which is greater than .2, the delta. Also, the p-value of .791 is greater than .05.

Either of these indicates that the Endeavor III clinical trial has failed to demonstrate the non-inferiority of the Endeavor DES when compared to Cypher in late loss.

But, missing data were found for 14.6 percent of the patients, and these patients were excluded from this analysis. Multiple imputation and worse case analysis were conducted to address the missing data problem. Both the multiple imputation and the worst case analysis give the same conclusion as the available case analysis, and they all failed to show non-inferiority of Endeavor to Cypher.

Although Endeavor III is a randomized trial, covariate gender was found significantly imbalanced between the two arms. About 35 percent of patients in the Endeavor arm are female while only 18.6 percent of CYPHER patients are female. Propensity score analysis was performed on the data to adjust for covariate imbalances, but the results of Endeavor III remained essentially unchanged.

Endeavor IV is the third pivotal trial. The objective was to demonstrate the non-inferiority of the Endeavor DES to Taxus. Like Endeavor II, nine month TVF was the primary endpoint, and the eight month in-segment late loss was a statistically-powered secondary endpoint.

A 1:1 randomization assignment resulted in 773 Endeavor patients and 775 Taxus patients. The sample size provided 84 percent power for the TVF claim. The first 328 consecutively enrolled patients were evaluated for eight month late loss. This number was determined to provide 80 percent power for the non-inferiority claim.

The hypothesis for TVF in Endeavor IV is a non-inferiority one with the non-inferiority margin set up as 3.8 percent in the protocol. This slide provides analysis results for the TVF in Endeavor IV based on all available patients. The table indicates the Endeavor's TVF rate as non-inferior to Taxus. The upper bound of one-sided 95 percent confidence interval 1.6 percent, which is less than the delta of 3.8 percent. Also, the p-value of less than .001 indicates

significant evidence of non-inferiority of Endeavor to Taxus.

However, the above analysis excluded 74 patients. Similarly, multiple imputation Similarly, Multiple imputation and worse case analysis were conducted to address the missing data issue. By looking at the p-values or looking at the upper bound of the one-sided 95 percent confidence interval, we can see that multiple imputation gives the same conclusion as the available case analysis, while the worst case analysis gives a different conclusion, indicating the data failed to show non-inferiority.

FDA also conducted an analysis to determine under what circumstances the conclusion of non-inferiority would be overturned. The result is that the odds ratio of being a failure for missing Endeavor versus Taxus patients needs to be at least eight to overturn the results of the available case analysis.

This slide provides analysis results of the statistically-powered secondary endpoint of eight-month in-segment late loss in Endeavor IV. P-value of .089 indicates a failure of establishing the non-inferiority

claim. Again, the upper bound of one-sided 95 percent confidence interval is .22 millimeters, which is slightly larger than the delta of .2, signifying the failure to demonstrate non-inferiority for 8-month late loss.

Missing data were found for 15.2 percent of the patients. Multiple imputation and worse case analyses were conducted to deal with the missing data problem. As can be observed from this table, all analyses give the same conclusion, indicating failure to show non-inferiority to Taxus in eight month late loss.

Here is the summary of statistical analysis results of the three pivotal trials. For nine month TVF, Endeavor DES demonstrated both superiority to Driver and non-inferiority to Taxus. For eight month in-segment late loss, Endeavor demonstrated superiority to Driver,

but failed to establish non-inferiority to either Cypher or Taxus. This concludes my presentation.

DR. FARB: For my final slides, I hope to put the clinical and angiographic endpoints of the Endeavor program into historical and current perspective. My

goal is to in some way reconcile an apparently less effective stent with respect to inhibition of in-segment neointimal growth compared to an approved drug-eluting stent with a stent that is non-inferior to an approved drug-eluting stent with respect to target vessel failure understanding that TVF is a composite clinical endpoint that includes both safety, that is cardiac death and MI, and effectiveness, TVR elements.

When one considers the clinical endpoint for drug-eluting stent versus bare-metal stent superiority trials, historically, for the currently approved drug-eluting stent and the current Endeavor stent program, randomized trials show that a significant reduction in the TFV composite endpoint by DES versus BMS. For example, as we've seen today, there was a 48 percent reduction in the rate of TVF in Endeavor versus Driver in Endeavor II, 7.9 percent versus 15.1 percent.

The superiority of drug-eluting stents over bare-metal stents in these randomized clinical trials was driven by a reduced frequency of repeat revascularization. For example, a 61 percent reduction in TLR in Endeavor versus Driver patients in Endeavor II

with no significant differences in low rates of cardiac death or MI.

When we evaluate angiographic endpoints for stent effectiveness in drug-eluting stent trials, we gain insights into mechanisms or restenosis prevention. Historically, for the currently approved drug-eluting stents in the U.S. and the Endeavor stents, angiographic studies within randomized trials show that the drug-eluting stents are significantly more effective in inhibiting neointimal growth as evidenced by reduced rates of late lumen loss, reduced percent stenosis and reduced rates of binary restenosis measures. For example, there was a 50 percent reduction in late lumen loss in the Endeavor stent versus the Driver stent as seen in Endeavor II.

Analyses of serial angiographic studies from randomized trials of drug-eluting stent and bare-metal stents show that late loss in percent diameter stenosis are strong surrogate markers predictive of repeat revascularization procedures. You have seen this curve from Pocock et al. generated from analysis of 11 randomized drug-eluting stent and bare-metal stent

trials showing the relationship between increases in in-segment late loss and the probability of TLR.

The 8-month late loss measurements of the Endeavor and Driver stents have been superimposed on the curve with the corresponding probability of increased TLR as observed with the Driver stent in the Endeavor II study.

With two approved drug-eluting stents in the United States, non-inferiority randomized trials are the expected designs going forward. Importantly, the Endeavor IV study was the first pivotal trial that we have reviewed in a PMA application that was powered both for clinical TVF and angiographic late loss endpoint. And as noted, the Endeavor stent met its TVF clinical non-inferiority endpoint but failed to meet its angiographic late loss endpoint.

Several issues are worth exploring in considering the dichotomus results in Endeavor IV. First, the rates of the components of TVF were low in both Endeavor and TAXUS groups. Next, target vessel failure includes target vessel revascularization, but target lesion revascularization appears to be a superior

clinical measure of stent effectiveness at the treated arterial segment compared with TVR, which includes lesions that may be present or developed during follow-up, proximal or distal to the stented segment and includes the impact of any procedural factors such as vascular trauma from catheters or guide wires that may lead to luminal compromise.

Differences in rates of TLR in Endeavor IV were consistent with a greater angiographic effectiveness of the TAXUS stent, albeit with low rates of TLR in both groups. Given the overall low rates of revascularization and the numerous factors that may affect whether repeat revascularization to the target lesion or vessel is performed, including symptom status, stress testing results, coronary anatomy, or overall propensity towards performing invasive studies, the clinical impact of small differences in low rates of TVR or TLR is uncertain.

Returning to the late loss TLR relationship, one notes that the late loss TLR graph is curvilinear. Based on the shape of the curve, a failure to achieve statistical non-inferiority and late loss between stents

may not translate into an important difference in clinical endpoints such as TLR since late loss values for both stents in Endeavor IV are located on the relatively flat part of the curve.

Considering long-term effectiveness of one drug-eluting stent versus another in a large pivotal drug-eluting stent versus drug-eluting stent trial such as Endeavor IV, it is uncertain whether the less effective angiographic results of the Endeavor stent will translate into significantly greater frequency of repeat revascularization procedures compared to the TAXUS stent in a larger study population or with longer term follow-up.

It is notable that follow-up for Endeavor IV is only available through 9 months, and longer term follow-up of the Endeavor IV patients will provide important information on this issue. From a review of the Endeavor program, cases of TLR and TVR continue to accrue over time in all treatment groups including Endeavor, Driver, and CYPHER without a pattern of reduced clinical effectiveness of the Endeavor stent.

In conclusion, PMA approval is dependent on a

reasonable expectation of device safety and effectiveness. What we've learned in the DES era is that in DES versus BMS studies, any short-term or long-term risk of putting a drug on a stent must be clearly outweighed by the clinical benefit of a drug-eluting device. Effectiveness of a DES over time should be evaluated in the context of long-term safety, that is death, MI, and stent thrombosis rates.

FDA welcomes the panel's review of our summary and their responses to our submitted questions. I'd like to turn the program to Dr. Duggirala to discuss the post-approval considerations.

DR. DUGGIRALA: Good morning. I have the pleasure of going at the end of a long morning right before lunch to talk about our summary and discussion of the epidemiology review of this PMA and the applicant's proposed post-approval study.

First, I will describe the general principles and rationale for the post-approval study, then comment on the post-market questions that the pre-market study was not designed to answer, but may be addressed in the post-approval study. Then I will summarize the

sponsor's protocol for the Endeavor post-approval study. Finally, I will describe the post-approval issues that we would like the panel to discuss.

