compare the two without the demographics.

MR. MIDDLEBROOK: Okay.

CHAIRMAN LASKEY: Dr. Vassiliades.

DR. VASSILIADES: I had a few questions. I'll just read them all now so you can have some time. If you can't answer them now, that's fine.

I was a little unclear as to why only 58 of the 138 patients in the continued access protocol, you had a complete dataset. Was that because you were not required to do so, or they haven't reached that end point? If you could just clarify that for me.

Question No. 2. I'd like to see some, a little bit more robust data or information regarding the reoperations for bleeding, in terms of the specifics of why they were, other than they just had bleeding problems, what the surgical findings were? Were they surgical bleeding or coagulopathy, etcetera.

Then I'm just curious as to the

three patients, two of which had a battery placement issue and one had a component issue. If you can elaborate on that.

MR. MIDDLEBROOK: Well, I'll take the first question. We may be able to answer the other two now or get back to you in a few minutes.

The 58 patients of the 138 CAP patients were presented because we had -- at the time of the analysis, we had six month follow-up on those 58 patients. So we wanted to present only data where we had at least six months' worth of follow-up.

So the 126 patients, we had full six month follow-up on those patients. Only 58 of the 138 we had six month follow-up on, and only ten of the 15 small patients had six month follow-up at the time of the analysis, which was March 16, 2007. At that cutoff point, we had six month follow-up on only those patients.

CHAIRMAN LASKEY: I'll go ahead and

ask mine. Well, sorry. Is the sponsor preparing responses at the moment for the rest of Tom's questions, or will you defer to the afternoon?

MR. MIDDLEBROOK: I think we can go ahead and answer them. Yes, I can quickly give you the answer to the two issues on the battery. One was the batteries weren't inserted correctly when they changed the power.

Of course, any VAD system, if it doesn't have a power supply stops, and that's what that came from. The other one, the patient fell asleep while on battery power. They're instructed not to sleep on battery power. They need to be tethered, for obvious reasons.

The other one was an inflow twist that happened during the implant. That was one of the changes made to the pump, to prevent that from happening again.

DR. SOMBERG: Is my understanding

correct that the intention initially was to include the patients with the small body surface area in the analysis?

MR. MIDDLEBROOK: The protocol, the FDA had asked us in the protocol to collect the data and do an analysis of the small patients separately.

DR. SOMBERG: But when you devised the protocol, I understand the FDA's intent. But your intent initially was to include those patients?

MR. MIDDLEBROOK: Well initially, when we originally submitted the PMA, we did do a separate analysis of the small patients. There were only seven of those, and we looked at all, everything that we could think of to look at, to compare those patients, those small patients.

DR. SOMBERG: Well, that's not what I'm getting at, though. What I'm getting at was was your intent when you designed the study to include those, not to separate them

out, but to include those patients in the analysis?

MR. MIDDLEBROOK: I would have to answer yes to that.

DR. SOMBERG: Okay, that's fine. Then if that's the case, do you have an analysis based on the intent, with the design of the protocol, of analyzing all those patients?

MR. MIDDLEBROOK: We did that in the original PMA, and we included those seven small patients in our analysis, and again in the deficiency letter that was issued to us in April --

DR. SOMBERG: Okay. But I'm not interested in the deficiency at the moment, but I'm interested in the data. If I remember correctly, that shows that you met the performance criteria when those people are included; is that correct?

MR. MIDDLEBROOK: No, we did not meet the performance --

DR. SOMBERG: Can you give that data again?

DR. HEATLEY: Yes. If you include the seven small patients with the 126, we have the same issue with patients that are not listed 1A or 1B at 180 days in the small cohort as well. So we come again about two patients short.

We're at about 64 percent lower confidence intervals. We can pop that slide up after lunch if you'd like us to.

CHAIRMAN LASKEY: If I can just follow that up. So for the 133, the original sample, that did not change either, the point estimate or the lower bound?

DR. HEATLEY: Right. If you include the small patients with the 126, we still come up with a lower confidence limit of 64 percent. We're still two patients short.

CHAIRMAN LASKEY: And the point estimate was?

DR. HEATLEY: 65 percent.

CHAIRMAN LASKEY: Okay.

MR. MIDDLEBROOK: The question regarding reoperations, we'll have to get back to you after lunch on that. We'll pull that data for you.

CHAIRMAN LASKEY: Thank you. Dr. Kelly and then Dr. Massie.

DR. KELLY: I have two questions. The first is also about the reoperations for bleeding, and I think Dr. Pagani mentioned it was similar with the Heartmate.

But at least in the multi-center study publication, we have it was 11 percent with the Heartmate. So if that could be clarified.

My second question is about the increased stroke risk and reoperation in women, and I wondered if we have data with the larger cohort, separating out the women, as opposed to just with the primary cohort?

MR. MIDDLEBROOK: We will answer those questions after lunch.

CHAIRMAN LASKEY: Dr. Massie?

DR. MASSIE: Yes. Just a follow-up to JoAnn's question, in terms of the comparison with the XVE. It seems to me that there is a great deal of experience that's been acquired, of using these types of devices over the time between those two.

You suggest or I think the implication is that this might be a better device, because of the better survival and long-term outcomes.

But I would offer an alternative explanation, which is that people have learned how to use these devices better.

Patient characteristics did seem similar, but that would be one point.

The other question I had is in what I think is a rather remarkable collection of quality of life and functional capacity type of data, I've never seen the data of the same patients from beginning to end.

In other words, the ends fall off,

as you expect. But perhaps the early sickness is related to the falloff, and therefore the comparable patients, the ones that were followed for six months, do we know whether we see the same striking gait increase in six minute walk tests, or did some of those start off being healthier anyway, and that's the reason?

The same with, you know, pertaining to the Minnesota Living With Heart Failure and the Kansas City questionnaires.

MR. MIDDLEBROOK: We will respond to that question after lunch.

DR. LINDENFELD: In the same vein, I noticed that there were no statistical comparisons in any of those outcomes. I know there's so much missing data that it's almost impossible, but even with the missing data, the standard deviations were large, of course, and my guess is there are no statistically significant --

I mean the data looks impressive

and the presentation is good, and I understand the problems with missing data. But were there any statistical comparisons in any of that data, because there were no P values on any of the slides?

DR. HEATLEY: Yes. I believe in the panel pack that we provided, we presented statistics on quality of life data.

DR. LINDENFELD: I don't think so.

DR. HEATLEY: It's in the panel pack. What we did was we matched data to baseline at one month, three months and six months.

DR. LINDENFELD: That's neurocognitive function.

DR. HEATLEY: No. This was for functional capacity, New York Heart Association class and quality of life measures.

For the functional class, six minute walk, and for New York Heart Association I believe we did T-tests that did

show very high statistical significance when compared to baseline.

For the quality of life, again, it's on page 72 of your panel pack.

DR. PAGE: Of what section?

DR. LINDENFELD: Okay. That's the six minute walk, right? Seven.

DR. HEATLEY: Section 7.5.

DR. LINDENFELD: Okay, all right.

DR. HEATLEY: Good.

DR. LINDENFELD: Now just in the same vein about the neurocognitive testing, if I might, the baseline was one month post-op, if I understand that correctly. Now we know from data published in bypass surgery that cognitive function goes down substantially just with surgery, and then improves over time.

So what I'd sort of like to see later on, I'm sure this will take a little time, is that yes, these patients improved. But just open heart surgery alone causes a

decrement in cognitive function that improves over time.

So that doesn't mean anything improved from the device. It just means that it improved from the time of surgery, which you would expect to happen. You may want to comment on that.

But in other words, there was a *New England Journal* paper in 2001 that demonstrated at least 50 percent of patients have a marked drop in cognitive function in post-op that improves over time.

Then I think a second problem with the neurocognitive analysis that you might want to discuss is that in that same study, there was clearly a learning curve by repeating the test, because in the patients who had no cognitive drop, their function improved from six weeks to six months.

So not only is there a problem with a learning curve on this neurocognitive analysis, but surgery itself causes a drop

that you expect to improve over six months. So that again, I just would like to hear your comments.

I appreciate the data, but you would expect that post-op and in any post-op surgical procedure, patients would improve over the first six months, not necessarily due to the procedure itself, but due to the initial decrement in surgery, and potentially bypass and then an improvement.

