 So I think the only dataset that I
20 see on the table that makes sense for
21 evaluation is the complete dataset, and that
22 seems to me to show efficacy.

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1 CHAIRMAN LASKEY: Just to finish
2 your sentence or your thought, using the
3 original pre-specified definition of efficacy?

4 DR. SOMBERG: Exactly.

5 CHAIRMAN LASKEY: Yes. Is there a
6 consensus on that at the table?

7 DR. NORMAND: Well, is it 194 or --
8 no, it's 194.

9 CHAIRMAN LASKEY: It should be 194.

10 DR. NORMAND: I'm looking at Slide
11 71 of the sponsor's handouts, because that
12 has the -- well, it's got the 194 and it's got
13 the pre-specified analysis for a March 16th end
14 point and a September 14th end point. You do
15 make different, slightly different inferences
16 if you look at it.

17 DR. SOMBERG: It should be
18 September, which was the last one, the cutoff
19 point.

20 DR. NORMAND: The last point. Page
21 71.

22 DR. SOMBERG: And as many patients

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1 as we can put in. By the way, this is very
2 smudgy company, so my number --

3 DR. NORMAND: It's on page -- well
4 no. There's not even any page numbers here.

5 DR. LINDENFELD: Is that right?

6 DR. NORMAND: So it's 71. I don't
7 know if you can find it.

8 CHAIRMAN LASKEY: All right. Well,
9 the gist of this is that we're moving towards
10 evaluating the data in aggregate, without
11 really evaluating it in aggregate, Dr.
12 Zuckerman.

13 We're certainly not pooling these
14 three studies, but it's hard for the
15 clinicians to not use the data before us.

16 DR. ZUCKERMAN: Okay, and that's an
17 interesting perspective. But I think again,
18 what I'd like to hear comment on is one, that
19 was not pre-specified. Two, for example, the
20 continued access protocol has a, as mentioned
21 by the sponsor and the agency, has a very
22 limited follow-up at this point.

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1 It really isn't a finished trial.
2 It was not designed as a finished trial. So
3 pooling these datasets, I'd like to hear why
4 that's justifiable.

5 CHAIRMAN LASKEY: Rick, why don't
6 you go ahead? But we're not talking about
7 pooling datasets here in the mathematical
8 definition.

9 DR. PAGE: I'm going to defer
10 answering that question exactly, Dr.
11 Zuckerman, although I do agree with you. I
12 think it is a reasonable expectation that we
13 look at the data as they were put forward. I
14 also agree with Dr. Somberg, however.

15 As I see it, when we take the data
16 in its entirety, they appear to be meeting the
17 performance goal. On the other hand, if we
18 don't take the data in their entirety and take
19 the study as it was performed, that's 64
20 percent, when we had a performance goal of 65
21 percent.

22 That seems close enough, based on

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1 my own clinical judgment and what I've heard
2 today, that I would see this as meeting its
3 effectiveness.

4 CHAIRMAN LASKEY: Rick, you were
5 about to say something?

6 DR. DOMANSKI: Yes, I think -- you
7 know, the business of the 64 versus 65, you
8 know, given the play, given the inaccuracy,
9 you know, it's good to make an estimate of
10 what's reasonable.

11 But that estimate is a guesstimate
12 really, and to try to then cut the thing so
13 far that one's talking about 64 versus 65 is
14 pretty hard to feel comfortable with that
15 level of, you know, formalism, because I just
16 don't think what went in in the first place
17 was that accurate.

18 DR. NORMAND: I'm not sure what you
19 mean by that. Can you elaborate? I don't
20 know if you're saying if it's worse or better?

21 DR. DOMANSKI: Yes. Let me say it.
22 Let me try to clarify what I'm saying. I'm

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1 saying that what happened was that a
2 reasonable estimate was made of what
3 represented appropriate performance for
4 efficacy.

5 But I think that that was based on
6 a lot of estimation, a lot of guesswork, and
7 it's not a very firm number, you know, in
8 terms of what's reasonable. So to talk about
9 the numerical difference between 64 and 65, I
10 think, is probably not meaningful.

11 I think there's too much play in
12 the original estimate of what represents a
13 reasonable standard. Is that clear? It may
14 not be right, but I hope it's clear anyway.

