long-term, unless that's the thing you're particularly studying. Do I have that right?

That's very important to us.

DR. BURMAN: Well, I think there matched for the non-glycemic effects.

DR. TEMPLE: What about glycemic effects? Are you going to leave somebody undertreated glycemically for five years?

DR. BURMAN: No, that's why the question was raised about how you treat those patients with hypoglycemic, then it does modify the paradigm, of course, and makes it more difficult to determine as long-term events, but it is unethical not to treat them.

DR. KONSTAM: You know, I wouldn't say I quite agree with what you just said. First of all, let talk about the non-glycemic things for a second.

I mean, if you have a drug that, for example, lowers -- also by the way, lowers LDL cholesterol, okay? And you don't -- do not in the protocol prescribe

that LDL cholesterol needs to me measured every month and statins suggest that accordingly, and we're going to tell you exactly how to do it.

Unless you go over and above the usual to do those things, you will wind up with LDL cholesterols in the two arms, okay? And I'm fine with that, okay, because when we're looking from the perspective of examining the clinical effects of the drug because as you -- I think what you're referring to -- I mean, I don't think that I don't think we should be specifically asking companies to explore the off target effects. I think we need to look at the integrated clinical effects and so I don't think I would go above and beyond the call of duty to match the other things prospectively, more than just go ahead and take good care of the patient myself.

As far as the glycemic control, yeah, I mean, in the long-term you're not

going to let people be significantly hypoglycemic and I just love people who do this every day to comment on it, but again, you could have -- I mean, if the HbA1c target is 7 -- I think you write that into the protocol, but you might not necessarily clobber the investigators with it.

So that you -- I don't know. I mean, if a drug for example, facilitated against hypoglycemia by some magical way, I suspect you're going to wind up with better glycemic control in that group and that would be okay. So I'm not -- I mean, I think we're looking at drug effect, not necessarily mechanism effect.

DR. TEMPLE: Okay, but you'd be telling them what target to go for. If what you said is true, if one of them is better tolerated, or something, you might do better.

DR. KONSTAM: I think that there's a difference between writing in the protocol. Investigators are reminded that that the

guideline recommends HbA1c of 7. And on one extreme -- and on the other extreme saying, you're going to measure HbA1c every two weeks and you are going to follow the following protocol in every patient, in order to drive it down to that point.

I think those are the two extremes and I'd love other people's opinion. I mean, I would generally lean toward the first side -- of making sure that people are good investigators, good clinicians, following guideline practices and then let chips fall where they may. That would be my approach.

In a protocol designed to examine the drug, is a whole other story because we've got to do studies to understand the, you know --

DR. TEMPLE: This all has a lot to do with whether the goal is principally -- or to show a benefit or to show harm. The harm's you're worried about are mostly off-target kinds. That's what we think might have

happened. So if that's what you're interested in, you'd really try to match up everything. But maybe if you want to show a benefit, maybe you wouldn't.

DR. KONSTAM: But if you wind up with a drug that facilitates better glycemic control, under normal use conditions and that contributes to a net acceptable safety level or maybe even better than that, what's wrong with that?

DR. TEMPLE: No, that's okay, but you'd still be trying for the same thing? That's what I'm asking.

DR. BURMAN: Okay, thank you very much. I think we should move on, unless there anybody -- any other comment?

DR. FLEMING: There is. Can I comment on this?

DR. BURMAN: Oh, sure.

DR. FLEMING: Yes. The response that I was giving earlier on to this issue I think in spirit is very close to what Marv has been trying to say. My sense is the optimal design

here, the comparator arm is agent Y plus standard of care. We're replacing Y with X. X plus standard of care.

I want to find out in the real world setting, based on totality of mechanisms here -- what is, in this particular case, what is the relative safety profile, relative to cardiovascular risk? I want a real world answer. So as Marv says, the overall totality of the effect of this intervention can be mediated through intended and untended mechanisms, some of which could be on these risk factors. Some of which are on other factors and unrecognized.

Well, to the extent that's unrecognized risk factors, then we should be treating two current guidelines, but not in an extraordinary, nonstandard way. But according to what would be responsible clinical management. And if that responsible clinical management still leaves some incremental difference on those risk factors,

that's part of what's inherently an effect of that experimental arm. I don't want to factor that out.

So I want a responsible management according to clinical guidelines for those risk factors, but I don't want to do something extraordinary or artificial, which I think in spirit is what Marv's saying.

DR. BURMAN: Thank you. I think we better move on. I think Marv was asking, and I think the consensus was to go over the other parts of the question and just see what the consensus is, so we can advice FDA. And as I mentioned, we're going to skip over the potential hazard ratio and come back to that in a minute.

I think and hope that the other questions seem to have more consensus. So specifically, what should the primary endpoints be? And I think virtually everyone agreed they should be hard endpoints, including a composite, but with specific

attention to the individual components of the composite, certainly not just the composite without consideration of the individual endpoints.

Is there any discussion or arguments there?

Okay, Dr. Genuth?

