

you needed one more month. You've cut off an awful lot of data that you do have in your database just guessing, if you're like every other study, that they didn't come in at exactly nine months. You had a window, I'm guessing, of plus or minus a month. So you've kind of left us just a little cold not seeing the data you have.

DR. KUNTZ: Let me make a response to that as well as the first thing. Your first question about the rates calculated, I stand corrected. The 740 represents the patients who were followed up, so that rate were patients who are missing and those who actually had a competing event like death and weren't available to have that event. That's a convention for reports on this type of analysis. We also did Kaplan Meier analyses as well to look for any differences in any of the major conclusions of the study.

DR. NAFTTEL: So you're saying that the first death thing, it's 5 deaths divided by 740?

DR. KUNTZ: That's correct. So there were 773 randomized, 33 patients were either missing for that follow-up point, or it included 5 who had died up to that point.

DR. NAFTEL: So the 740 includes the 5 deaths?

DR. KUNTZ: Correct. It does, yes.

DR. NAFTEL: Okay. Great. Thank you.

DR. KUNTZ: Getting back to the 9-month endpoint, one of the reasons that we use 9 month is there's a long history of looking at the kind of restricted hazard of restenosis which has generally been around 6 to 8 months, and there have been a lot of -- the history of studies have been at least a study of restenosis at 6 months and just measure it. As a matter of fact, there's a lot of data to suggest that most of the narrowing occurs only between 3 and 6 months and then it stops occurring. So this is a very unusual event.

After you get angioplasty, you have a very restrained risk, and that's usually over by about 7-8 months. In the most recent studies, in the last, I'd say, 5 to 8 years, most Food and Drug Administration trials have extended the follow-up from 6 months to 9 months. There's been hope to look at 12 months, but the competing issues there are that once you start to extend

way beyond 9 to 12 months, you start to get interference with new coronary disease. So it's always a tradeoff of what to pick. So the 9 month has always been chosen as a middle zone that reflects the events occurring at the target lesion, trying to minimize the amount of events that might occur at adjacent lesions with coronary disease per se.

So you're right that you can always do better by following further, but I think the convention has been that we tend to sometimes get more noise. And then in addition and this 9-month endpoint also has plus or minus 14 days, so it actually includes 9 months and 2 weeks, you know, to include as well.

DR. NAFTEL: But not on this plot, though, because it's strictly intervals? I mean you don't have that plus 14 days?--

DR. KUNTZ: I think if it was after 14 days, it was included.

DR. NAFTEL: Well, it couldn't be because you stop at 270 days, so if you had an interval of 280, it's not on here.

DR. KUNTZ: It's a very good point. I think

what was done was that anything between 270 and 284 was put on the 270th day on this graph. Maybe it's a little bit silly.

CHAIR YANCY: So I think the whole panel is following this and just so we can crystalize it and not get lost, just in terms of summary, the table that we see in slide 101 is inclusive of all patients for whom you have follow-up on and only excludes those lost to follow-up or otherwise withdrawn?

DR. KUNTZ: That's correct.

CHAIR YANCY: Okay. And then the second issue is that the 9-month endpoint was pre-specified because that was presumably the window where you would likely see restenosis? Is that correct?

DR. KUNTZ: That's the convention that everybody uses, right, in restenosis these days, so.

CHAIR YANCY: Okay. And so what is your exact protocol for following ongoing events that occur in the patients that are in that study, Endeavor IV?

DR. KUNTZ: To continue on?

CHAIR YANCY: Yes.

DR. KUNTZ: Will be followed for a minimum of

5 years and --

CHAIR YANCY: Okay. And so that is embedded a data set that we can access in due time?

DR. KUNTZ: That's correct. I think that the next lock for 12 months is occurring right now. Yes. So the clinical events committee has now adjudicated the 12-month lock. And a year from now, we'll do the 24-month lock and continue to evaluate these overall. The convention has always been to report the 9-month TLR rates and TVR rates as restenosis and what you'll see is the next report from this being 12 months and 2 years and so on.

CHAIR YANCY: And so the last issue, just so we can all be clear. The negative influxion on the Endeavor curve that we see corresponds with the protocol-specified angiogram?

DR. KUNTZ: Well, that's an easy answer. In this case, it was only about 20 percent of the cases actually had angiograms, so there was an effect that was due to that but probably not as pronounced as it normally is in a study that has a lot more angiographic follow-up.

CHAIR YANCY: Okay. David, do we need to pursue this any further?

DR. NAFTEL: Just one more question and then I'll -- and one more statement. I really do like the analyses. However, if you'll go to slide 125, just one more comment that puzzles me, if you can. That's the combined analyses. It's a little hard to tell there. I can tell better in the handout you gave me, but it looks like the confidence limits get bigger and then smaller and then bigger across time. And I think that's mathematically impossible with Kaplan Meier. If you were using some kind of life table thing, it's extremely possible, but just if your statisticians will look at that, you'll see that the yellow bar at whatever it is, 980 days, it's quite wide, and then it gets narrower at the next time point. And that's -- I don't believe that's possible. So just maybe if you -- I don't expect you to answer but if you guys could look into that.

DR. KUNTZ: I would agree. I think, hopefully, it's just a graphical error. You're right. The people at risk will continue to be decreasing.

DR. NAFTEL: And that happens on all these

plots by the way. They go up and down so just revisit how you plotted it.

DR. KUNTZ: Okay. Thank you for pointing that out.

DR. NAFTEL: Okay.

CHAIR YANCY: We're almost done with our panel queries. I think we haven't heard from our pharmacology expertise for any outstanding questions, nor have we heard from Dr. Zuckerman. Dr. Somberg?

DR. SOMBERG: Boy, I wouldn't want to have a traffic ticket in your court. This is very helpful. Thank you. Well, this is going back to a point that was made about the duration of dual antiplatelet therapy and what would be recommended. And I just wanted, since our Chairman, Dr. Yancy, pointed out on a table in the FDA summary, I think in reference to that, a table should be pointed out which was 62, that is the duration at 6 months of dual antiplatelet therapy across the studies. And it ranges, I guess, from a low of 59 percent to a high of 95 percent of dual antiplatelet therapy.

This a very important issue at our last panel meeting on stents, and I think to say anything other

than 6 months would be completely inappropriate and there is nothing -- and I'll ask this as a question -- is there anything in the data you presented to us that would suggest that you should not go to 6 and possibly 12 months which was the panel's recommendation for all antiplatelet therapy? And I think this talk of 12 weeks is very disturbing to me, because that will be taken by a lot of doctors to immediately say that's an excuse, let's do it.

So -- and it's also an advertisement if I may be a bit pejorative to the sponsor here that we have less. And there's nothing to support that because the actuality is that people were going 6 months and then I -- and you came to the microphone, Dr. Mauri. I think you said that there was a majority open for a year.

DR. MAURI: I said in my presentation, it was the minority that took it for a year or more.

DR. SOMBERG: What was the number? Can you tell me the number?

DR. MAURI: The number, I believe, was 26 percent.

DR. SOMBERG: So it drops from at 6 months

across this maybe 60 percent to 20 percent at a year you're saying?

DR. MAURI: Yes. It was approximately a quarter at a year who were still taking dual antiplatelet therapy --

DR. SOMBERG: An was that before --

DR. MAURI: -- sorry -- 29 percent --

DR. SOMBERG: -- the last meeting? When is this --

DR. MAURI: So, yes.

DR. SOMBERG: I'm confused with your lock points. When was this? Was this before the late stent thrombosis problem, or was this after the late stent thrombosis problem?

DR. MAURI: Yes. It's a very good question. So most of this safety data that we've acquired beyond one year is in patients who were enrolled and treated before the December 2006 meeting, so the context for the observed rates of stent thrombosis is prior to the inclination to extend dual antiplatelet therapy. So I think that's an important reference. I think the other issue to comment on is the quality of the data that we

to try to ascertain when patients stopped their antiplatelet therapy.

I would agree with the comment that we don't have hard data to say 3 months versus 6 months. All we have is what the recommendations were under the protocols, and we have observations acquired prospectively from case report forms in these studies which asked at 30 days and at 6 months, were you following the protocol recommendations for antiplatelet therapy.

You can see how if somebody filling out that form at 6 months could interpret that perhaps differently in terms of filling out what the compliance was with antiplatelet therapy. For example, a patient who took antiplatelet therapy, dual antiplatelet therapy through 3 months could be construed as complying with the protocol. So I think there's some ambiguity as to whether really, truly 50 percent or more of patients were on therapy at 6 months.

Certainly, in the Endeavor IV trial, we can say with some certainty that 90 percent or more were on dual antiplatelet therapy for the prescribed 6-month

recommendation.

