occurs beyond 360 days and this is in the context of over 1900 patients being followed beyond 360 days in the Endeavor arm and over 570 in the Driver group.

So to summarize these results according to the time intervals, the first thing that these time intervals, according to the ARC definitions, the first thing that I would point out is that we looked at the proportional hazards assumption, and there was not a significant finding. And that basically confirms that we didn't see any apparent trend to different patterns over time of stent thrombosis between the two treatments.

Looking specifically at the very late period, which we were most concerned about, the 360 day and beyond, the rate of events for the Endeavor group was 0.1 percent and for the Driver group was 0.2 percent, each of these reflecting one additional event in each group but the different denominators reflecting the difference in percentages. Overall, the cumulative incidence was 0.8 percent and 1.5 percent for Endeavor and Driver respectively.

Looking at the overall safety analysis at all

of these hard clinical endpoints plus the endpoints of stent thrombosis according to protocol and ARC definitions, and I would note that we looked at stent thrombosis according to the more restrictive definite ARC as well as any ARC and found consistent findings with a low rate for the Endeavor stent compared to the Driver stent. You can see that in each endpoint, there is a low observed rate of adverse events in the Endeavor group. And the confidence intervals and the upper limits of these intervals are important to note in terms of providing the confidence around these estimates based on the density of clinical follow-up.

Looking at these results, graphically, you can see that the rate of death overall at 1080 days was 3.1 percent versus 4.5 percent, and cardiac death in the Endeavor group accounted for 1/3 of those deaths and was lower for the Endeavor group than for the driver group. In looking at myocardial infarction or the compositive cardiac death and MI, the rates were low for the Endeavor group as compared to the Driver group.

And finally, stent thrombosis, one can see again that whether looking at the more restrictive

definition using the original protocol definition, we saw a rate of 0.5 for Endeavor versus 1.2 for Driver, or the more inclusive ARC definition of definite and probable, 0.8 for Endeavor versus 1.5 for Driver.

These are the overall results summarized with a 95 percent confidence intervals of the upper bounds, and you can see that some of these intervals are actually fairly tight, particularly looking at stent thrombosis compared to what we're accustomed to seeing. And that reflects the density of follow-up beyond one year and out to three years.

So in summary, from the Endeavor clinical program, which is a data set that includes 2,132 patients treated with the Endeavor stent and 596 patients treated with Driver, we found no evidence of increased rates of death, cardiac death or myocardial infarction for the Endeavor stent treated patients compared with Driver out to three years of follow-up. And there was no evidence of increased stent thrombosis risk whether one looked at the period within one year or in years one through three in patients treated with the Endeavor stent compared with those treated with Driver.

And these results should be considered in the context of the available clinical follow-up and the concomitant antiplatelet therapy, and that is to say that 1287 Endeavor stent patients have been followed out to two years, and 675 patients out to three years. And that follow-up is ongoing for all of these trials and that the majority of Endeavor stent treated patients were off of dual antiplatelet therapy by one year and almost 90 percent were off by two years so that these observed safety results are in the context of fairly limited durations of dual antiplatelet therapy compared to what some of the trends have been in recent years.

So with that, I'm gong to pass the presentation on to Dr. Richard Kuntz who will conclude on the Endeavor clinical program.

DR. KUNTZ: Thank you. Good morning. My name is Rick Kuntz and I'm an employee of Medtronic. This is the last presentation and I will provide a high level summary of the presentations as well as introduce the overview of our post-market studies. You've seen a lot of data so far in the presentations in the last hour and a half. I'm going to provide just an overview of

the key points that were presented so far.

Let's first start with the safety overview presented by Dr. Mauri. I think we can conclude that in looking at the density of the data so far, both in the size of the sample and the length of follow-up that we don't see a signal of adverse safety events either prior to one year of follow-up, which has historically been the norm, or one to three years, which has recently been the new interest in looking at the affect on drug-eluting stents.

We can summarize that comment in the following graph. On the left side is a graph of the experience of stent thrombosis. We chose the most common definition used today which is the definite probable definition by the Academic Research Consortium. It's a very workable kind of practical definition of stent thrombosis.

If we look at the direct comparitor available in the Endeavor II study, a randomized controlled study, the frequency of stent thrombosis was not higher in the drug-eluting stent Endeavor stent compared to its bare metal counterpart, the Driver stent. And here you can

see the rate is .8 percent for the drug-eluting stent and 1.5 percent fo the bare-metal stent.

If we take the overall large experience of the studies and pool them as we've shown earlier, the frequency by Kaplan Meier estimate at three years of stent thrombosis is 0.8 percent. The high density of data we have in follow-up of over 1,000 patients at two years and almost 700 patients to three years provides an upper boundary that we can measure on that Kaplan Meier estimate that almost includes the rate seen in Driver to suggest that the likelihood that a rate higher than the bare-metal stent is very, very unlikely.

If we translate that into what it means from a very practical clinical perspective, the probably most basic definition to use for safety is a combination of death and myocardial infarction. In the direct comparitor, that is the randomized controlled study, the rate was 4.4 percent at 3 years compared to 6.6 percent demonstrating no evidence that there is a higher frequency of cardiac death and MI for the drug-eluting stent Endeavor compared to its bare-metal stent counterpart.

If we then take again the pooled data where we have a sufficient amount of sample and also follow-up, we can see that the Kaplan Meier estimate is 3.5 percent for the combined experience with an upper boundary due to the density of follow-up on the Kaplan Meier estimate that actually is lower than the mean result seen in the Driver stent clearly showing that there is no evidence that the drug-eluting stent has a higher frequency of cardiac death or MI in the experience so far from these Endeavor studies.

We saw Dr. Leon's presentations of the overall randomized trials experience. I think we can summarize those in two points. One is that there is clinical angiographic superiority in a double-blinded one-to-one randomized study. Now that was the Endeavor II study. The operators, the assessors and the patients were blinded to that treatment assignment. The second was the comparison with an existing drug-eluting stent using non-inferiority design or equivalency study in which we had a single-blind randomized study that demonstrated a slight increases in segment late lumen loss but no differences in clinical outcomes.

I think this is an important slide as well. It addresses one of the points raised by Dr. Ferguson earlier in the Society for Thoracic Surgery about an important concern about studies, that is when one does non-inferiority studies, is there a drift. And we can address that issue. First, we can say that, in fact, compared to the old standard bare-metal stents, we show superiority in the Endeavor II study, 15.1 percent versus 7.9 percent and a primary endpoint of target vessel failure.

(Whereupon, off the record to adjust microphones.)

DR. KUNTZ: All right. Great. Back to the slide, it's important to point out I think that the point Dr. Ferguson raised in the STS four studies -- we're doing non-inferiority, is their drift? It's important to always measure the precedent or the previous control. Here we did that with the Endeavor II study. We're fortunate to be able to have a study against the old bare-metal stent that demonstrates superiority, and that was maintained in the non-inferiority comparison demonstrating parity with an

existing stent.

Now the second point I think was also raised by Dr. Ferguson which I also think is an important point by the Society is comparison of components versus composite endpoints. And we can show, as Dr. Leon previously showed, that almost all of the components demonstrated value and safety in what we measured and efficacy. Here the potential and most important endpoint for clinical restenosis or target lesion revascularization demonstrates substantial reduction in the head-to-head stud, bare-metal stent, and again, to show that there's no drift, parity in the non-inferiority study with the existing control TAXUS stent.

Finally, Dr. LeNarz presented earlier the pre-clinical and drug substance presentation, and we can summarize that as follows. In this stent, we chose a well-categorized drug, the limus family that has a longstanding safety profile. We designed in a biomimetic polymer with non-cytotoxic drug preserves or preservation of endothelial function with low inflammation profile as by design. And finally the advanced proven cobalt alloy design could be classified

as a true second generation stent in the drug-eluting stent era.

And I think mainly when we look back at the slides that have been presented earlier, this stent could be viewed a one that was designed for better deliverability and safety and truly represent a next generation drug-eluting stent.

Now to put into context of where we stand right now, the drug-eluting stent era of therapy for patients who suffer from coronary disease, one basic place to start off from are the conclusions from the FDA panel in December of 2006. At that time, addressing the potential issues of safety concerning drug-eluting stents, it was observed that there was an increase of risk or rate of stent thrombosis beyond 1 year seen in drug-eluting stents compared with bare-metal stents.

Our large experience so far presented today shows, in fact, the Endeavor program has no demonstration of an increased stent thrombosis risk seen either before or after one year regardless of the definitions, either protocol or the new Academic Research Consortium.

The FDA panel pointed out that despite this increased risk, the overall rate of death and MI was equal between drug-eluting stents and bare-metal stents due to two things, either the effect of low revascularization seen with drug-eluting stents or insufficient discriminating to demonstrate a difference that might come out later. What we've seen in our program is that we, in fact, enjoy the lower TLR rates seen with drug-eluting stents but don't demonstrate the increased risk of very late stent thrombosis.