DR. GENUTH: I don't have an argument. And those should be the hard endpoints. But I wanted to address that in combination with the later question of who are the proper patients to enroll in this kind of a trial? And the point was made several times that if we enroll patients late in their course, that's good because we'll have more events. And so we'll have better power with fewer subjects, less cost.

If we enroll participants early on, say after diagnosis of diabetes as in the UKPDS, or even before that point in so called pre-diabetes, we'll be intervening earlier, which might be more beneficial, but we'll

have fewer events and it will take us a long time to get an answer.

I think that issue should be looked at a little bit differently. I think we should look to the biology that was learned during animal experiments in drug development and we should design a trial with as much information as possible on whether we think the drug is more likely to influence atherosclerosis, and the slow development of risk? Or whether the drug is more likely to influence events because of thrombosis, plaque ulceration, et cetera.

If we think the drug is going to have a benefit or a risk, is going to be working on thrombosis, fibrinolysis, plaque ulceration, then we should do the trial in people at high-risk for those events. People who've already had an event, or have many risk factors.

But if we think a drug is likely either to be beneficial or noxious because it

effects the atherosclerosis process, then we have to bite the bullet of recruiting patients much earlier in their disease and accepting the fact that it's going to take longer to get an answer. But we're more likely to get a biologically believable answer.

DR. BURMAN: Thank you and, if you will, those are very cogent comments.

And what I'd like to do is just hold those comments for the group for a second, because I think the next question before the one on which population -- which you just addressed -- is the size and duration of these trials. And I think there was consensus they should be long-term trials of five years or so. And I think Tom is going to give us some more information on that shortly.

Yes?

DR. FRADKIN: It just occurs to me that in discussing the duration, maybe we didn't

explicitly address that the duration that you would want, which would be, say, five years for a cardiovascular endpoint. If we're trying to do this at the same time that people are also demonstrating the efficacy in terms of glycemia, those two durations may not really meld. I mean, often glycemic efficacy is shown in a shorter duration trial and the way the study might be designed -- it might be, for example, if you have a comparator that you would have the time and total insulin was needed, or something.

So it might not be that you'd need the full five years for the glycemic efficacy to be established and maybe we should just explicitly say that.

DR. BURMAN: Agreed. And thank you for doing that. Any other comments on the duration? The size, I think Tom is going to talk about a little bit, to see if there's some consensus there.

And now, what type of population? Dr. Genuth already had some nice comments. I

open that up for discussion, yes?

DR. HOLMBOE: Yeah, I was going to say that I agree with you, so I think the question becomes, though, is that something that necessary for regulatory approval? Or is that something that -- you know, NVLHI or NVDAK -- you know, the NIH organizations would take on? I mean, I'm not sure that population would have a very long lag time.

It would be necessary from a regulatory point of view to -- clearly from a scientific point of view -- those are really important questions and they need to be answered. I'm just not quite sure where that sits in our current kind of paradigm?

DR. BURMAN: Any other comments on that issue?

Dr. Genuth?

DR. GENUTH: Yeah, I'd like to make one other point about which populations we should study. We've been assuming, I think, that we only will accept hard outcomes. And

that's a reasonable position to take, but I think at least it's worth pointing out that if we think atherosclerosis is what we are trying to intervene on, then measurement of carotid artery intermedial thickness or measurement now more recently proven of coronary artery calcium are pretty good surrogates for events, particularly carotid intermedial thickness.

I think it's been pretty well-demonstrated to predict higher event rates. So it might be that the agency should consider accepting trial evidence on those grounds for either harm or benefit for atherosclerosis. And those trials are shorter: Generally within three or four years you can see progression of either of those two parameters.

DR. BURMAN: Thank you. My understanding is, at the moment, no cardiac surrogate is accepted. And that's a whole separate topic and I just -- if the FDS wanted to respond -- and to listen, if they go with my

comments, that's fine. Sure?

DR. GENUTH: I just didn't want everybody to make their flights.

DR. PARKS: I was just going to confirm that, indeed, no drugs have been approved based on that surrogate, but if the cardiac imaging is done.

DR. BURMAN: Thank you. Oh, I'm sorry, Dr. Savage?

DR. SAVAGE: I just wanted to make a quick comment on the same issue. I think one of the problems with diabetes is it's a diffuse metabolic disease. It has effects on coagulation factors, there are components of it, like hypoglycemia, that can trigger arrhythmias and so forth. And therefore, a strictly atherosclerotic endpoint, runs the risk of missing something that might be particularly important in at least some subgroup of the diabetic population. So I don't know the answer to the question, but I think that needs to be kept in mind. We don't understand enough about

the mechanisms by which diabetes causes cardiovascular events to be able to choose a surrogate endpoint with real confidence, at the present time.

DR. BURMAN: Thank you.

And let me -- we're trying to get a consensus here and I'd say the consensus, which may not be total consensus, is studies should include diabetics -- these studies we're talking about. And probably, mostly, diabetics with pre-existing cardiovascular disease for these type of trials. Anyone strongly disagree with that for this particular group?

Then I'd like to go through the other questions, hopefully quickly, and then get to Tom before we then get to the voting question. There wasn't much controversy on -- and there was a consensus it seems that we should use drug plus comparator. And how exactly that is performed, whether it's not drug versus placebo, but drug versus

comparator, even though it has potential difficulties, that seems to be what everyone recommended, or at least most people recommended. Any discussion? Okay, good.