MR. MIDDLEBROOK: We'll respond to your question after lunch, Dr. Lindenfeld.

CHAIRMAN LASKEY: Dr. Edmunds.

DR. EDMUNDS: This is going to be an after lunch answer too probably, but I would like to really drill down on the indications for reoperation for bleeding, and what you know or what the etiology of that bleeding was then found, and how you stopped it.

In other words, you have a very high -- this is a big problem, bleeding and

thrombosis.

The other question I'd like to ask that maybe you can answer now is you've used the word "languishing." Does that mean existing or sepsis, in reference to the patients that are alive on the machine at 180 days?

DR. HEATLEY: I used that term, and I just meant to say that they were doing poorly on support.

DR. EDMUNDS: They were doing poorly on support because they were septic?

DR. HEATLEY: No.

DR. EDMUNDS: Because they were brain dead, or they had no kidneys? What?

DR. HEATLEY: One was suffering from muscular dystrophy that they had prior to entering the trial, which progressively got worse as the trial progressed. Laura, can you describe the other patient?

DR. EDMUNDS: But we don't need to get the details. They weren't complications

from the device?

DR. HEATLEY: No. They weren't stroke patients. They weren't patients who were languishing because of sepsis, I do not believe.

DR. EDMUNDS: Okay.

DR. LINDENFELD: In that same vein, I think the ten patients that you have reclassified for the new analysis, that were not reversible, I would just to like to see, just to be sure, that there were several patients who refused transplant.

Could we just be certain that those patients were not stroke patients? You've said they weren't, but is that correct? These were not patients who had some major complication; therefore said I don't want another operation?

DR. RUSSELL: Stuart Russell. I'm a cardiologist at Johns Hopkins. I have some research support from Thoratec. I, from one way or another, took care of six of those ten

patients.

One of those patients wanted to see if we could recover them. Went back to work, was doing well. We realized we couldn't recover him; he's now been transplanted. Another one was a 17 year-old in Bermuda, who got life-flighted over here.

He wanted to go home for Christmas. Was not then listed for transplant at six months. Came back after Christmas and was subsequently transplanted.

DR. LINDENFELD: I think he wasn't listed until April, according to at least -- so it wasn't just the holidays.

DR. RUSSELL: Okay, I'll give you that. A third patient had some surgical complications. Required a partial colectomy. Subsequently transplanted, doing very well.

A fourth patient has -- was transferred to us from Duke, is a smoker, is doing fine. But because of his smoking, we're not going to transplant him. He moved up here

because of some social issues down at Duke.

A fifth patient was very debilitated, has slowly recovered. Is now doing well, no strokes whatsoever. The sixth patient actually was transferred to us from Spokane, and you met her earlier.

I think we would all agree that she hasn't had a stroke. She's doing very well. Because of her PRA and because she feels very good on the pump, has not elected to be listed for transplant. So that's at least six of the ten.

DR. LINDENFELD: That's great. We might find out about the other four, because there's at least one, I think, that you didn't mention, whose Minnesota Living With Heart Failure and KCCQ scores were remarkably good, remarkably good, almost Class 2 heart failure prior to the device.

So I think that when these are -- the important here is that two or three patients that switched from the ten you've

added into the primary end point as positive, I think we just want to know about all those ten and be certain that there weren't other reasons.

I think all those six and the explanations are good, but --

CHAIRMAN LASKEY: Dr. Page and then --

DR. PAGE: I'd like to just ask a question. In terms of the practical management of patients with this device, the panel pack actually includes a fair amount of hemodynamic analysis of the pump, and I understand that it tends to augment the pressure pulse from the left ventricle, as long as there is some left ventricular action.

In terms of managing the blood pressure, how does one assess a patient who is living with this device? There's some discussion about blood pressure monitors being variably effective.

Perhaps the LVAD coordinator who's

with the group can comment on just the practical management of a patient who is being maintained on this device.

DR. MILLER: It is an interesting development to find someone talking with you, that you can't discern a palpable pulse very frequently. We frequently use a Doppler probe to define blood pressure.

It's obviously, since it's non-phasic, it's a very narrow pulse pressure; frequently ranges 110 over 80 or 90. It's an important observation; it's a difference. But we are able to maintain a pretty accurate look at their blood pressure monitoring and it has been not a big problem since familiarity with this phenomena.

DR. PAGE: And one other question I have. As an electrophysiologist, I've seen patients with VADS suffer ventricular fibrillation out of hospital, without a shock and actually be brought in in ventricular fibrillation.

Do you have any experience with this device? Have patients survived to hospital transfer, or do they still require an ICD if they're at high risk?

DR. MILLER: As you saw, many of these patients have ICDs in place at the time. There's been somewhat of a variability of people turning them off. We've been able, with this technology, to effectively deliver a cardioadversion shock without injury to the device or short-circuiting it and so forth.

As you've alluded, as long as right ventricular function is reasonably good, we've had patients in ventricular flutter, a very fast VT that tolerated it quite well. As long as there's reasonable right ventricular filling, they seem to tolerate this.

But we have not empirically across the board in all the centers placed an ICD going home if they did not have one on the front side.

DR. PAGE: If I may, in ventricle

fibrillation, have you seen a patient survive to admission to the hospital in --

DR. MILLER: Absolutely.

DR. PAGE: Yes. Thank you.

CHAIRMAN LASKEY: Dr. Blackstone.

DR. BLACKSTONE: This question is about the device exchanges. There appear to be, I believe in the primary cohort, five of these. They seem to be handled differently in your analysis, depending on whether the device that was exchanged was the Heartmate II or yet another VAD.

One could argue that if it's exchanged in another Heartmate II, that is like now evaluating another of the Heartmate II devices. Why did you handle these patients differently, and where do they appear in your analyses?

DR. HEATLEY: Three of the patients had their Heartmate II exchanged for other devices. In consultation with our DSMB, those patients were judged to be treatment failures,

and were considered study failures.

The two patients that required a Heartmate to Heartmate exchange are considered ongoing in the trial, and whatever their outcome -- we'll find out what their final outcomes were.

But if they received a transplant, which I believe they did, they would be considered study successes. The reason we adjudicated it that way was because in the VE trials and other analyses, we do pump exchanges, and usually look at survival to transplant.

If the patient survives a pump exchange and eventually is transplanted, they're considered a success. So we adjudicated these patients the same way.

DR. BLACKSTONE: So the bottom line is that they were handled totally differently, depending on what they received at that exchange?

DR. HEATLEY: Right. If the

Heartmate II supported them to the transplant, they were considered a success, even if they received a second Heartmate II.

DR. LINDENFELD: May I ask --

CHAIRMAN LASKEY: We'll get Dr. Normand, to have her first, and then we'll come back to you.

DR. NORMAND: I have two questions, a clarification and then perhaps two questions that I suspect you'll elaborate on this afternoon.

So the questions of clarification, first of all, how are the sites selected, the 11 sites of the 26 to perform the neurological testing? Were they randomly selected or were those that agreed to do it?

MS. DAMME: There were 11 sites selected, and how we selected them, in the protocol, we indicated that we'd be selecting sites that were high, medium and low enrollers, just to get a spectrum of sites enrolling that could be a representative kind

of sample, doing these neurocognitive tests.

We looked at from our previous history with these sites, as far as how high of an enroller they were. We categorized them into these categories, and then looked at which of these sites were now Heartmate II sites, and that's how we selected them.

DR. NORMAND: So again, it wasn't based on looking at any outcome data. It was a priori. They were selected in advance?

MS. DAMME: Correct, correct.

DR. NORMAND: The second question of clarification, and this is just my lack of knowledge, is I don't understand how a patient gets transplant-listed as 1A or 1B in 2006, and how that was done earlier. This is obviously related to the use of the OPC.

DR. PAGANI: I'm not sure I understand the question.

DR. NORMAND: So I'll tell you the reason why I'm asking you the question. That may help you answer the question. Part of the

outcome that we're using in the current study is whether or not they're transplant-listed into 1A or 1B.