Finally, the panel recommended larger and pre-market clinical analyses in order to address these issues. And I think the dossier presented today with three or more years of sufficient follow-up to power and show durable lower TLR rates and very safe low stent thrombosis rates in the very late period with measurable high confidence boundaries. It is the most dense data dossier today for a drug-eluting stent.

I want to introduce the post-market studies that are planned or ongoing. This study which has enrolled 290 patients to date at 235 sites is an 8,800 patient randomized controlled study comparing the

Endeavor stent to an existing marketed stent, the CYPHER stent. The endpoint is the ARC definition of definite and probable stent thrombosis at three years. We are powering this study to demonstrate superiority of the Endeavor stent over the comparitor stent based on the data we've seen so far to suggest that we have a very low rate of stent thrombosis after one year.

There are two registries that are either ongoing or completed. The E-Five single-arm registry is completed in its enrollment. It's an 8,000-patient study that addresses the third element also raised by Dr. Ferguson earlier this morning -- do we measure the application of these studies outside the label. This study is an all cumber study intended to look at the affect of this drug-eluting stent in all cumbers in a more practical application and practice and has been fully enrolled in outside the United States. The results of this study will be focusing on the one and two year outcomes. It will be a great benchmark to use to see how we can compare when used on and off-label when the follow-up data is available.

A second study required by the Food and Drug

Administration is the U.S. post-approval single-arm registry, and this is a sample of 5300 patients drawn, in part, from the PROTECT study and in part from a new registry which will commence shortly in the United States of 2,000 patients. This will look at both on-label cases and off-label cases as well and provide even more data in density and follow-up looking for durability and other subsets outside the label and within the label when this gets expanded to people and places that weren't in the clinical trial.

So if we look at the final issue addressed at the December FDA panel meeting, that is that they recommended that after a drug-eluting stent be approved, there are larger and longer post-approval studies. I think that we are prepared to do these very large studies including the post-market 1,800 patient randomized controlled study which has already initiated enrollment to test the hypothesis that this stent has a low, very late stent thrombosis rate.

So final slide, in closing -- substantial density of safety and efficacy data in today's dossier. We have seven clinical trials, three randomized and four

single-arm studies representing 2,232 Endeavor patients, 1,287 patients with two or more years of follow-up, and 675 patients with three years of follow-up. Overall, we look at the density as measured by patient-years represents nearly 4,000 patient-years of follow-up.

The clinical and angiographic superiority to BMS is clearly shown, mainly anchored on the Endeavor II study, and the treatment effect has been sustained through three years of follow-up. The clinical non-inferiority, which is the proper way to compare against an existing drug-eluting stent, has been demonstrated. There is consistent clinical and angiographic outcomes across all the geographies and studies that have been studied and, as Dr. Leon showed in the variety of different odds ratios analyses, these are very consistent results.

And finally, we have seen no observed safety signals before or after one year as we've demonstrated with high degrees of follow-up and density and high degrees of confidence, low rates of stent thrombosis, death, cardiac death, myocardial infarction

Thank you very much. That concludes the

presentation.

CHAIR YANCY: Thank you very much. I'd like to complement the sponsor for very clear and thorough presentations and especially for including the post hoc extended follow-up analysis. That's quite helpful. Before we go forward with our panel questions, we've had one member of the panel join us, and I'll ask Dr. Domanski to introduce himself and describe his affiliation and area of interest.

DR. DOMANSKI: I'm Mike Domanski. I'm a cardiologist in Lanham, Maryland.

CHAIR YANCY: Thank you very much, Dr. Domanski. If you can check his microphone? We didn't hear that. We have approximately 25 minutes to pose questions to the sponsor. Let me remind the panel that we will be able to revisit the sponsor with additional questions and as well, this is an opportune time to raise questions that may require a little bit more evaluation that the sponsor can bring back to us later in the afternoon. So this is a time to seek clarity and to request more information if such is needed.

I actually would like to begin the questions

and, if you would allow, I'd like to focus the first question to Dr. Leon. As I look at the data and specifically focus on Endeavor III and Endeavor IV, Endeavor III had an endpoint of late loss and Endeavor IV, Endeavor III had an endpoint of late loss and Endeavor IV had an endpoint of target vessel failure. There was also an analysis that you showed us of target vessel failure for Endeavor III at two years.

Target vessel failure includes in the definition MI, and it's interesting to me that in both Endeavor III and Endeavor IV, there was a lower incidence of periprocedural non-Q MI and that in point of fact, that lower incidence may have buffeted some of the higher target lesion revascularization seen, and that contributes, obviously, to the endpoint.

So I'm curious about why you think we may have seen lower episodes of periprocedural non-Q MY. Is this related to the deliverability issues that you discussed or this a play of chance? So if you could address that for us, I'd appreciate it, I'd appreciate it.

MR. SALMON: Thank you. It's a very

insightful question. I don't think it's a deliverability issue as there were no differences in device success between the Endeavor and the drug-eluting stent arms in Endeavor III and Endeavor IV. I do think it's a meaningful difference and you might recall that in the TAXUS V study, there was a significant increase in periprocedural MI's associated with the TAXUS stent. And I think it does reflect the intrinsic properties of the Endeavor stent, a much thinner, biocompatible polymer, a rapid drug release with improved healing responses.

We did additional angiographic analysis done in the core angiographic laboratory by Dr. Popma looking for specific angiographic markers for why this might have occurred -- side branch occlusion, reduced flow. We could not find that. But it is a consistent observation, and I think it's a meaningful observation. It does in a composite index tend to offset some numerical differences in revascularization events, as you pointed out. But in both studies, those numerical differences were not statistically meaningful given the sample sizes of the trials.

CHAIR YANCY: Thank you. Additional questions. Dr. Somberg?

DR. SOMBERG: I'd like to ask a pre-clinical question first. In fact, I have two pre-clinical questions and maybe I'll come back to ask some clinical ones later. And maybe Dr. LeNarz, I think was the one who brought these things up.

My first question is that earlier in the early DES concerns with Sirolimus and Paclitaxel in the pre-clinical area, there was an interaction. It's known from pharmacology data that Sirolimus and Paclitaxel interact and one can inhibit to Paclitaxel to inhibit the activity of Sirolimus.

Has there been any work with Zotarolimus, your compound with this? And the reason ask this is that I have seen cases of old DES one with, you know, a CYPHER stent with a TAXUS stent. Now there is some clinical literature that claims on the basis of small observation that there is no clinical interaction if you put one stent next to each other. But I don't know if since this is more a lipophilic agent, maybe it would have a greater inhibitory effect. So that's my first

question while you think about.

And my second one is I believe this endothelial dysfunction is a very interesting surrogate for potential clinical downstream problems, and you are to be congratulated for doing an animal study which I think is very important, but, you know, different people reach different conclusions. And your slide on your Pack 43 shows in this canine model, I guess it's eight if I count the blues -- sort of a -- anyway, eight subjects and two go very dramatically one way and six dramatically the other way. Two over six, you know, 30 -- 25 percent, so I mean you can interpret there's no endothelial dysfunction. And I can say in that model there is a minority that has a very dramatic and, you know, not everyone gets late stent thrombosis, thank God. So maybe this is a portent of something to come. What is your response to my interpretation?

DR. LeNARZ: I will defer to Dr. Bob Melder who runs our preclinical program and has first-hand experience.

DR. MELDLER: Good morning. I'm Robert Melder, Medtronic Cardiovascular. Actually, let me

address your first question that while we do not have any specific studies that look at interaction of Zotarolimus and other drugs, I think that we have seen a tremendous amount of similarity between Zotarolimus and Sirolimus. And given that similarity, I think that it would be safe to speculate that there is a possibility for the same sort of interactions that might have been observed with Sirolimus. In the absence of specific studies that address that, I would defer to that possibility but can't say that with any definite possibility.

DR. SOMBERG: So that should be clearly addressed at some point?

DR. MELDER: I think that I'd have to confer with my colleagues and we'll respond further to that point.

Now with regard to your second point, the studies that have been looking at endothelial function were done within a context of a broader set of studies that were trying to understand the biology of the vascular response to DES. Within that context, we've been looking safety issues, particularly restoration of

normal function. In this particular study, we were looking at three different endpoints -- transcriptional responses, particularly MRNA for eNOS, functional responses, vascular dilation inresponse to acetylcholine challenge, and protein translational responses in terms of immunohistology detection of eNOS protein.

In this particular slide, you can see a profile of the transcriptional responses, particularly the Zotarolimus eluting stent, ZES or Endeavor, in comparison to a Sirolimus and Paclitaxel eluting stents and a bare-metal stent, Driver in this case.

At the 28-day and 90-day endpoints, you can see differences in the transcriptional responses with two of the other DES unites. However, we do have, within the proximal arterial region, a high level of transcriptional response with the Zotarolimus eluting stent. Within the instant region of the artery, we have also a depressed response of eNOS mRNA production. This is less severe with the Zotarolimus eluting stent, but there are significant differences there.

May I have the next slide, please? Here you can see some of the immunohistochemistry of the bare-

metal stent on the left and the Zotarolimus eluting stent. Again, this is the proximal section. And on the bottom, we have a endothelial staining by means of a specific collectant, just above that, the eNOS expression.