How should deteriorating glycemic control be handled -- defined and handled? We really didn't talk about the definition. That could be discussed in a different forum, but it has to be handled, everyone agrees, from a clinical standpoint. And it's a confounder that the statisticians emphasize, but it's something that we have to do in real-life studies. Further?

Dr. Genuth?

DR. GENUTH: I thought there was a little confusion in the previous discussion that went back and forth about that, on the other side of the room.

I think two different objectives were being a little bit confused. One objective to make HbA1c level equal in two groups, which then puts you completely in the

off-target zone of looking for benefit or risk with a different objective, which is not to allow any participant in the trial to be at -- continuously above some ethically acceptable level that exposes them to microvascular risk, for sure. And those are a little different.

So I think it's more important to the second question, that we agree on in any trial, the level above which we will not consciously permit a participant to remain. At least we will make our best effort to bring them down. And that can either be by a protocol prescribed recipe or it could be left up to the investigator how. But the critical point would be to bring them below some unacceptable upper level.

DR. BURMAN: Agreed. Thank you for the clarification. Any comments on that?

DR. BERSOT: What I heard in the previous discussion is, you'd tell them what the American Diabetes Association goals are, but you

wouldn't overdo it. You wouldn't tell them they've got to measure every two minutes, and stuff like that. So it's a blend of what you're talking about. It's partly a goal towards where we were supposed to get and probably, also some escape value, too. But not just totally leave them alone, but maybe I didn't hear that right?

DR. BURMAN: I think that's my understanding. Good, thank you for the clarification for both of you.

And the last question, there shouldn't be any disagreement on. It seemed like everyone agreed there should be encouragement to manage all of the other parameters to goal in these patients.

So what I'd like to --

DR. KONSTAM: I'm sorry, but, again, I would say it the same way Bob just said it vis-a-vis glycemic control.

DR. BURMAN: Yeah, this question, as I read it, is looking for control of other parameters.

DR. KONSTAM: No, I understand. But, again, I wouldn't overdo it. I wouldn't be, you know -- I mean, I would be trying to assure that clinicians are generally following practice guidelines and are aware of it. But, again, if the drug has a favorable effect on LDL cholesterol, it will show up. Unless you go crazy trying to keep it from showing up. And I'd be fine with that if that's contributing to the effect.

DR. BURMAN: Thank you.

It's 2:30, and for the next 15 minutes, before we get to Question No. 3 and the vote, Tom, I think you were kind enough to respond to Dr. Rosen and some of our other questions regarding specific parameters. And really, regarding the question -- the second subtext of Question No. 2; hazard ratios.

His slide should be coming up in a minute.

Yes, Tom, thank you for preparing this on short notice.

DR. FLEMING: Sure. So in response to the request, I did the best I could over the lunch hour to try to distill some of the essence of the illustration that I had provided in responding to the question about how big the trials might be. And so here is an illustration of what size trials might be done for a confirmatory trial for cardiovascular safety and a screening trial. And the assumption under which this is based is suppose that we're looking at a population with a 2 percent per year rate of the composite endpoint that we've been talking about: cardiovascular death, stroke, and MI.

So in the confirmatory safety trial, for illustration, suppose it's determined that we need to rule out a one-third increase, or we need to rule out a 50 percent increase. And certainly, what that increase would be is specific to a lot of issues that we have been talking about. What is the level of benefit that you would

be expecting with this intervention, other domains, for example, microvascular domains.

To give some sense about how this plays out, as a number of my colleagues said, it's not just relative risk, what's the overall absolute impact. And of course, that depends on what the event rate is. But if the event rate is 2 percent per year, or 20 per 1,000, a one-third increase would be in excess of about 6 or 7 events per 1,000 person years. A 50 percent increase would be saying you're okay up to, but not beyond, 10 excess events.

And as I was mentioning, in the precision trial, in rheumatoid arthritis and in osteoarthritis, the bar was set at 1.33 and a 1 percent per year because that translated to three excess events.

But, here, it's logical that some additional excess could be allowed because of the microvascular benefits. But this is an issue taking into account these kinds of

considerations that need to be done on a study-specific basis based on how impressive the evidence is for this particular agent in terms of its efficacy.

So under this context, suppose that you were, let's say, using the 33 percent increase. You're trying to discern the difference between no increase and a 33 percent increase, in a setting where -- I'll make the assumption here, where you want to have 90 percent power i.e., if, in fact, there's no increase, you want to have 90 percent chance of coming out with a positive result. But you want to have a low false positive. If there really is an increase, traditionally, if it's 2.5 percent false positive conclusion of being safe when you're not.

If that's the case, it takes 508 events. And that would take, if we -- and most of us have said, look at something along the lines of a five-year trial. If it is a

five-year trial and you have a 2 percent per year event rate, that would be a sample size of 5,000, or 2,500 per arm.

Now, in contrast, if it was acceptable to rule out a 50 percent increase, because you're saying it's okay to have up to 10 excess cardiovascular deaths, strokes, and MI per 1,000 person years, then it would take only 256 events, or 2,500 people followed for five years.