15 CHAIRMAN LASKEY: Norm?

16 DR. KATO: Well, you know, I think
17 just to combine both approaches is probably,
18 you know, in a way I think that's a lot of
19 what we're all wrestling with, is that we can
20 slice and dice in a couple of different ways.

21 The two ways that it seems to be
22 coming down to is well, you can pool the data

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1 in a rough kind of way, not strictly
2 aggregated one for one, but just look at the
3 totality of the data and it looks, and I think
4 it looks efficacious.

5 On the other hand, to agree with
6 Dr. Domanski, that 65 percent is a number that
7 reasonable people came up with, which is has
8 some standard deviation to. The outcomes
9 achieved by the sponsor, given the variability
10 of the patients, the variability of the
11 facilities they're in as well as the surgeons
12 and the patients themselves creates, if you
13 will, a standard deviation, if you will,
14 around that 64 number.

15 The difference between 64 and 65
16 just seems to be very, very small.

17 DR. LINDENFELD: Can I?

18 DR. NORMAND: There's a delta of
19 ten percent in there that you need to keep in
20 mind. That's like the fudge factor; that's
21 the standard deviation, if you want to think
22 of it. So is my mike on? Sorry. I have to

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1 talk in it apparently.

2 So I think you should think of that
3 does include the standard deviation, if you
4 want to think about it that way. It does
5 include a leeway of ten percentage points.

6 DR. LINDENFELD: It's not they
7 didn't meet the performance measure; they
8 didn't meet the confidence intervals around
9 the performance measure. We're not discussing
10 -- I mean the performance measure was, I know,
11 at the lower confidence intervals.

12 But it was actually closer to 70, I
13 think, and the confidence intervals were down
14 to 65. So it was below the confidence
15 intervals around -- it's a little bit
16 different than saying it didn't meet 70. It
17 made 69.

18 CHAIRMAN LASKEY: All that is true,
19 but the clinicians are saying is there a
20 difference between 64 and 65?

21 DR. LINDENFELD: No, I understand
22 that. But there might be -- I think it's a

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1 little bit of a subtle point, but if you're
2 expecting 70 percent and you say the
3 confidence intervals around that are 65 to 75,
4 making 69 is a little bit different than not
5 even making the confidence intervals.

6 I agree. We have to look at the
7 totality of the data I think overall. But I
8 mean it isn't that we're trying to make 70.
9 We're trying to make the confidence intervals
10 around 70.

11 CHAIRMAN LASKEY: But if we had
12 said delta of 11 for the same rationale as the
13 delta of ten, we'd be having a similar
14 discussion.

15 DR. NORMAND: But if we stay with
16 the pre-specified plan.

17 CHAIRMAN LASKEY: That is correct.

18 DR. NORMAND: I mean I think it's
19 very slippery slope to say that -- again, it
20 would be different if it was the point
21 estimate. We'd say, you know, what's 69 and
22 70 versus -- it only has the interval estimate

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1 around it. Again, in perspective of what was
2 decided.

3 CHAIRMAN LASKEY: Cynthia?

4 DR. TRACY: Just if you do take the
5 three separate potential components of this,
6 the small BSA; fine, we can approve for small
7 BSA obviously, because it makes 70 percent. I
8 mean that's ridiculous.

9 But you've got 64 percent, 66,
10 although I'd be happy. Small size. If you
11 take the CAP, the small and the original 126,
12 we're talking 64, 66 and 70. I don't know
13 what the relevance between the important
14 relevance from a clinical standpoint is
15 between 64 and 65.

16 Granted, it's outside the
17 confidence interval, but what is the
18 implication of that, given trying to keep in
19 mind the other two groups that are there, that
20 we can't ignore. What is the relevance of
21 that?

22 CHAIRMAN LASKEY: And that is part

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1 of the issue. I think Rick has stated it
2 well, a number of people have stated it well.

3 We have the aggregate and we have the
4 pivotal. The pivotal is live or die by one
5 percentage point, and the clinicians say well
6 no, not so fast. Maybe it's not quite so hard
7 and fast. Marcia?