DR. SOMBERG: Now I'm even more confused. So at 6 months, the case report form asked that you comply, and you could say I complied and that would be counted that you were three months, but you didn't comply could be that you're on dual antiplatelet therapy or you're not on dual antiplatelet therapy? The negative could be construed either way then?

DR. MAURI: I think there are limitations to the way the case report form was constructed during the window between 30 days and 6 months. So to say with certainty whether there's an advantage to continuing therapy at 6 months is difficult from the data that we have.

CHAIR YANCY: Dr. Zuckerman, did you have a question?

DR. ZUCKERMAN: No. I just wanted to point out, one, I think the panel is doing a great job of hitting key issues, and so my comments per protocol always stay at a minimum. But I would ask panel members to refer back to FDA Slide 110 when they are challenged by thinking about, in this challenging area, what's

meant by a reasonable assurance of safety and effectiveness. Again, none of the devices that we deal with have absolutely safety and effectiveness.

And number two, if we have x number of drug-eluting stents on the market, there is no criteria that says that the n plus one drug-eluting stent has to be better than other devices out there.

CHAIR YANCY: Thank you very much. With that having been said, we will now specifically address the questions that were brought forward by FDA for panel to consider, and I think Elizabeth is going to restate the questions for the panel.

Just for the panel's benefit, while Elizabeth is doing that, we'd like to see if we can get through these questions in about 45 minutes or so which will get us back on time so we can have our second open forum and have sufficient time to deliberate on our ultimate decision.

MS. HILLEBRENNER: The first question is did the data submitted to date on the Endeavor drug-eluting stent provide adequate assurance of safety in the population identified in the proposed indications for

use.

CHAIR YANCY: Let me prompt this discussion by calling on Drs. Domanski and Lincoff since they've already made some comments about the safety issues. So if you can crystalize some thoughts that you've shared already?

DR. DOMANSKI: I think that the sponsor has done a very good job of putting together a clear indication of safety to the extent that this process, you know, contemplates that, so I think it's -- there's no safety signal at all that I can see.

CHAIR YANCY: Michael, did you want to answer that?

DR. LINCOFF: I agree both from the standpoint of the long-term thrombosis rates, and I think -- and we've talked about it sort of counting into the target vessel failure definition and helping. But it's not trivial that the periprocedural MI rates look that they may be lower as well, and I wouldn't want to discount those to be a real finding as well. So I think they've gone very far to assure adequate assurance of safety.

CHAIR YANCY: Other comments from panel members regarding safety? Dr. Somberg.

DR. SOMBERG: Well, I just didn't want to leave it as unanimity of opinion. Yes, I feel that I'm quite perplexed at what the safety signal is beyond 2 years, and I thought that was a concern for ongoing stents. So I think knowing in 600-and something patients what very late stent thrombosis is inadequate.

CHAIR YANCY: So that's a very fair comment. Dr. Weinberger, you also indicated that seeing no signal of risk is not a signal of safety.

DR. WEINBERGER: I think that in real life, we -- there was a number that was actually proposed by the FDA that sort of sounds like a number that we will discuss, that is will we accept what we, as regulators, accept, a 1 percent per year late stent thrombosis risk, a number underneath that 1 percent. And I think that the data suggests that it's likely that it's certainly in there 1 to 2 years is going to be well under 1 percent and likely that in the 2 to 3 years. But I think that I'm quite comfortable that if you set a liberal number for your annual acceptable thrombosis rate, we will be

there.

Question to be discussed is whether or not the number of 1 percent per year is truly acceptable. But if we're going to use a number like that, then this certainly falls within the acceptable range. That's the number proposed by the FDA, not the sponsor. That's the reason I'm using that number.

CHAIR YANCY: Dr. Hopkins?

DR. HOPKINS: Yes. The question is, "...identified in the proposed indications for use." And the proposed indications for use by the sponsor reads, "The Endeavor system is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo lesions of length. . ."

But every study, including Endeavor IV, talks about to assess the equivalence and safety and efficacy of the Endeavor system for the treatment of "single" de novo lesions in native coronary arteries. Somehow that "single" has gotten dropped and, therefore, all the studies reflect data in single de novo lesions. And, therefore, I would have to say that in answer to this question of the FDA, the proposed indication is not

supported by the study design and should reflect the study design.

CHAIR YANCY: So the indication comments are accepted but right now we just want to kind of crystalize this issue of safety based on what have before us. Let me see if I can frame then a statement from the panel unless there's another person who wants to contribute to this.

So what I'm hearing the panel saying in response to the first question is that the data that are presented in aggregate do provide reasonable assurance of safety, but there are some questions about the long-term safety that require ongoing follow-up and the data should be interpreted in the context of the way they were obtained, vis-a-vis single lesions?

DR. HOPKINS: But it's also in the group of single de novo lesions. That's what the study studied. The indication is written without the word "single", so the answer to this question has to be no, because that's not what was studied.

DR. DOMANSKI: But isn't that a labeling issue?

CHAIR YANCY: That's my comment that that label can be modified as we go into this. Dr. Somberg, you had an objection?

DR. SOMBERG: Well, I just -- I think the summary, it's not going to be able to pave over a difference that I and Dr. Domanski have over this issue, and that is that I think the sample size is inadequate for very late stent thrombosis and that's the major safety concern with DES. So I think -- I don't say it right now -- I think this is a premature PMA to the panel, and I think that data set could be captured in 6 months. That would be adequate.

CHAIR YANCY: Dr. Domanski?

DR. DOMANSKI: Yes. I must say, though, that if one's looking for an assurance about late stent thrombosis, I'm not so sure that the very low numbers we're talking about with this and, frankly, other stents that there's -- I'm not so sure it is practical. I get some help from my statistical colleagues, maybe from other people that it really is practical to ask them to make that kind of reassurance at these low levels, not arguing perhaps that I'm wrong, but I'm worried about

that. I'm not so sure that's right.

CHAIR YANCY: Dr. Lincoff?

DR. LINCOFF: And I would like to add -- and, again, I'm talking about the past only because as you brought up, the issue we're concerned about with drug-eluting stent is late thrombosis -- is that this isn't an event that comes out of nowhere from a flat Kaplan Meier curve and suddenly appears. All the prior evidence that led to this concern was a monotonically increasing risk over time that didn't go away like it did with bare-metal stents.

We've seen the landmark analysis here that shows no events or one event, depending on the definition used, after 12 months. So, yes, we do want to continue to have the data, but I think there's some point where it's reasonable to say everything looks pretty good and we'll continue to look. But it's a reasonable level of assurance, and I think that the data that we have is for those reasons.

CHAIR YANCY: We do also need to remember the context in which these data were described. The studies that we're using are studies are studies that were

designed and completed prior to the sensitivities that came forward in December 2006, and it was at the FDA's request, appropriately, that the pool post hoc analyses were being done, and so an effort has been made to capture information relevant to this question, but it's not the same as prospectively acquired data. And as many have pointed out, it's a very finite event rate. It would take a large denominator with significant years of follow-up. So let's try to reframe an answer that reflects the flavor of the committee, if we can, understanding that we will have maybe some strong voices of dissension.

But with regard to the question of reasonable assurance of safety based on the aggregate data that's presented and the way that it was obtained, the panel feels that generally, there is reasonable assurance with what we have available but persistent questions vis-a-vis late stent thrombosis and that we understand the context of the way in which this information was obtained does, in fact, give us some reason to continue to want to acquire information.

I can wordsmith that later, but does that

capture the flavor of the majority of the panel without going through a vote? I see sufficient nods. Dr. Zuckerman, does that satisfy the FDA?

DR. ZUCKERMAN: Yes. And in looking at the subsequent questions, I would just go back to the point that you and Dr. Lincoff have made. One can always change the intended labeling, but the thought here is to capture the practical relevance of these questions as Dr. Lincoff tried to summarize in his comments.

CHAIR YANCY: Elizabeth, can you proceed?

MS. HILLEBRENNER: Yes.

CHAIR YANCY: Thank you, Dr. Zuckerman.

MS. HILLEBRENNER: The second question is does the application include adequate follow-up in a sufficient portion of the patient population. If not, how much additional follow-up, the number of patients or duration of follow-up is needed prior to approval to confirm a reasonable assurance of safety?

CHAIR YANCY: For the sake of discussion, I'd like to ask the panel to strike the phrase that says "prior to approval", because that prejudices our comments, so let's just answer the question in the

context of how many more patients for how much longer will you need if you are already -- if you're not yet at a comfort level, how much more do you need to see to get there? Dr. Naftel?