The critical value, what we as statisticians call the value at which success occurs, would be if the excess can't be more than about 12 to 15 -- 12 to 17 percent, which would be an estimated three excess events per 1,000 person years. And if the rates are less than this, that would be a success. If the rates are higher than this, then that would be problematic in terms of not having ruled out a 3three- to five-0 percent increase.

Now, if in fact we decide this has

to be done, but we would argue that doing this entirely pre-marketing, unless you had a signal, unless the FDA has already said -- if there's a signal, then -- or clear signal -- then they would require pre-marketing. But if one wanted to take a measured step in a pre-marketing setting as a screening trial, following the example that Steve Nissen had indicated, if, for example, you were to use a 125- event trial in the screening trial -- and 125 events, technically speaking, is sufficient to discern the difference between no increase and an 80 percent increase.

Now, an 80 percent increase probably isn't the smallest excess that would be at clinically acceptable. But that's formally what you're able to rule out, is an 80 percent increase, when you see a 25 or 26 percent increase.

The appeal to this, from my perspective, is it's not only able to

rigorously rule out an 80 percent increase, it's able to screen out a 50 percent increase, meaning that if the agent truly was unacceptably giving a 50 percent increase in cardiovascular death, stroke, and MI, you'd only have about one chance in seven of seeing a result as favorable as a 25 percent increase or less.

So in essence, if you were to use this criterion of 125 events, and needing to see no more than about a 25, 26 percent increase, then that has the property that you can be comfortable that this agent doesn't have an 80 percent increase, and reasonably comfortable it doesn't have a 50 percent increase. That's essentially where you would be.

This would be a trial that would take 2-1/2 years -- let's say it would take 2-1/2 years.

Then that would take 2,500 people, or 1,250 treated people. To contrast that

with what the Agency has said, now they would require 1,500 treated people for at least a year, this would be 1,250 treated for 2-1/2 years. So the most tangible difference here is that you're needing to go 2-1/2 years, not a year. But for many reasons that have been laid out, there are very substantial -- not just getting more events, it's getting a better sense about at least a more intermediate timeframe. But it's not five years. That's the advantage of doing this as a screening trial.

Now, Dr. Temple has raised a valid point. The world isn't dichotomous. If this estimate is more than a 25 percent increase, it's problematic. But if it's less than 25 -- what if it's actually favorable? If the point estimate is a 30 percent decrease, you have superiority. Even though it's in fact a smaller screening trial, you have a claim, or at least you have evidence, the FDA can judge whether it's persuasive, but you

have statistically significant evidence of a favorable effect on this. If, however, you're just better than neutral, a 5 percent estimated decrease, then you're actually able to rule out a one-third increase. So this 25 percent increase doesn't conclusively rule out a one-third increase, it just rules out an 80 percent increase. It's allowing you to go on. But if the results are much better than a 25 percent increase, if you have a 5 percent decrease, it's, from my perspective, a very reasonable consideration that that might be enough, without, therefore, needing -- you haven't proven superiority, but you've ruled out a one-third increase.

So there's a continuum here. If it's a percent reduction or better, it's superiority.

If it's a 5 percent reduction or better, it's ruling out a one-third increase. And then if it's between 25 percent and the

26 percent worse, you're going on, but you certainly would need the confirmatory trial.

And then, the worse case scenario is if it's greater than 25 percent.

DR. BURMAN: Thank you, Tom. And I think we have a -- very nice of you to do that on short notice. And to me that clarified and put more objectively a lot of the information. Thank you for doing that.

We do have a couple minutes for discussion. Dr. Temple?

DR. TEMPLE: Well, it doesn't really address what I asked before, which is, suppose you decide, in your wisdom as a company, I want to do 1,250 people. Okay? I don't want to do 2,500 for three years, or whatever it is. I want to do 1,250 and I think I can do it in a year and a half. I now get a point estimate of 1.1, which nicely -- I'm just guessing -- nicely rules out the 1.8 I was looking for. That may not get you out of the task of doing the follow-on study, but maybe that's not their

goal. Maybe their goal is to get in the marketplace.

DR. FLEMING: Fair point, Bob. So let me expand on this to say, suppose you take the approach of saying, I'm only going to put in a total of 1,250 people. And with 1,250 people instead of 2,500 people, my standard error is about 40 percent higher. But, I can still win. I can still win by ruling out an 80 percent increase, but not by seeing a 25 percent increase by estimate, but by seeing a 5 or 10 percent increase.

The price that I'm paying for that is, with this approach, if you truly have no excess, then you have a 90 percent chance of getting -- of going on; i.e., the worst mistake in a screening trial is to declare that you're unacceptable when you are acceptable. Okay, in a screening trial. And this particular design has the property that if you truly have no excess, you've got a 90 percent chance you're protected to see a

result that's acceptable.

If you take the 1,250-person trial, you're right: You can still win. But winning, now, is a 1.05. Now, you have about a 60 percent chance of winning.