Before we talk about post-approval studies, we need to clarify that the discussion of a post-approval study prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean 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.

The main objective of post-approval studies are 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 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. One main reason to conduct a post-approval study is to gather post-market information. As we all know pre-market clinical data are collected from patients that are highly selected and treated by highly trained physicians. In contrast, when a device is permitted to be on the market, patients that receive the device are less restricted, and physicians who treat these patients are not limited to the best trained physicians.

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

Another reason for conducting post-approval studies is to address issues and concerns that panel members may raise based on their observations.

As discussed in the December 2006 Drug-Eluting Stent Thrombosis meeting of the Advisory Panel, post-approval data collected on currently approved drug-eluting stents have signaled a potential increase in

late stent thrombosis after one year compared to bare metal stents. However, it is not known if this rate plateaus or continues to increase over time, nor is the impact of stent thrombosis on the cumulative rates of cardiac death and MI completely understood.

Therefore, FDA currently recommends that post-market data be collected on a series of consecutively enrolled patients. FDA suggests that the cohort of patients enrolled in accordance with the labeled indications be pooled with pre-approval pivotal trial to reach a sample size sufficiently large to provide adequate power to evaluate a hypothesis comparing the rates of cardiac death and target vessel MI between the new DES and the control stent used in the pivotal study. This cohort of post-approval patients may be in a single-arm or randomized study, and data pooling may be based on either a frequentist or Bayesian perspective.

Drug-Eluting Stent post-approval studies to date have demonstrated that routine clinical use of drug-eluting stentS typically includes treatment outside of the labeled indications to include higher risk

patient and lesion subsets. Based on this previous experience, FDA recognizes that a post-approval study of consecutively enrolled patients will likely include patients representing a broader use of the product and recommends that data from such patients be analyzed to better understand whether significant safety issues exist in the treatment of these patients.

A sufficient number of patients should be enrolled to confirm that the upper bound of the one-sided 95% confidence interval around the observed rate of stent thrombosis for each 12 month period after 1 year is less than 1% for patients treated in accordance with the labeled indication. Depending on how the study is designed, it may be appropriate to include an adjustment for multiple comparisons in the statistical analysis plan.

FDA suggests that all patients be consented for 5 years of follow-up. If stent thrombosis rates are demonstrated to plateau or decrease in prior years, shorter follow-up may be sufficient. Alternatively, if stent thrombosis rates continue to increase, longer term follow-up or specific labeling changes may be

appropriate.

FDA recommends that the statistical plan include planned descriptive statistics on certain subgroups of interest including demographics, patient characteristics, and lesion characteristics.

Medtronic has proposed to address FDA's concerns outlined above by conducting two Endeavor stent studies, the Endeavor U.S. Postmarketing Registry and the Outside U.S. PROTECT Study. Data from 5,300 Endeavor patients, 2,000 from the U.S. registry and 3,300 from the PROTECT study will be collected and pooled for an analysis of stent thrombosis rates. Data will be analyzed separately for the patients enrolled in accordance with the labeled indication and collectively for all patients enrolled in the studies.

The sponsor has submitted a post-approval protocol for the U.S. Postmarketing Registry. Patients receiving the device will be enrolled in up to 100 sites in the U.S. The proposed sample size is 2000 patients.

The objectives of the registry are to evaluate the overall stent thrombosis rate of the Endeavor stent over the course of 5 years and to compare

the rates of cardiac death and MI with those patients with similar characteristics to those enrolled in Endeavor IV with a control group from the pre-approval trial population.

The second objective is to assess the safety and efficacy in patient subgroups with specific demographics, clinical indications, and/or vessel or lesion characteristics.

The sponsor has also submitted a post-approval protocol for the PROTECT study. The PROTECT study is already on-ongoing. However, the sponsor intends to pool a portion of PROTECT patients with the U.S. Registry patients to conduct an analysis of stent thrombosis rates. Patients receiving the device will be enrolled in up to 200 study sites outside of the U.S. The sample size is 8,800 patients.

The objectives of PROTECT are to compare overall stent thrombosis rate of the Endeavor stent versus the CYPHER stent, to compare the composite endpoint of total death or cardiac death combined with the number of patients with all non-fatal MIs as well as the number of patients with large non-fatal MIs for

Endeavor versus CYPHER, and finally, to assess the safety and efficacy in patient subgroups with specific demographics, clinical indications, and/or vessel or lesion characteristics.

The null hypothesis is that the true Endeavor definite/probable stent thrombosis rate per ARC definition during each yearly interval post-implant is greater than 1.0% when used in accordance with the labeled indication. The parameters/assumptions for this analysis were that the annual increase in stent thrombosis rate is 0.5%, and the power of the study is 80%, and the one-sided alpha error is 5%.

The co-primary endpoint is of cardiac death and MI, the null hypothesis being for the co-primary endpoint that the incidence of cardiac death and MI in patients treated with the Endeavor drug-eluting stent will exceed the endpoint incidence by 50% or more for patients treated with the Driver stent. The power for evaluation of the endpoint at each timepoint is greater than 80%, and the one-sided alpha error is 5%.

The sponsor plans to pool the U.S. post-approval registry with a portion of PROTECT patients.

For your consideration this afternoon, the post-market study has design to identify rates of stent thrombosis through 5 years, assess rates of cardiac death and MI to confirm long-term safety of the Endeavor stent when implanted in accordance with its labeled indications for use compared to the Driver bare-metal stent, and to evaluate use of the Endeavor stent for potential safety signals associated with higher risk lesion and patient subsets, recognizing from published literature that such patients are likely to receive drug-eluting stent in clinical practice.

Are the objectives identified above appropriate? Please discuss what additional objectives should be considered.

Finally, presented on this slide are key issues we have identified in our review of the post-approval study. The sponsor has powered the study to detect an overall stent thrombosis rate. It is uncertain whether the sample should be powered to detect stent thrombosis in any subgroups. In addition, the sponsor proposes up to 5 years of follow-up. However, it is unclear whether this is sufficient time

to study long-term stent thrombosis rates.

Finally, it is unclear what potential impact the difference is in antiplatelet therapy regimen between the Postmarket Registry and the PROTECT study will have when the study populations are pooled. Please discuss if the study protocol should be revised to address these issues. Thank you.

CHAIR YANCY: I'd like to thank FDA for very cogent and crisp presentations and I appreciate your clarity. We have a bit of a schedule overrun, so we'd like to have a brief Q and A by the panel to the FDA referable to that presentation. And I'd like to start with, hopefully, just two very succinct questions with almost yes or no answers.

One of the questions that I'd like to raise is referable to the statement of the unblinding in Endeavor III. In FDA's opinion, does that unblinding lead to any persistent concerns regarding the data integrity for Endeavor III?

DR. FARB: To keep it brief, the answer would be no.

CHAIR YANCY: And the second question is a

follow-up on a very important question that Dr. Weinberger raised earlier that was answered by Dr. Leon, but I'd like FDA's answer referable to Endeavor IV which is a single-blind study and the question of bias. Is FDA comfortable that the issues of bias have been addressed in Endeavor IV?

DR. FARB: The answer is yes. We looked at specifically the questions that were addressed about procedural endpoints looking at the different baseline lesion characteristics and approaches to the lesions per the investigators, and there were no obvious signals that favored one or the other.

CHAIR YANCY: Thank you. Open this up for questions. Dr. Naftel?

DR. NAFTEL: Just one general question where I need a little help. So there are these five or six studies and at this point, every one of us could through the details of them. We know them very well. But what I'm not clear on is should -- so this is to FDA -- should I be giving equal weight to each of these studies or should I be just looking at three, or what are you expecting on the panel?

DR. FARB: I believe that the studies should be looked at individually for the questions that they're asking that the study is supposed to address. And then look at -- the way we've approached it -- then following that to look at the program as a whole with emphasis on safety. So when we think about the current interventional cardiac practice when there are various alternative therapies, medical therapy and interventional therapy, how does this device meet criteria for safety and effectiveness to an appropriate level versus what is available so that when we think about the Endeavor II trial, which is a bare-metal stent trial, what are the relative clinical endpoints that are present and does the Endeavor meet those.

And then for the angiographic studies, substudies, really, those are more mechanistic kind of questions that get to how the device works in and of itself and relative to other devices out there, be it the bare-metal stent in Endeavor II and the drug-eluting stents in Endeavor III and Endeavor IV.

So long-winded answer to the question, I think the individual trials need to be looked at

critically on their own and then pooled together for the important safety concerns.

DR. NAFTEL: I think I was asking a little different question. That helps but just as far the pivotal study and is it Endeavor II that was designed without any input from FDA? I'm thinking just the regulatory wait.