DR. NAFTEL: So the question this morning of FDA as to which of these studies should we be looking at and what sort of weight, I think the answer was look at all of them and I agree with that, too. And then it makes this combined analysis so much nicer. You know, for sure, we're not going to have 5-year follow-up. We don't have anything like that, but I have to say I'm kind of going the other direction from some of the discussions. I'm incredibly impressed that there's 648 patients out at 3 years, 1,200 at a year and a half, 2,000 at a year. That's a lot of patients and an incredibly small number of events.

And Dr. Mauri, as you pointed out, the confidence limits, that's the best way to get an idea of what we have here, because it's more a reflection of the amount of patients than anything and the events. But that's what you look at to say how much confidence do I have in this estimate. And those confidence limits are

incredibly narrow.

So within the context of 2 to 3 years, I personally think we have great follow-up and great information. Now if you're wondering about safety at 4 years, we got nothing. That's a Alabama term.

(Laughter.)

CHAIR YANCY: We understand that in Texas as well. And so actually, David references this information that appears in Table 8 in our question packet. That's your position. And it shows that at 3 years, there are 675 patients available, 2 years 1,287, and at 1 year 1,301.

There were comments from others that the 1,200 number was a reasonable denominator, the 675 was not. So can we just develop that for just a little bit more so we can see if we can come up with an answer to this question? It sounds like David is saying that you have reasonable comfort that we're capturing enough patients, longitudinally, to address this issue? Dr. Hirshfeld?

DR. HIRSHFELD: Yes. I think the Postmarketing Registry and the PROTECT trial, if I

understand their design correctly, they will have something on the order of 6,000 patients under surveillance for late and very late stent thrombosis. And if we start out with a presumption that Endeavor might have the same late stent thrombosis rate that CYPHER and TAXUS have, that would mean we would expect about 12 events per year in follow-up.

And so I would think that, not having done the statistics, that sounds to me like a number in which if there is a important difference, we would see it and if it's actually better than what we expected, we would probably see that also.

CHAIR YANCY: So I think there are two panel members that have spoken in the affirmative for question two. Are there other comments we need to entertain here?

(No response.)

CHAIR YANCY: So what I hear is that with regards to the first part of the question, does the application include adequate follow-up in a sufficient portion of the patient population. Dr. Naftel has led the way and is suggesting that that's a yes. And it

sounds as if apart from whether the issue is approval or not, that the ongoing plans to acquire more information will be helpful in further resolving any residual questions about safety. Am I overstating that? Am I representing the flavor of the panel? Dr. Zuckerman, does that satisfy the FDA?

DR. ZUCKERMAN: Yes. I just would like to hear from Dr. Somberg one more time. Do you have a dissenting viewpoint to what Dr. Yancy just summarized?

DR. SOMBERG: Well, I can't answer the two, because it says if the answer to one was yes.

DR. ZUCKERMAN: Okay. Then you have a dissenting viewpoint?

DR. SOMBERG: Yes, I do.

DR. ZUCKERMAN: Thank you.

CHAIR YANCY: And we do respect that.

DR. SOMBERG: Thank you.

CHAIR YANCY: Elizabeth?

MS. HILLEBRENNER: The third question is regarding antiplatelet therapy. Do you believe that the language in the proposed endeavor stent label adequately conveys a recommended course of dual antiplatelet

therapy following Endeavor stent implantation?

CHAIR YANCY: Let me just restate that language, or if you have your handout, you can see it at your place. But it's in the Endeavor study is clopidogrel or ticlopidine was administered pre-procedure and for a minimum of 12 weeks post-procedure. In Endeavor IV, clopidogrel or ticlopidine was administered pre-procedure for a minimum of 6 months post-procedure in order to ensure proper blinding to the randomization comparator, and there is some other verbiage as well, and you've heard Dr. Mauri's comments about Endeavor IV especially. Dr. Somberg, do you want to lead this discussion?

DR. SOMBERG: Do I want to? It's an interesting way to put it. The -- in light of what's recently come out, I feel we have very inadequate information here and, in fact, the way the studies were designed and the data was captured and I think there was a compromise on the part of the sponsor to deal with OUS and US approaches and reimbursements, etcetera.

So with all that said, I think we have very little information on how long the people were actually

on dual antiplatelet therapy. I think this is critical for the safety issue, and since we have no data, I think we have to defer to what has generally been recommended by consensus views from the different societies, also from the previous panel when we looked in to this.

And therefore I think, clearly, the statement that 3 months or the implication that 3 months is sufficient is not correct, and 6 months preferably in the higher risk patients, 1 year, is probably appropriate unless they change and do a study to actually look at that. It may be with Endeavor. You know, I don't want to get me wrong that I'm -- I think this, you know, has tremendous possibility.

But it may -- but the studies are not designed to test that hypothesis that we can only give it for three months, stop everybody and follow them out for a safety outcome. So I think this is mislabeled.

CHAIR YANCY: Well, I thank you for taking the lead, because I think you'll find some consensus with your opinion. So what you're saying is that the answer to 3(a) is no. And the answer to 3(b) would be yes?

DR. SOMBERG: Yes.

CHAIR YANCY: So what you're saying is that the labeling, which is insufficient and we would embrace the panel deliberations and the published statements for 12 months. Is there any dissension to that?

DR. LINCOFF: It's not really dissension. I would just like to clarify for my own -- what is the attitude of FDA for labeling with regard to making it concordant with such ACC/AHA or other guidelines of professional committees? Because they change and your labels change less frequently, so. Now granted it was an FDA panel that came up with the 12, so maybe that's the precedent, but how do you generally bring those together if you do at all?

DR. ZUCKERMAN: Okay. Before I answer that, I just want to respond to one point that Dr. Somberg made, because I think he hits part of the safety issue right on the nail. He has stated that there's a real need to do the appropriate antiplatelet trial and certainly I want to underline FDA's interest in working with any sponsor or sponsors and quickly getting that trial done.

Now because we don't have the data that Dr. Somberg is seeking and that we all seek, we need to carefully consider the limited available data. And we have some backup slides to show you how we interpret the data for the two other approved stent labels, and that might give you a sense of what our thinking is.

CHAIR YANCY: May we see that, Elizabeth?

MS. HILLEBRENNER: So since the December panel meeting, FDA is recommending some changes to labeling for drug-eluting stents with regards to antiplatelet use. This wording has been specifically requested. In clinical trials of the DES, clopidogrel or ticlopidine was administered pre-procedure for a period of 3 or 6 months post procedure.

Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies suggests that a longer duration of clopidogrel than was recommended post-procedurally in

drug-eluting stent pivotal trials may be beneficial.

Current guidelines recommend that patients receive aspirin indefinitely plus a minimum of 3 or 6 months of clopidogrel with clopidogrel therapy extended to 12 months in patients at low risk of bleeding. It is very important that the patient is compliant with the post procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction or death.

Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a drug-eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy.

Patients who require early discontinuation should be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

CHAIR YANCY: Thank you. So if we go back to question three, it seems as if our feeling is the language that we have before is not adequate to convey what the panel believes should be a recommendation for a course of antiplatelet therapy.

DR. LINCOFF: Can I just -- what I like about that is because saying 6 months is just as arbitrary as saying 3 months. You know? So I'd rather than do that, I like the idea of saying it's been tested at 3 or 6 depending on the trial, but there's evidence to suggest that you should go longer and the organizations have suggested up to a year. Because one of the questions here is do we say 6 months, and I don't think we can justify that any more than we justify three months.

DR. SOMBERG: Well, can I address some of this. If it's the -- with Endeavor, it's my understanding that was we do not know the duration.

Okay? That's the first thing. So that has to be studied in my opinion. But with the CYPHER and TAXUS, it came out that -- the two things that I believe influenced the committee and other people were there to make other statements -- but the things that came out was that a majority of patients were on antiplatelet therapy for at least 6 months, so that's why it was felt to be consistent for 6 months.

And there was a concomitant paper that was being published simultaneously and everyone had a copy of this pre-print from Harrison and colleagues from Duke that suggested, and it wasn't from, you know, acute coronary syndromes, but it was people with stents that the longer you were on the stent -- I mean the longer you were on dual antiplatelet therapy with a stent, the better you did.

And those people who had a DES plus dual antiplatelet therapy did the best, and those people who had a DES but off dual antiplatelet therapy did the worse, and the BMSs were in the middle.

And because of that, the committee recommended that although we didn't have definitive

evidence, it was suggested that at least 6 months and maybe a year in high risk patients were indicated. And I think this is a terribly important thing, because I practice not just a pharmacology, I practice clinical cardiology and I get the people back from the interventionists, and they say, well, you know, should I stay on my dual antiplatelet therapy, should I not stay on it. When should you stop it.