Could I have the next slide, please? When we did the same thing with the Sirolimus and Paclitaxel eluting stents, we found that while there was endothelium present, we were unable to detect a staining with the eNOS protein. So this confirms the suggestion that there was a deficiency of normalization of endothelial response.

Could I have the next slide? Again, just looking at the acetylcholine responses when they are summed up, you can see that the Zotarolimus eluting stent, Endeavor, had less of a decrease in response relative to the bare-metal stent as compared to the Sirolimus and Paclitaxel eluting stents. This is part of an ongoing effort to try and understand these responses and we hope to have further such studies in the near future.

CHAIR YANCY: Thank you. We have two more

panel questions we need to entertain. Dr. Lincoff, please?

DR. LINCOFF: Yes. Given the apparent difference in the angiographic reduction of neointimal hyperplasia that seems to be on the flat part of the clinical revascularization curve, one wonders, though, if in higher risk patients, angiographically at least, that may be on a part of the curve that does manifest a difference in clinical revascularization rates as well. So I wondered if you had data specifically with relationship to diameter or for vessel length and whether or not, you know, in those groups, you had relative TVR rates.

Also, on a separate issue, I recognize that the goal of the studies, the inclusion criteria were to cover with one stent, but if you had any data for the use of overlapping stents, either, you know, unplanned or whatever as that had been an issue or at least a potential issue with some of the drug-eluting stents?

DR. LEON: Thank you, Dr. Lincoff. We did look at that very carefully. As you pointed out, I think it's relevant to consider that if you're on the

flat part of the curve but close to what might be an S-ending slope, that if you're treating higher restenosis risk patients, perhaps the TLR rates would be significantly higher. So what we did was both look at those rates in high risk subgroups including diabetics, long lesions greater than 20 millimeters, small vessels less than 2.5 millimeters, multiple stents which includes all of the overlapping stents and even the LAD location, those five subgroups.

And we did not, when we did an odds ratio comparison, look at either TVR or TLR, either for the entire cohort or just the clinically followed up cohort, see any significant differences that would suggest that the Endeavor stent performed any less well than the TAXUS stent in Endeavor IV. So we did look at that. Certainly, for both of these devices, in the higher risk subgroups, numerically, you can see a slightly higher frequency of clinical revascularization events, but they were equal in both arms of the study.

DR. LINCOFF: Will you be able to share those data with us later today? Do you have them with you?

DR. LEON: If you can slow that slide.

Actually, maybe the odds ratio plot from the presentation would be the better one from Endeavor IV. I can see that but I -- you can see this is late loss across subgroups for Endeavor I through IV, not just the randomized trials. And you do see, for instance, in diabetics, there's a slightly higher late loss, .66 versus non-diabetics, .61.

This is the one that I meant to show. In these five subgroups, and there are significant numbers in each of these subgroups -- and, of course, this was not a study designed to look a high risk patients, but with more than 30 percent diabetics and a significant percentage of longer than 20 millimeter lesions by the core lab, and almost a third of the patients had less than 2.5 millimeter reference vessel diameter and with multiple stents and LAD lesions, there really is no suggestion that there was a difference in either target lesion or target vessel revascularization favoring TAXUS or Endeavor.

DR. SOMBERG: Excuse me, are those numbers there? Are we 4 over 86, 11 over -- is that the number of patients?

DR. LEON: Yes.

CHAIR YANCY: I think Dr. Hirshfeld wants to follow-up on this.

DR. LEON: They're a small number. The multiple stent group, by design, is a small number of patients. The intent of the study was not to implant multiple stents.

CHAIR YANCY: And we recognize this post hoc?

DR. LEON: Yes.

CHAIR YANCY: Dr. Hirshfeld?

DR. HIRSHFELD: Yes. I would just like to pursue what you were pointing out, Marty. The confidence intervals are enormous here, and so just seems to be given the kinds of subset analyses that you're doing here, that it's really, with the amount of data that you have, with the confidence intervals that you have -- are we not -- you can't say that there's an effect. On the other hand, I think it's a little hard to say that there's not an effect as well with those confidence intervals.

DR. LEON: Certainly, the confidence boundaries do reflect the relatively smaller number of

patients in this post hoc subgroup analysis. But if you look at the raw data looking at late loss, angiographic restenosis, target lesions or target vessel revascularization, or if you do a multi-variable analysis looking at predictors of either clinical or angiographic endpoints, these higher subgroups do not come out as being predicting a higher or worse clinical outcome.

But you're right, this study was not designed to look at a real world population of high risk individuals, so there are limitations to this post hoc subgroup analysis.

CHAIR YANCY: Dr. Lindenfeld?

DR. LINDENFELD: Just two comments. Dr. Mauri, you showed us the safety data with the endeavor patients and you showed us three baseline characteristics that were comparable. But I wonder if you would be prepared to show us all the baseline characteristics in those two comparisons just so we can be certain that the groups are similar because you've taken Endeavor patients from a number of different trials.

And while you're answering that, one other -- just this is a minor comment for Dr. LeNarz. I think the inflammation data that was shown, as I understand it, your stent struts are much smaller for the Endeavor stent, so I'm not sure the number of inflammation cells per surface area -- and I think it should be done for surface area as opposed to per stent -- I'm not sure that's a fair comparison if the actual strut sizes are smaller.

DR. MAURI: So we certainly can show you the baseline characteristics for a broad range of baseline characteristics. I would say that overall on balance, it appeared to be that the endeavor group had a slightly higher risk characterization than the Driver group, but that full table is presented in your panel pack. But we can certainly present the slide --

DR. LINDENFELD: Yes. It would be great to see --

DR. MAURI: -- for the detail.

DR. LINDENFELD: -- because we're basing our safety data on that, so we'd like to make sure the groups are comparable.

CHAIR YANCY: Dr. Domanski:

DR. DOMANSKI: I'm almost scared there because it's working, I guess. You know, I -- we've been looking at a lot of that data that relate to safety and so far, it's pretty compelling. I guess one question I have for you is a practical clinical question, and, Marty, maybe it's for you. What would cause somebody, based on the data you've presented, to walk into the cath lab and use this device as opposed to a TAXUS or a CYPHER? I mean where would that come in just from a practical way -- I turn around to the techs and say give me an Endeavor instead of TAXUS or a Driver? Marty, it's a friendly question. I'm trying to make this --

DR. LEON: This will not be a high-style response, I promise.

MR. ROBERTS: -- trying to make the case for Endeavor here. I give you a chance to do it.

DR. LEON: I think you could have -- Dr. Mauri, who's an accomplished interventionalist could have answered this as well, or Dr. Kuntz. I tried to point out in the beginning we look at three things. We

look at deliverability, safety and efficacy. I believe that this device has essentially comparable efficacy in the kinds of patients that were studied in these trials, but certainly has superior deliverability and safety. So in any patient where I thought that deliverability of the device was going to be more problematic, this would be my preferred choice.

In any patient where there's a question about safety, based upon the data that I've observed, I believe this device would be the preferred choice, especially those patients where I'm uncertain about their ability to extend dual antiplatelet therapy beyond the first few months.

DR. DOMANSKI: Where is the deliver -- in these data, where -- is there anything that reflects that deliverability clearly?

DR. LEON: I mean as you know, in these clinical trials, measuring deliverability is extremely subjective.

DR. DOMANSKI: Sure.

DR. LEON: I think the performance of the Driver stent which is the predicate platform, it is an

advanced superior deliverable device. It is a cobalt alloy thin strut flexible deliverable device. It represents an advanced stage of stent technology which is not to say that the other devices cannot be delivered, but it's more problematic, as you know as an interventionalist, and they represent older versions of stent and delivery system technology.

DR. DOMANSKI: Okay. But I'm not -- and so I'm not going to be able to, other than sort of the impression, I'm not going to be able to make that case from these data? I know the data weren't -- the trials weren't designed to do that but I'm just curious about whether you can parse --

DR. LEON: The only metric that we did point out was this metric of device success which is the ability to take the assigned stent, bring it to the lesion, inflate or expand the stent and achieve a good angiographic result. and in the three clinical trials, it was 99 percent, 99 percent and 97 percent.

CHAIR YANCY: That shows on your slide 61?

DR. LEON: Yes.

CHAIR YANCY: Do you have comparable data for

the other DES stents for that same metric?

DR. LEON: Yes, although I don't have it in front of me.

CHAIR YANCY: Maybe we can deal with that later. Dr. Weinberger, please?

DR. WEINBERGER: Marty, very nice presentation. The most important piece of information in terms of efficacy revolves around revascularization, because death washes out, it's identical, MI washes out pretty much, and we're down to understanding revascularization. And I was wondering if you could explain to me the TLR definition that is parsed in a very difficult way in the writeup here. So I would like to know whether every patient who had a revascularization in the artery, regardless of what the diameter was subsequently adjudicated to be, whether that counts as a TLR?

DR. LEON: No, it does not. As with all of these clinical trials, we have a definition of what we call clinically driven or ischemia driven target lesion revascularization. And that means that a patient has either symptoms or a functional test indicating ischemia

or, by angiogram, a core laboratory analysis showing a 70 percent or greater diameter stenosis which, as you know, visually would be an 80 or more percent diameter stenosis. That is the definition in all these were adjudicated by a clinical events committee.