DR. FARB: Yes. FDA did not review the Endeavor trial prior to it's initiation and it was an OUS trial. That said, the structure of Endeavor II in terms of the patient characteristics, inclusion/exclusion criteria endpoints and monitoring were of a level that we expect to see in pivotal trials. So I think it would fit that characteristic of pivotal trials and shouldn't be downgraded because it was just -- because of OUS.

CHAIR YANCY: Dr. Somberg?

DR. SOMBERG: Andrew, in your study and your study summary, you sort of -- in fact, you did suggest that there was no safety concern in terms of very late stent thrombosis. How can you justify that in terms of the small number and the -- probably the inadequacy of

seeing a very late stent thrombosis, especially since that's the major concern with safety verus efficacy consideration, and on the stent panel, it was stated that we should have some sort of point estimate to balance that against our efficacy consideration?

DR. FARB: Right. And this is a challenge that we have retrospectively looking at the approved devices and going forward to reviewing new devices of how to balance that safety and efficacy equation. And what we're looking for here are signals from individual studies and pooled studies and the rates and the confidence intervals around those studies. And what we've seen to date doesn't rise to the level of a safety signal for increased rates of stent thrombosis.

Now there are limitations of that that you recognize, that you brought to attention with your question. But of the data that we've seen, we don't perceive a safety signal for this device compared to the bare-metal stent which is a decent stent and performed as expected which is, I think, fairly important to consider and the other approved drug-eluting stents out there, keeping in mind that we are following that

situation as closely and as it's developed, since our December 2006 panel meeting.

CHAIR YANCY: Additional questions? Dr. Lindenfeld?

DR. LINDENFELD: You showed the Pocock slide as did the sponsor, and maybe you can comment now and the sponsor later. We've seen target lesion revascularization correlated with late lumen loss, and I know the numbers are much, much smaller, but do we have a similar correlation with clinical events? In other words, we've see a difference here between clinical events and late lumen loss which was disappointing. And I wonder if those two things are equally predicted by late lumen loss, that is clinical events and target revascularization, or do we have any data at all? Was I clear there?

DR. FARB: I think if I can broaden that and say clinical events would be something like since these are clinically driven either by a recurrence of symptoms or a positive functional study, then, yes, they would be generally correlated, not specifically correlated with, as far as I know, to death or MI.

DR. LINDENFELD: I think --

CHAIR YANCY: I have a question --

DR. LINDENFELD: Go ahead. I think that might be a little bit of an important point.

CHAIR YANCY: Let's go with our industry representative, please. Dr. Yaross?

DR. YAROSS: Dr. Farb, I appreciated your commenting that Endeavor II should not be downgraded just because it was performed OUS. However, I did notice in the FDA executive summary memo that that was listed as a study limitation. Could you clarify?

DR. FARB: Okay. Clearly, we -- our mission is to regulate devices for use in the United States. And for that, part of that mission is to be able to assess studies that are performed -- that meets our standards so that we can make a reasonable judgment. We do accept studies are performed OUS as complementary data to an entire program that help, in our judgment, so that while we would not find that a single pivotal study that was performed OUS to be necessary sufficient, we would want to see that studies are performed in the United States so we have assurance that the drug or

device, when used is appropriate in the U.S. population. So there may be other regulatory language that others could add on that.

CHAIR YANCY: Dr. Lincoff, please?

DR. LINCOFF: I'd like to come back to the Pocock curve because this continues to bother me exactly where this elbow is, and I recognize that it may vary depending upon the population. But the differences that we're seeing in late loss on this curve are comparing, say, to the TAXUS are of a magnitude as large as or larger than between, say, CYPHER and TAXUS, and that difference, which is further down on the curve, more on the flat part of the curve, has been associated now with two recent metanalyses with higher rate of revascularization.

So I think it's hard to say that this difference which is further along and more toward the elbow is not going to translate. And I think your analyses where you can find -- you took out target vessel failure because that has the compensatory effect of the reduction in other ischemic events, your analysis seems to indicate that may be something there. And this

is in the simple population of patients.

So it raises the question, and I'm not sure, you know, how -- because I've not been on a device committee before, but if we're concerned that a device may not be quite as effective as another device that already exists but clearly more effective then, say, bare-metal stent, how does that fit into the regulatory decision?

CHAIR YANCY: One of the things to bear in mind, Dr. Lincoff, is that our responsibilities to look at these data stand alone and do these data demonstrate a reasonable signal of efficacy and safety. And so we discuss that in some more detail.

DR. LINCOFF: But that Pocock curve was derived from data from lots of other studies, so --

CHAIR YANCY: Correct.

DR. LINCOFF: -- we're using that and we're using it often. So it's based upon previous data and that previous data also suggests that maybe that elbow is not where we think it is.

CHAIR YANCY: So clearly an issue we need to address after lunch. Yes, Dr. Morrison?

DR. MORRISON: I'd like to ask a question right now in the context of the proposed post-marketing analysis, but I think it's going to come up again when we discuss later, if we get to that point, labeling. If I understand it correctly, in all of the Endeavor trials with the exception of the one that compared to TAXUS, the duration of antiplatelet therapy was specified at three months although data has been presented that greater than 50 percent of patients in most of those trials were getting dual antiplatelet at 6 months.

Now as I look at the post-marketing proposal, at least the 8,800 patient Outside U.S. is still targeted at 3 months, and it wasn't clear to me whether that's the case in the proposed additional 2,000 patients. But it seems to me, as a clinician recognizing especially the probable or possible late stent thrombosis, there are a lot of implications of 3 months versus 6 months versus 12 months antiplatelet drug.

DR. DUGGIRALA: So allow me to pass the buck. That's going to be one of the questions that we ask in the afternoon of the panel. What should the proposed

labeling be, and then that will be what will be used for the 2,000 patient registry.

DR. MORRISON: Okay. But before we get to labeling, is it or is it not correct that the two arms of this pooled post-marketing trial include, number one, an Outside U.S. trial where it's already 3 months.

DR. DUGGIRALA: Right.

DR. MORRISON: And then an additional 2,000 patients where it's what, 3 months, 6 months, 12 months --

DR. DUGGIRALA: We don't know yet?

CHAIR YANCY: We get to suggest if -- when we get to that point.

DR. DUGGIRALA: And so one of the post-market questions was is that going to affect the pooling, the fact that you have these patients OUS who have a 3-month regimen and then some other regimen for the other group.

CHAIR YANCY: Are there other questions. I just have one brief question. FDA brought up this issue of incomplete stent apposition. How concerned should be about that?

DR. FARB: This issue is not decided yet in

terms of the clinical importance. Incomplete stent in apposition is not uncommon right after the procedure is done and can persist. We really focused where we thing, mechanistically, is this late acquired stent apposition which may have to do with inflammatory responses. We don't have a good -- we only have some retrospective data that have been published that suggest this may be important. But so here and in our review of the Endeavor program, we are looking for excess number of cases that might have been present and there weren't any.

CHAIR YANCY: Seeing no additional questions, let's go ahead and break for lunch and try to make up some time, so let's see if we can reconvene at 1:15. Thank you very much.

(Whereupon, the proceedings went off the record at 12:28 p.m. and back on the record at 1:19 pm.)

CHAIR YANCY: Prior to the break, we had prompted the sponsor with three or four specific issues that we were hoping to get more insight on with some fairly succinct responses. And the sponsor, I believe, is ready with about a 10 or 15 minute response to the

queries.

Following the sponsor's response, we will then have comments from three members of the panel who have independently reviewed the PMA. The order of presentation for the panel will be Dr. Hirshfeld first, Dr. Weinberger second, and Dr. Lincoff third.

We'll then have an opportunity as panel to discuss all of the things we have heard and we can pose additional questions to the FDA, to the sponsor or ourselves.

And then this afternoon's session will end with yet another public hearing.

So if we can proceed with the sponsors' response to our queries from earlier today, that'd be great. Thank you.

DR. MAURI: So I'll begin with a response to Dr. Lindenfeld's question which was regarding baseline characteristics. These are provided in the panel pack, but they're also shown up here on the slide. These are baseline characteristics comparing the Endeavor-treated patients versus the Driver-treated patients in the pooled safety analysis. And you can see that there are

some significant differences as this is a pooled analysis. It's not a 1:1 randomization.

But as I said, overall, the risks tended to favor the Driver stent group, and basically I'll focus on what is significant or of borderline significance. You can see that although the number of men was higher for Driver, that would tend to favor Driver. The number of prior PCIs was higher for the Endeavor-treated group. That would tend favor Driver as well. The incidence of various comorbidity such as hyperlipidemia, diabetes, hypertension, prior bypass surgery and this group of risk factors was higher, tended to be higher for the Endeavor arm, which would tend to favor the Driver arm.

It's a little bit difficult to interpret revascularization for angiogram MI in this slide since that's a combined group. It's uncertain which would favor one stent versus the other. So that's presented in the context of the pooled safety analysis.