And these are, you know, important considerations. And right now the evidence is minuscule for the other stents. And with this stent, it's completely confusing. So I think instead of putting in more confusion, we should probably recommend longer and then have studies to either shorten it which may work or to even extend it beyond that.

CHAIR YANCY: Dr. Domanski?

DR. DOMANSKI: Yes. I'd like to comment on this one, too. I think this actually is a big -- I think this is a big point, and it's a big point because if it goes out labeled, you know, it's really a problem keeping people on dual antiplatelet therapy. They come off it because they can't afford it, because they don't

want to take it, because they don't understand it for whatever reason. But people come aboard because they have to, because they're going to surgery. This would make this stent look like a good -- this would be a great reason for putting it in.

If this were true, if it turns out to need less of a duration of antiplatelet therapy, it becomes a compelling reason for not worrying one bit about small differences in restenosis and using this thing, it's probably a very good stent in terms of crossing. And that probably is a totally false impression to send, at least based on the data. Not that that may not be how it works out, but I think there's nothing to suggest it.

So I think having a difference between the suggestions relative to antiplatelet therapy and between this and the other stents is really inappropriate.

CHAIR YANCY: No. I think we all agree in principle with the comments. The context of our task right now, though, is to look at the statement that the sponsor brought forward that really describes the use of dual antiplatelet therapy in the different studies, so it prompts Endeavor I, II and III, there's a minimum of

12 weeks. In Endeavor IV is a minimum of 6 months.

And our question is whether or not this is adequate language, if we agree with it or if we don't. If we don't agree with it, then the next question is should we emphasize a recommended course of 6 months, and Michael points out that there is an arbitrary cut point, whether it was 3 to 6. And then our next prompt is should we just simply embrace the stated guideline documents.

So that's the advice the FDA wants -- for us to advise them on whether we accept the language that's been brought forward, do we modify it with a 6-month metric, or do we modify it with the prevailing guideline statement, or do we add item C which is to capture everything that Elizabeth has just shared with us in the backup slide? Yes. Dr. Morrison?

DR. MORRISON: Well, having been at the December meeting and being on the guideline committee, I would be inconsistent with myself if I didn't embrace 12 months. But I think besides the very important point that Drs. Somberg and Domanski have both made that labeling this anything less than 12 months would give

patients, doctors a false hope. I think the results, though, you might argue that have such a low signal or nearly no signal on a lower dose of antiplatelet therapy is almost a form of sensitivity analysis.

But looking forward instead of backwards, we're going to presumably all of us be looking back on this when the data that we have is larger numbers of patients, larger follow-up and clinical endpoints such as cardiac death and MI. And I think it really doesn't make sense to label this anything other than 12 months so that we, to at least the degree humanly possible, wind up comparing apples with other fruit rather than with vegetables.

CHAIR YANCY: So we're trying to reach a decision if we accept 12 months for patients who are not at high risk for bleeding with the provisos that have been outlined in these two slides, are we as a panel generally comfortable with that understanding that compromise is part of what has to rule? Dr. Domanski, do you have a comment there?

DR. DOMANSKI: No.

DR. SOMBERG: I think you've said it and

that's the appropriate thing to do. And the only proviso I would say is that guidelines change and I suggest the sponsor or other sponsors come up with a real answer to this issue.

CHAIR YANCY: Well, I think you put it squarely when you said we don't have the data. If there are no other strong opinions -- Dr. Yaross, you seem tentative?

DR. YAROSS: I just think that typically class labeling is a useful concept in the absence of specific information one way or another. And so to the extent that FDA has promulgated class labeling, that may be an appropriate way to go.

CHAIR YANCY: Thank you. Dr. Zuckerman?

DR. ZUCKERMAN: Okay. I'm glad that the panel is spending an appropriate amount of time on this point, because it is such a critical point and Ms. Ashley Boam from our interventional group would like to give us additional contacts for the discussion.

MS. BOAM: Thank you, Dr. Yancy. Just a point of clarification to some question that Dr. Lincoff brought up about why the current labels have stated what

they did. Because we did not have the data collected in the initial trials of either CYPHER or TAXUS to tell us definitively what the actual usage was of dual antiplatelet therapy in those trials, then the labeling could only reflect then what was recommended in the protocol.

So then following the December meeting, the recommendation was again, in the absence of any other definitive data about what should the length of time be rather than the label making a firm recommendation to physicians, it was felt appropriate to include again what was done in the protocol but then strengthen that language by including the language from the guidelines. And so that is the approach that we have taken today.

So I hope that answers Dr. Lincoff's question. The label does not recommend a duration, it simply reflects what was done in the trials and then the guidelines.

CHAIR YANCY: All in favor.

MS. BOAM: Thank you.

CHAIR YANCY: Looks like we have an opinion that we can accept. Is that acceptable Dr. Zuckerman?

DR. ZUCKERMAN: That's very helpful.

CHAIR YANCY: Great. Elizabeth, question four?

MS. HILLEBRENNER: Do the data presented on the Endeavor stent provide a reasonable assurance of effectiveness. The first part of this question is in the Endeavor II study, the Endeavor stent was demonstrated to be superior to the bare metal Driver stent with respect to TVF along with reduced rates of TLR and TVR. Has a reasonable assurance of effectiveness of the Endeavor stent been demonstrated versus bare-metal stent implantation?

CHAIR YANCY: Dr. Hirshfeld, you set up a beautiful template for us to resolve this very question. Would you mind leading this discussion?

DR. HIRSHFELD: I think it can be stated quite simply that there is very good evidence of superiority to bare metal, both in terms of safety and effectiveness.

CHAIR YANCY: And then b? A is Endeavor versus bare metal and "b" is Endeavor versus CYPHER and TAXUS.

DR. HIRSHFELD: I think b versus CYPHER and TAXUS is more complex, and it really hinges upon whether a device that does inhibit late loss compared to bare metal but does not inhibit it as much as the other devices that are out there will in the long run prove to be equally effective in all subsets of patients. And I think that the sponsor presented data that was intended to demonstrate that that's the case.

However, I think they're short on statistical power to be absolutely certain that the diabetic with a 2 and a half millimeter reference diameter in a 20 millimeter long stenosis is going to be as well off with a Zotarolimus-eluting stent as a stent that elutes something else. So I think that probably remains to be sorted out with more acquired clinical experience.

CHAIR YANCY: So I think that Dr. Hirshfeld addressed question 4.a. succinctly, and I suspect there's no deviation in the panel from that? Is that fair? Is that correct?

(No audible response.)

CHAIR YANCY: So let's have some more discussion on 4.b., because obviously, we saw that

compared by CYPHER or TAXUS in late loss, there was a failure to meet that endpoint. But then we saw other data referable to clinical events. So let's have some dialogue. Dr. Somberg?

DR. SOMBERG: I don't know the clinical significance of these disparate findings, and I've hear everything presented. So my recommendation, I think, one that would facilitate things would be is that this all be placed in a label, that the differences between small neointimal hyperplasia versus clinical outcomes totaled vessel revascularization, etcetera be stated. And that physicians will make up their mind with this information, with the information about being able to use this device and with other understandings.

And I think that's very fair, especially if we don't give them -- or not give them -- but we don't overly overstate the benefits of dual antiplatelet therapy that this thing might have. Then physicians can make a reasoned discussion. Because I don't think we're going to resolve whether because it didn't meet its non-inferiority endpoint in terms of luminal considerations whether that really means something.

CHAIR YANCY: Let me just remind the panel that referable to Endeavor IV, the primary endpoint was reached which was non-inferiority with TAXUS. It was a powered, pre-specified, secondary endpoint that was not met that had to do with late loss. Dr. Domanski?

DR. DOMANSKI: Yes. I entirely support that view. I think the differences, if there are differences, are very, very small. And they don't seem to be reflected in what actually to the patients. So, you know, if you see a patient and it's discussed with them, not that we usually discuss it in this detail, but if you discuss with them the stents, you can certainly at least say that based on the available data, it's really no more likely that we're going to be back here doing this again, at least on clinical grounds, then if I use one of the other stents. So I think it's fine to show it in the labeling, but I think there's a reasonable assurance of the efficacy here as well.

CHAIR YANCY: Dr. Weinberger, I haven't heard from you.

DR. WEINBERGER: Yes. I think I'm in agreement with the tenet of what's been said. I don't

think can shed any more light when there's no more data to be added.

CHAIR YANCY: Dr. Kato?