If we look at the total number of revascularization events, total -- forget clinically driven, forget CECs -- the actual number is -- we have it --

DR. WEINBERGER: That would be fascinating to see.

DR. LEON: In fact, I can get it. If you ask the next question, I'll get it for you in a second. I know exactly where it is, but it's an important question.

DR. WEINBERGER: All right. And the other question I have is for Dr. Mauri, and that is I know that -- I understand the motivation for censoring TLR patients and not considering them for thrombosis, but I was wondering if you have an analysis of thrombosis risk in patients who had TLR or if you did an analysis where you included those patients as well?

DR. MAURI: Right. We have looked at an analysis of patients who had TLR. Basically, that is actually the main distinction between the original protocol definition and the ARC definition. And there were three additional stent thrombosis events that were counted, and one of them occurred in the bare-metal stent arm, the Driver arm, late. And that was a specific case of a patient who'd had multiple treatments for in-stent restenosis and eventually had a stent thrombosis but after having had three revascularization procedures including treatment of in-stent restenosis with another drug-eluting stent, with, actually, the first drug-eluting stent for that patient.

CHAIR YANCY: Thank you. Dr. Somberg? Are you ready, Dr. Leon?

DR. LEON: Sorry for the delay, Dr. Weinberger. There were a total of 24 additional revascularization events that were not clinically driven, 10 in the Endeavor arm and 14 in the TAXUS arm. The event rate was 1.4 percent versus 1.9 percent, Endeavor versus TAXUS. So the total lesion revascularization, clinical and non-clinical was 5.5

percent for Endeavor and 4.6 percent for TAXUS.

DR. WEINBERGER: And one follow-up. Since this is a single-blinded study, the operator knew if he was looking at an Endeavor stent or the CYPHER stent or at a TAXUS stent. What sort of -- was there any way to -- the operators were disincentivized from treating those two groups of stents differently?

In other words, this is a TLR and you're looking at a stent where there's some schmutz in the stent and you and you can tell the difference between the CYPHER stent and an Endeavor stent optically very, very simply. If -- and given the fact that when you're around 70 percent, you may fall into a non-clinically or clinically-driven TLR. I was wondering how do we assure ourselves, since the vast majority of the data that you're presenting is not from the double-wide study but from single-blind studies, that we're not having a lot of operator overlay?

DR. LEON: Well, it's a good question, Dr. Weinberger, although you may have to define what the word "schmutz" means.

DR. WEINBERGER: Not to a New Yorker.

DR. LEON: First, we considered the single-blind nature of the study and the fact this is a cobalt alloy stent that may be more visible and might be more apparent to the operator, so for follow-up, each of the sites was asked that the follow-up physician not be the implanting physician and no identification of the device was revealed to the follow-up physician. I cannot say with absolute certainty that in absolutely every case that occurred, but in the vast majority of cases in those patients with angiographic follow-up, the follow-up physician the did not know the identity, at least before hand. So that was one safeguard.

The second safeguard I would argue is that Endeavor IV, the larger trial, 1548 patients, there was no angiographic follow-up in over 80 percent of the patients, so this was largely a more real world clinically driven study, and the events were quite comparable to the overall patient groups.

CHAIR YANCY: We need to take two very brief questions -- Dr. Somberg and then Dr. Morrison. Well, three -- and Dr. Zuckerman.

DR. SOMBERG: This is for Dr. Mauri and I

think it goes to the crux of the safety data. You have about 1200 plus patients at two years, but you have half that number at three years. Convince me that there's enough power in this study, based on the experience with other DES's and the late stent thrombosis to make a statement beyond two years, because I'm very concerned that if you have that small number, and 670-something patients is small, you have that small number of patients, you are oblivious to events that may occur, maybe less as you hope and maybe far more as you may fear or we may fear. So please address that issue.

DR. MAURI: All right. So from a quantitative perspective, what you'd like to look at is the upper limit of the confidence interval for the rate at three years in that it's not higher than you'd like to see. And what we saw was the upper limit on that confidence interval, I believe, was 1.49 for the rate of ARC definite and probable stent thrombosis. And that upper limit actually excluded what we observed in the Driver control arm, which was an observed rate of 1.5 percent at 3 years.

So I think that that is reassurance. I would

furthermore add that the performance of the Driver stent in that group was consistent with what we've observed in the literature of previous analyses looking at bare-metal stent controls in larger pool data sets of other drug-eluting stents out to four years. That rate is actually spun on with what we would have expected to see from that literature.

So first, the Driver performance was consistent with what we know in long-term follow-up of other bare-metal stents. And second, that the upper limit of the confidence interval at three years excluded the rate that we observed in the bare-metal stent arm.

DR. SOMBERG: Ma'am, I'm asking for the DES experience with CYPHER and TAXUS and then with 670 patients in three years, would you have seen a rate higher than bare-metal stents with those two DES's with 675 patients, or did you have to wait until you had several thousand patients or at least 1200 patients in year three to see that rate?

DR. MAURI: Right. I think even if you look at the number of patients that have been reported in those trials, that they are not that much larger than

what we've observed at three years, not having the direct comparison in front of me. So these are numbers --

DR. SOMBERG: What I'm saying is we sat through a panel meeting on late stent thrombosis, and initially, when these devices were presented were very small numbers. This was not seen. But it was a problem and we all talked about it. In fact, Dr. Leon says it's now established that they have -- which I'm not sure I agree with -- but it's now established that they have a higher incidence of late stent thrombosis and there's a safety problem with those, and the implication I got from the Medtronic presentations was that we don't have this. And I want to know what statistical basis you have for making that implication? That seems to me one of the most crucial things to your argument, and I don't see any justification for it.

DR. MAURI: Right. So I think the best way to do that is to go back and look at the observed data at 4 years that's been presented here back in December of 2006, and the confidence intervals around those rates, the upper limits are actually higher at the time

points.

And part of that is that the numbers of events are higher for the drug-eluting stent arms in those studies and the numbers of patients followed to three years are actually not that much larger than 675.

So if one looks at the paper by Stone at all, 3 years in the Sirolimus eluting stent pooled arm, you have 795 patients to 3 years. And in the Paclitaxel eluting stent arm, you have 1106 patients to 3 years at risk.

So it's not -- there is a difference in the numbers which is consistent with the duration of those stents being on the market. But the density of data at this point in the pre-market application is much higher than what has previously been available, for example, at the time of 2003 for these other stents.

DR. WEINBERGER: Let's get to our last several questions so that we don't get too far off schedule, and we do appreciate that this is a post hoc analysis, so we understand there are some limitations. Dr. Morrison?

DR. MORRISON: I think this was a terrific

presentation, but I'd like to follow-up on Dr. Lincoff's question. Despite the elegance of the Pocock analysis and despite the obvious recogniton that clinical outcomes trump surrogate measures, how concerned are you and how concerned should we be that in Endeavor II, the Zotarolimus stent didn't meet its late loss non-inferiority measure against CYPHER. And in Endeavor III, it did not quite meet its non-inferiority late loss specification against TAXUS? And I say that with a clear response to Dr. Domanski that I think the Driver stent is terrific, and we're, I think, all reassured by the previous use of phosphorylcholine. But the late less measures, are you, Dr. Leon or Dr. Mauri, concerned about that? Should we be or is the fact that the target lesion revascularization rates are clearly non-inferior with this sample size adequate.

CHAIR YANCY: So really Endeavor III and Endeavor IV?

DR. MORRISON: Endeavor III and Endeavor IV. I'm sorry, II is the drug.

DR. MAURI: So I would say the first reply would be that our understanding of late loss has changed

somewhat that we have a more refined understanding. Analyses that we've done as well show that there's a curvilinear relationship that we published for the more sensitive relationship to angiographic restenosis which means that with smaller differences on the lower end of the spectrum of late loss, that is within in the drug-eluting stent range from 0.2 to 0.6, that differences translate to small differences in restenosis, if any.

But I think the most important finding is that in a trial where you have predominantly clinical follow-up, there was a consistent finding of, even in the higher risk groups in the secondary analysis, of not seeing significant differences in TLR between the stents.

CHAIR YANCY: Let's take that as an acceptable answer, Dr. Leon, just for the sake of time. Dr. Zuckerman, a very brief question.

DR. ZUCKERMAN: Yes. Dr. Lincoff began the discussion where he wanted to get a better sense of how the so-called Pocock curve shown on Slide 51 changes as a function of lesion complexity so that he can better understand the answer to Dr. Morrison's question, you

know, does it shift to the right or to the left with different complexity lesions. Given that these are curves instead of odds ratio, we can better appreciate the data. We don't lose power, etcetera.

So does Medtronic have any of those visual presentations that they can try to better address this question as to where the knee starts with the Pocock curve as a function of lesion complexity?