DR. TEMPLE: But someone might --

DR. FLEMING: I'm not going to --

DR. TEMPLE: Someone might choose that approach, even if it's --

DR. FLEMING: You could.

DR. TEMPLE: Not the smartest thing to do.

DR. FLEMING: You could, if you're a gambler and you're willing to take a 50/50, 60/40 shot of passing this screen when you're truly safe.

DR. BURMAN: We have a few other questions. Yes, please.

DR. PROSCHAN: Yes, I mean, still, the idea that ruling out an 80 percent harm is somehow a great thing to do, I think is not right.

So you know, if you have -- so I think you ought to couch it in terms of letting go a little bit on the confidence level and ruling out a more reasonable harm. So a small trial ruling out an 80 percent harm would not be convincing, at all, to me.

DR. FLEMING: And I would agree. It's why when Steve put this forward with the 1.8, that's essentially looking at preserving a 2.5 percent false positive error rate, here. And my sense is, as a screening trial, the real way that I look at this trial isn't this column, it's right here. It's saying, if you would argue that a 50 percent rate is, in fact, the limit, then this trial has the property that if you truly had a 50 percent excess rate, the probability that you would see a 26 percent excess rate here is sufficiently low; i.e., what you're saying here is that I'm going to go on with a 26 percent rate. And yes, that would be incredibly unlikely, 2.5 percent chance if it was 1.8, but it's still only one in seven if

it's 1.5. So if you're willing to say that a 1.5 is that smallest excess -- and I agree, 1.8 doesn't make sense to me, but 1.5 could -- then the reassurance here is, for those agents that would have a 50 percent increase, 6 out of 7 are not going to pass this screen.

So it's not perfect. If you want perfect, you have to do the entire, fully powered trial in a pre-marketing study. But at least this way, we're getting rid of 6 of 7 agents; we're not going on without more data for 6 of 7 agents that truly have a 50 percent increase.

DR. BURMAN: Thank you. Please.

DR. JENKINS: Just one point of clarification and a question for Dr. Fleming.

It's important for the Committee and others to note that the screening trial that you're proposing is 2-1/2 years of controlled, randomized assignment. And that's very different from the safety databases that Dr. Joffe presented to you

earlier, where he showed that we ask for 1,300 to 1,500 to be exposed to drug for more than a year. Most of those exposures are going to be open label or extension exposures. They're not going to be randomized, where you have a control group to look at. He also said we ask for 3- to 500 exposed for greater than 18 months. Again, those are open label, not randomized.

So the screening proposal here would provide a lot more patient years of exposure in a randomized, controlled setting, which would be on top of, probably, the Phase 2, Phase 3 exposure that we already get, where you're demonstrating benefit.

So it is an addition, and it's a very different dataset than what we normally get. So. Not a criticism, just to clarify.

DR. FLEMING: Right. It's a very key and accurate clarification. So it is different from status quo in that, as I was mentioning, you're getting a lot more experience beyond six

months; you're getting it out to 2-1/2 years. But you're absolutely right, John, you're also getting it in a far more informative way, with a randomized comparator. And if we were looking for tenfold increases, or a hundredfold increases, we don't need that randomized comparator. But when we're trying to sort out no difference versus a 20, or a 33, or a 50 percent increase, those uncontrolled studies provide very uninterpretable evidence. This would be, in contrast, very interpretable evidence about what is the true impact of the intervention on that risk.

DR. BURMAN: Thank you.

DR. JENKINS: My question --

DR. BURMAN: We are going to have to move on in a minute, but please --

DR. JENKINS: Dr. Proschan, earlier, had suggested you could have an interim analysis approach where you could start the trial, do an interim analysis for the screening purposes, and then confirm after approval. I want to hear

your comment about that aspect of it.

But also in the era of adapted trial design, I'm wondering if you could also address -- say they start this trial and they want to analyze it after a year for efficacy, to look at glycemic benefit, to provide part of the package for efficacy. They also analyze it at 2-1/2 years for safety for this interim analysis. Talk a little bit about the validity and the concerns about multiple looks at this for multiple purposes.

DR. FLEMING: Yes, that's a very important point and my concern is, to really delve into this, would take more than just a minute or two. So let me just take a minute and inadequately answer your question.

You're absolutely right that there are subtleties here that are needing a lot more discussion. If you allow more flexibilities, adaptive -- well, we speak a lot now about adaptive methods, where, in essence, bottom line, trying to build in

flexibilities in the discovery phase with the confirmatory phase. And it sounds better than it actually plays out. We're always best off in a setting where we can formulate the hypotheses that we're trying to confirm and then prospectively proceed to confirm them.

There are some options that could be done here. You want to learn the most you can from this study. And so you certainly could use this study, along the lines of what Marv has talked about, this could be, in fact, an aggregation of a number of elements of your Phase 3 program that also carry efficacy aspects to it. And where there are some nonoptimalities as that plays out to the integrity of the aggregate data for safety, that may be a tradeoff you'd be willing to do, as long as we can set this up in a prospective way.

From an interim analysis perspective, there -- it is possible that

this could be an interim analysis of that larger study. It would be, for some reasons, I think, preferable for it to be separate, where the confirmatory trial can be, in fact, altered in its size -- in fact, it might not even have to be done, based on the results of this study.