CHAIR YANCY: Is that acceptable, Dr. Lindenfeld?

DR. LINDENFELD: Yes, thank you.

CHAIR YANCY: Next item, please?

DR. LeNARZ: Dr. Lincoff asked for some information about multi-stented patients, and I think the first thing I'd like to just point out is the Driver analysis from Endeavor II. And I highlighted a couple of areas that I think will allow for an appropriate comparison. One is that the procedure success does change as one goes from single-stented to multiple stents. In addition, you can see quite a step up in the target vessel failure rate as well as TLR in the bare metal.

Next slide please. This is a pool comparison and just so that we understand the totality of the data, we have 215 multiple stented patients and we have reviewed the number of patients beyond 30 millimeters of stent length, and it's 163 and roughly 3.3 percent beyond 40 millimeters of stent length.

So with that as a background, you see one, a maintenance of the procedure's success even with the multiple stents. You see a significant drop over the 32 or so percent in target vessel failure with the Driver stent, and TLR that I think is quite acceptable for the types of patients that we're encountering.

Next slide. If you then look at the data that is the TAXUS study for multiple stents in Endeavor IV, you see one of the more interesting things is that the late loss, both in-stent and in-segment, step up more than I would have frankly anticipated. And you see a target vessel failure rate that's 15 percent and a target lesion revascularization rate of 6.8 percent.

Next slide. This is then the data from TAXUS against our pool, and you can see that the target vessel failure rate is represented on the left from TAXUS from Endeavor IV and on the right against the pool data, the 215 patients. It's consistent with the Endeavor data from Endeavor IV, and we see basically target vessel failure rate that's consistent across the groups.

Dr. Lincoff, is this the information you were looking for?

DR. LINCOFF: Yes, Thank you.

DR. LeNARZ: Okay. I have a couple of more things -- points to clarifying. Next slide, please? Dr. Somberg required some information about the interaction of Zotarolimus with the other drugs, and I wasn't at the podium, but I think it's important to

point out that it is not just the drug-drug interactions but also the polymer. And our instructions for use in this Section 5.3 contains, at the bottom, potential interactions of the Endeavor stent with other drug-eluting or coated stents have not been evaluated, that it is discouraged in basically all trials.

One last slide. And then there was a question from, I think, the industry representative regarding information about gender and this is the information. So again, you can see that we have 339 females in this analysis combined across EI, EII, EII-continued access, and EIII. And this was an earlier analysis done, and we see, frankly, that the late loss in-stent and the late loss in-segment are as good as the male population and that the target vessel failure and the target lesion revascularization rates are also consistent with no statistical difference and that the stent thrombosis in these two groups prior to Endeavor IV are quite comparable.

So I hope I've answered your questions regarding late loss.

CHAIR YANCY: Next item, please?

DR. POPMA: My name's Jeff Popma. We were the angiographic core lab for this study. My disclosures are that we did perform the angiographic analysis for this study and received research grants for that. I'm also on the Medtronic Advisory Board and my travel and hotel were reimbursed for this meeting.

I would like to take just a minute or two. I would like to go quickly and try to summarize five years of work that has really been done within our core laboratory, I think as well as with Dr. Alexander Lansky's core laboratory. You'll see that. And with the statistical assistance of Dr. Laura Mauri and Dr. Rick Kuntz. And Dr. Kuntz will speak in just one moment.

When we talk about in-stent and in-lesion late lumen loss, we have to understand exactly what we're measuring. When we do our analysis with in-stent/in-segment late lumen loss, the in-stent measurements are determined over the axial length of the stent where the stent has been placed within the artery.

Understanding that elastic recoil does generally not occur, the amount of lumen loss that

occurs over the follow-up period is a good surrogate for the amount of intimal hyperplasia that is occurring within the stent.

In order to determine whether there's been any effects of balloon injury on the edges, our analysis also includes the 5 millimeters of edges that occur on either side of the stent, and that's the in-segment late lumen loss rate. Five millimeters proximal, 5 millimeters distal. That's where we make our measurements, and we make our measurements how the lumen looks immediately after the procedure and then we subtract from that what the lumen is at the follow-up period.

If I could have the next slide, please? We have become very precise in our measurements within the angiographic core laboratory for the determination of late lumen loss. And I'll show you two angiograms. The on the top the stent has been placed in the left anterior descending artery between two septal branches. And this is a magnified view of that stent at its late follow-up and the amount of measured late lumen loss in this example was .2 millimeters.

Now in contrast, I'll show this is immediately after the procedure in a patient who has also had a stent in place between this branch and this branch. And if I could have the next slide, please? We've blown that up. And this represents .6 millimeters of late lumen loss measured. Now what I mean by this is we've become very precise in our measurements of differences of late lumen loss that most of us would agree may not have clinical importance to patients. This is not a significant narrowing and no interventional cardiologist, I don't think, would dilate this lesion even though there are differences between this .6 millimeter late lumen loss and the .2 late lumen loss. As I said before, our measurement tool has become very precise.

Next slide please. Now we begin to look at this specifically in trials like the reality trial where there were statistical differences in a well-designed randomized clinical trial using the CYPHER stent and the TAXUS stent. And in that study done by a different core laboratory and a different set of investigators, significant differences in late lumen loss but no

differences in the occurrence of target lesion revascularization. And we began to understand that there was an important relationship between simply looking at the angiogram by the investigator and then what the patients felt.

And I wanted to emphasize in a couple of different slides, very quickly, the fact is that in those patients who are scheduled to undergo angiographic follow-up, the target lesion revascularization rate is significantly higher -- this is the bare-metal Driver stent -- then in those patients who are not scheduled to under go clinical follow-up. And in the bare-metal stent group, from 16.2 percent down to 8.3 percent, the occurrence of TLR was affected by the individual looking at the angiogram. In the Endeavor limb, this was not quite so dramatic.

Next slide, please. The reason that this is so important as we talk about the concepts of the relationship between late lumen loss and target lesion revascularization is we saw a similar trend in patients enrolled in the Endeavor IV trial where less than 20 percent underwent angiographic follow-up.

And in those patients who underwent angiographic follow-up, as presented by Dr. Leon earlier, the target lesion revascularization was 6.9 percent with Endeavor, 3.0 in those patients treated with TAXUS, potentially attributable to the fact that the investigator saw the angiogram and made a decision based on what they saw in the angiogram.

When we removed that angiographic follow-up which occurred in 80 percent of patients in the Endeavor IV trial, then these differences were between 3.5 and 2.7 percent. The occulostenotic reflex has affected many of our measurements with respect to the late lumen loss-TLR correlation.

My last slide, please. Next? Now does this make a difference? Let's look at the non-angiographic cohort. The question that we specifically said is is there a late catch-up that occurs in those patients who do not undergo this occulostenotic target lesion revascularization?

This is from Endeavor II and we'll take the Endeavor stent and the non-angiographic cohort 5.2, 5.9, 6.9 percent, not much of a catch-up and certainly not

different than the catch-up that occurs with the Driver stent and just slightly lower than that occurred in those patients who underwent much higher rates of revascularization in the angiographic cohort.

So we have noted over the past five years that there has been a discordance between the degree of late lumen loss that occurs within the vessel and the need for target lesion revascularization. There are two reasons for that. The first reason is we're influenced by what we see on the angiogram. Investigators and all their good intentions look at the angiogram and say, oh, that's narrowed, I have to fix it.

But the second one my colleague, Dr. Kuntz, will address is the fact that this relationship between late lumen loss and target lesion revascularization is not a linear one. It's a curvilinear relationship. I'll turn things over to Dr. Kuntz.

DR. KUNTZ: Thanks, Jeff. Just really quickly.

CHAIR YANCY: Dr. Kuntz, just one minute. There's a question from Dr. Domanski about Dr. Popma's presentation.

DR. DOMANSKI: Yes. I mean I'm impressed with the safety profile of this device and all of that. And I know these numbers are all small but I'm not -- I must -- I guess it's more a comment than a question, but perhaps you could respond to it. I'm -- there are a variety of reasons why somebody doesn't go back to the cath lab, the pain is not all that much, they don't want to go back, there's a certain threshold to taking them back, so I'm not so sure that there's some mysterious discordance. I mean it sounds like the difference is that there's less angiographic restenosis with the TAXUS but, in fact, that it's, you know, the severity is such that, you know, the patients are going back for whatever reason.

Again, I must say, perhaps you can enlighten me, but I'm not so impressed this is either surprising or anything else. Again, granting that the numbers are small, the conclusion I'd draw is that TAXUS does a better job of preventing restenosis. It's a small number either way. It doesn't necessarily say anything terribly bad about the stent, but I guess I'm not impressed with that --

DR. POPMA: Again, we have two measures that we're measuring for effectiveness. One is the amount of tissue growth --

DR. DOMANSKI: I understand -- well, it's not tissue growth, though, Jeff. It's target lesion revascularization, I mean based on your angiogram. I'm not talking about just small numbers by IVUS.