CHAIR YANCY: And let's just do that as a request for additional information, because there have been several requests that the panel has generated. Dr. Lindenfeld would like to see more detail of the baseline characteristics. If you can find that simple metric of what the DES stents have experienced vis-a-vis deliverability, then if you can address this issue not only of higher risk but how this analysis that goes from being monotonic to curvilinear would change if we'd have greater complexity in the lesions. I think that would help all the panel members. Dr. Hopkins, a very brief question?

DR. HOPKINS: Very brief. Do your TLR data capture the crossovers to surgery or are those censored?

DR. LEON: We would never a censor a crossover to surgery. TLR includes any revascularization, either PCI or surgery, although there were relatively few number of patients who actually did cross over to surgery, probably reflecting the fact that this was largely a single or most double-vessel disease population.

CHAIR YANCY: So what we'll do now is take a break. I'll ask the sponsor to address the issues that are outstanding, and we'll give you time after lunch at 1:00 p.m. to bring those answers forward. Thank you very much. We will reconvene at five minutes to the hour.

(Whereupon, off the record at 10:45 a.m. and back on the record at 10:59 a.m.)

CHAIR YANCY: Once again, if everyone could take a seat. If we could let the outer group know that the meeting is resuming? It's time to start.

Before beginning, let me bring to the sponsor's attention that two questions have arisen from the panel that the Chair failed to acknowledge. And I've asked them to pose their questions and I would

request that the sponsor incorporate your answers to these two questions in your brief presentation at 1:00 o'clock. We'll start with our statistician, Dr. David Naftel.

DR. NAFTEL: So this is, obviously, a very complex thing to pull together all these studies, and I'd like to complement the sponsor. I think the way you've laid out the data with the various tables, the various plots, and you've kept the terminology to look the same actually has helped ver much as we try to compare.

My question for you to think about, and we can revisit after lunch when Clyde lets us, is I'm going the other direction from the earlier questions, that is how can -- the earlier question how can you say something with 600 patients at three years.

Well, I'm going the exact opposite direction and that is I want to look at the follow-up with you and understand better why chopped your plots at the end of, I think, the protocol-driven follow-up when -- I'm guessing, and you'll have to tell me, of course -- I think in all these studies, you probably have -- like

the Endeavor IV -- I'm assuming you have follow-up beyond nine months and that you know about death up to 12 or 15 and some of the major events.

So I'm going to go the other way. Instead of why didn't you stop sooner. I'm going to ask why didn't go later and show me data that I imagine you have but you haven't shown me? And, of course, that's going to be extremely important as we talk about follow-up studies and as we talk about stent thrombosis.

CHAIR YANCY: So you're making a request for protocol-specific follow-up data instead of the pooled information?

DR. ZUCKERMAN: Yes. Well, it's part of the pooled question, too. But I'm not sure that we've seen all the information that they actually have. I don't think we've seen all the follow-up, but I might be wrong.

CHAIR YANCY: Very brief statement, please?

DR. LEON: You have seen all the follow-up that we have in all of these clinical trials. In approximately two weeks, we will have 12-month data on Endeavor IV, but we haven't even looked at that data

yet. So you are seeing the last available time point for all the clinical trials that we have, although all of these studies will be followed to at least five years.

CHAIR YANCY: So, Ms. Rue, if you would, please?

MS. RUE: On your Endeavor III study when you talked about the late loss, that seems to me the only one that you had that there was a difference in the Endeavor and the CYPHER as far as the sex of the population, that you said that the women were higher. And I was wondering on your late loss in any of the other studies if, even though you've taken the diabetic population out, if there's anybody -- any specific looking at the female population and their differences, and if this has been thought about as a difference in this study, and if you're going to be looking at nay of those, because in your mean age variants, it takes them from various stages in the menopausal years, and if that has any effect?

CHAIR YANCY: So let's do this, Dr. Mauri or Dr. Leon, in your afternoon presentation, if you can

address the gender issue and if there's any additional information you have on protocol-specific longer term follow-up to address Dr. Naftel's concerns, that'd be appreciated.

We'll spend the next hour now for the FDA presentation. I don't want to truncate that, and we'll have an abbreviated Q and A and make every effort to get back on time. So thank you very much.

MS. HILLEBRENNER: Good morning. Sorry for the delay. Thank you to the panel members for their time and effort to review this device. My name is Elizabeth Hillebrenner. I'm a biomedical engineer and the lead reviewer for this PMA, and I would like to present the FDA review of the Endeavor Zotarolimus-Eluting Coronary Stent System.

This is a device-drug combination product for which lead review was conducted by the Center for Devices because the device component, the stent, is considered the primary mechanism of action. The stent platform is the FDA-approved Driver balloon expandable cobalt alloy stent in sizes ranging from 2.5 to 3.5 millimeters in diameter and 8 to 30 millimeters in

length. The stent is first coated with phosphorylcholine, referred to as PC polymer. This polymer is similar to one used to coat an FDA-approved stent.

Next, the stent is coated with a mixture of PC polymer and the active pharmaceutical ingredient, Zotarolimus. This drug is a new molecular entity that has not been previously reviewed by the Center for Drugs for any indication. After coating with the drug, a thin PC over-spray layer is applied.

The final coated stent is provided pre-crimped onto one of three delivery systems -- the over-the-wire, rapid-exchange or multi-exchange systems.

The sponsor has proposed that the device be indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo lesions less than or equal to 27 millimeters in length in native coronary arteries with reference vessel diameters between 2.5 and 3.5 millimeters.

FDA has conducted a very comprehensive review of this PMA. Since this is a drug-device combination product, our review has spanned two Centers, the Center

for Drug Evaluation and Research and the Center for Devices and Radiological Health. As outlined in this slide, members from eight offices across these Centers have worked together to complete this review.

I would like to acknowledge these individuals for their contribution to the review of this device. The reviewers listed here reviewed various forms of animal studies, biocompatibility, and pharmacokinetic data. These contributors evaluated in vitro finished product testing. These individuals reviewed various aspects of the manufacturing process. And these members of FDA staff provided reviews of Medtronic's investigational device exemption submission under which three U.S. clinical trials of this product were conducted.

FDA's review began with drug safety data including safety pharmacology, toxicology, absorption distribution, metabolism and excretion studies and human IV dosing studies. Preliminary review at the time of the IDE indicated no concerns and U.S. clinical studies were approved. At the time of the PMA, FDA has reviewed additional data provided and notes no outstanding

concerns. Testing of the finished product consisted of stent functional testing, coating testing, delivery system testing, animal studies and biocompatibility testing.

The sterilization and manufacturing, both CMC from a CDER perspective and Quality Systems and GNP's from a device perspective were also evaluated. FDA has no major concerns regarding data provided. As noted in your panel pack, minor deficiencies remain.

There were 7 clinical trials in the Endeavor program provided for review in the PMA. I would like to bring to your attention Endeavor II, III, and IV. These are randomized trials which comprise the bulk of data under review. Endeavor II consisted of a superiority angiographic and clinical comparison to the Driver bare metal stent, Endeavor III consisted of a non-inferiority angiographic comparison to CYPHER, and Endeavor IV consisted of non-inferiority angiographic and clinical comparison to Taxus. Each of these trials will be discussed in more detail later.

I would now like to introduce Dr. Andrew Farb. Dr. Farb will present a clinical review of the

Endeavor program.

DR. FARB: Good morning I'm Andrew Farb. I'm one of the medical officers at FDA, and I'll be presenting the FDA clinical review of the Endeavor stent. Here's an outline of my remarks.

First, I will discuss the important study outcome definitions and key inclusion and exclusion criteria that are common across the Endeavor drug-eluting stent program. I will then discuss the three randomized clinical trials, Endeavor II, Endeavor III, and Endeavor IV followed by a brief summary of non-randomized study data.

Pooled data from the Endeavor clinical program will be discussed to follow with clinical outcomes presented, first, for all patients following by a separate analysis for outcomes in diabetics. A discussion of stent thrombosis and dual antiplatelet therapy will follow. I'll conclude my remarks with a summary of the Endeavor stent clinical program and discuss clinical and angiographic stent effectiveness issues within the context of DES trials.

These are the important Procedural and

angiographic endpoints for the Endeavor stent trials. Device Success was attained by attainment of less than 50 percent in-stent residual stenosis of the target lesion using only the assigned device and device-specific procedure success was device success plus no in-hospital MACE.

For angiographic endpoints, late lumen loss was the difference between the post-procedure minimal lumen diameter and the MLD at follow-up angiography . Binary restenosis was an angiographic follow-up percent diameter stenosis of greater than 50 percent.

Presented here are the important clinical endpoints. TVR is clinically-driven repeat intervention of the target vessel. TLR is clinically-driven repeat intervention of the target lesion within the target vessel. Target vessel failure or TVF, the primary endpoint for Endeavor II and Endeavor IV is a composite of TVR, cardiac death or MI that could not be clearly attributed to a vessel other than the target vessel. Finally, MACE was defined as the composite of death, MI, emergent bypass surgery, or TLR

Moving next to stent thrombosis definitions.

The protocol definition of stent thrombosis included any death not attributed to a non-cardiac cause within the first 30 days. Late stent thrombosis, here defined as an event occurring beyond 30 days, was conservative as it required angiographic or pathologic confirmation.