This could also be -- you could even do an interim analysis before you got the, in this case, 125 events. I think it would play out to a sponsor's best interest, in most places, to let this study play out till you had the entire 125 events.

One of the consequences here, as I've already tried to mention, it follows what Bob Temple was saying before, is the conclusion here is not just dichotomous, are you able to rule out an 80 percent increase or a 50 percent increase. The results could be sufficiently favorable that you might not need to do that confirmatory trial, and you might even, in fact, get a superiority claim.

So that overall insight needs to be factored in. And I think a lot more could be said, but in the interest of time, it probably needs to be discussed later.

DR. BURMAN: A very important issue. Dr. Temple, did you have a quick comment?

DR. TEMPLE: Well, as Tom said, you could talk about this for a long time. Seems to me a company might well look at the first 40 events, figure out that they're going in the right direction, and say, oh, I'm not worried about being 1.25. I think I'm gonna be all right. I can do a much smaller study.

And then we'd have to figure out what price he'd pay in the final analysis.

I did have one other question, though. Tom's been talking about a 2-1/2 year study. Is that the same as twice as many people, but only for a year and a quarter? I mean, are we committed to very long duration, here?

DR. FLEMING: You're right, Bob.

There are tradeoffs of this, so that you could do this in a year and a quarter for twice as many people. Many tradeoffs. One of them to be thinking about is if there is, in fact, a varying effect of treatment over time on the these cardiovascular complications, where the longer you look, the better it is, I would argue that that sponsor would be well-served; i.e., they could cut their sample size in half, but they would also be well-served by having a greater chance of a favorable conclusion.

DR. TEMPLE: All right. But it's possible you could think of the definitive postmarking study as the place to look for long-term effects.

DR. FLEMING: That's true, but suppose -- I don't know if this is true -- but suppose there is, in fact, true adverse effects for the first 6 months to 12 months, and then not thereafter, then, I don't want my screening trial sending me in the wrong direction either.

DR. TEMPLE: Stuff happens.

DR. BURMAN: Very critical points. Good -- Dr. Parks.

DR. PARKS: I'm sorry, I'm afraid I'm going to muddy up the waters a little bit. I do need some clarification here, Dr. Fleming.

The 2-1/2-year duration here that you -- on the previous slide, I'm assuming this is going to have to be on top of the Phase 2 program. I would assume that the company would want to do the dose- finding studies first, a 12 week to 24 weeks.

But the other thing I want to point out here is that this is based on, I'm assuming, selecting one dose of the investigational drug. It's conceivable that a company may want to test two doses, and that will certainly modify the sample size, as well.

DR. FLEMING: I would agree with you that it wouldn't make sense. While I agree with Marv, this could be based on an aggregation of elements. I would think of your Phase 3

Program. But even as you've described it, the Phase 2 Program would be a very small number of person years, anyway, relative to what we're talking about here. So you're not giving up that much by not including the Phase 2 Program.

And yes, I would think that you would be, ideally, doing this as a two arm; i.e., as a given strategy against a control.

DR. KONSTAM: You know, I'm not sure about that. I mean, first of all, we haven't gone into dosing issues, at all. And we don't know, at the end of the day, whether the company is going to wind up with a single dose recommendation or a multiple does recommendation.

So I'm not so sure about -- that I would agree that that this critical safety analysis necessarily has to be around a single does. And I agree that most of the contribution will be in the Phase 3 program, but if in -- but you're not going to independently test the safety of every single

does. So you're going to have to make compromises.

And at face value I don't see why you couldn't -- in the Phase 2 program you're having three doses, if those wind up being the three doses that go forward, well you've got a randomized -- I mean, Tom's focusing on the randomized -- prospective controlled randomized effort, as opposed to uncontrolled, which is a whole different ballgame. But if it's controlled, even if it's a 3:1 randomization with three different doses, I would hope that somehow or other that could contribute to your overall safety signal.

DR. FLEMING: And just to respond. You certainly -- if you aren't, in your Phase 3 program, in a position to have clarification of the dosing schedule, I'm okay. It's less optimal, but I'm okay with that. The Phase 2 is such a small fraction of the person years' aspect of this that, from a practicality

perspective, it would make more sense to really think of this as the aggregation of evidence across the Phase 3.

DR. BURMAN: Other questions before we move on?

DR. KONSTAM: Can I just, at some point -- and maybe we can do it after the break, but I -- you know, I, again, I mentioned earlier that if you wind up with a two-phase effort here, I wonder whether you'd have to throw out the prior information. And I would just wonder if we could have any comments, and maybe we could save it for after the break, about is there another approach to this.

DR. BURMAN: I forgot to mention, there's not going to be a break.

DR. KONSTAM: Okay.

DR. BURMAN: We're running too short on time --

DR. FLEMING: Just one -- I would hope that we would all say, you wouldn't throw it out. It's just a matter of what is the

structure for obtaining totality of information. Is it two separate sources or is it one with an interim. So there's no question, you wouldn't throw it out. It's one of the key contributing sources of information. Might be the only one required.