DR. POPMA: Well, if we could go back to just the one last slide just to speak to what Dr. Domanski's talking about, just back one, for these pieces here. You know, I think that you'd have to postulate that the patients in the Endeavor group were having more angina, and the doctors who were treating them were having more angina. If you look at this differential, there is a numeric but non-statistical significant difference between these two numbers, but there are less than 1 percent absolute rates at follow-up.

And I think that's the area tha we're talking about where there is a curvilinear relationship. It's not 0. It's monotonic. But it's very, very small in the broad scheme of things.

DR. DOMANSKI: But the number that I'm

looking at is if you do an angiogram, it's a simple point, but if you do an angiogram, the fact is there's less angiographic restenosis if you actually know the answer. Is that true or not? I mean it's 6.9 versus 3.0.

DR. POPMA: Those are the target lesion revascularization rates.

DR. DOMANSKI: Based on angiogram?

DR. POPMA: On the left side.

DR. DOMANSKI: Right. So if you don't have an angiogram --

DR. POPMA: On the right side --

DR. DOMANSKI: -- you're less likely, you know, to go do something. But if you have an angiogram, you see the restenosis and you go after it. I mean that's the other way to define --

DR. POPMA: Right.

DR. DOMANSKI: You know, I understand the term occulostenotic is a prerogative term, but maybe the problem is that there's angiographic restenosis and the people are reopening it. I mean --

DR. POPMA: Well, hopefully, we do this --

DR. DOMANSKI: -- appropriately --

DR. POPMA: -- for a reason, for symptoms. I mean the idea is that is there any change that the simple measurement affected what we do. And I think every trial we had in Europe and here says that we do.

DR. DOMANSKI: Sure. Well, one would --

DR. POPMA: But where we would want us going clinical practice is over in the clinical side.

CHAIR YANCY: So why don't we let Kuntz finish this up, and I guess the hope is that this occulostenotic reflex will go away one day, particularly in the context of courage.

DR. KUNTZ: Thank you. Next slide, please? Just very quickly. I've had a 15-year interest in this area that Dr. Lincoff brought up earlier, the relationship between angiographic narrowing and clinical restenosis, and my colleague, Laura Mauri, has had a long interest. My old colleague, Don Baim did. We did a lot of work in this area.

And what's interesting is if we look at this Pocock analysis, which was used by the Food and Drug Administration -- we showed it as well today -- this is

an analysis of the relationship between any single patient and a probability of a narrowing, of a revascularization. So you wouldn't be surprised that the inflection point occurs at around 1 to 1.5 millimeters because for any 3 millimeter vessel, for example, it's going to take 50 percent narrowing before you would dilate. It's not really a great curve to look at means, that is a mean of .6 or .4 or .2. They're all falling in an area where nobody would ever dilate.

So there is another way to do this. Can I have the next slide, please? This is also the same analysis of a single-patient we did with the actual data showing, again, that really, the curve starts to inflect up at about 1.1 to 1.4 millimeters. For any given patient, you have to have that much narrowing. Since the averages of most drug-eluting stents that are of contention here are way down here, it's really in an irrelevant area, because the question isn't does the stent have .2, .4 or .6 narrowing. It's if you have a mean of this, what's the probability that it'll have a 1.2 or 1.5. That's really what the question is. So that's been addressed.

Next slide. That was address by a paper that Dr. Mauri and I published about two years ago on circulation where we used instead of TLR, binary angiographic restenosis , which is obviously more sensitive and shifted up, we found that this is a very soft curvilinear relationship, that the probability of any mean narrowing from a stent that has on the right side of its curve a 1.4, 1.5 or greater goes up very gradually.

And the real question is what is this slope. That's really the question here. And there's no question tlhat if you have lower late loss for any probability, you'll have a lower chance of having a TLR. It's whether it's practically different or not is really what the question is.

Next slide. What we saw was that across a wide variety of different risk groups, we didn't see big differences in late loss. So one question would be does this stent tend to have late losses in the .8, .9, .10 range for vessels that are really long or diabetic patients. We saw relatively flat relationships. So the first answer would be that in the high risk groups that

we could look at within these groups, we didn't see them really creeping up the curve.

Next slide. And then the other analysis is to then look at purely the clinical response, that is we did have patients with high risks even in this relatively low risk group, those with over 20 millimeters and those with diabetes. And we didn't see strong signals that would favor the lower late loss stent, TAXUS versus Endeavor.

And then finally, I just want to point out that while the network study that you referred to by Dr. Stetler, which is a very complex meta-analysis that used kind of novel statistical techniques, they're contrasted with two head-to-head studies, one of which was the reality study which compared CYPHER and TAXUS, two different stents with different late losses and also the SORT-OUT II study done in over 2,000 patients, both of which head-to-head randomized trials showed no differences in clinical restenosis for at least those differences in late loss.

So what we would contend is that in the range that we're working with in late loss and what we've

observed in our risk, we are still in the relatively potion of the relationship between the mean of the late loss for any given patient and the probability that the TLR would creep up. Hopefully that answers the question.

CHAIR YANCY: Thank you, Dr. Kuntz. Any other comments from Medtronic referable to issues we raised this morning. Dr. Leon?

DR. LEON: There was a question posed about deliverability showing all of the data from the three randomized trials, Endeavor II, III and IV. Looking a device success, procedure success, and then device specific procedure success to see if there were any differences in the endeavor versus the control arms. Again, device success is crossing the lesion and being able to achieve a less than 50 percent diameter stenosis. Procedure success requires that you achieve device success without a major adverse event, and then, of course, the device specific procure success means that you've crossed the lesion without an adverse event.

And you can see Endeavor versus Driver, the first observation is that they're quite similar, and

we've said the Endeavor really is based on the driver stent, this very deliverable bare-metal stent with a device success of 98.8 versus 99.2 for the Driver stent.

The procedure success is about the see -- 97, 97, as is the device specific success. Endeavor III which involved the CYPHER comparison was intersting. I think most of the five interventionalists, I think most people would agree that the CYPHER stent is the least deliverable. And what you see is the device success is 98.8 with Endeavor, 94.7 with CYPHER which was a statistically significant difference, and if you add MACE to the equation, an event greater difference with a device specific procedure success falling to 91.2 for CYPHER versus 98.1 for Endeavor, a highly significant difference.

In Endeavor IV, the comparison to TAXUS shows pretty much the same, device procedure and device specific procedure success, TAXUS being a somewhat more deliverable stent than CYPHER, but I would hasten to add that these measures do not incorporate all of the multi-variate factors that lead into this issue of deliverability. And most people who work in an

interventional laboratory would concede that the Driver and Endeavor stent is certainly more deliverable than the first or currently available drug-eluting stents, CYPHER and TAXUS.

CHAIR YANCY: Thank you very much and thanks to the sponsor for responding to all the queries we had this morning. We will start our panel presentation with Dr. Hirshfeld. While John is getting his presentation up, Dr. Lincoff, did you have a response for any additional questions about Dr. Kuntz' and Dr. Popma's comments?

DR. LINCOFF: No. I thought they answered very completely and I appreciate it.

CHAIR YANCY: And Dr. Domanski, did you have any other comments about deliverability?

DR. DOMANSKI: No. That's actually very interesting.

CHAIR YANCY: Okay. We'll proceed with Dr. Hirshfeld. Thank you again Dr. Kuntz.

DR. HIRSHFELD: I took the liberty of making a couple of slides, because I felt that this was complicated enough that it would go over better with

some illustrations. While they're finding the slides, I'd just like to make the remark that I think we've had some really good quality data presented today, and I think it's going to be very helpful in this.

And the real issue that I think that we have to think about is how do we apply these data to an approval decision. And the first thing I'd like to point out is if we go back in the history of stenting in general from the stress trial to Sirius to TAXUS and now to Endeavor, I think it's very clear to me that we have come a long way with respect to both methodology and data quality compared to where we started, and I think it's a reflection of the agency's understanding of this and also the companies and sponsors understanding of how to do this.

So we're supposed to decide about safety and effectiveness, and so for openers, a completely safe device would have no adverse events ever. And a completely effective device would have no restenoses. But what we're asked to deal with here is what about something that's incompletely safe and/or incompletely effective.

And that makes us ask the question, what is our appropriate comparitor. Is it plain old balloon angioplasty. I think everybody would agree not. Are we to compare this to a bare-metal stent or are we to compare this to existing currently approved drug-eluting stents?

And with that in mind, the question is how do we set the bar, and if there's a tradeoff between safety and effectiveness, how do we adjudicate that. And also, how must the candidate device compare to currently approved similar devices in the same class.