As discussed in the December 2006 FDA meeting on drug-eluting stent thrombosis, the definitions of stent thrombosis has varied among DES sponsors. And as we've heard this morning, FDA participated in the Academic Research Consortium of ARC to propose working definitions for all types of DES adverse events The proposed definition of stent thrombosis was based on available clinical evidence and the timing of the thrombotic events. Here is the timeframe established for these stent thrombosis definitions with early being an event occurring between one and 30 days, late -- greater than 30 days to one year, and very late -- beyond one year.

The levels of evidence of stent thrombosis per the ARC definitions are presented here. FDA believes that events that meet the criteria of definite plus probable provide the optimal level of clinical

sensitivity and specificity. We requested that the sponsor have their stent thrombosis events independently adjudicated per the ARC definite plus probable definition in addition to their protocol definition.

These are the key clinical and angiographic inclusion criteria for the Endeavor stent program. Patients in the Endeavor program had evidence of ischemic heart disease with single non-complex de novo lesions up to 27 millimeters of length in all studies except Endeavor I. The target vessel reference diameter was greater than or equal to 2.25 millimeters in the Endeavor II continued access registry and greater than or equal to 2.5 millimeters in Endeavor III, Endeavor IV, Endeavor PK, and was greater than or equal to 3.0 millimeters in Endeavor I.

For the key inclusion criteria, it is notable that patients with acute MI within 72 hours were excluded so that enrolled patients were clinically stable or stabilized without advanced left ventricular or renal dysfunction. The coronary lesions were non-complex and did not involve the left main osteal segments or bifurcations.

I will next discuss the three randomized clinical trials in the Endeavor stent program. Beginning with Endeavor II, this was a randomized, prospective, double-blind superiority trial conducted to compare the safety and effectiveness of the Endeavor stent compared to the Driver stent which is the bare-metal stent platform for the Endeavor stent. The primary endpoint was target vessel failure at 9 months.

Important secondary endpoint included measures of acute stent performance such as device-specific procedure success. MACE was a secondary endpoint as were rates of death, MI, revascularization, and stent thrombosis assessed over time. Angiographic in-segment late lumen loss at 8 months was a pre-specified powered secondary endpoint to demonstrate superiority of the Endeavor stent versus the bare metal Driver stent.

Angiographic and IVUS follow-up was required in the first 600 and 300 patients respectively enrolled in Endeavor II. As you've heard, Endeavor II was conducted completely outside the United States in Europe, Israel, Australia, New Zealand and the Asia

Pacific region.

There were 598 patients randomized to the Endeavor stent and 599 to the Driver stent. Here are the baseline demographic and clinical characteristics in Endeavor II patients which were similar between stent treatment groups with the exception in insulin-dependent diabetes, which was more common in the Driver arm, 7.4 percent versus 4.5 percent.

Pre and post-intervention, lesion and vessel characteristics were similar between stent treatment groups. For procedural success in 30-day MACE, the device-specific procedure success rate in Endeavor stented patients was 96.5 percent. The 30-day MACE rate was 2.9 percent for Endeavor patients versus 3.7 percent for Driver patients with non-Q-wave MI's comprising the majority of these adverse events.

Next primary endpoint. The primary endpoint in Endeavor II was the rate of TVF at 9 months. In the Endeavor patients, the TVF rate was 7.9 percent compared to 15.1 percent in Driver patients resulting in a 7.1 percent absolute and a 48 percent relative reduction in the TVF rate. The corresponding P-value was less than

0.001. The Endeavor stent met its primary endpoint.

Here are the rates of the important individual clinical outcomes in Endeavor II through 9 months. The study was underpowered to detect outcome differences between treatment groups for death, cardiac death, MI or stent thrombosis. What is apparent from an inspection of these data is that the reduction in TVF in patients treated with the Endeavor stent was largely driven by a greater than two-fold reduction in the rate of TVR. The ARC definite for probable stent thrombosis rate was 0.5 percent for Endeavor patients and 1.4 percent for Driver patients.

As you recall, angiographic in-segment late lumen loss at 8 months was a powered, secondary endpoint. There was a 0.36 millimeter absolute reduction and a 50 percent relative reduction in late lumen loss in Endeavor patients who participated in the angiographic substudy. The Endeavor stent met its angiographic late loss endpoint with a P less that 0.001. Other angiographic parameters such as percent diameter stenosis and the rate of binary restenosis plus IVUS measurements such as percent, volume

obstruction by neointimal tissue favored the Endeavor stent versus the Driver stent.

Thirty-six month follow-up data are available for Endeavor II patients. There remains a 40 percent relative reduction in the rate of TVR at 36 months in patients treated with the Endeavor stent driven by a 46 percent reduction in TVR. The ARC definite plus probably stent thrombosis rate was 0.9 percent for Endeavor and 1.4 percent for Driver.

As noted, Endeavor II was conducted completely outside the United States and FDA did not review the protocol prior to initiation. Endeavor III was designed to be completed in the United States with results used in conjunction with the results of Endeavor II to support a U.S. marketing application. After the approval of the CYPHER drug-eluting stents, the sponsor believed that it would not be feasible to conduct a randomized trial in the United States that utilized the bare-metal stent as a control device.

Thus, Endeavor III was a randomized, prospective, single-blind, non-inferiority trial conducted to demonstrate the equivalency in in-segment

late lumen loss at 8 months of the Endeavor stent compared to the FDA-approved CYPHER stent. Patients were randomized at a 3:1 ratio, Endeavor versus CYPHER. The primary endpoint was angiographic in-segment late lumen loss at 8 months. An equivalency margin, or delta, of late lumen loss was set at 0.2 millimeters.

The null hypothesis for the study was that the Endeavor stent would have a mean in-segment late lumen loss equal to or exceeding that of the CYPHER stent by 0.2 millimeters or more. The alternative hypothesis was that the Endeavor stent would have an in-segment late lumen loss less than the CYPHER stent plus 0.2 millimeters.

Secondary endpoints included measures of acute stent performance, TLR, TVR, and TVF at 9 months and rates of MACE, death, MI and stent thrombosis through 5 years. There were 323 patients randomized to the Endeavor stent and 113 to the CYPHER stent.

Here are the baseline demographic and clinical characteristics in Endeavor III which were similar between stent treatment groups with the exception, as you've heard, of a higher percentage of

women in the Endeavor arm.

Pre and post-intervention lesion and vessel characteristics were similar between stent treatment groups. For procedural success in 30-day MACE, the device-specific, procedure success rate in Endeavor patients was 98.1 percent. The 30-day MACE rate was 0.6 percent for Endeavor patients versus 3.5 percent for CYPHER patients with non-Q-wave MI's comprising the numerical difference between treatment groups in favor of the Endeavor treatment arm.

The primary endpoint in Endeavor III was angiographic in-segment late loss at 8 months. In Endeavor patients, late loss was 0.36 millimeters compared to 0.13 millimeters in CYPHER patients. The upper bound of the one-sided 95 percent confidence interval of the treatment difference was 0.32 millimeters which was greater than the prespecified non-inferiority margin of 0.2 millimeters. The P-value was greater than 0.05.

Thus, the Endeavor stent failed to meet its late loss endpoint versus the CYPHER stent. And in fact, the post hoc analysis showed that the treatment

difference significantly favored the CYPHER stent. all other imaging parameters such as percent diameter stenosis, binary restenosis and percent volume obstruction by neointimal tissue favored the CYPHER stent versus the Endeavor stent.

Here are the rates of the important individual clinical outcomes in Endeavor III through nine months. Although there were some numerical differences in rates of MI's, specifically non-Q-wave MI's favoring Endeavor and rates of TLR and TVF favoring CYPHER, it is important to note that Endeavor III was underpowered to statistically evaluate these clinical outcomes. There were no stent thrombosis cases in either treatment arm.

Twenty-four months of follow-up data are available for Endeavor III patients. These results demonstrate a similar pattern to those seen at nine months with MI, specifically non-Q-wave MI rates numerically favoring Endeavor and repeat revascularization procedures favoring CYPHER. The ARC definite plus probable stent thrombosis rate was 0.3 percent for Endeavor and zero percent for CYPHER.

Moving to Endeavor IV but before discussing specifically about Endeavor IV, I'd like to bring up some background. During the Endeavor III trial, after nearly 40 percent of the anticipated enrollment had been completed, a safety update reported had inadvertently disclosed the randomization scheme to the sponsor. Medtronic continued the ongoing Endeavor III study with a new patient randomization scheme to preserve blinding for the remaining patients.

In response to FDA concerns regarding the unblinding of the original Endeavor III study, but before the results of the reinitiated Endeavor III study were known, Medtronic changed the design of their originally proposed Endeavor IV study from a single-arm registry to a randomized drug-eluting stent plus a drug-eluting stent study. Endeavor IV thus became a randomized, prospective, single-blind, non-inferiority trial conducted to demonstrate the equivalency of the safety and effectiveness of the Endeavor stent compared to the FDA approved TAXUS stent.