DR. KATO: I'm moving along in the direction of Dr. Somberg in that, you know, I think much like some of other labels we've discussed, I think in this case, because there is a fair amount of uncertainty, the data is in flux. You know, we know this stent does work in a very large number of patients, and basically an explanation of how the data plays out, at least currently, until, I guess, the PROTECT study comes out and is published is probably the best we can do. And at least it creates a dialogue between the patient and the physician, which I think is an important part of the label.

CHAIR YANCY: Dr. Lindenfeld.

DR. LINDENFELD: I agree. I think there's been good effectiveness demonstrated, but I think including the information about late lumen loss is valuable to physicians who maybe they apply the stent in patients other than the ones described here. And I think we don't know yet what it means, but I think

people may want to consider that, so I think it would be valuable to have it in the label.

CHAIR YANCY: Dr. Zuckerman?

DR. ZUCKERMAN: Yes. If I could just interrupt the panel discussion a moment which has been quite important on 4.b, the panel today is asked to use both its clinical and regulatory hat. And much of the discussion is compared to FDA approved stent 1 or 2, how effective is it.

But I'd like you to understand the philosophy of this question, besides addressing that, is also to understand the regulatory definition which we will hear again later. But the regulatory definition is the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

And I'd like also panel members to comment on whether this particular product hits the regulatory definition of effectiveness.

CHAIR YANCY: I appreciate that clarification. From those who've already spoken, do you

support this device reaching the bar that Dr. Zuckerman has just described? Dr. Somberg?

DR. SOMBERG: The -- it's an interesting question you ask, because the device does work compared to Driver. There's mixed information in other areas, but I think my feeling, and maybe the rest of the panel, is that when one looks at the clinical implications of this, the efficacy of the device is significant.

CHAIR YANCY: Other comments. We haven't been here. Dr. Hopkins.

DR. HOPKINS: Again, I think we have to take the efficacy into adjudication by the fact that this is a combination device which makes our mind set a little bit different. I think the mechanics of the device, the deployment, the operator technical abilities with this has shown to be superior. The biology of this is not yet very clear, but it's certainly in the ballpark of the other drug-eluting stents. So to have multiple drug-eluting stents available in the context of post approval studies makes sense to me.

CHAIR YANCY: So it sounds as if the panel is saying that unequivocally the Endeavor stent does show

more than reasonable assurance of effectiveness compared to the bare-metal stent and that with regards to comparing it to CYPHER and TAXUS, there is at least one drug-eluting stent with which the panel thinks it has similarity based on the primary endpoint of achieving non-inferiority, but there are differences in late loss and that there is a reasonable assurance that this device will achieve a clinical result that is meaningful. Is that a fair response to these questions? Is that acceptable, Dr. Zuckerman?

DR. ZUCKERMAN: That's very helpful.

CHAIR YANCY: Thank you. Elizabeth?

MS. HILLEBRENNER: With regards to labeling, please comment on the indications for use section as to whether it identifies the appropriate patient populations for treatment with this device.

DR. HOPKINS: I would have to say no for the reason I was talking about earlier that all of the trials identify a single de novo lesion but the labeling refers to de novo lesions, and I think that since what was studied was single de novo lesions, the labels should, in fact, reflect that.

CHAIR YANCY: Dr. Kato?

DR. KATO: Well, going back to the sponsor's list of indications, if I can just quote that. It says, subject was greater than 18 years of age. Subject was an acceptable candidate for angioplasty, stenting or immersion CABG. Subject had a clinical event of ischemic heart disease or positive functional study. The subject had single-vessel disease or had multi-vessel disease with only moderate stenosis in the other vessels. The target -- and it actually says -- the target lesion was a single de novo lesion that had not been previously treated with any interventional procedure. And then there's the anatomic requirements.

From my perspective, I think that the indications for use should reflect the trial indications primarily because, again, this is new technology, new therapy. And in order to optimize outcomes, you know, we have to take reasonable steps forward and in trying to avoid, you know, what happened -- you know, what brought together our meeting in December.

CHAIR YANCY: Dr. Lincoff?

DR. LINCOFF: By that argument then, we would

also have, under contraindications, all the angiographic contraindications. You know, some of these indications of contraindications are done to do a trial, for the practicalities of doing a trial and correlating the events. Now the way that these angiographic exclusions are handled in this proposed document is in Section 5.7 which says the safety and effectiveness have not been established with these criteria because they weren't in the trial.

And I would suggest that may be a reasonable alternative for the issue of whether or not they have multiple stenoses or single stenosis, because I don't know where you draw the line. If you're going to take the inclusion as inclusion criteria explicitly, then why don't you do it for all of them?

CHAIR YANCY: Dr. Hirshfeld?

DR. HIRSHFELD: Yes. I'd like to emphasize that I think the labeling should not be up front restrictive in the ability to use this device. And I think that, as we all know, the majority, there's a high frequency of what we call off-label use, and I think if the label is written in such a way that it explicitly

states that a particular circumstance is the wrong circumstance in which to use the device, that unnecessarily ties the hands of the clinician who's trying to make the best decision for the patient.

If we were only limited to only those indications that have been proved in trials that were designed to gain approval of the device, we would be quite handcuffed in terms of what we could do in terms of patient care, so I'd be --

DR. DOMANSKI: That's wrong.

DR. HIRSHFELD: -- opposed to having labeling that says you can't use it in this circumstance.

CHAIR YANCY: Just so we can all be on the same page, be certain to look at section 9, page 9, items 2.0, 3.0, 4.0, and 5.0, just so we can use the same language. Dr. Domanski.

DR. DOMANSKI: Yes. I want to really agree with the gentleman to my left and totally disagree with what was just said. I think that one has every expectation that any device, any of the stents might behave differently in different lesions. In fact, nobody's hands are tied one bit by giving an indication

based on, you know, FDA labeling based on what they actually showed.

We're not talking about a black box warning or any of that kind of stuff. We're just saying that they showed reasonable safety and efficacy in a particular type of lesions, and to go beyond that in the labeling or to fail to indicate that is very different than listing every single parameter of the trial. This is a very important parameter. Again, not tying anybody's hands, but it's totally inappropriate to give them an indication for something they didn't show.

CHAIR YANCY: So trying to follow this, Drs. Lincoff and Hirshfeld, you feel a more broad statement would be beneficial and Dr. Domanski and Dr. Kato, you feel a little more narrow statement, is that what I'm hearing -- oh, Dr. Kato?

DR. KATO: Well, let me just say that what I'm suggesting is that the labeling reflect the lesions that were actually -- where safety and efficacy is actually shown. That's what I mean.

CHAIR YANCY: Okay. Dr. Hirshfeld, you want to respond?

DR. HIRSHFELD: Yes. I don't think we're actually disagreeing. What I was advocating was that the labeling should not explicitly state that merely because the efficacy of device has not been shown in a given situation, that therefore it's not correct to apply it to that situation. And --

DR. HOPKINS: So, could this be used in the carotid, the renal? No. This is absolutely wrong. The labeling is the crux of the issue --

DR. HIRSHFELD: Well, let me --

DR. HOPKINS: Because off-label use is covered by your clinical capabilities. You can use it however you want. They already have a study to study off-label use. For the panel to say that this is safe and efficacious in settings which have not been tested is malarkey, and it goes back to what Dr. Ferguson brought up this morning. If you're going to do that, then the studies have to be designed with appropriate control groups, which in this case, if you're going to extend that use by the labeling -- I'm not saying by the clinician, but by the labeling -- then all of these studies have to control -- have concurrent surgical

controls, concurrent medical controls so that you're really comparing apples to apples.

Now if you're going to say that all of these 5.7 lesion vessel characteristics are inconsequential and you can use it however you want, then why are we even here.

DR. HIRSHFELD: Again, I don't think we're disagreeing. I don't want to prolong this but let me give one example. There was discussion about whether given the fact that this was studied only in single-lesion application as to whether it should be labeled for single lesions only, and I don't think any interventionalist would agree that you couldn't generalize this information base to the patient with two-vessel disease who had two lesions to be treated.

DR. HOPKINS: We don't disagree.

CHAIR YANCY: Dr. Somberg.

DR. SOMBERG: I think there's a middle pathway here and that is you have to have biological common sense, if you will, and just what you -- that was my feeling that if you have a non-complex lesion in the LAV and then you have one in the RCA and one in the

CIRC, then you can look at it as 1 plus 1. They're each discretely different. They weren't studied in a combination trial of doing two lesions, but that's different than you do a left main, a long lesion, a bifurcation and maybe a very, very small vessel and this is an oversized stent.