I just wanted to know how that factor has changed, because you're using --

DR. PAGANI: That factor is not --

DR. NORMAND: Just let me finish my, just so that you understand what I'm asking. Because you're using an OPC based on historical data, and I want to know based on the historical data, if we were looking at those and had those data, then how would the decision to transplant-list the patient 1A-1B. So that's basically what I'm asking.

DR. PAGANI: The criteria for listing a patient 1A or 1B has not changed. Those criteria have been in place since 1999-2000, and that's the same criteria that has been used to determine listing status for heart transplantation. Through the time, it's been consistent.

DR. NORMAND: Okay. Thank you very

much. I'm a little surprised about patient mix, that somehow that wouldn't change. But in any event, you're the expert, not me.

MR. MIDDLEBROOK: Just to add to Frank's comments, the requirement for the listing status was new with the Heartmate II study. We did not --

DR. NORMAND: Oh, I understand, that it was a new thing for your study. I'm just asking historically and currently.

MR. MIDDLEBROOK: Yes, and historically, the data wasn't collected, and in that way, we didn't have a way to analyze it in a previous clinical trial.

DR. NORMAND: No, I understand. I was just wondering from your knowledge base, if theoretically, based on rules that people used to get wait transplant-listed. I'll just give you my two questions, that I hope we'll get some information on for this afternoon.

That is, and I'll just tell you what I'm concerned about. I'm concerned about

the fact that for some outcomes, you're using an OPC, and then for other outcomes you're using the Heartmate VE.

You've actually switched the comparison groups, and this is quite confusing, for the reasons Dr. Lindenfeld suggested. We have no basis on which to believe the comparison between the Heartmate VE and the Heartmate II, because you've provided no information, at least that I could find, comparing those two groups.

Moreover, we don't know how those three groups line up. That is, the OPC group, some demographics regarding them. Not only demographics, but clinical, clinical information, and for the Heartmate VE and then for the Heartmate II.

So that would be important, if you could supply some information regarding those groups, because switching the comparison groups in the middle is quite confusing, and makes it difficult to interpret the data.

Then the second question I hope that perhaps you can provide some information on for the afternoon relates to the missing data. I realize we're not -- we know that the missing data is going to be a problem, especially when you're administering the questionnaire.

But you're down to about a third of the responders as time goes on. For this type of an analysis, you know, perhaps some people didn't make it because they died. But that's actually informative of various questionnaires, in terms of their quality of life clearly.

So getting some information regarding characteristics of who were responders and non-responders over the time frame, would also just be helpful in interpreting those data. Thank you.

CHAIRMAN LASKEY: Okay. Everyone seems to be assuming we have endless amounts of time this afternoon. That of course is not

true. So as much as you can respond to us before the break.

We'll go for another 15 minutes here. So if there's other information you can provide, because otherwise the afternoon will get rather urgent. JoAnn and then Barrie.

DR. LINDENFELD: Another question about the population. In a recent publication by Lietz, et al., Dr. Miller I think was the senior author, discussing the potential survival of low and high risk candidates.

Now that was a destination therapy analysis. But if one were to put this cohort of patients into that analysis, the expected mortality would be well less than ten percent at 90 days, probably closer to four percent at 90 days.

So at 20 percent, 160 day mortality looks pretty high, and I'm sure there's an explanation there. But maybe we can hear about that. While this mortality looks good compared to the XVE, if you look at it in that

post rematch destination therapy cohort, I think these patients, admittedly you can't use the mean to assess individual patients.

But if you make a rough estimate of the mortality, the score here would be six to eight, based on those criteria outlined. That would be a 90-day mortality of four percent expected. I may have interpreted that wrong, but that would mean that this mortality seems to be higher than what you would predict for a destination therapy population, which is sicker and considerably higher.

DR. MILLER: That's an interesting question, JoAnn, and we'll probably come back and give you a little more data. But remember that this population is 100 percent inotrope-dependent.

Twenty-five percent are on two drugs, whereas not quite three-quarters or two-thirds of the patients in the destination therapy were inotrope-dependent.

When Wayne Levy has looked at this

cohort and factors in intra-aortic balloon pump, multiple inotropes and so forth, that risk of survival is quite high.

This data, as we've seen in the OPC and most published, and I think even the FDA's assessment is 65 to 70 percent survival at six months, is a pretty accurate portrayal I think this reflects that.

So I don't think you could look at this dataset and say that they have an expected survival in the ten or twenty percent. I think it's amazing to get to 70, 75 percent survival at six months.

We'll go back and look. We're actually looking at that risk score.

DR. LINDENFELD: Yes. I think from the risk score, they only meet two of the high risk criteria. In fact, no inotropes in that score gives you a higher --

DR. MILLER: That's a paradox in that trial.

DR. LINDENFELD: So I don't know

that you can use the inotropes at all in that particular one.

DR. MILLER: Yes.

CHAIRMAN LASKEY: Dr. Massie.

DR. MASSIE: Two other questions. One is you're proposing in your labeling cohort to use the 194 patients with six month follow-up in March of 2007.

It's now eight months later, and I don't know if you've had a chance to do an analysis, so we would actually have a much bigger cohort, and whether that would show any differences.

Because among the people who have the, you know, the continuation protocol approval, a lot more of those would be at six month follow-up now.

MR. MIDDLEBROOK: We had the pre-specified end point analysis as of September 14th that we presented to you earlier. That's the only analysis that we have updated since the March analysis, where we looked at

everything, outcomes, adverse events, and so forth.

We have not done and FDA has not seen or reviewed an updated analysis on those additional patients, and the additional CAP patients beyond the ones that we've presented here today, that we have enrolled into the Heartmate II study. We have not done that analysis yet.

DR. MASSIE: As I remember, refresh me if I'm wrong Doug, but clearly they looked about the same; is that right?

MR. MIDDLEBROOK: That's correct.

DR. MASSIE: The other thing gets to the post-approval study and the INTERMACS, and I don't know whether that's something we want to talk about now or this afternoon.

But why only 50 patients, when systematic data is being collected? The second issue would be what are you doing to ensure fully complete data, for those people who are going to be part of the post-approval?

Because INTERMACS is to some extent, you know, you get what you get. Whereas a study, you would expect there would be lots of efforts to make sure you get 100 percent of the data.

MR. MIDDLEBROOK: Right. As I mentioned earlier, we did anticipate that it would be a requirement for a post-approval, condition of approval post-market study.

But we didn't know exactly what those conditions were. We had typically done, in previous post-market studies, around 50 to 100 patients.

Because of the size of this study, which has been larger in the pre-approval phase than any of our previous studies, we proposed a 50 patient study initially.

But we've had dialogue with Dr. Dale Tavris, the epidemiologist at FDA assigned to review the post-market study, and he has indicated to us that that is probably an inadequate sample size. We're in an

interactive dialogue. We have proposed a hypothesis-based new sample size. It's greater than 50.

But again, those exact patient requirements will be worked out with FDA.

DR. MASSIE: Surely, there is a difference between when you roll it out to everybody who does these types of procedures, from those that you selected to be in your trial.

I think it would take quite a large number to decide whether or not what you found with these sites is what it's going to be in the future.

MR. MIDDLEBROOK: As I said, we're working with FDA on the sample size of the post-market study. Regarding your second question, in addition, as you mentioned, the INTERMACS registry is a volunteer registry.

In addition, what we are planning to do is working with INTERMACS, to get more frequent updates or downloads of the data, so

that we can evaluate, assess for compliance, and then follow up with those sites where we might have missing data, more frequently than the standard published reports that INTERMACS prepares.

CHAIRMAN LASKEY: We were scheduled to hear from James Kirklin. It's not clear if that will happen, but that would provide more detail. Just one more question for Thoratec, if I might.

In the expanded arms, beyond your pivotal trial, the continued access and the small size, did you keep your DSMB and your CEC employed?

MS. DAMME: Yes. Under the continued access protocol, those patients were followed identically, just like the main study cohort. So the same thing. The CEC has reviewed all AE deaths, and DSMB reviews all that data, all the same way.

DR. MILLER: Can I just make one response, because I think Barrie raised a very

important point. There is actually published information about can you take trial results and extrapolate them into the general population when it gets commercially available?