The primary endpoint in Endeavor IV was TVF at 9 months. The 9-month TVF rate in Endeavor and TAXUS

subjects was assumed to be 7.6 percent with a non-inferiority margin set at 3.8 percent. For the study, the null hypothesis was that the Endeavor stent would have a ninemonth TVF rate that exceeded of the TAXUS stent by at least 3.8 percent. The alternative hypothesis was that the Endeavor stent would have a ninemonth TVF rate that is no more than that of the TAXUS rate or exceeds that of the TAXUS rate by less than 3.8 percent.

Secondary endpoints included measures of acute stent performance in rates of MACE, death, MI, revascularization, and stent thrombosis. Angiographic in-segment late lumen loss at eight months was a pre-specified powered secondary endpoint to demonstrate non-inferiority of the Endeavor stent versus the TAXUS stent. Angiographic and IVUS follow-up was required for the first 328 patients enrolled in Endeavor IV. An equivalency margin of late lumen loss was at 0.2 millimeters.

The null hypothesis for the angiographic substudy was that the Endeavor stent would have a mean in-segment late lumen loss equal to or exceeding that of

the TAXUS stent by 0.2 millimeters or more. The alternative hypothesis was that the Endeavor stent would have an in-segment late lumen loss less than that of the TAXUS stent plus 0.2 millimeters.

There were 773 patients randomized to the Endeavor stent and 775 to the TAXUS stent. These are the baseline demographic and clinical characteristics of the Endeavor IV patients which were similar between stent treatment groups. Pre and post intervention lesion and vessel characteristics were also similar between the stent treatment groups in Endeavor IV.

For procedural success in 30-day MACE, the device-specific procedural success rate in Endeavor patients was 96.5 percent. The 30-day MACE rate was 1.2 percent for Endeavor patients versus 3.0 percent for TAXUS patient in favor of the Endeavor arm driven by a numerical difference in non-Q-wave MI's.

The primary endpoint in Endeavor IV was the rate of TVF at 9 months post stent implantation. In Endeavor patients, the TVF rate was 6.8 percent compared to 7.4 in TAXUS patients. The upper bound of the one-sided 95 percent confidence interval for the treatment

difference was 1.6 percent which was less than the 3.8 percent pre-specified non-inferiority margin. The Endeavor stent met its non-inferiority primary endpoint compared to the TAXUS stent with a P-value of less than 0.001.

The important individual clinical outcomes in Endeavor IV through nine months are presented here. Endeavor IV was underpowered to statistically evaluate individual clinical outcomes. The MI rate, mostly non-Q-wave MI's numerically favored Endeavor and the TLR rate numerically favored TAXUS. The ARC definite plus probable stent thrombosis rate was 0.9 percent for Endeavor versus 0.1 percent for TAXUS.

The secondary endpoint of angiographic in-segment late lumen loss was assessed at 8 months. In Endeavor patients, late loss was 0.36 millimeters compared to 0.23 millimeters in TAXUS patients. The upper bound of the one-sided 95 percent confidence interval for the treatment difference was 0.22 millimeters which was greater than the pre-specified, non-inferiority margin of 0.2 millimeters. The P-value was greater than 0.05. Thus, the Endeavor stent failed

to meet its late loss endpoint versus the TAXUS stent.

Other imaging parameters such as percent diameter stenosis, the binary restenosis rate and percent volume obstruction by neointimal favor the TAXUS stent versus the Endeavor stent.

Turning next to non-randomized study data. Endeavor I, the Endeavor II continued access registry and Endeavor PK study are single-arm studies that provide additional data on Endeavor stent use. Endeavor I was actually the initial feasibility study of the Endeavor stent. the primary endpoint was MACE at 30 days, and important secondary endpoints were TVF and clinically-driven TLR at nine months.

There were 100 patients enrolled in Endeavor I, the MACE rate at 30 days. The primary endpoint was one percent. The rates of individual clinical events through nine months were all less than or equal to two percent. The rate of stent thrombosis was one percent.

The objective of the Endeavor II continued access registry was to collect additional acute safety information and performance data on the Endeavor stent. The primary endpoint was MACE at 30 days with secondary

endpoints including measures of acute stent performance and rates of MACE, death, MI, revascularization, and stent thrombosis. Two hundred and ninety-six were in enrolled in Endeavor II continued access. The 30-day MACE rate was 5.4 percent. The rates of TVF and the individual clinical events through nine months are shown here. The rate of stent thrombosis was zero.

The objective and primary endpoint of the Endeavor PK study was to assess the in vivo pharmacokinetic profile of the Endeavor stent. Important secondary endpoints included acute stent performance, rates of MACE, death, MI, revascularization and stent thrombosis. Endeavor PK enrolled 43 patients. These PK curves that show that in multiples of the total Zotarolimus dose, blood concentrations reached low levels by 14 days for all dose exposures.

FDA concluded that pre-clinical toxicology studies in animal models escalating in multiple IV studies in human healthy subjects, and these PK did establish the clinical safety of Zotarolimus in multiples of clinically relevant drug exposure. The rates of TVF in the individual clinical events through 9

months for the patients enrolled in Endeavor PK are shown here. The stent thrombosis rate was zero.

Overall, the clinical results from these non-randomized, single-arm registries were qualitatively in line with the randomized controlled trials with no apparent new safety concerns.

FDA requested post hoc analyses of the clinical outcomes for patients treated with Endeavor stents pooled from available clinical trials consisting of Endeavor I, II, II-continued access, III, IV, and Endeavor PK. Separate analyses were completed for all patients and patients with diabetes. Additional analyses were performed to evaluate stent thrombosis. Survival analysis was completed for followup through to 3 years. In the Kaplan Meier graphs and tables that follow, patients treated with Driver stents in Endeavor II are shown for comparison with 597 Driver patients followed through three years. It should be noted that the results are unadjusted for baseline covariates and multiple comparison with pool ability assumed.

For new molecular entities such as Zotarolimus, FDA requested a minimum of 2,000 patients

exposed to the drug for a demonstration of drug safety. Across the endeavor program, 2128 patients have received the Endeavor stent of which 1287 have been followed through two years and 675 through three years.

In these Kaplan Meier plots, the Endeavor-treated patients are represented by solid lines and Driver patients by the dashed lines. No differences were observed for freedom from all death and non-cardiac death between treatment groups with freedom from cardiac death and freedom from MI favoring the Endeavor stent group.

Freedom from cardiac death or MI favored the Endeavor stent group. No differences were observed for any definition of stent thrombosis between treatment groups.

Freedom frm TVR and TLR favored patients treatment with Endeavor stents indicating no loss of the effect of reduced repeat revascularization procedures versus the boilermaker Driver stent.

Diabetic patients represent an important patient subgroup that is at increased for cardiovascular morbidity and mortality. Like previous DES applications

for PMA approval, including the currently approved drug-eluting stents in the United States, diabetic patients were included in the Endeavor clinical trials. Although there are no pre-specified hypothesis or trial designs features to warrant a specific labeled indication for the use of the Endeavor stent in diabetics, FDA believes that clinical outcomes in diabetics should be considered in the review of all DES programs.

The total number of diabetic and non-diabetic patients in the Endeavor clinical program with 270 days follow-up are presented in this table. FDA requested post hoc analyses of clinical outcomes for patients treated with Endeavor stents pooled from the available clinical trials. Two analyses were preformed -- Endeavor diabetic patients versus Endeavor non-diabetic patients and Endeavor diabetic patients versus Driver diabetic patients taken from the Endeavor II study. Analyses were stratified by the insulin and non-insulin dependent status and clinical outcomes were assessed at 270 follow-up. Results are unadjusted for other baseline covariates and multiple comparisons.

In an analysis of pooled Endeavor patients

with all non-diabetics shown in blue, all diabetics in yellow, insulin-dependent diabetics in lavender, and non-insulin diabetics in white, there were no apparent safety signals for death, cardiac death, MI, cardiac death or MI, or stent thrombosis between groups. As expected, revascularization rates were numerically higher in diabetics, both insulin-dependent and non-insulin-dependant compared to non-diabetics.

In analysis of the pooled Endeavor patients versus Driver patients, rates of all death, cardiac death, MI, death or MI through 270 days numerically favored Endeavor patients for all diabetics, insulin-dependent diabetics and non-insulin-dependent diabetics. With the exception of stent thrombosis in insulin-dependent diabetics, rates of stent thrombosis and TLR and TVR through 270 days numerically favored Endeavor patients for all diabetics, insulin-dependent diabetics and non-insulin- dependent diabetics.

Considering long term followup in diabetics, the following Kaplan Meier plots compare Endeavor stent treated diabetic patients pooled from the Endeavor studies compared with diabetic patients treated with

Driver stents in Endeavor II. Results are post hoc and unadjusted for baseline covariates and multiple comparisons. In these Kaplan Meier graphs of diabetics, Endeavor patients are presented by the red lines and Driver patients by the blue lines.

No differences were observed for freedom from all death and freedom from MI between treatment groups. Freedom from cardiac death and freedom from cardiac death or MI favored the Endeavor stent group. No differences were observed for any definition of stent thrombosis between treatment groups in diabetics. Freedom from TVR and TLR in diabetics favored patients treated with the Endeavor stents.