8 DR. YAROSS: Yes. From a
9 regulatory standpoint, to me the debate about
10 pooling or not pooling feels a little bit
11 excessively academic. The reason I say that
12 is it's not a matter for this panel to try to
13 determine if the study met or did not meet the
14 end point.

15 I think it's clear that it didn't
16 meet the pre-specified end point. But the
17 challenge is whether or not all of the
18 evidence in the PMA leads to a reasonable
19 assurance of safety and effectiveness. That's
20 the clinical judgment piece.

21 So maybe we can move it along by
22 not debating, you know, whether it meets the

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1 end point, but just talk about whether or not
2 that probable benefit exceeds probable risk.

3 CHAIRMAN LASKEY: Some of that
4 information was posed to the sponsor this
5 morning, so perhaps it's time we did ask you
6 folks to prepare answers to some questions
7 that perhaps may help round out the picture.
8 So welcome back.

9 MR. MIDDLEBROOK: Thank you. We
10 have taken all of your questions into
11 consideration, and I believe we have answers
12 for all, if not most of the questions that you
13 raised, and I'd like to call on Dr. Les Miller
14 to come to the podium.

15 DR. MILLER: Thank you. I'll try
16 and be brief in answering the questions
17 somewhat in the order they were posed by Dr.
18 Lindenfeld, the comparability of the VE data
19 that was shown in the Kaplan-Meier curve.

20 What I have is not in your panel
21 pack, but was in the PMA R-5 clinical trial,
22 so pretty objective data, that have occurred

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1 in the last 15 years, including the VE data,
2 which was collected between '96 and '98.

3 The consistency of the data is
4 rather astounding. The standard deviation may
5 be as small as .5. For example for age, the
6 age in our group was somewhere between 52 and
7 49, and the average in the trials was 50.

8 The gender breakout is exactly the
9 same, of 80-20 as it's been in transplant for
10 30 or 40 years. Etiology was almost an
11 identical overlap at 46 in the VE trial and
12 similar in our cohort.

13 Body surface area was identical,
14 1.9 to 2.0. Creatinine was a little higher in
15 the VE trial. Ours was 1.4 and 1.7 in that
16 trial, but the VE-1 was nearly identical.

17 Bilirubin was slightly higher, as
18 was ALT in the VE trial. But when you look in
19 these five trials, the range and the mean from
20 those trials is almost identical.

21 The wedge pressure was identical,
22 27. Cardiac index was 1.7 versus 1.9. It was

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1 slightly higher. In our group, the blood
2 pressure was not recorded in the VE trial, but
3 in the other trials, it ranged very similarly
4 to the blood pressure in this cohort.

5 Importantly, the intra-aortic
6 balloon pump was 49 percent and the VE trial
7 and 41 percent in the Heartmate trial. The
8 time of support, though, I think is one of the
9 most important variables. Over time, the time
10 to getting a transplant has certainly
11 prolonged, and the range in these trials over
12 this last 15 years ranged from a low of 35
13 days to the high of 96, which was in the VE
14 trial and more contemporarily reported.

15 It reminds you that in the
16 Heartmate II trial, the time of support
17 averaged 177 days. So almost twice as much
18 support time and still saw a reduction in most
19 of the adverse events.

20 Finally, the question about right
21 ventricular support. It went down by 64
22 percent, comparing the VE trial specifically

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1 to the Heartmate II trial. I think that would
2 say the data's fairly comparable and is
3 consistent, and I think reassuringly. I have
4 that data if you want it.

5 The second question I wanted to
6 address was stroke, particularly was addressed
7 an increased incidence of stroke in women. We
8 looked at this fairly extensively, and did a
9 lot of analysis, including men and women,
10 with, without stroke, side by side comparisons
11 and looked at a large number of variables
12 including age, blood pressure, flow rates,
13 flow index, anticoagulation.

14 We really found almost nothing that
15 seemed to be a signal to indicate an increase
16 or a different risk. Interestingly, the women
17 without stroke had a greater, much greater
18 incidence of atrial arrhythmia, which did not
19 seem to predispose to stroke.

20 The one variable that did turn out
21 to be correlated in both genders for risk of
22 stroke was infection, and that was a pretty

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1 consistent signal across all of that.