The REMATCH study had 20 centers, and the post-REMATCH database that we reported on the risk score that JoAnn alluded to were 66 sites. Only 12 of them had been in REMATCH. So 50 sites that had no experience.

The outcome was in fact ten percent better over the next three years. So it looks like that technology could be put forward. The guidelines and lessons learned, I think, can be extrapolated to suggest that we would get at least as good if not better.

CHAIRMAN LASKEY: I'll come back to you, Norma, in a second. A quick question for Dr. Zuckerman. Although it's certainly of scientific merit to pursue the discussion of the comparison between the two populations, the present one and XVE, it is a bit off the

mark.

I just wonder how much we should delve into this topic, when we have a much larger issue at hand.

DR. ZUCKERMAN: Okay. Well, that's an excellent point, Dr. Laskey. As you'll see in the upcoming FDA presentation, I think one needs to put the lack of appropriate control literature in context.

The FDA presentation will delve into why we came up with the number we have, what are some of the limitations of the other control data sets internally, when we talk about a post-approval study this afternoon, with new developments in this area, what might be better controls.

So I would certainly agree with you. Getting a better feel for what's really available will be very helpful for the ensuing panel discussion.

Perhaps if there aren't any other key questions for the sponsor that they'll

need to address this afternoon, we can go on to try to compliment this very fine presentation this morning, such that the panel can understand the whole gestalt here, from th FDA's perspective.

MR. MIDDLEBROOK: I would just like to make one comment, and maybe we'll answer one of the questions earlier. The data we presented, really we were presenting data comparing outcome results to the pre-specified end point, based on the OPC.

That really was the purpose of the study, and that's what we presented. We put in there the Kaplan-Meier comparisons for the VE, because the VE today really represents the standard of care. It's probably the most widely implanted VAD worldwide for bridge to transplant in the history of this technology.

So we had the data from control data from previous clinical trials. So because none of these studies for any of these devices have been randomized prospective

control trials, we wanted to give the panel and the FDA some sense of how this device looks in comparison to that VE, and that's the reason we've made that comparison and that presentation.

DR. MASSIE: It just would be interesting if you gave us the VE data in a contemporaneous manner, as opposed to VE data that dates back quite a long time. That might solve some of the issues in a more simplistic way.

CHAIRMAN LASKEY: And we still need to see the specifics of the patient populations, of course. I think we should take a short break. I would like to keep this moving, because we're doing quite well, and obviously we need sufficient time this afternoon.

So I have about 10:15. If we can regroup at 10:30 back here. Thank you.

(Whereupon, a short recess was taken.)

CHAIRMAN LASKEY: Okay. It's just a little past 10:30, 10:32. I'd like to call this meeting to order again. Thank you all. We'll now have the FDA's presentation. The first presenter is Eric Chen, the review team leader for this PMA. Eric?

MR. CHEN: Thank you, Dr. Laskey. Mr. Panel Chair, panel members and members in the audience, I'd like to thank you for taking your time out to be here with us today, to review the application at hand.

So this is the Circulatory System Devices Panel. The PMA that we're discussing today is P060040 from Thoratec Corporation, in regards to the Heartmate II left ventricular assist system.

My name is Eric Chen. As indicated, I was the lead reviewer for this application. I'll be providing a brief history of the clinical study and some of the pre-clinical evaluation that we've reviewed.

Dr. Ileana Pina and Dr. Julie Swain

will be discussing the clinical evaluation. Dr. Chul Ahn will be discussing the statistical evaluation, and Dr. Dale Travis will be discussing the post-market study proposal that's been provided by the sponsor.

FDA's panel questions that we have for this panel will be in the afternoon session.

As indicated by the sponsor before, this is an anatomical picture of the implantation position of the device. We have the inflow cannula that's inserted in the apex of the left ventricle.

We have the full graph that’s anastomosis to the ascending aorta, and then we have a percutaneous lead that exits the skin to the right of the abdomen, that's connected to a controller. The controller can be powered by two batteries, or as indicated previously, can be powered by a battery or AC power.

This is an exploded view of the

device. The inflow cannula is here, with the textured service, outflow cannula, and then the single moving part known as the impeller, that causes the centrifugal force that's provided to the blood, in order to inject it to the systemic circulation.

We have the patent hydrodynamic variance as indicated by the sponsor, and we have two blades here that cause the blood to go in continuously and then similarly in the exit sites.

So the mode of operation for the previous bridge to transplant devices that we've seen previously were pulsatile blood pumps, in which the devices were to make the systolic and diastolic functions in the native heart function properly.

This is a continuos flow rotary blood pump, so it's the first of a kind, in which the volume of blood that's ejected to the systematic circulation is based on the rotational speed of the impeller, and the

pressure differential that exists across the pump, the pressure differential being the pressure in the left ventricle and the ascending aorta.

The FDA has classified this as a Class 3 device. Therefore, the data that needs to be submitted to the FDA in order to demonstrate a reasonable assurance of safety and effectiveness needs to be reviewed.

The relevant factors that need to be considered in regards to the review of this type of application is the patient population for which the device is intended to be used, the conditions of use, which are described in the labeling; the risk benefit ratio of the probable benefits that the device may cause against the probable injury that it may; and lastly is the device reliability.

So the proposed indications for use for this device is intended to be a bridge to transplant in cardiac transplant candidates at risk of imminent death from non-reversible

left ventricular failure.

The device is intended to be used inside and outside the hospital and during transportation purposes. The sponsor has proposed to contraindicate the device for patients whose body surface area is less than 1.3 meters squared.

FDA's engineers have performed a review in regards to the pre-clinical evaluation of the device, and we've indicated that these following components have deemed to be satisfactory. We still have some minor outstanding issues that need to be resolved. However, we believe those to be completed very shortly.

So a brief overview of the clinical trial that's in regards to be discussed today is that the trial was a single arm prospective multi-center pivotal study.

The trial was powered for 133 patients, and the sponsor chose to implant these at 26 investigational sites. The study

was to be prospectively determined successful if the one site at 95 percent lower confidence limit of the true success rate exceeded 65 percent, which is known as the performance goal.

As discussed earlier already in the morning session, there were three patient cohorts in regards to this PMA. The primary cohort that we have enrolled 126 patients, and these are patients with a body surface area greater than or equal to 1.5.

The protocol had specified that those patients who had a body surface area of between 1.2 and 1.5 would be analyzed separately from the main cohort. That's why seven patients from the original 133 that were implanted were removed from this primary cohort.

The continued access cohort allowed the sponsor to continue to enroll investigational patients, and allowed FDA time to review the PMA application.

138 patients have been enrolled so far, with body surface area greater than 1.5. As of March 16th, 2007, 58 patients have reached a clinical end point.

The small BSA cohort, 15 patients were enrolled, and these were patients that had body surface area between 1.2 and 1.5. Seven of these patients, as indicated earlier, were from the primary study cohort known as the pivotal study; eight patients were enrolled in the continued access; and ten patients have so far reached a clinical end point as of March 16th, 2007.

There were seven device replacements that occurred in regards to the three patient cohorts. Five came from the primary and two came from the continued access. Four patients received another Heartmate II device based on pump thrombosis that was seen in the original pump.

Three patients received other approved devices, other approved LVADS. Four

of these device replacements, in which the patient received another Heartmate II, was because of the pump thrombosis, and the implanting -- the post-implant days are shown here.

The other replacements were due to a pledget that was found in the pump, an outflow graph kink and poor infill valve positioning. Those patients received approved LVADS.

There were a total of 108 suspected device malfunctions reported in the initial submission, and device malfunctions were classified as certain components of the device not operating as intended. Nineteen of these were determined to be not malfunctions or failures.

Of the 68 reported malfunctions, 13 related to the implanted components. 55 were related to the external components. 21 of the events related to various technical errors during implantation, user errors or wear and

tear on the system.

So therefore from an engineering conclusion, we believe that the pre-clinical testing demonstrates that the device performed to the specifications proposed by the sponsor. The corrective actions have been proposed for the malfunctions and failures that we have, and FDA has reviewed those.

We believe that the technical errors may reduce with more experience with this device, especially since only 26 investigational sites were in the pivotal study.

From an engineering standpoint, because of the low pulsatility that this device has, compared to previous pulsatile pumps, it doesn't appear that we observed any physiological problems. But due to the small sample size, our experience is limited.