I think this slide sort of illustrates the core issue that we're looking at. This is a plot of the in-stent and in-segment late losses for the four stents that have been discussed today, and you can see that there's a gradient of degree of inhibition of neointimal growth from the bare-metal stent down to the CYPHER stent.

And so the question is how do we interpret this in terms of making decisions aobut safety and effectiveness. And just parenthetically, I'd remind you that if you go back to the stress data, the QCA data are

not directly applicable but the difference between plain old balloon angioplasty and bare-metal stenting with a palmage shaft stent was .18 millimeters in minimal lumen diameter at angiographic follow-up. So it's a smaller difference than we had between Endeavor and Driver at this particular time.

So then the question is what about late loss, and we've talked about it, and the question which is sort of circulating underneath all of this, is there actually an optimal amount of late loss? And how does late loss reflect both safety and effectiveness? And is there an optimal late loss effectiveness range? Too much late loss, obvously you have excessive restenosis. What about too little late loss? Does too little late loss actually constitute a safety issue making one more at risk of having late or very late stent thrombosis? So then the question is is there an optimal late loss which gives you an acceptable balance between restenosis and late or very late stent thrombosis?

So in putting this together, I sort of though this kind of a matrix is the way we should be thinking about this, and what you see here is a 9-cell matrix

with safety on the horizontal axis and effectiveness on the vertical axis. And so if we have a new device that we're comparing to existing devices, obviously if it has better safety and better effectiveness, it's a 4+ approval decision, and so the obvious approval decisions are the green cells where you either have similar safety with better efficacy or better safety with similar efficacy.

And in the lower right hand corner, you have the obvious non-approval ones where the safety is worse and the effectiveness is similar or they're both worse. And then the rest of the cells are sort of in the grey zone. The one in the middle where it's similar and similar is most likely an approval decision. The two extremes where one is better and one is worse is one where one would have to scratch one's heads a little bit. And then the final issue is what about a device that has similar safety but has somewhat worse efficacy. Where does that fall in the hierarchy?

Now with that paradigm, what are we looking at so far from what we have seen today. If we compare Endeavor to Driver, I think we fall right here. We have

similar to somewhat better safety, and we definitely have better efficacy than a bare-metal stent. However, if we do an Endeavor-Taxus comparison, we fall somewhere around here. We have similar safety and we have somewhere between similar and worse efficacy depending upon which metric one looks at. And so this is the issue that I think we're going to have to think about over the afternoon.

So I think for our approval recommendation basis, it ultimately has to be based on clinical performance rather than theoretical performance characteristics, which is going to be the balance of safety and efficacy. Safety is going to be defined mainly by the adverse event rate, and there are multiple metrics which we can choose from to judge effectiveness including the various aspects of the restenosis rate and clinical.

And the final point I'd just like to emphasize is that although we have a lot of safety data, I think the experience with the other devices in this class is that we really will not be able to fully judge safety until we have a long-term real world experience

tabulated.

CHAIR YANCY: Thank you very much. That was very clear and very succinct and really helps us frame our thought process. Dr. Weinberger?

DR. WEINBERGER: I think what I"m going to try to just increment the very nice presentation that you just heard. We've heard a lot of very professional presentations this morning, a huge amount of data. I congratulate the sponsor on very thoroughly investigating their device.

My comments fall into several categories. First of all, I'd like to say something about the basic science of this particular device. This device is unique in ways that have not been underlined by the sponsor to my satisfaction in a positive fashion, that is the elution of the drug is complete by one month and it's very likely that the stent will be completely endothelialized, and that's what the animal study had showed. And one would expect, based upon basic science alone, that this device ultimately, from the point of view of late stent thrombosis and very late stent thrombosis will be more safe if one were to take the

animal studies at face value.

The animal studies also raise another question which nobody has discussed up to now, and that is there reports in the animal studies of embolization of material from the stents and fine microscopic areas of embolic material. Whether that is going to translate into a clinical problem when this device would be released on large populations, whether this will be an arrhythmiagenic focus or not, whether this will be a clinically relevant problem or not is one which should be built into consideration of subsequent investigations. So that's from the point of view of basic science.

The clinical studies, I think that the -- we're going to be framing our decision ultimately in terms of the paradigm that Dr. Hirshfeld just put up. I think that one thing I've learned, and it's been brought home by these studies, is what an outstanding stent the Driver bare-metal stent really is and what an advance it is. I think that one thing that has been brought home is that the definition of TLR and one which we're using is itself a perturbation in the nature of the

Heisenberg Uncertainty principle. You cannot observe a system without perturbing the system.

And as Jeff Popma just put up, if you look at TLR in groups of patients with time who have not had angiographic look, their subsequent TLRs actually increase at a faster rate than in groups of patients where they had a TLR look at one point so that looking at a TLR and deciding what to do something about it will perturb the subsequent natural history of the population.

That being said, we now live at a point in the history of drug-eluting stents that we're dealing with very good devices. We're dealing with devices that, in general, operate at a very high level where safety and efficacy have been reassured by various means in numerous studies. I think that we can break out the studies now into questions of effectiveness and are we convinced that the Endeavor is an effective stent.

So we just heard that -- I think there's really no argument that if you compare this to the Driver stent, that this is certainly a superior device. The question really becomes in comparison to the

existing drug-eluting stents is this device as effective or is it within striking range of being as effective as the existing devices. Well, we don't have the -- I think that the data speaks to that in terms of clinical effectiveness -- is the data from Endeavor IV. And the non-inferiority that was demonstrated, I think, at least provides some assurance that we're not dealing with a device that's inferior, so we're dealing with the devices that are fairly comparable.

The problem becomes that we have a discordant signal and the discordance signal is what we've spent a lot of time talking about as the angiographic signal. We've been trained that if you loose lumen, that's bad. And ultimately that loss of lumen is what translates into clinical events. Given the excellent draw-up that was done by the operators in getting very good, final luminal geometry, a loss of an additional .2 millimeters has not translated in these studies into clinical events.

I think the question for -- one of the questions that will occupy us will be what happens when real-life operators get a chance to use this device?

Will the ultimate payment of an additional .2 millimeters of late loss, will that translate to clinically relevant loss of efficacy of the device. In the hands of Dr. Leon and his colleagues who performed the study, a .2 millimeter incremental late loss did not translate into clinical events. But it's far from certain that in the hands of an average interventionalist who achieves very average results that that will indeed be the case.

So I think with that being said, I think that we really have to dwell a little more not just on the efficacy issues but also on the safety issues. It's my opinion that the signals that we see from the cohorts of size that we have do not give a confidence interval that says that this is a "safe device."

However, we are always -- the mandate for the FDA and for us as advisors of the FDA is to make a relative decision, that is is there sufficient safety to say that the effectiveness of the device is acceptable. In other words, would you be willing to when you balance out the safety and effectiveness that you know about. Obviously, we cannot know what will happen with the

device several years after the device is implanted prior to the device being released.

What is a little bit perturbing is the repeated statement that there is a lack of worrisome signals in the data. A lack of a worrisome signal is not a signal of safety. So lack of evidence is not evidence of lack. I think that what would have been the expected number of patients to have had late stent thrombosis if there is a .2 percent per year late stent thrombosis risk or a .4 or a .5 percent late stent thrombosis risk, and you're talking about relatively small numbers of patients in the 1200 patients that have gone out to 2 to 3 years.

So I think that if I had my druthers, we'd be sitting here evaluating the data 6 to 12 months down the line when more patients would have passed through further time points.

Finally, one last comment. It has to do with deliverability which really just came up in the follow-up, and that is we're told that in the Endeavor cohort, overall, there was a statistically significantly higher rate of patients who had had previous PCIs. I assume

that we're not talking about restenosis lesions. Otherwise, that would make deliverability a whole different issue. So I'll stop with that and go on. Thank you.

CHAIR YANCY: So the way this process unfolds is that over the next indefinite time period, we have a chance to query the sponsor, FDA or discuss among ourselves based on the very scholarly reviews that panel members have provided. If FDA or a sponsor has a response to something you've already heard or to something that you're about hear, we haven't prompted it with a question, there is another opportunity later in the afternoon for each of you to provide that response in a very limited way.

So with that proviso, we have several different skill sets on the panel, and I'd like to entertain questions from everyone. So let me start with our consumer representative. If you have any questions about either the presentations or about the internal review that our panel members have done so that we can give a fair opportunity to participate. Dr. Yaross?

DR. YAROSS: No comments at this time.

CHAIR YANCY: So we have a number of individuals on the panel that have experiences as interventional cardiologists. Do you have questions or comments that you'd like to make at this time? Dr. Morrison?

DR. MORRISON: Since you put it like that, I guess I can't resist. I'm grateful for this afternoon's data. I don't consider myself one of the most experienced interventionists around. As a matter of fact, I'm feeling like perhaps I'm the token real world person here. But I do have the experience from the real world of a handful of patients who have driver stents because I couldn't pass either a CYPHER or a TAXUS, so I'm greatly relieved to see that that's not necessarily a reflection of technical incompetence.