2 The data that hasn't been perhaps
3 submitted in your panel pack was interesting,
4 and I'll use this as an observation. There
5 were 26 centers in this trial. Twenty of the
6 centers had no reported strokes. Three of the
7 centers had one and three of the centers had
8 more than one.

9 So it's an interesting question
10 about whether this is as profound a risk
11 across all patients as it seemed to be a
12 little bit of a center effect in that regard.

13 This third question regards paired
14 data, and I think that's an important aspect.

15 Slide 43.

16 This is not the paired data, but it
17 does give you a sense of, in the blue bars,
18 the progression of people who could walk 200
19 meters, and I think would give you a sense
20 that there must have been high percentage of
21 patients who collectively improved.

22 I went back during the break and

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1 looked at specifically six minute walk, and
2 found 41 patients in whom I could quickly
3 identify paired data at one, three and six
4 months, and had 35 of the 41 patients who had
5 a consistent increase over time, somewhere
6 near 80 percent, which is I think really what
7 you're seeing on the graph there.

8 Only four of the 41 patients had a
9 reduction at either the three or six month
10 interval. So what we have by paired data
11 would suggest this same consistent improvement
12 in six minute walk.

13 The same thing was true for Kansas
14 City Cardiomyopathy, which I think probably
15 reflects the same improvement in functional
16 capacity.

17 Finally, the question that I think
18 was an appropriate one about risk estimates,
19 and Dr. Lindenfeld posed the question about
20 the recent report that said if you do risk
21 ratification, you can have a fairly good
22 prediction of in-hospital mortality. It

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1 didn't say anything about long term.

2 I think that the inference you made
3 was that if you took the means of each of the
4 variables that we outlined here, you would say
5 they would have a very low risk. As I showed
6 you, there was a huge variability in BUN,
7 creatinine, bilirubin, etcetera.

8 So the individual may have quite a
9 spectrum of that. But if you accepted that,
10 and suggested that they were in the best
11 outcome cohort, we had exactly that, 90
12 percent, which is what the article suggested
13 for in-hospital risk of mortality.

14 So it looked like they were right
15 on target, 75 percent at six months. So I
16 think they met what we would predict they
17 would do in that regard.

18 I'd finally remind you that Wayne
19 Levy, who's done a lot of work with the FDA
20 and others with regard to risk ratification of
21 these patients, with regard to concept of a
22 control group, he looked at the cohort going

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1 into the trial and predicted their mortality
2 to be 100 percent at nine months or 12 months.

3 So there is no opportunity for a
4 medical control group to ever be done with
5 mechanical support. I think the suggestion of
6 a concurrent control we really hope is what
7 INTERMACS will provide, when all the VE data
8 is in there and now we can begin rolling these
9 things.

10 I think that's our whole hope. We
11 will have a legitimate, contemporary,
12 concurrent control to begin to compare
13 subsequent devices. Thank you.

14 MR. MIDDLEBROOK: There was a
15 specific question about reoperations and
16 particularly for bleeding, and I'd like to
17 bring back Dr. Frank Pagani to address that
18 question.

19 DR. PAGANI: The majority of sites
20 for reoperation for bleeding were non-
21 specific, including chest wall, abdomen,
22 preperitoneal pocket, mammary artery, thorax.

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1 So this was a sense of generalized bleeding
2 and reoperations.

3 There was a mention made of 11
4 percent reoperation quoted from the Frazier
5 article. That 11 percent was device-specific
6 bleeding. If you look at the total number of
7 patients in the Frazier article that were
8 reoperated on specifically for bleeding, there
9 was 133 patients out of 280 or 48 percent.

10 The corresponding number of
11 patients reoperated for bleeding in the
12 Heartmate II trial was 37 patients or 29
13 percent. So it's not 29 percent compared to
14 11 percent; it's 29 percent compared to 48
15 percent. Thank you.

16 DR. MASSIE: A quick follow-up
17 question to that. What kind of protocols were
18 using interoperatively for, you know, to
19 minimize bleeding?

20 DR. PAGANI: There was a
21 standardized perioperative anticoagulation
22 protocol, but there was no standardized method

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1 of controlling bleeding. It was left up to
2 the discretion of the usual care at each
3 center.