DR. BURMAN: Please.

DR. PROSCHAN: Yes, I mean, there's an impression, unfortunately, among non-statisticians that the only way to take into account prior information is through Bayesian methods. That's not true at all. We take into account prior information as classical statisticians, as well. And you could take into account the difference in HbA1c; you could take into account all kinds of things. It's just that a Bayesian methodology is a very specific way to do that, where you specify a prior distribution before starting your study and, you know --

DR. KONSTAM: How do you go from, let's say you wind up with the right-hand

column, at the end of at the end of your approval, and what you want to be is at the 1.33, how do you get there with a frequentist approach?

DR. FLEMING: I completely agree. And you would use, I mean, there are different ways of doing it as a frequentist, but you would be looking at totality of data. You could look at totality of data through a meta-analysis.

DR. KONSTAM: I see.

DR. FLEMING: You can look at totality of data as the aggregation of evidence for strength of evidence to rule out excess risk. I'm okay with a Bayesian approach, but it doesn't buy you anything --

DR. KONSTAM: I mean, I'm not --

DR. FLEMING: That frequentist can't do.

DR. KONSTAM: I'm not stuck on Bayesian, at all. I just think that -- but we haven't talked about -- I mean, it's been presented as if you do something in pre-approval

and then you start -- it sounded like --

DR. FLEMING: No, no --

DR. KONSTAM: Then you start over --

DR. FLEMING: It's totality of information. And the benefits for thinking of it as separate studies is the first study would be fully analyzed and would have impact on how you would then subsequently design that second study.

But this is fine-tuning, I think, relative to what the Committee has to discuss. I think we're in agreement. In principle, what we're trying to say is we're in agreement. The totality of these data would be used if you had two studies that were providing the information.

DR. BURMAN: Let me -- we really have to move on. And I apologize that there really isn't time for a break because we really have to end by 4:30. And there's a tremendous discussion and I appreciate everyone's interaction. It's really important.

But quite equally important is the question for vote.

MR. TRAN: Once Dr. Burman read a questions into record, for all voting members, this would exclude Dr. Veltri, our industry rep, and Dr. Genuth. Starting from Dr. Fradkin, and around the room to Dr. Holmboe. Our FDA panelist members are non-voting and including myself.

Once we are ready, you can hit yes, no, or you can abstain from voting. You have three choices on your microphone right in front of you.

So after Dr. Burman -- yes?

DR. KONSTAM: Can I ask for some clarification? So I mean, we've talked about a few things and so I want to understand. When we talk about the conduct of a long-term cardiovascular trial, are we including in that the concept of actually a pooled assessment across a number of trials.

Is that responsive --

DR. BURMAN: I would suggest and agree that that be a slash: a cardiovascular trial and/or a cardiovascular assessment, as we've discussed.

DR. JENKINS: Actually, I think we would really prefer that you answer the question for a standalone, long-term cardiovascular trial.

DR. BURMAN: Okay.

DR. JENKINS: We addressed, under Question 1, the issue of whether you think we should do a better job of pooling trials. But we really need for you to answer the question should there be a standalone, long-term cardiovascular trial, yes or no?

DR. BURMAN: Okay.

DR. HOLMBOE: I hate to be difficult, but it's hard for me on this question in the absence of context. I mean, if we had a screening study that reached the result that Tom just showed, then I would vote differently than if I didn't have that data. If I only have the

data that's currently available using your current program, I would vote differently. So I guess I need some help on what exactly is the amount of information that this long-term trial would be based on?

DR. JENKINS: The screening trial that Tom just described, I would characterize as a long-term cardiovascular trial -- that's not what we currently get.

DR. BURMAN: Thank you. Any other points of clarification? Those are excellent. Oh, I'm sorry, Dr. Day.

DR. DAY: So question No. 3 looks like yes/no, in the absence of a cardiovascular signal. And then, if yes, there are two choices below, but there are really three: when would such a trial be pre-approval, post-approval, or straddling both? So the straddle strategy has an option for voting, might make it easier for us to answer the question.

DR. BURMAN: The question itself, let me read the question. It is -- which is up

there.

It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, there should be a requirement to conduct a long-term cardiovascular trial. Yes or no. And then the category is either pre-approval or post-approval.

But we're going to go around the room, individually, after the vote, and everyone will -- can then make their comments about how they would caveat it. Dr. Savage.

DR. SAVAGE: Can I just get a clarification as to what this -- the data is, again?

I'm not sure that I understood what someone just said a minute ago. The information that would be available during the Phase 2/3 development is exactly what?

DR. BURMAN: My understanding -- you want to answer that question?

DR. JENKINS: It would be the type of trials that Dr. Joffe described yesterday morning. The 12-week Phase 2 trials, the 24- to 48-week Phase 3 trials, that's the data, and then the extension. You know, that's the type of data we're getting now.

We asked you in Question 1 to describe things that we could do to make that dataset better.