So I think there are times when you want to label, because there's appropriate concern and there's times you can't label for everything, otherwise no one will read the label. So it's a balance. So I think the de novo point you made, I must say, I don't agree with. But I think the other point you made, that labeling is important is certainly the case and it should be in the left main, bifurcations, very long and, you know, oversized are concerns that have to be pointed out, that would be -- you know, haven't been studied.

CHAIR YANCY: Dr. Kato?

DR. KATO: Well, you know, the reason why I brought this up is because this is essentially the crux of what happened back in December of '06, which is that we had a restatement by not only this panel, the FDA as well as the manufacturers that these drug-eluting stents

are supposed to be used and were safe and effective, quote unquote, under the circumstances in which the label had been written which was based on scientific data, the best scientific data on hand at the time.

And, therefore, the -- much as Dr. Yaross has said before, this is a class of devices now. This could potentially be the third one. And I think that the label has to be written in a similar manner to the other two labels that out there. But I think that in both of those situations there, many of the so-called on-label indications, you know, were taken -- and correct me if I'm wrong -- were taken from the way the trials were designed.

CHAIR YANCY: So the way the indication would read right now says that the Endeavor stent system is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo lesions of length less than in native coronary arteries with reference vessel damage greater than or less than. Is there great discord with that statement?

DR. HOPKINS: Yes.

CHAIR YANCY: What would be different?

DR. HOPKINS: I think that the label should reflect the data. The data does not go beyond single lesions. That's all they're taking about. Now if they entered patients who didn't have single de novo lesions, then we need to see a subset of the data on the patients who were identified as the focus of the study of single de novo lesions. That's what they're talking about. If we're going to talk about triple vessel disease, bifurcation lesions, LA ostial stenosis, then that has to be studied in the context of the other therapeutic alternatives.

CHAIR YANCY: So I respect that we have one strong opinion that disagrees with the language. Are there other statements that disagree with the language that I just read.

I've been asked to read the language again. The Endeavor Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo lesions of length less than 27 millimeters in native coronary arteries with reference vessel diameters of greater than or equal to 2.5 millimeters to less than or

equal to 3.5 millimeters. Yes?

DR. KATO: Under that circumstance, I would agree with Dr. Hopkins because, again, what I read before was it says, the target lesions was a single de novo lesion. Now if a cardiologist wants to go ahead and put in, you know, put one of these things in the LAD, in the circ, and the right coronary, then that's off label. I mean I think here we're talking about an on-label indication, and as far as I understand it, the on-label indication is a single de novo lesions.

CHAIR YANCY: Other comments?

DR. DOMANSKI: You know, I have one comment to make and this is sort of a general one. You know, what's reasonable to do in practice is not necessarily congruent with what we're doing here. What seems reasonable, what seems entirely reasonable may go beyond the available data. And I think in this setting, we have to act in terms of indications on the available data and not go beyond it even where it seems reasonable to do it. I don't know whether I'm right about that. Bram, maybe you can -- Dr. Zuckerman might want to comment on that comment?

DR. ZUCKERMAN: Okay. This has a been an interesting clinical discussion but, again, with respect to 5.a, where you can most help the FDA, is both putting on your clinical and regulatory hats. And certainly in an IFU indication statement, we're looking for a concise statement that adequately summarizes the intended patient population and what the device does. So from what I'm hearing, the main question on the table is whether or not to add the word single. And Dr. Yancy, can you try to see where the panel sits on that issue, individual panel members?

CHAIR YANCY: I'm happy to do that. I'm just quickly reviewing to see how much variance there is from the language that was brought forward and what was identified as the inclusion criteria for angiographic descriptions in Endeavor IV, and indeed it says the target lesion must be a single de novo lesion in a native coronary artery, with the rest of it following the language that we've heard.

So is there a sense from the committee that we need to be consistent with the inclusion criteria for the clinical trial or respect the statement that's been

brought forward by the sponsor? That's really where we are.

DR. SOMBERG: Isn't it true that the predominant reason to have written the inclusion criteria that way is it would become a real conundrum if you had two vessels in one person and one would respond one way and one would respond another way? So they want to study -- it's like a -- it's a biology experiment. They want to study the effects of this stent with this elution material in a vessel. So I don't think it's one vessel or two vessels is relevant biology here.

What is relevant is what they state is the lengths, the, you know, it's oversized, undersized, and I'm not sure -- I didn't read all the thing, but obviously left main would be a very special case, and ostial lesions and bifurcations, because that's the biology is different, but the biology in a right-sized LAD, CIRC, or what's the other one -- I missed one -- okay, I thought I said the RCA, but the CIRC also. Okay. But the biology in each one of those is going to be the same, so I think your point is well taken about labeling and biology, but that single versus two or

three, I think, is just not well taken.

DR. DOMANSKI: And I'm going to agree with Dr. Somberg, you know, for what it's worth on that.

CHAIR YANCY: So let me see if I can move this forward. I think -- I'm sorry. Dr. Morrison?

DR. MORRISON: Well, I'd just like to say that whatever hat I try to fit on my head, I can't feel real threatened by the labeling being just what's in the Endeavor II and IV statement. To me, this is analogous to thinking, as a surgeon, that the Heart-Lung Bypass Machine is a device that was approved and had some labeling, and when I went around the country to look at all of the sites that were in my prospective randomized trial comparing bypass to intervention, what the surgeons put in the bath at different places was incredible.

And whether, you know, one person thought thyroid hormone was good and somebody else used vitamins, someone else thought inflammatory agents was great, some people used cold cardioplegia, some used warm, some used retrograde, some used antegrade, they had no prospective randomized trials and that just falls

under the category that the FDA doesn't regulate practice.

So it seems to me the label that's just copied right out of what was in the trials is perfectly adequate, and then if the product is released, people will use their best judgment.

CHAIR YANCY: So let me suggest this as an answer to 5.a. The majority of the panel believes, in general, that the statement that already exists as a proposed indication is, in fact, reasonable, but as we've done before, within the label, we can develop the language from the individual trials and make specific reference in that language that the trial has prompted single vessels as has been outlined in these inclusion criteria. Would that be acceptable to Dr. Zuckerman?

DR. ZUCKERMAN: Well, there's a clinical trial section. The clinical trial section will, as in the draft, fully describe all the inclusion/exclusion criteria for the individual trials. Yes.

CHAIR YANCY: So will that be acceptable to the body of the panel. Dr. Hirshfeld?

DR. HIRSHFELD: I would just like to point

out that neither the CYPHER nor the TAXUS instructions for use mention single lesions only.

CHAIR YANCY: And so that gets back to the class issue. So again, I think we have -- yes, sir.

DR. HOPKINS: I'm sorry. I wasn't on the panels for those, or I would have made the same -- if, in fact, that was the language of the studies that -- I mean why don't we just drop out coronary arteries and just say arteries with lesions of x amount of diameter. I mean --

CHAIR YANCY: No, because --

DR. HOPKINS: -- you start dropping out words --

CHAIR YANCY: -- so what we need -- I appreciate that and I think --

DR. HIRSHFELD: -- from --

CHAIR YANCY: -- the points that have been made are well put, but from a pragmatic context, looking at the aggregate information we have addressing ischemic heart disease, which is very clear, I think that with the language before plus the appropriate explanations in the clinical trial section and consistent with the other

devices, I believe we have a consensus with strong statements that we will acknowledge and reflect as you move forward.

DR. HOPKINS: Mr. Chairman, could I ask for a vote on how many members of the panel are bothered by the dropping of the word "single?" I just would like to --

CHAIR YANCY: Or what I --

DR. HOPKINS: -- you're saying that there's a broad consensus that there's no concern with that. If it's two of us, it's two of us, but I'd like to know quantitatively how many people are comfortable with the studies being done and then that word being dropped in the indication when that's the primary indication for the study.

CHAIR YANCY: That's an absolutely fair question, and we have a time designated where we will vote on precise language.

DR. HOPKINS: Okay.

CHAIR YANCY: And I'm certain that you will have any opportunity to enter that issue. Let's move on to 5.b. Please comment on the contra -- I'm sorry,

Elizabeth.

MS. HILLEBRENNER: Please comment on the contraindication section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefits.

CHAIR YANCY: We're back in Section 99, Item 3.0, contraindications. "Patients with a known hypersensitivity to Zotarolimus or strokes-related compounds, patients with a known hypersensitivity to the cobalt based alloy, i.e., cobalt, nickel, chromium or molybdenum, patients with a known hypersensitivity to PC polymer or its individual components, described elsewhere" , and then there's some statements about in general, when coronary stenting is contraindicated. There's not a consensus here?