Turning next to stent thrombosis. Cumulative rates of stent thrombosis defined per protocol or ARC definite plus probable through 3 years numerically favored the Endeavor stent verus the Driver stent at all time points. We point out that the Endeavor IV study data are only available after 270 days. Drug-eluting stents that utilized drugs that interfere with the cell cycles such as Sirolimus, Paclitaxel, and Zotarolimus inhibit in-stent neointimal growth but also delay

neointimal healing and endothelialization. This affect prolongs the window of thrombotic risk versus bare-metal stents.

Autopsy studies suggest that incomplete or delayed neointimal healing may be an important mechanism of late drug-eluting stent thrombosis. Although overall rates of stent thrombosis may be shown to be similar between drug-eluting stents and bare-metal stents, any observed increase in the rate of late stent thrombosis in patients receiving drug-eluting stents is an important safety concern.

FDA requested post hoc analyses of the data pooled from all Endeavor patients for potential signals of late cardiac death, MI or stent thrombosis. The following Kaplan Meier curves depict late safety outcomes beyond the 1-year landmark in patients treated with Endeavor stents pooled from the Endeavor trials. Patients treated with the Driver stent in Endeavor II are shown for comparison. These results, as others, are unadjusted for baseline covariates and multiple comparisons. The number of patients available for follow-up from one to three years are shown in the

table.

In these graphs, Endeavor-treated patients are represented by solid lines and Driver patients by the dashed lines. No differences were observed for any definition of stent thrombosis or death between treatment groups beyond one year. Beyond one year, no differences were observed for MI, freedom from cardiac death. And freedom from cardiac death or MI favor the Endeavor stent group. Incomplete stent apposition may be a mark of late stent thrombosis. Incomplete stent apposition data are presented in this table. No that although persistent incomplete stent apposition was no uncommon, late acquired incomplete stent apposition was rarely seen in patients treated with Endeavor stents.

Turning next to dual antiplatelet therapy, here are the per protocol recommendations for dual antiplatelet therapy for patients enrolled in the Endeavor clinical program. For all studies, the recommendation was for indefinite aspirin and thienopyridine for three months, at least three months, except for the Endeavor IV trial in which six months was recommended to match the TAXUS stent control group.

In considering the recommended course of dual antiplatelet therapy in the labeling for the Endeavor stent and the clinical outcomes in the Endeavor stent program, including stent thrombosis rates, data on the actual use of dual antiplatelet therapy through six months may be relevant.

Per the case report forms, data on antiplatelet therapy use was captured by asking whether the patient was taking antiplatelet therapy per protocol rather than a yes or no. And a question was posed whether there was a change since the last interview. As the table indicates, a large majority of patients treated with Endeavor stents were taking dual antiplatelet therapy through six months.

In summary, for clinical endpoints, the Endeavor stent met its primary TVF superiority endpoint versus the bare metal Driver stent in Endeavor II, and the Endeavor stent met its primary TVF non-inferiority endpoint versus the TAXUS stent in Endeavor IV. For the angiographic endpoints, the Endeavor stent met its late loss endpoint versus the bare-metal stent in Endeavor II but failed to meet its non-inferiority late loss

endpoints versus the CYPHER sten in Endeavor III and the TAXUS stent in Endeavor IV.

The Endeavor clinical studies include a total of 2,133 patients assigned to receive Endeavor stents with 1,287 followed out to 24 months. For the individual randomized trials, Endeavor II, III and IV, increased rates of death, cardiac death, MI, cardiac death or MI, or non-cardiac for the Endeavor stent versus the control stent in these studies have not been observed. Outcomes from an analysis of patients treated with the Endeavor stents pooled from the submitted Endeavor clinical trials do not demonstrate unanticipated safety signals.

I will now turn the podium over to Dr. Gao who will discuss statistical issues.

DR. GAO: Good morning. I am Yonghong Gao representing FDA's Division of Biostatistics. My division colleague, Gary Kamer has been the FDA statistical reviewer throughout the entire development, conduct and review stages of Endeavor trial.

I have been involved throughout the entire PMA review process. Today, I will present the

statistical results of the studies conducted to established and effectiveness of Medtronic's Endeavor drug-eluting stent.

There are six prospectively designed clinical studies to evaluate the various aspects of Endeavor DES. This slide provides a general overview of the six studies. While each study provides some degree of information necessary for the evaluation of the safety and effectiveness of the Endeavor stent, my presentation will focus on the three pivotal studies -- Endeavor II, III and IV. Since these are randomized, confirmatory clinical trials and they provide the most statistically valid results.

Endeavor II's study objective was to demonstrate the superiority of the Endeavor DES to that of the Driver bare-metal stent in clinical measures. This study was conducted completely outside of the United States. A 1:1 randomization resulted in 598 Endeavor patients and 599 Driver patients, and this sample size provided 90 percent power for the primary endpoint, which is target vessel failure. The first 600 consecutively enrolled were evaluated for eight month

in-segment Late Loss. The sample size was determined to provide 90 percent power for this secondary endpoint.

This slide gives Endeavor II's results for the nine month TVF. Recall, this is a superiority testing, and the goal is to show that Endeavor's TVF rate is significantly lower than that of Driver. The table shows a 7.9 percent rate for the Endeavor compared to a higher rate of 15.1 percent for the Driver.

The two-sided 95 percent confidence interval for the difference in rates is -10.7 percent, to -3.5 percent. This interval does not exclude zero, providing evidence of Endeavor superiority. The p-value for the superiority testing is less than .001, and that also supported Endeavor's superiority in TVF.

The above analyses were based on available case analyses where 14 patients, whose 9-month TVF information was unavailable, were excluded. However, patients with missing data should still be included in the analysis. To address this missing data issue, FDA requested a sensitivity analysis, multiple imputation and the worst case analyses were conducted, and the results are shown in this slide.

In the worst case analyses, we impute success for missing Driver patients and impute failure for missing Endeavor patients. Usually, the worst case analysis is very conservative and provides a reference point about the worst possible result for the device. The table shows that the p-value for the worst case analysis is still smaller than .05, so the missing data problem did not affect the conclusion, which is Endeavor II data indicated Endeavor superiority over the Driver in TVF. Multiple imputation analysis confirmed the Endeavor superiority also.

Eight month in-segment late loss is a power of secondary endpoint in Endeavor II. The goals is to show that the mean late loss of the Endeavor arm is significantly less than that of the Driver arm. The table shows that Endeavor arm had a mean late loss of .36 while the mean late loss for Driver arm was .72. The two-sided 95 percent confidence interval ranged from -.452 to -.267. The interval excludes zero, which provided significant evidence of Endeavor superiority over Driver.

Also, the p-value for the superiority testing

is less than .001, which indicated statistically significant difference favoring the Endeavor DES. However, 75 patients, which is about 12.5 percent, were excluded from this analysis of all available patients.

Multiple imputation and worse case analyses were conducted to address missing data problem. Late loss is a continuous variable. The Worst case imputation was implemented in the following way. Missing patients in the Endeavor arm were imputed the worst possible value, which is the maximum value observed in the Endeavor arm. Missing patients in the Driver arm were imputed the best possible value, which is the minimum value observed in the Driver arm).

The worst case analysis gives a p-value of 0.975, so the worst case analysis failed to show superiority of Endeavor over the Driver. However, multiple imputation gives the same conclusion as the available case analysis indicating superiority.

A second pivotal trial of the Endeavor DES was conducted in the United States. The objective was to demonstrate Endeavor's non-inferiority to Cypher in eight month in-segment late loss. The non-inferiority

margin was specified as .2 millimeters in the protocol. A 3:1 randomization ratio was applied, and 323 patients received the Endeavor stent while 113 received Cypher. The sample size was calculated to provide 90 percent power for the non-inferiority claim.

Before proceeding, it may be helpful to say a few words about non-inferiority trials. If the objective of a clinical trial is to establish that an experimental treatment is no worse than a control treatment by an allowable margin, a non-inferiority trial is conducted. The allowable margin is referred to as the non-inferiority margin, or delta, and represents the agreed-upon maximum clinically-acceptable difference. The margin should be pre-specified in the protocol and is clinically meaningful.

The set-up of the non-inferiority hypotheses are the following. Assume that a smaller mean value is better as in Endeavor studies. The null hypothesis is that the testing device is worse than the control by more than the margin delta. The alternative hypothesis is the opposite, which is that the testing device is no worse than the control by the margin delta.

The sample size estimation and hypothesis-testing methods are unique to non-inferiority trials. One-sided statistical testing and one-sided confidence intervals of the differences are employed for making inferences. Usually, the upper bound of the one-sided 95 percent confidence interval of the difference is constructed and compared with the margin delta. If the upper bound is less than the margin, then we say the data provided is significant evidence of non-inferiority.

Now back to Endeavor III. This slide shows the failure to reject the null hypothesis, which is the Endeavor III failed to establish non-inferiority. First, the upper bound of the one-sided 95 percent confidence interval of the difference is .32,