A review of the literature also indicates that there's no conclusive evidence in regards to reduced pulsatility in

ventricular assist device patients.

This device was reviewed by a whole list of specialists in regards to statisticians, clinicians and engineers, and I've listed their names here for their recognition. I will now turn the clinical parts over to Dr. Julie Swain and Dr. Ileana Pina.

FDA Presentation

DR. SWAIN: Thank you, Eric. I want to go over generally a little bit about the history, and then a review of these data.

There are five approved bridge to transplant devices. None were approved with randomized control studies, and none really had comparable control groups that are scientifically validly comparable.

So in 2002, we decided we really needed to try to advance the field a little bit with the FDA, and develop a performance goal, because there are basically three choices.

Keep doing what we're doing, single arm studies without a good comparator, or require randomized control trials for bridge to transplant, which has never been done.

But the problem is with a level playing field, we thought is certainly an option for any company, but probably was not going to be requirement by the FDA.

The third was to try and develop a performance goal. You know, I say "performance goal," not OPC. Because we looked at the literature very extensively, and had inside and outside consultants look at the literature and vetted this to the heart failure society and other groups.

The literature is somewhat difficult to evaluate. But in 2002, we came up with what we thought was a reasonable performance goal. It was based on criteria for the journal articles that we looked at, and again it's all publicly-available data, published in peer review journals.

It is not appropriate to use confidential data that the FDA had. So we needed public data, and we came up with this list. We came up with a performance goal of survival to transplant.

And again, I'm going to repeat this over and over in my presentation, the performance goal was for survival to transplant. We came up with a number of 65 to 70 percent, based on six papers in the literature, comprising 797 papers.

At the same time and concurrently, Marv Konstam's group was doing a meta-analysis, and came up with a goal of 74 percent, with some of the same papers and a different number of patients.

Again, this is a goal that because the literature, unlike heart valves, where we developed an OPC, where the investigators, the journal editors stepped up to the plate in the early 90's and had common reporting of complications, we really didn't have that in

the literature for bridge to transplant. So it made it somewhat difficult.

Well, the Heartmate study design was a multi-center single arm trial, again compared to this performance goal. The primary end point, which was pre-specified and agreed upon, and was published -- you have it in the protocol in your pack, and it was submitted by the sponsor to clinicaltrials.gov, the website of clinical trials, was survival to cardiac transplantation or 180 days while listed 1A and 1B.

Again, I'm going to talk a lot. One of the times I chaired this committee in the last decade, I think I mentioned that clinical studies are kind of scuba diving. Plan your dive and dive your plan.

So we depend on pre-specified end point analyses. The statistical hypothesis was that the lower confidence limit would exceed 65 percent, and for the non-

statisticians, the way I like to look at it is you could propose an N equals 1 study and if the first patient succeeded 100 percent, you would have beat the 65 percent. If it was a three patient study, two out of the three succeeded, 66.6 and you'd win.

So therefore the only reasonable way to look at a performance goal is looking at lower confidence limits. Again, these are the criteria list.

Dr. Pina, who's the heart transplant expert, as well as several of the panel members, the question that I think Dr. Somberg asked earlier or someone asked is did these criteria change.

Dr. Pina tells me that the criteria for a Status 1B listing has changed somewhat with mechanical devices. But in general, these are the UNOS listing requirements for 1A and 1B, and you know it takes a committee to list a patient.

There are three PMA study groups.

I'm going to speak generally only about the primary study cohort, which had the pre-specified analyses. These were 126 patients with BSA greater than 1.5. The other data is supportive data for the application.

There's been a lot of comparisons to the XVE data. We don't have the line listing that the company presented for the XVE data, so we cannot comment upon the validity of that or anything about that data, because we don't have those data.

Baseline characteristics of this group appear to be similar from the literature papers used to develop the performance goal. In particular, the etiology. 39 percent ischemic; 52 non-ischemic. That's pretty much the balance in the papers we use to develop our performance goal. The creatinine, bilirubin sodium are consistent with patients in this category.

You can tell for transplant listing, each site has different criteria for

listing patients. The categorization of 1A or 1B is standardized, but whether a patient gets listed varies between institutions. So it's somewhat subjective.

Well, here are the results. I have them on the right. The purple is the not successes and the yellow successes. These are divided out into really how they met or didn't meet it.

Again, think of the performance goal was survival to transplant. There's been a great bit of discussion this morning about that bottom right. Can people from the bottom right be switched over to the left, who weren't listed at 180?

There's been a lot of discussion of that. But let's discuss the other side a little bit first. First of all, there are two of the devices changed to Heartmate II, as Dr. Blackstone was just saying, because of pump thrombosis. You know, is that clinically a success?

Well, we're judging it a success, because again we have a pre-specified plan, and this really didn't fit in it. But we're allowing that to count as a success.

How about patients listed 1A-1B at 180 and then they later die, those four patients? Again, the performance goal is survival to transplant.

Obviously, these patients did not survive to transplant, but with the performance goal that we agreed with, the 180 days, because it made a discrete time limit on a study, that's listed as a success.

The patients that are ongoing at 180 days, that were listed at 180, are viewed as a success. So there's a question of whether anything on the left should go to the right? What about the right on the bottom, the ones that were not listed at 180 and ongoing?

As the company has presented multiple times this morning, they are eligible

with no contraindication to transplant, some of these, and they've given some examples.

My example, I think, is that I am eligible and I have no contraindication to be drafted by the NBA. Most likely that's not going to happen. But again, I'm eligible and I'm not contraindicated to be drafted by the NBA.

If you have a patient that perhaps had an extremely stormy course with the device, maybe two devices, things like that, and really doesn't want any more operations, the patient is transplant eligible but is probably not going to get one.

Likewise, if you have complications from the procedure and the device, require lots of blood transfusions, ends up with very high PRAs, you can want to be transplanted but it's probably not going to happen.

So we needed, when we made this 180 days and transplant-listed, we did not agree and would not agree to say transplant-

eligible, because that's really not an objective definition.

We wanted something that could be quantitated a little better. Again, the performance goal was made survival to transplant; not survival to 180, survival to transplant.

So we're counting transplants after 180 as successes. So that makes it again somewhat fuzzy on judging risk-benefit of this device, and whether it met a performance goal or not. But we again have a pre-specified agreed upon performance goal.

But what about the causes of death? These are broken up into yellow is the brain type causes, and again look at this pi chart, just dividing up the causes of death. Pretty common with what we found in the literature with the other devices.

Adverse events. Again, we don't have -- we can't make comparisons to the literature for lots of reasons. The

definition -- there are no definitions listed in many of the studies, and retrospectively it's very hard to come up with adverse events.

There are different definitions than what is being used currently, especially for things like stroke. The rates differ among the approved devices, and our performance goal was based on both of the approved devices or several of the approved devices.

The rates for the same device may well change over time. So it's very difficult to compare adverse events. This is a listing of the percent of the patients with each type of adverse event, which again is similar to that seen in the literature -- death, stroke, especially bleeding, thrombosis, sepsis. Those are the complications that we worry about the most.

As Dr. Edmunds has mentioned, you have the balance between thrombosis and bleeding, and that is the most difficult

factor to clinically manage these patients.

What about infections? Smaller device than the previous devices, but there's a 20 percent incidence of sepsis, 20 percent instance of local infections, as well as some pocket and some lead infections.

That indicates just the sickness of these patients and the recovery time it takes for any of these devices that are implanted.

There have been several questions about reoperations, and this is my take on the reoperation list, that 63 percent of the patients needed reoperations. 57 percent of the patients under 30 days, 23 percent after 30 days. These are all reoperations.

Look at the middle part, and those are the reoperations for bleeding. Red is under 30 days; blue is post-30 days. So there are multiple, and the other consists of many operations, things like tracheotomy, gall bladder operations, things of that sort.

So these patients really do have a

stormy course, and again, it's not substantially different than what we see in the literature. These are the other serious adverse events.

Two percent device thrombosis rate and some hemolysis. As Eric Chen was mentioning, some malfunctions. Low myocardial infarction. Cardiac arrhythmias; the definition is so broad that that's difficult to interpret.