DR. KATO: I just want to bring up the fact that the, you know, again, and I'm taking this out of the sponsor's submission, that the general exclusion criteria name no less than 21 major points, and there's actually 4 -- A-B-C-D -- subsets of 1 point, which makes it 4 plus 21 or about 25.

DR. ZUCKERMAN: Dr. Kato, if I could just interrupt here a moment. You know, again, I think Dr. Somberg summarized the situation well. For clinical trials, there's always attention between inclusion/exclusion criteria. You need to make the trial reasonably homogeneous such that at the end of the day, you can interpret the trial. Again, going back to our regulatory hat, contraindications are statements that need to be taken extremely seriously.

From a clinician's viewpoint, if you were to do something that stated, as a contraindication, you should think that a lawyer should take you to court and you should be sued over it and lose the case, that's how strong the contraindication -- that's the implication of a contraindication statement.

CHAIR YANCY: That's pretty sobering.

DR. KATO: I'm sure we'll be hearing from attorneys today after that statement.

DR. HOPKINS: Do you think we should ever lose the case. I mean come on.

DR. KATO: So let me just --

DR. HOPKINS: Yes, please.

DR. KATO: Since I came on so strongly about Question A, I will say I have no problem with Question B, contraindications.

CHAIR YANCY: And with the language of -- oh, please.

MS. RUE: I just wanted to ask -- there was a lot of discussion about the anticlotting drugs. Is that something that needs to be in the contraindication that if they can't be on that medicine?

CHAIR YANCY: It is a good point, but I think that's dealt with elsewhere.

MS. RUE: Okay. Thank you.

DR. KATO: Getting back to the contraindications, one thing the sponsor did mention during the presentations today was the mixing of different types of drug-eluting stents. And again, I don't know how important that really is, but -- and again, I would have to defer back to the basic science. And again, I don't remember if there were any interactions between the drug-eluting stents, whether that's been tested, but if that is of concern from the sponsor, then we should definitely add that.

DR. ZUCKERMAN: Yes. And it's section 5.3. When we get to the warning/ precautions, you'll be able to comment.

CHAIR YANCY: I think Dr. Zuckerman's point is a contraindication, is something where you found from the study that it's just really reprehensible. A warning is we don't know and there's so many things, and that's why it's warned. And I mean I'm the one who's been talking about mixing stents. But it really shouldn't be a contraindication, because in all probability, it may not be a problem. But if something --

CHAIR YANCY: Just to complete the thought, Ms. Rue, the statement about not being able to tolerate antiplatelet therapy is one of the included statements. So getting back to this question for 5.b, are we comfortable, the body of the panel, that this is acceptable as listed? Dr. Zuckerman, are you good with that?

DR. ZUCKERMAN: Yes.

CHAIR YANCY: Okay. Elizabeth?

MS. HILLEBRENNER: Please comment on the

warning/precautions section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

CHAIR YANCY: And so now we're looking at sections 4.0 and 5.0 and under 5.0, there are 9 specific entries that deal with general precautions, antiplatelet therapy, use of multiple stents, brachytherapy, pregnancy lactation, gender, ethnicity, pediatrics, geriatrics, vessel characteristics, drug interactions, and MRI. Any comments?

DR. SOMBERG: It looks acceptable.

CHAIR YANCY: One person has said it looks acceptable.

DR. KATO: I concur.

CHAIR YANCY: Two, three, four.

DR. WEINBERGER: I have a small comment.

CHAIR YANCY: Please?

DR. WEINBERGER: Under lesion characteristics, this statement is made, "The safety and effectiveness of the Endeavor have not yet been established", and then gives a long list of things. I would strike the word "yet". When it's established,

it'll be established. I'm not sure it's going to be studied in thrombus or calcification or whatever. So when it's established, they can put it in.

CHAIR YANCY: Point well made. David, was that an Alabama yes? Did I see that?

DR. NAFTEL: Yes.

CHAIR YANCY: Okay. All right. Will you accept that we are good with the one precaution section, Dr. Zuckerman?

DR. LINCOFF: I just have a small point as well.

CHAIR YANCY: Yes, please?

DR. LINCOFF: I had noticed in the patient guide, there was a comment that you may want to talk to your physician about antibiotics if you're going to have dental work, yet there's nothing in the package, at least that I could find, about antibiotic prophylaxis. And I don't know if this would be the place to do it if we even wanted to do it -- I'm aware of any data -- but I just wonder if there should be -- if you're going to suggest that patients contact their doctor, should we provide some guidance to the doctor on that topic?

CHAIR YANCY: Certainly the language that we suggested for antiplatelet therapy prompts the discussions about discontinuation for dental procedures. But I know you're talking about antibiotics, but we've already provided the entree for that sort of thing to happen, so I think it's a point well made.

DR. SOMBERG: I have a question. Is there any data at all that suggests -- I mean I didn't catch that in the -- I didn't read the patient -- I must say -- but there's really no data on that point whatsoever. And from my understanding of infectious disease, they're very low to expand the things you use prophylactic antibiotics for.

So I think, unless there's data or anything suggesting that, and we should ask the sponsor, that -- you know, if it's just something a lawyer added in, because it's -- that's just afterthought -- it should be omitted.

Is that a legal thing or is that based on some sort of idea? Can I ask the sponsor, Mr. Chairman?

CHAIR YANCY: Absolutely.

DR. SOMBERG: Okay. I mean it's your --

MR. SALMON: Thank you for the question. We just adopted standard language. We are unaware of any empirical evidence to support that statement.

CHAIR YANCY: The other thing is that I don't if there's language in the label for clopidogrel that prompts a discussion about the interaction of clopidogrel with antibiotics. Are you aware of that, Michael? I don't know. Because that would be another place it would be captured if someone's already on at least antiplatelet therapy. There's a separate question about zotarolimus obviously. Okay.

Any strong feelings about suggesting that the antibiotic issue be captured, or is this something to be dealt with at a later time, because we won't address all the issues right now, and there certainly will be things that will need a little bit of homework. Later is acceptable. Okay. Dr. Zuckerman, are you good with that?

DR. ZUCKERMAN: Yes.

CHAIR YANCY: Okay. Great.

UNIDENTIFIED SPEAKER: Homework to whom?

CHAIR YANCY: Not the panel.

DR. ZUCKERMAN: The FDA and sponsor to see if there's any rationale for including a notation about antibiotics in the IFU for the Endeavor stent and that can be simply handled offline.

CHAIR YANCY: Thank you. Elizabeth, 5.d?

MS. HILLEBRENNER: Please comment on the operator's instructions as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

CHAIR YANCY: Any comments from our interventionalists? Yes?

DR. LINCOFF: On page 41 of this binder, it's section 12.7, removal procedures, which I assume falls under that, it says -- the last thing it says, "Observation of patient angiographic evaluation --

CHAIR YANCY: Dr. Lincoff, I'm sorry, which binder?

DR. LINCOFF: It's -- well, it's the first binder, so it's any one of the -- there's three different examples of the information, so it's section 12.7. I can just read it.

CHAIR YANCY: Under which tab?

DR. LINCOFF: Under attachment 9.a, IFU over-the-wire. It's page 41 of 44.

CHAIR YANCY: Proceed.

DR. LINCOFF: Okay. The key is it recommends fibrinolytic therapy of thrombus is formed. Now my understanding of the literature, what there is of the use of intracoronary thrombolytic therapy in the presence of thrombus, has never shown a benefit of any kind. And given that there are other agents that there seems to be more suggestive data -- I'm not suggesting that other agents be recommended, but I think this is antiquated.

I don't know if the other information packets for other stents have it, but I think may be irrelevant since we can evaluate on their own, so I'm not sure what the basis of recommending fibrinolytic therapy. It's not even -- it doesn't even say it can be considered. It says it's recommended and I would propose that that's too strong. The statement should be deleted entirely.

CHAIR YANCY: Other comments? Dr. Hirshfeld?

DR. HIRSHFELD: I'd just to like to ask the sponsor -- there are statements in the about handling in

the description that imply it's possible to damage the coating either by getting the stent wet or by touching the stent, and these are more -- stronger statements than exist in the other marketed drug-eluting stent IFUs. And I wonder whether this coating is more fragile than in the TAXUS and the CYPHER stents or -- and is this something that interventionalists really need to be warned about actively or whether this is just being very cautious in your labeling?

MR. SALMON: I really cannot comment on the other devices that are available. We have adopted language we felt was appropriate to ensure that the device would be adequately handled, and that language was consistent throughout the clinical trials as well and the instructions for use for the clinical trials.

CHAIR YANCY: Any other comments in this area? So is there a general sense that the operator instructions are reasonable and that there may be some offline work, but we are reasonably content with this? I think there's a consensus, Dr. Zuckerman?