(Laughter.)

DR. MORRISON: I think that the driver is an excellent stent, not only for deliverability but the thin strut. And as I mentioned earlier, I'm greatly reassured by that just as my colleague is reassured by some of the animal data. And Similarly, I'm reassured by the world experience with the BiodivYsio stent and

knowing that of the components of this produce, two of them we have clinical experience of, a fairly substantial amount with the Driver stent and with the phosphorylcholine polymer.

And so I'm reassured and I'm very excited about -- I did not find reading the data that I was compelled with the notion that maybe there's a right amount of late loss. I mean thinking about it theoretically, I thought the right amount of late loss was one layer of endothelial cells. That would be perfect. But I am very reassured that the animal data may suggest endothelial healing has taken place, and I'm particularly excited by the sponsor's doing acetylcholine testing down the line and demonstrating even over and above cells that there may be resumption of proper endothelial function.

CHAIR YANCY: Dr. Domanski or Dr. Lincoff, do you have any questions from the perspective of invasive cardiology?

DR. LINCOFF: I wanted to go back to the confidence that we have in terms of safety, because it's my impression, looking at the numbers of patients that

we have in the upper limit of the confidence interval, that we are at a range that with some degree of safety, at least out to 2 years, we do have confidence that the acute thrombosis or late thrombosis rates in total don't exceed that which would be expected from the bare-metal stent. Now that, of course, still leaves open the time beyond 2 years.

But unless I'm wrong, there were 1,200 or so Endeavor-treated patients who had data out. Now that's as large of a data set that I think had been sort of calculated in prior forums on this topic to provide some degree of confidence for that time period for this range of thrombosis rates.

So can we get some clarification on that, because I think this is an important number. I recognize the whole story isn't over. We only have gone out some confidence to 2 years and that's what all the post-marketing we're talking about. But in terms of the level of evidence that we have for any other device of this type, of a drug-eluting stent or a bare-metal stent, are we that far off from a fair degree of confidence at two years?

CHAIR YANCY: Let's get a response.

DR. SOMBERG: Yes, I wanted to --

CHAIR YANCY: Oh, please.

DR. SOMBERG: At the 2-year time point, that was the number in our panel discussion on -- you know, general stents was discussed and by one person, and it's statistical. The trouble is with very late stent thrombosis, it's the 2-3 year period that is a concern to see what's going on.

And while everything seems to indicate -- and, you know, this is -- I'll turn it around as a question -- while everything seems to indicate that we are headed in the right direction, I still would like somebody, and I, you know, ask the company, maybe before the afternoon is out to say, okay, based on the tumult that occurred in Barcelona and subsequently and, you know, Swedish analysis 2 years, 3 years, and maybe now is 4 years, a little different, is -- how many patients would you have had to expose your stent to pick up a difference?

And I think 675 is inadequate and I think 1,200 or 1,500 patients would have been adequate. And,

you know, did we just miss it? Are we going to get more data? I mean there is a process. And when is this data going to come in? So if, you know, we make a panel recommendation and in 6 months there's all this information is in, well, usually things don't come out in 6 months, so there is a time frame, but if it's going to take 2 years for this to come out, are we doing this prematurely? That you can't answer but the other things you can.

CHAIR YANCY: Well, one other thing we can consider is that in our panel pack in Volume I, Table 59 brought forward by the FDA, it kind of captures this thrombosis rate and time sequence is 0 to 30, 0 to 180, 0 to 360. It's page 67 under Section 1, FDA Executive Summary, Table 59. That's probably as close as we have. And I would agree with you, Michael, that the denominator is at least as good as we've seen in most other data sets.

Now if somebody from FDA -- Gary, if you want to comment on this table or if there's another person from FDA. But otherwise, I think it's an appropriate representation of what is available, and I certainly

agree with Dr. Somberg that this has to be an ongoing evaluation, and it requires prospective acquisition of new data. But I think this is well collated here if you've had a chance to look at this. Dr. Domanski?

DR. DOMANSKI: You know, one of the things I think is important to consider as this deliberation goes on is that to the extent, there's been a lot of well-done safety data presented and certainly this device looks, on the face of it, to at least be minus any safety signal at all, number one.

Number two is that although we can argue about angiographic restenosis being a little more or a little less with TAXUS, I guess I'm impressed that the numbers are extremely small with a device that's, you know, been attested to being very deliverable.

So I guess as we consider reasonable demonstration of safety and effectiveness, one also has to consider the usefulness of having another device in one's quiver. You can recognize that maybe the angiographic restenosis is a little more, but when you're in the lab, you would now have a third option of a device that, at least in its Driver format, has proven

useful where the stents that are out there haven't.

So I think it's important to take that whole picture into account as opposed to trying to refine the science to the nth degree.

CHAIR YANCY: Andrew?

DR. FARB: Thank you. We just would make two quick points. One is looking at the absolute rates of the particular product are important, but we also have to consider the rates of stent thrombosis in any comparitor, be it the bare-metal stent or any other drug-eluting stent. And specifically getting to the late stent thrombosis issue that came up such a big issue last year and events that are occurring after some landmark, in this case we asked the company to provide data after the 1-year landmark in patients who have not had an event, looking for, particularly, those late stent thrombosis signals now that the denominator is somewhat smaller, obviously. But we do not see late stent thrombosis occurring when we compare the Endeavor stent to the Driver stent. But we are really keyed into this late stent thrombosis question.

CHAIR YANCY: Great. And it does look like

this rate is actually slightly less than 1 percent consistently. I appreciate the comments from our interventional cardiologists. What about from our surgeons on the panel. Do you have any specific comments. Dr. Kato?

DR. KATO: Thank you. One question for the sponsor is that in -- since, you know, from the surgical side, we always have to worry about the clopidogrel being on board, you're saying that, at least in your clinical trial design, that clopidogrel was recommended for at least 6 months. And yet we saw a lot of data that said that perhaps it really wasn't being used for 6 months, and it certainly wasn't being used for 12 months.

Where exactly is this -- you know, if you had to do this again, I mean are you advocating now you only need it for a month or two months? Or is this part of some -- you know, in terms of your future studies, how long are you going to recommend dual antiplatelet therapy?

DR. MAURI: I'll speak to that in terms of what was performed in the clinical studies that have

been presented. So the minimum duration that was recommended was 3 months in all of the studies except for Endeavor IV. Endeavor IV recommended six months minimum duration of clopidogrel. In terms of aspirin usage, an indefinite course of aspirin was recommended.

There was a query prospectively in each of these trials at defined endpoints to look back over the periods of time preceding the data acquisition, so at 30 days and at 6 months, 9 months, 12 months, 2 years, and subsequently ongoing, to see in that previous period did patients comply per protocol with therapy. So we have an indication at 6 months of whether patients complied with therapy. Unfortunately, it's difficult for us to tell whether they actually stopped at three months to 6 months, so there is incomplete information to know whether there's a difference between continue to 3 months versus 6 months.

The current ACC/AHA Guidelines are based primarily, I think, on data from ACS trials showing that there's a benefit to extending clopidogrel therapy out to as long as a year. But what we can say is that from the clinical trials that were conducted, the

recommendations were primarily for 3 months, and that reflects most of the data that we -- all of the data that we presented beyond one year in terms late stent thrombosis outcomes. And the Endeavor IV trial used clopidogrel out to 6 months.

So I think, at a minimum, the range is going to be 3 months of clopidogrel therapy, and it certainly is reasonable, as a clinician, to consider extending that for patients who are high risk for future events according to the ACC/AHA Guidelines.

CHAIR YANCY: If I can extend this just one step further, the one trial that you have actively enrolling is PROTECT. Is that correct? The others are registries?

DR. MAURI: You know, I think I'll let the sponsor answer that question.

DR. LeNARZ: We're actively enrolling PROTECT. We have, I think, 208 patients as of today.

CHAIR YANCY: So in a context of the recent statement from the ACC/AHA and the Society of Angiographers regarding concurrent use of dual antiplatelet therapy, what is the protocol specified

requirement for antiplatelet therapy in PROTECT, and have you changed it if it wasn't consistent with that statement?

DR. LeNARZ: The design of the student was to not mandate for any patient population the duration but to first state the IFU's for both Endeavor and CYPHER, the comparitor, and both of those would indicate 3 months. Obviously, during the design of the study with the new guidance documents, we then added the language that is consistent with those guidelines.

However, there are many geographies outside the United States in which the reimbursement of clopidogrel is on a limited basis. Recognizing that, therefore, recognizing the real world practice, we have set the study that we do not mandate abut ask the local physician to consistently apply the duration of clopidogrel across the Endeavor and CYPHER patients at his site and to collect that with case report forms. Obviously, to Dr. Yancy, the information that we will gather is now consistent with feedback from regulatory bodies indicating that we should identify when patients stop, for what reason, whether it's for surgical

intervention, and that's really the design of that study.