4 DR. MASSIE: I mean the reason why
5 I ask that is, as you're probably aware, when
6 an antifibrinolytic drug was just taken off
7 the market, and I wanted to find out whether
8 that had any, would have any impact on
9 bleeding, anti-bleeding protocols in the
10 operating room, in that these, you know, the
11 percentage of bleeding and reops can actually
12 go up in the future?

13 DR. PAGANI: Aprotinin was not part
14 of our recommended protocol for interoperative
15 management of bleeding. There was no
16 specified protocol for interoperative
17 management of bleeding.

18 DR. MASSIE: But you said it was
19 left up to the individual centers?

20 DR. PAGANI: Correct.

21 DR. MASSIE: So do the centers use
22 it?

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1 DR. PAGANI: Yes. Specifically at
2 our center, we used it for every patient.

3 DR. MASSIE: And was that a fairly
4 common theme throughout all the other centers?

5 DR. PAGANI: I can't speak for most
6 of the centers, but my guess would be yes,
7 probably for a large majority of centers.

8 DR. MASSIE: So your thought or
9 your best guess would be that the bleeding
10 instance would probably go up substantially?

11 DR. PAGANI: I don't know. We can
12 use other antifibrillitic drugs to take that
13 place, would be our first protocol. There's
14 other ways of managing bleeding
15 perioperatively other than Aprotinin.

16 CHAIRMAN LASKEY: Hank?

17 DR. EDMUNDS: So you don't have a
18 protocol, that there was no consistent
19 protocol across for managing coagulopathy at
20 the time of implantation?

21 DR. PAGANI: The management of
22 coagulopathy was the standard of care at that

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1 Hospital.

2 DR. EDMUNDS: But that's no
3 standard at all across multiple institutions?

4 DR. PAGANI: Correct.

5 DR. EDMUNDS: I think this level of
6 bleeding, 48, 29 percent reoperative rate
7 during the first 48 to 72 hours after
8 operation, has to be considered unacceptable,
9 at this time in our history.

10 That needs to be addressed by
11 getting good data. You have a consumptive
12 coagulopathy going, thrombin formation at the
13 same time has fibrinolysis.

14 You don't really have the tools to
15 measure that in the OR late at night. You
16 can't get the technicians to do the ELISAs.
17 So you have a platelet count maybe. You're
18 flying blind.

19 This is a need of a real good
20 protocol, that takes in such things as tissue
21 factor, how you measure bleeding, how often
22 you respond. Now I'll just drop that, but

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1 this is totally inadequate.

2 DR. PAGANI: I appreciate your
3 comments.

4 CHAIRMAN LASKEY: One hopefully
5 more benign question. Is there an interaction
6 of bleeding and gender? There is in a lot of
7 other areas in cardiovascular intervention.

8 DR. PAGANI: We saw no definitive
9 association between bleeding and gender.

10 DR. LINDENFELD: Were all the
11 devices preperitoneal?

12 DR. PAGANI: Yes, all the devices
13 were preperitoneal.

14 DR. PAGE: I have a question for
15 the sponsor and then for the panelists who are
16 experts in this area, and that is do you see
17 this as exchange technology for your previous
18 generation, or do you see the two devices
19 being used in tandem?

20 I'd be especially interested in
21 your perspective as a surgeon, as to whether
22 you want both of these on the shelf, or

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1 whether it's going to be a transition from one
2 technology to the other. Then I'd be
3 interested in the other physicians in the
4 panel's opinion as well.

5 DR. PAGANI: I think it's very
6 important that both devices be left on the
7 shelf, because I think there's specific
8 reasons why you might not choose one device
9 over the other.

10 For example, if a patient has an
11 intolerance to anticoagulation or
12 contraindication to anticoagulation, the
13 Heartmate XVE would be an appropriate device
14 to use in place of the Heartmate II device.

15 So I think clinical judgment plays
16 a very important role in device selection, and
17 no one device is appropriate for every
18 patient. So I think several devices are
19 appropriate, and that decision should be left
20 up to the physicians taking care of that
21 patient, which is the most appropriate device.

22 DR. PAGE: That's the important

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