DR. ZUCKERMAN: Good.

CHAIR YANCY: 5.e, please, Elizabeth.

MS. HILLEBRENNER: Given the information on the drug substance proposed for inclusion in the labeling, please comment on whether modifications are needed or whether any additional information should be added to the labeling to maximize benefits and minimize adverse events.

CHAIR YANCY: There is a drug component description under tab 9, page 97, starting at 1.2 with several subheadings. It's fairly detailed. My own sense is that this is something else that can be worked out in a more deliberative way unless there's some strong opinions about something that doesn't appear here. With that having been said and Dr. Zuckerman nodding approval, let's go to 5f.

MS. HILLEBRENNER: Please comment on the remainder of the labeling as to whether it adequately describes how the device should be used to minimize benefits and minimize adverse events.

CHAIR YANCY: Let me ask FDA for a point of clarification -- "the remainder of the labeling?" Just tell me where to look.

MS. HILLEBRENNER: Any sections of the

labeling that we have not yet already discussed, if you have any --

CHAIR YANCY: I have three volumes.

DR. ZUCKERMAN: Just the big ticket items in the IFU. Is there something that we're missing. We've been pretty deliberate in going through the IFU, but if anyone has any last minute suggestions.

CHAIR YANCY: So that's a great way to truncate that question. So did we miss anything major? I'm looking around the table once. We didn't.

So what we need to do before we have a break is to go forward with out second open public hearing. Elizabeth, thank you very much for moderating that discussion.

Seriously, if there are any other comments, because this is an important part. This was our opportunity to address the FDA questions and this information will be used in a very real way to modify any language that might go forward depending on our decision.

DR. ZUCKERMAN: Dr. Yancy, I think we forgot question 6 which is on the back.

CHAIR YANCY: So a point of clarification and a mistake on the Chair's part. There is a question 6. Dr. Morrison?

DR. MORRISON: Well, I'm just wondering where all of this stuff in the labeling about the impact of magnetic resonance imaging came from. I wasn't aware of the data to support all this. It follows immediately after the -- on tab 9, page 9 of 44.

DR. ZUCKERMAN: Okay. That's a standard part of the pre-clinical review, and we're very confident that those data are correct. Do you need a FDA reviewer to give you further explanation of why it's written that way?

DR. MORRISON: No. I don't need an FDA reviewer to go through all that. I was just unaware of data showing that there's ever been a problem with the patient getting an MRI after a stent, drug-eluting or bare-metal. And so this incredible detail implies that there's all sorts of data and information and I was expressing surprise.

CHAIR YANCY: Point duly noted. Elizabeth, let's go ahead and do question 6, please? So we can

hold 6. Okay. So we would like --

DR. ZUCKERMAN: Can we just take a time out for 30 seconds? Okay. So Ms. Wood has informed us that the procedure is to go to question 6 now, realizing, again, that we've taken no formal vote, and this is a hypothetical planning situation.

MS. HILLEBRENNER: Okay. The post-market study has been designed to identify rates of stent thrombosis through five years; assess rates of cardiac death and MI to confirm long-term safety of the Endeavor stents 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 stents in clinical practice.

The first question is are the objectives identified above appropriate and should additional objectives be considered?

CHAIR YANCY: We've had some discussion earlier today about post-market issues. Dr. Somberg?

DR. SOMBERG: Yes. That's my feeling. Yes.
And I wish we had that --

CHAIR YANCY: That's a great answer.

DR. SOMBERG: I wish we had the data now.
I'm sorry I can't stick to just yes.

CHAIR YANCY: Other comments about this 6a?
Are the objectives identified above appropriate? Should
additional objectives be considered -- identify rates of
stent thrombosis through five years; assess rates of
cardiac death and MI to confirm long-term safety;
evaluate the use of the Endeavor stent for potential
safety signals? Remember again that the post-market
studies are not to determine efficacy. We have to make
that decision based on what we have. Dr. Lincoff?

DR. LINCOFF: That having been said, I think
for the randomized trial, again, CYPHER, it should be a
key secondary endpoint to assess target vessel
revascularization rates. I recognize that that won't
influence the issue of approval because we've discussed
the -- you know, we had evidence of effectiveness. But
on the other hand, to allow the medical community to
make a decision regarding the relative choice in certain

patient subsets, that information should be available. Because of the randomized trial design, that's possible to obtain.

But if it's not prospectively defined -- and I saw it was this a -- an endpoint. But we all know how, you know, very minor endpoints are less carefully adjudicated or taken -- or acquired -- or ascertained than our the key secondary endpoints. So I would encourage that to be a key secondary endpoint is revascularization rates.

CHAIR YANCY: My understanding is that with regards to post-market surveillance study, that would have to be started after the fact, after approval, if approval occurs. And so if indeed PROTECT is already ongoing, comments well-made from another recognized figure in the field, but I don't know that this panel can influence an already established trial. But going forward with a post-market study, point would be well made. Usually, that's a single-arm experience as well. Dr. Hirshfeld was next.

DR. HIRSHFELD: I'd just like to comment that I think that these two planned studies also represent an

unparalleled opportunity to define the variables that are associated with late stent thrombosis. And I hope that the data collection is going to collect all the baseline variables that we will want to know about their association with late stent thrombosis. It's a matter of how much effort the sponsor wants to invest in gathering baseline data, but I hope they will gather a lot.

CHAIR YANCY: No. And I would strongly encourage the sponsor to heed what Dr. Lincoff said with regards to revascularization and what Dr. Hirshfeld just said as well, because this should be more than about registration. It should be about moving the field forward. So I appreciate both comments. Dr. Naftel?

DR. NAFTEL: This is maybe a question for FDA, because I'm a little unclear with post approval studies in general. I read through the whole study and it sounds very good, and there are some precise comparisons with expected thrombosis rates. But my question is will there actually be a point in time where the study will be examined and a decision would be made to unapprove? And this has nothing to do with

Medtronic. This is an in general question.

DR. ZUCKERMAN: Yes, and those are great questions, and this is exactly the reason why this system has been such that we spend a lot of time now talking about a hypothetical post-approval plan rather than after the vote so that people understand what we're dealing with. And while I make a few comments, I'm also going to ask Dr. Duggirala from our EPI Department to also be ready with a few slides. But I think the discussion today has been a rich one, and we want to make sure that in any design post approval study, we're really asking the right questions.

And although Dr. Lincoff's comment was interesting regarding PROTECT, and we'd like to know about a TVR rated, the first question the agency would have based on today's discussion is help us develop a post-market study such that we can identify rates of stent thrombosis through 5 years using appropriate pharmacology.

And the reason why I put in that addendum, and I'll ask Dr. Lincoff and others, is that we heard that the PROTECT study has pharmacology to 3 months.

And that may be great for European practice, but are those results going to be extrapolatable to the to the U.S. practice to answer Dr. Somberg's key question. And so if Dr. Somberg and Dr. Lincoff can try to develop these ideas, I think that would be issue number one -- what is our principle objective and how do we incorporate an appropriate pharmacology here such that we can meet that objective.

CHAIR YANCY: They're not ready to show.

DR. ZUCKERMAN: Okay. The -- if you'd like, our EPI staff can show you the design again of PROTECT and the U.S. post-approval registry. But a key point, again, is that we have differing durations of pharmacologic therapy, and this is an issue, to predict stent thrombosis.

CHAIR YANCY: Dr. Somberg?

DR. SOMBERG: You know, it's not that Yancy made a very valid point here that if the study is initiated already, it's going to be very hard to, at least for that part of it, to do that. And I wanted to also raise when we were discussing before is that, no, it does not answer the question of what is optimum

pharmacologic therapy. And I'm not even sure whether it will capture whether these patients are -- you know, it's the detail, are the answers in the details, and how you ask the question is very important.

So I'm not sure whether it's going to capture whether they're on dual antiplatelet therapy, whether they were compliant, whether they stopped it, they started it. There -- it will someone's saying -- Dr. Boam is saying, so. I mean even if it does, I think they're going to be -- there's going to be a need for a study that looks at different durations of antiplatelet therapy for -- and you can't look at all durations, but you have to look at some wide differences and look at outcome. And the trouble is I'm not sure one sponsor can really address that.

CHAIR YANCY: So I think what Dr. Zuckerman is really saying is that in addition to PROTECT, there is another 2,000-patient study that has been proposed as a post-marketing study, and the input they want from us is how should the pharmacology be constructed and are there any other thoughts about that particular study that can be given to the sponsor from this panel.

DR. LINCOFF: But the other study that's being proposed, is a non-randomized registry. I mean you can't study the pharmacology if you don't do it randomized,