Well, what about the secondary end points? There's been a lot of discussion about the significance of those, and there weren't things listed in the slides. There were no hypotheses listed in the pre-specified analysis plan. Plan your dive; dive your plan.

Therefore, they're not for labeling, because there was no correction for multiplicity. Nothing Bonferroni, home step down, nothing of that sort proposed. So we're left with a descriptive data for multiple end

points, and these are the multiple secondary end points.

NYHA class, I'll show you the QOL and NYHA class six minute walk. Again, it's a single arm study, and we have to worry about both placebo effect and assessment bias, because it's an unblinded study.

So we expect that with the ritual of an intervention, one has increased placebo effect. It's hard to get more ritual than a thoracostomy.

But again, I think there's, you know, good evidence here that these patients started at Class 4 and improved at three and six months, the patients who were tested. Very little missing data on NHYA class, and the sponsor is to be congratulated on fairly complete collection of data, on patients who could have data collected.

Same with the six minute walk. It improved, and again, these are not paired data, but it's the group data. Again, we have

no P values because of the lack of a hypothesis and a pre-specified analysis plan, taking into account multiplicity.

Same thing with quality of life. On the Minnesota scale, lower is better. On the Kansas City, higher is better, and Dr. Miller has presented this data very well.

What about the neurocognitive evaluation? We congratulate the sponsor. It's the first trial that's finished that has collected systematic neurocognitive data. We decided to make that a requirement for trials in 2001 or so, and had many consultants, including Dr. Petrucci, who's here, develop a suggested battery of tests.

It was again, collected at 11 sites, and five different domains were evaluated. We decided to define profound defects as something that everybody would agree as a serious adverse event. That would be three standard deviations below the normative mean.

If you think of IQ, the norm being 100, three standard deviations is 70. Until recently, you couldn't get in the Army if you were below 85. So 70 is profound defect, that you have a hard time functioning in society.

So we found that there were really no profound defects, although there was a good amount of missing data. So the question is do people who did not get tested may have defects? No way to tell that.

Only between six and ten patients for each of these five domains had paired baseline and six month data. So we think that it is impossible to say that patients either improved or got worse or didn't get worse, that you really can't make a conclusion regarding neurocognitive performance with this amount of data.

Well, what about the continued access protocol? Again, the performance goal was based on survival to transplant, and you can again see in these boxes we have listed

for you, and you have copies of the slides and can examine them closely, about what fell into which box as success or not success.

The 58 patient one, lower confidence limit of 55, with a performance goal or agreed-upon end point of 65.

What about the small BSA? Again, plan your dive and dive your plan. The plan, what we find often in many devices is that smaller patients are mostly women, and women mostly do not as well as men, in a lot of especially cardiac studies.

So if you look at the protocol, you'll see that it was not proposed to pool small BSA with 1.5 or greater in the pre-specified analysis plan, and we agreed with that. That is what's written in the protocol that you have in your panel pack.

So there was no pre-specified analysis plan. Therefore, *post hoc*, when it turned out these small BSA patients actually did fairly well, then one wished to pool them.

That's really not planning your dive and diving your plan. So again, they are not pooled in the primary analysis.

We would like a qualitative look at this data, and see if it can be extended. Again, here is the breakout on what happened to the seven patients that are included in that kind of pooled cohort.

Here is a distribution of BSA, and numbers of patients in the study. As a person who's on the left side of this curve, I'm very anxious to have devices approved for small BSA. We're thinking of small BSA as a surrogate for body habitus to have these devices. That's not a perfect correlation.

So that the surgeon's evaluation of body confirmation is, I think, far more important than the actual BSA. There may be some 1.7's or 1.8's that really don't have the right body to have some of these devices.

But again, you look at ten patients with 1.3 or 1.4, look at the other end of the

spectrum, which we don't hear a lot about. Nine patients with 2.5 and 2.6. So if you think there's enough data to approve 2.5 and 2.6, maybe there's enough data to approve 1.3 and 1.4.

Okay. Secondary end point, adverse events for these other cohorts. They're qualitatively similar to what we see in the literature, and that's about the only statement we can make.

So what are our clinical conclusions? That the registry really came close to meeting the primary end point of 65 percent. I think this committee and many members of this committee knows the meeting an end point does not mean approval by either recommendation by the committee or the FDA approving a device.

Likewise, not meeting an end point doesn't mean disapproval. If it did, we could have the statisticians and the secretaries. Statisticians can see if the end points met,

and the secretaries could see if the box's checked, and then approve or disapprove a device. We don't really work that way.

So I think the clinical judgment and the totality of data is very important, rather than is there a one point difference in drilling down, whether you can switch patients from one side or another to that graph.

The safety results for this study were qualitatively within the range of what is expected from the literature. Not a huge advance, but certainly qualitatively within the range.

The study was not powered to determine the effects of low pulsatility. This is the first really continuous flow device, and the small sample size limits safety and effectiveness considerations about small BSA patients, and I think I'll about large BSA patients.

So thank you very much, and Dr. Pina is going to talk about gender.

DR. PINA: Thank you, Dr. Swain. I'm Ileana Pina. I'm a professor of Medicine at Case Western. I'm a heart failure transplant cardiologist and I'm a consultant to FDA-CDRH.

We felt at FDA that it was important to take a look at the women. Historically, women have been underrepresented in heart failure trials, and there's been this sense that by the time the women do get into trials, they are considerably sicker.

There's a lot of impact now in the literature, looking specifically at women, the female group of large clinical trials. We felt that this was appropriate.

Having taken a look at some of the articles that were used for our FDA performance goal, and looking at the number of women that were actually entered into the primary cohort, I felt that the number was comparable enough that we could at least take a look at the data.

So in the gender analysis and notice this includes now the primary cohort, the 58 continued access patients, and ten of the small BSA, and all of these BSA happen to be women.

Something that we have seen, particularly in some data that FDA and I have been looking at in Ohio, we see a lot of African-American women getting listed for transplant.

The ischemic number lower in the women; again, not surprising. Very similar background characteristics of bilirubin creatinine. However, the hemoglobin of the women was lower; it was at about 10.7, and there's also very strong interest now in anemia in the population of heart failure.

But very striking. The incidence of stroke was more than triple in the women compared to the men, and the majority of these were beyond the two days post-operative.

I really want to thank the sponsor

came through. We asked for an analysis of the women and they came through and gave it to us. So I really congratulate them on this.

The reoperation after the first 30 days was also higher in the women; rate of infection was higher, but again reminding everybody we're dealing here with small numbers, and I think this is something that really needs to be explored.

So obviously not all women were enrolled in the small BSA group except for the ten that we're looking at here were in fact all women. Although the number of women are small, we see a signal here for a higher stroke rate, and for reoperation beyond -- for it being after 30 days.

So we think that this needs to be prospectively looked at. If we have a post-approval study here, that this is something that needs to be also prospectively looked at in a post-approval study.

Dr. Ahn will now proceed with the

statistics.

DR. AHN: Even after Julie's presentation, I suppose you still need some statistics, right?

Good morning. My name is Chul Ahn. I'm a statistician in the Division of Biostatistics, CDRH. This is the outline. I will discuss OPC and performance goal, and then present study design and results, along with statistical issue of poolability. Then I'll conclude with the summary.

Objective performance criterion is a fixed target with an appropriate delta based on sufficient data. The sponsors derived an OPC from historical data, including the clinical trials for the target patient population, with body surface area greater than equal to 1.5 square meter, and proposed a value of 75 percent.

Then they set up the study goal of success rate being greater than OPC minus ten percent delta.

There are some confusions about OPC. Some define it with a delta included and some don't. So should it be 75 percent or 65 percent?

The FDA prefers using a performance goal because of the limited data. A performance goal is a fixed value to which the device's performance is compared to, and which appears in the statistical hypothesis a perimeter value. Here, it will be at 65 percent.

A performance goal was developed by FDA in 2002, with a rate of survival to cardiotransplantation. It was developed based on six publications, reporting on the majority of approved devices, where there exists a lower BSA limit of 1.5 square meter.

I'd like to make some general comments on performance goal. First, a performance goal should be developed for the intended patient population. Second, the current patient cohort and the historical

patient cohort that was used to develop the performance goals should be comparable.