CHAIR YANCY: Thank you, Dr. LeNarz. Dr. Hopkins, did you need to follow-up in the surgical -- actually, Dr. Kato, did you have another?

DR. KATO: That was my follow up. Go ahead.

CHAIR YANCY: So we're in sync. Dr. Hopkins?

DR. HOPKINS: Sort of a comment just to pull all this data into a slightly different context, that is as a combination device, this puts the panel, I think, in a little bit of a conundrum in that the device components of this application appear to be excellent. The biology part, the Seeber part, is a little less compelling, but we have to vote on the entire device. It is a combination device. So I just bring that up for the panel to think about.

The other issues that I have are really at product labeling, and I'll hold them until we get tot that.

CHAIR YANCY: Okay. Thank you. Dr. Lindenfeld, did you want to raise any new issues or follow-up any that we've already discussed?

DR. LINDENFELD: No. I have no more questions.

CHAIR YANCY: Dr. Naftel from a statistical standpoint, are you satisfied?

DR. NAFTEL: No.

CHAIR YANCY: No.

(Laughter.)

DR. NAFTEL: Is that the end of my comment?

CHAIR YANCY: No. Just realize we have to leave some time this evening.

DR. NAFTEL: Okay. I'll try to keep this short. One again, I really am impressed at how you've put it together, all the different studies, and it's easy to dance from study to study, but I do have a few questions. First of all, in studies that I'm used to dealing with, you have a period of enrollment 1 or 2 years. And maybe your endpoint is some event at, say, 1 year or 9 months, but it takes awhile for all those patients to hit that point. Now the early enrollers, they pass that point and, ordinarily, you follow those patients also for death or whatever the major endpoints are.

Now as I understood it, Dr. Leon, you said, in fact, in all these studies, it stops dead at a certain point in time, if I understood it right. And in fact, this nice table in our panel pack, it's Table 58 on page 60, that shows the patient follow-up for all the different studies, I mean it's just unbelievably -- I didn't mean to say unbelievable -- it's wonderful follow-up through, well, like for the Endeavor IV, great follow-up through months, and then it has nobody followed up at 12 months or 2 years.

So first of all, I just want to make sure I understand the data. Did you indeed stop the data -- let's stick with Endeavor IV -- do you really have no follow-up beyond 9 months for, say, death or for anything?

DR. LEON: All of the patients in all the randomized trials are planned to be followed-up for no less than 5 years. The follow-up is updated on an annual basis, and we report the follow-up when a complete cohort has achieved that annual follow-up. So, yes, there are certainly some Endeavor IV patients that have been, relative to the index procedure, they have

been out for more than a year, some maybe even close to two years at this point, but we do not have those data. They have not been submitted to the FDA as yet, but certainly that follow-up is continuing.

DR. NAFTEL: Okay. So let's just push a little farther. So when you stop to do the analysis for the panel pack or for the PMA, even though you have these patients scattered through time so, for some of them, the 9-month follow-up was, you know, months ago, for others, it was like yesterday, but you actually said to your statistical data managers, you said, now take all the data that's in place, because I'm sure it was, and you said, censor or chop it off for this patient who hit 9 month last January you really said truncate and the fact that there's some deaths or stenosis or thrombosis, you really did chop it cleanly?

DR. MAURI: Maybe I can clarify this. So as we enroll these studies, you're right, there is an extended period of enrollment so patients may reach different durations of follow-up. And there certainly are patients in Endeavor IV study who have longer periods of follow-up. We lock the data sets when all

patients achieve a certain endpoint, so for Endeavor IV, the last lock was for the 9-month data.

As Dr. Leon mentioned earlier, in a few weeks, we'll have a lock data set for the 12-month data. And in order to maintain the integrity of the randomization and be sure that we have a complete follow-up over a certain time interval, we wait until we have a lock data set to be able to analyze it, and that's what's been presented today is the complete date for each of these lock data sets at the last available time point of follow-up. So that's why you have follow-up in Endeavor IV to 9 months.

DR. NAFTEL: Okay. So, you know, we're just so hungry for information and we've talked so much about, you know, what's happening next, so I want to make sure the panel is aware, there's a big hunk of information sitting there that could be there. But I understand what you did. It's clean and neat. But you need to understand we could stop today and reanalyze and have a whole pile more data on all of these.

DR. MAURI: Yes. So I think it's important to stress that we do intend to follow every patient out

through 5 years in all of these studies and for some of the trials, obviously for Endeavor I, we have 4 year follow-up. For Endeavor II and III, I believe it's 3 years of follow-up. So there has been an attempt to use as much of the available data as possible while maintaining using the highest integrity of data using only the locked data sets to do the final analysis.

DR. NAFTEL: Okay. So a locked data set, normally I think of it as a point in time, but it's a point in time relative to each patient the way you did it, not a calendar point but at 9 months post patient?

DR. MAURI: It's relative to the last patient enrolled in each study.

DR. NAFTEL: Okay. So that's fine. Now the second thing, just to help me understand -- I think I do -- but in the presentation this morning, and I'll stick with Endeavor IV because it's easy to work with, looking at the clinical events to 9 months, I just want to make sure I understand the statistical part -- it's slide 101 if you want to -- it's where you've got all the clinical events in Endeavor IV to 9 months, and I just want to understand the calculation a little bit, because you had

740 Endeavor patients followed at 9 months, so that's good. Incredible follow-up, good job.

And then when I calculate these various numbers like just the first one, death, there are 5 deaths if you're looking that and divide it by 740 and you get the .7, so I have a question. It's actually important for me to understand it. That 740, how do you get in that denominator? How do you get in the -- who is the 740 or who isn't there?

DR. KUNTZ: If you're referring to is the number a simple rate for numerator/denominators divided, the answer is no. They're -- we do a Kaplan Meier estimate, so patients who -- the very few patients that aren't followed are censored, so we have kind of a proper estimator, which I think will be a better estimator than just doing the rate. So if that's the question?

DR. NAFTEL: Totally. That is the question. Thank you. Well, when I did all the arithmetic through there, it kept looking like array, and so I'm glad you did a Kaplan Meier estimate. But then the 740 is a bit misleading because, for example, I bet those 5 deaths

aren't included in the 740, because I'm guessing the 740 is who's alive at 9 months. So I mean that's my guess. So it sounded like you did the calculation correctly, but the slide's just a little bit misleading, because I was just wondering where those dead people were in the 740. But I'm satisfied that I understand why it's confusing.

Okay. Let's -- so one more thing and then I'll let it go, Clyde. The next slide, slide 102 also makes a good point. This is on TVF at 270 days. So this is nice Kaplan Meier and I've dealt with this all my life, so I understand the possible pain. So this is the 270 days. That's supposed to be 9 months. Now if you look at the Endeavor group, you see how they're speeding up close to 9 months? We had all noticed this.

Now, okay, so let's talk about how you actually did the calculation. For each patient, you had an interval and you had the event. I mean that's how you do a Kaplan Meier. Now so 9 month follow-up, I'm betting you went plus or minus one month, maybe two months, because, you know, patients come when they come. You had some window. So first off, 270 days is 3.9 days

less than 9 months. That's fine. But there's a window. Like I'm betting you had a bunch of patients who came in between 270 days and 300, that came in from 9 to 10 months. And because you chopped off the plot here, the thing that anyone looking at this is saying, oh, wow, look how Endeavor is catching up late, I wonder if they catch and even cross.

Well, you chopped off -- you should have given me at least one more month to look at, because I think you used one more month of data. And at the rate it's going, it actually would have crossed. Your assumption of proportional hazards would have been shot. You wouldn't have used log ranks. So it sounds like a small detail but it's actually very important to me that you chose to cut this off prematurely.

DR. LeNARZ: Can I make a clarifying comment here? The reason you're saying a change here in day 240 is that is the timing of the angiographic follow-up, and a part of the ARC effort, the Academic Research Consortium effort was to take out this influence of angiographic follow-up and to then move it beyond the clinical follow-up, and in subsequent studies, we'll do

that. So the tail that you see there is what has been described by a number of individuals today indicating that that is the angiographic influence.

And as to the data, the last patient enrolled in Endeavor IV was a year ago the end of June, and so if you know the follow-up of individuals, we're in the process of trying to clean that data and then get this data locked. And it will be presented at TCT, and the Medtronic effort consistently is that as we lock databases, we present it publicly to the next available public forum. As an example, we historically lock the follow-up data on Endeavor II the first week of May and present that by the end of May at Euro PCR. So we're very timely with getting all of our data crunched and out to the public and to the regulatory bodies.

DR. NAFTEL: So you said your last enrolled patient was a year ago June, so that's important. But the first enrolled patient was more important to me because he's well past but I'm hoping that you'll still either agree with me or disagree with me that