Third, it is neither a superiority nor non-inferiority comparison. The appropriate claim should be such that the pre-specified performance goal is met.

This is a multi-center single arm clinical trial comparing to an OPC, with a null hypothesis of P less than OPC minus delta, against alternative hypothesis, P less than OPC minus delta.

Here, P is the proportion of successful patients in the intended patient population. P is a fixed constant, but only in value. It can be estimated using the data we collected from the study.

The patient success was defined as survival to cardiac transplantation, 180 days of LVAD support, with UNOS status 1A or 1B. The nominal point of hypothesis may be written as follows, and accordingly, the study success criterion is the lower bound of one-sided 95

percent confidence interval for P greater than 65 percent.

Now how do you apply this decision? First, we get an estimate of the true proportion P by counting all the successful patients and dividing it by the number of patients in the primary cohort. This is a point estimate.

But this is not a good estimate, since it does not consider its variability. This estimate will vary from sample to sample or study to study. The better way is to estimate P using an interval. It will be an interval estimate.

When we put a confidence on it, it is called confidence interval. We can now calculate 95 percent confidence interval, so that we can be 95 percent confident that this interval contains the true proportion, P.

If the lower bound of this 95 percent confidence interval is greater than 65 percent, we will declare that the study is a

success.

For the secondary end point, most statistical hypothesis will specify. So any statistical claims regarding secondary end point will be problematic.

This line shows the result of the primary cohort. The number of patients in this cohort is 126, with BSA greater than or equal to 1.5 square meter. There were 89 successes, among which 73 had transplants, full recovered, and 13 had 180 days of LVAD support, with UNOS status 1A or 1B.

The lower bound of one-sided 95 percent confidence interval was 64 percent, and therefore the study failed regarding the primary end point.

I noticed that there were some confusions about sponsors previously presenting OPC and comparison of survival curves of Heartmate II and Heartmate XVE.

Note that this transplantation survival is not the primary end point, but we

were interested in finding out the survival probability at each time point and compare with INTERMACS data.

This represents the survival curve for primary study cohort as of September 14th, 2007. We can see that the survival poolability at 180 days is roughly 75 percent, which is similar to data from the INTERMACS registry.

As well, we can see that the majority of patients, actually there were 55, were transplanted before 180 days. This graph illustrates the CAP survival curves for the Heartmate II, compared against the Heartmate XVE.

A CAP curve for Heartmate II is slightly higher than the Heartmate XVE, but we should note that Heartmate XVE was approved in 1998. So a comparison of survival curve is confounded by difference in the practice of medicine and differing patient populations.

Only 86 patients were enrolled in

the Heartmate XVE trial, but the sponsor continued enrolling patients through the approval process, eventually enrolling 280 patients.

This competing outcomes graph provides illustration of the four possibly outcomes for patients implanted with the device.

We are unable to compare this graph to the literature reports that were used to develop the performance goal, because the literature did not specify the time point at which patients were transplanted.

INTERMACS registry has competing outcomes graph, but their graph includes both bridge and destination patients. Among 138 CAP patients, there were 58 evaluable patients, and out of 58 evaluable patients, there were 38 successes. So the success rate is 65.5 percent, with a lower bound of 55.3 percent.

In the small size cohort, there

were a total of 15, among which seven patients were from the pivotal study and eight from the CAP. Out of these 15 patients, there were ten evaluable patients and seven were a success, with a success rate of 70 percent, with a lower bound of 46.2 percent.

You may wonder why the lower confidence interval varies a lot among these three patient cohorts, even though their success rates are almost the same. That is because of the sample size.

In the next slide, we'll show how the sample size affects the confidence interval. In this slide, you will see three scenarios, all of which have a similar success rate of 70 percent.

The first scenario shows the small BSA cohort, where there are seven successes out of ten, with a success rate of 70 percent, and a lower bound of 46 percent.

The green line indicates the confidence interval. Note that the upper

confidence interval of this confidence interval is always 100 percent, because it is one-sided.

The second scenario is the primary study cohort, with 126 patients, with 71 percent success rate.

The third scenario is hypothetical situation, where we have 1,000 patients with 710 successes. Here, the lower bound of one-sided confidence interval is 69 percent.

You will notice that as the sample size increases, the width of confidence interval becomes narrower, and the lower bound becomes higher.

What is the message of this slide? The result of the small BSA cohort tells us that even though the success rate or the point estimate of the true success rate P is 70 percent, in fact the true success rate, P, could be as low as 46 percent. For the primary cohort, it could be as low as 64 percent, and this is what we compare with the

performance goal of 65 percent.

There is a statistically issue of poolability. Assessment of data poolability across investigational site is challenging, since the primary success rates are different among centers.

This graph shows the success rate of the primary cohort by hospital, with five or more patients. The Y axis is the success rate and X axis is number of patients in each site.

Each bar corresponds to each site. So for example, the first bar is a site with 16 patients, and its success rate is more than 90 percent. The last bar is a site with 12 patients, and its success rate is about 40 percent. The rest are in between.

This table includes all the hospitals. The first column shows the number of patients in each site, with the same success rate.

There are eight sites in the first

row, and three, two, two, and five ones are the number of patients in each site, and their success rates are all 100 percent.

There is only one site in the second row which enrolled 16 patients in the primary cohort, and its success rate is 93.8 percent. In the middle, there are four sites which enrolled three patients, and their success rates are all 66.7 percent.

On the bottom, there are two sites which enrolled one patient each, but no successes. You will notice that the success rates are all over the place, ranging from zero to 100 percent.

We did some statistical testing, to see if there is a homogeneity of success rate across the investigational sites. The Fisher's Exact gave us a P value of .068.

However, when we include only sites with five or more patients, we have a P value of .02. So it seems to suggest that the success rate may be different across the

investigational site.

We also used a random effects model to account for variation among sites. For this model, we treated the success rate of each site as random effect arising from a common distribution. We are interested in the meaning of this common distribution.

The following are the statistics from this posterior distribution of this mean. You can see that this mean of 70.15 percent came very close to the success rate of the primary cohort, which was 70.6 percent.

The five percent point of the distribution of this mean is 61.9 percent, and this is slightly smaller than the previous lower bound of the confidence interval, which was 64 percent.

This slide tells us that the random effects model accounts for the variation among sites, and produces the wider confidence interval.

In summary, the study failed

regarding the primary end point. There is not enough information to draw a statistical conclusion of this device for patients with BSA less than 1.5 square meter.

There is a statistical concern of data pooling across investigational sites, and this may be due to unknown covariant. This is all of my presentation. Thank you.

DR. TAVRIS: Good morning. My name is Dale Tavris and I'm one of the epidemiologists at the Division of Post-Market Surveillance in the Office of Surveillance and Biometrics.

Today, I will talk about some general principles that we utilize when thinking about the need for and designing post-approval studies.

Then I will discuss the post-approval study that has been proposed for the Heartmate II left ventricular assist system, if the PMA is approved.

Before we talk about post-approval

studies, we need to clarify a few things. The discussion of a post-approval study prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean that FDA is suggesting the panel find the device approvable.

The plan to conduct a post-approval study does not decrease the threshold of evidence required to find the device approvable. The pre-market data submitted to the agency and discussed today must stand on its own, in demonstrating a reasonable assurance of safety and effectiveness, in order for the device to be found approvable.

As we all know, pre-market clinical data are collected from patients who are highly selected and treated by the best-trained physicians.

In contrast, when a device is permitted to be on the market, patients who receive the device are more representative of general population of device recipients, and

physicians who treat these patients are not limited to the best-trained physicians.

Additionally, some rare adverse events that were not observed in the pre-market studies might occur on the post-market phase, as the observation period extends and the patient population broadens.

Therefore, the main objective of conducting post-approval studies is to evaluate device performance and potential device-related problems in a broader population over an extended period of time, after pre-market establishment of reasonable evidence of device safety and effectiveness.

Post-approval studies should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial establishment of device safety and effectiveness.

The reason for conducting post-approval studies are to gather post-market information, including longer-term performance

of the device, data on how the device performs in a real world in a broader patient population that is treated by average physicians, as opposed to highly selected patients treated by leading physicians in the clinical trials.

Evaluation of the effectiveness of training programs for use of devices, the evaluation of device performance in subgroups of patients, since clinical trials tend to have limited numbers of patients or no patients at all in certain vulnerable subgroups of the general patient population.

In addition, post-approval studies are needed to monitor adverse events, especially rare adverse events that were not observed in the clinical trials.

Finally, we conduct post-approval studies to address issues and concerns that panel members may raise based on their experiences and observations.

The sponsor proposes to use the

inter-agency registry of mechanical assisted circulatory support, otherwise known as the INTERMACS registry, to prospectively evaluate the success rate of patients receiving the Heartmate II left ventricular assist system for bridge to transplant indication.

The primary objective of the study is to assess the success rate, defined as the percent of patients who are transplanted, weaned from the device due to myocardial recovery, or supported on the device for at least 180 days.

Secondary objectives include the rate of adverse events, the rate of device malfunction or failure, quality of life, difference between baseline and follow-up, the rate of reoperations, cognitive function, difference between baseline and follow-up and the rate of rehospitalizations.

The hypothesis for the study is that one-sided lower bound for the 95 percent confidence interval for the success rate will

be 60 percent or above, which is five percent lower than the performance goal of 65 percent that was used in the pivotal trial.

In order to do that, the sponsor proposes to enroll the first 78 patients from the registry who signed consent forms. Inclusion criteria are all patients receiving the device for bridge to transplant indication, in accordance with device labeling, which includes being refractory to medical therapy, at imminent risk for death, and a body surface area of at least 1.3 meters squared.

The sponsor proposes follow-up assessment at discharge, one week, one month, three months and six months.

Since the INTERMACS registry provides the whole patient population for the proposed post-market study, I'd like to say a few words about it.

INTERMACS is a national registry for patients who are receiving mechanical

circulatory support device therapy to treat advanced heart failure.

This registry was devised as a joint effort of the National Heart, Lung and Blood Institute, the Centers for Medicare and Medicaid Services, the Food and Drug Administration, clinicians, scientists and industry representatives.

The purpose of the registry is to provide data for analysis, which will facilitate improved patient evaluation and management, while aiding in better device development.

It currently includes 81 transplant centers out of a total of approximately 150 transplant centers in the United States. Enrollment began on June 23rd, 2006. As of November 9th, 2007, 489 patients have been enrolled, and well more than half had six month data available.

We believe that approximately 100 to 120 patients annually will receive the

Heartmate II left ventricular assist system for bridge to transplant indication, if the device is approved.

FDA has four areas of concern for which we would like to have comments from the panel.

First, we would like comments on the basic study design. We question whether or not we have an appropriate basis for comparison of safety and effectiveness without the use of a concurrent control group, and we would like input on the appropriate length of subject follow-up.

Secondly, we would like comments on the need for subgroup analyses, especially with regard to separate analyses in women. In the pivotal study, only 21 patients or 17 percent of the total study subjects were women.

There is reason to believe that this device could perform differently in women, because women tend to have a much

smaller body surface area than men; numerous studies of cardiac catheterization in women have shown a much higher rate of local vascular complications in women than in men; and the sponsor's pivotal suggested that women have higher rates of some adverse events than do men.

Thirdly, we are concerned about the adequacy of the proposed success criterion for a few reasons. A, because of well-established limitations with performance goals, we feel that the use of a concurrent control group would provide better information.

B, the sponsor is proposing a success criterion for effectiveness of only 60 percent, which is five percent less than the performance goal of 65 percent used in the pivotal trial.

C, the sponsor makes no mention of patient status at 180 days when defining success. Thus, a living patient who lasted 180 days on the device would be considered a

success, no matter what their status at that time, according to the sponsor's proposed success criterion.

Fourthly, we are concerned about the adequacy of the proposed neurocognitive assessment. The sponsor proposes that the Trailmaking Part B test be used alone to assess neurocognitive function.

The Trailmaking Part B test provides an inadequate assessment of the full range of neurocognitive function, which includes such aspects of neurocognitive function as memory, verbal fluency, activities of daily living, adverse symptoms and quality of life.

We look forward this afternoon to hearing your responses to our specific questions regarding the post-approval study should this PMA be approved. Thank you.

CHAIRMAN LASKEY: I'd like to thank the FDA representatives for their presentations, and the panel. Dr. Normand.

DR. NORMAND: I've got a question and a clarification for Dr. Swain. Specifically in Slide 24, you seem to indicate -- I'm going to sort of paraphrase this; it's going to sound harder than it actually is, that the sponsor was given credit for some successes that I think you had said initially, when you circled those boxes, that that wasn't really what you were looking for. You needed survival to 180 days or something. I'm trying to recall that conversation.

DR. SWAIN: Well, no. I think what is demonstrated on this slide, left-hand side, is pre-specified agreed-upon analysis plan.

If one wished to start switching patients from right to left side, then you ought to start also looking at left to right side, according to what the performance goal is based upon. But the pre-specified analysis --

DR. NORMAND: Right. So the reason why, I just wanted to make sure that you were

just saying hypothetically, if you're going to move thing around.

DR. SWAIN: Right. If one wanted to drill down, you need to drill down on each side.

DR. NORMAND: Okay. Then I have one question of clarification for Dr. Ahn, and that relates to the analysis that you undertook to assess between site variation.

Now this is an observational study, so although the same inclusion criteria were applied across the sites, one would, I think, have -- I may be wrong about this, but have every reason to believe that the patient severity might vary across those sites.

So it wouldn't make much sense just to do a test, to see if there was between-site variation that could be totally explained by patient characteristics.

So I just wanted to get your sense of did you look at that, and why didn't you adjust for patient severity? I'm just

assuming that the high volume centers, maybe they're getting sicker patients relative to the patients that they're accruing.

DR. AHN: I didn't adjust for those criteria.

DR. LINDENFELD: I think that's really important, because that could change your lower confidence interval. If in fact you calculated and observed to -- tell me if I'm wrong, Sharon, but if you calculated and observed to an expected ratio.

The point here is that is it the centers themselves and something they're doing that makes the difference in outcomes, or are some centers entering sicker patients?

If the variation is not accounted for by some centers entering sicker patients, then it seems like that would change the lower confidence interval, than if there are just different results in centers.

I mean if you correct for that, that might totally change your lower

confidence interval, which would totally change the outcome of this study. Is that correct, Sharon?

DR. NORMAND: That's correct. It means you'd partition out of some of that between-study variation and attribute it to the observed patient characteristics. So the amount that the intervals increase would be decreased.

DR. SWAIN: Let me just comment. This is Julie Swain. We really don't have a validated risk prediction scale to look at all the covariants that could lead to who's sicker in this particular number of patients.

There's a lot of things that aren't captured, that we all know clinically affect status, but they're not captured for various reasons.

So there's really no way to do that correction. Which speaks to the --

DR. NORMAND: I would say that there is at least some correction you could

do. I would conjecture that the estimate that you presented is penalizing too much the amount of between-study variation.

I agree, that you know, there's some unmeasured characteristics. They weren't randomized certainly, but surely for some of the observed characteristics, I would conjecture that the between-study variation would be reduced by some amount.

Now whether that amount is enough to make it, you know, 64, 63. But it would seem prudent to at least adjust for the observables. No one can get over your concern about unobservables. But at the very least, if you adjusted for the observables, you would reduce that size.

DR. AHN: I agree with you, Sharon. If we adjust for those, some of the covariants will be reduced. Even with the random effect hierarchical model, if we include those covariants, we may see some improvement, yes.

CHAIRMAN LASKEY: In any event, maybe you can do that by the afternoon.

(Laughter.)

CHAIRMAN LASKEY: Standard general estimating equation. First Mike Domanski and then you, Hank.

DR. DOMANSKI: Yes. I'm actually having a major problem with that part of the analysis, because it looks -- you know, it would be a worrisome thing if there were really substantial variation across those centers.

But I wonder if we can't save them the time of doing that this afternoon, because I'm not sure what difference that would make. I think that that --

I don't think that we can in any reasonable way, or at least again, the statisticians can help me out I guess with this -- but with the small numbers that we're talking about, the difficulty with making any kind of adjustment, I'm not sure it makes any