You talked about adjudicated cardiovascular committee. You talked about other things that we could do, meta-analysis, for example. We really are asking you should we go beyond that, in our cardiovascular assessment, in asking for a specific, long-term cardiovascular trial, yes or no. And then we'd like you to tell us, well, should you do that pre-approval, should you do that post-approval, or should you do a mixture. And you can give us that in your

comments as you go around, should it be a mixture of screening, interim analysis followed by confirmatory. But again, this is for a situation where our best available risk estimate, at the time, does not show a cardiovascular signal. That's what the question says.

DR. SAVAGE: But it does not include a short pre-approval trial of the sort we've been talking about.

DR. BURMAN: It does not, but --

DR. JENKINS: The screening trial that Dr. Fleming described, I would categorize as a long-term cardiovascular --

DR. SAVAGE: Right. That's what I thought you said --

DR. JENKINS: A 2-1/2 year trial --

DR. SAVAGE: That's why I wanted to make sure I understood, because --

DR. JENKINS: So if you liked that perspective, you would probably vote yes. And then in your comments, you would say, I like the

screening approach pre-approval and the post-approval confirmation, but --

DR. SAVAGE: Yes, that's the clarification I wanted. I wanted to make sure I understood what I thought I heard.

DR. JENKINS: We're really asking you, do you think we should be having a specific cardiovascular long-term safety trial above and beyond the usual Phase 2, Phase 3 control trials and extension studies.

DR. BURMAN: Yes --

DR. SAVAGE: Above and beyond an enhanced version of what exists now.

DR. JENKINS: Yes. Yes.

DR. BURMAN: Dr. Temple and then Marv.

DR. TEMPLE: Well, I think Tom described some circumstances in which the Phase 2, 3, whatever study could obviate the need for further long-term study. And maybe there are some circumstances for that. This question asks, in the absence of something like that, where you haven't gotten anything, do you

always need a long-term study. And then when should you do it. Right?

What Tom described, I think, is a case where a short -- a relatively short-term result could be so persuasive you wouldn't want to bother anymore. And maybe there are cases like that. But that'd be a little unusual. Right?

DR. FLEMING: Indeed. I think, if I understand the essence of what you're really asking here, is, is it necessary, in a development plan, before an agent is approved, to be able to have sufficiently comprehensive and reliable evidence, or at least, then, in a post-marketing, the Committee can decide when it would be done, pre or post. But if you believe that an agent needs to have sufficient evidence to be able to reliably rule out unacceptable cardiovascular safety risks on a routine basis, then it's -- my understanding is the answer is yes. And in that context, Marv, you were saying there's another way -- there are different ways

to do that.

DR. KONSTAM: I mean, I think that's where what we were proposing amending the question or clarifying the question to that effect. But I guess I'm worried about the reaction to that because I think your reaction to that is setting up an unfortunate and potentially misleading dichotomy --

DR. FLEMING: So it's essentially such a trial or equivalent evidence --

DR. KONSTAM: That's what I'm saying --

DR. FLEMING: Such a trial or equivalent evidence. And what Bob Temple keeps saying is that equivalent evidence could come from an aggregation of somewhat less Phase 3 trial data, where you have a really favorable point estimate that allows you to rule out an excess. But it would be a little risky for a sponsor to presume that would be the case before they embark on Phase 3. So if this answer was yes, then the sponsor would know that they would

be required to provide a long-term trial or the equivalent evidence. And then later we'll discuss whether that's -- to what extent pre-marketing, post-marketing.

That seems to be the essence of what you're asking. And that's the fundamental difference from today, where you're not requesting, routinely, that you would be able to have the equivalent of this kind of evidence to be able to discern and rule out an unacceptable safety risk, cardiovascular.

DR. JENKINS: I think that's correct. If that's what you need to do to modify the question to make it clear, I think that's okay. You have to understand, the Agency has heard calls, now, for a year or longer, that every anti-diabetic agent should have a cardiovascular outcome study. So we're trying to get you to pen down that answer as far as your recommendation to us, as well. So I'm nervous about wiggling too much, so that we don't come

out with a clear advice from the Committee.

DR. KONSTAM: Well, you have to remember that we -- we're in we're smarter than all those people who have been speaking to you, and we've been talking about this for a day and a half, and we're trying to identify pathways to establish cardiovascular efficacy in a least burdensome manner. And I think that's been the spirit of the discussion here, and I just I think just it's another way of saying what I think we've been -- you know, Tom has been saying, and others, is, you know.

So I've been in a number of programs in which there were pre-specification that there are three trials to also be aggregated as a single additional trial with a different endpoint. I mean, there are numbers of programs in cardiovascular development like that.

So you know, I just -- I'm just concerned that, I mean, I think there's just an unnecessary dichotomy of saying, a trial.

I think -- and what we mean by that.

DR. ROSEN: Okay, okay. And this is a critical vote, and I don't understand it. So I think we need one more clarification, without a lot of adjectives and other things.

What you're saying is in the current situation with all the data that you have, currently, at the FDA, and you don't see a signal for cardiovascular risk, should there be a long-term cardiovascular trial for an anti-diabetic drug. Is that the question you're asking us to respond to?

DR. JENKINS: I think that's the question we were trying to ask you to respond to.

DR. ROSEN: Yes. Okay. Okay. That's fine. I think that's the question. And you've also clarified a bit that a long-term trial, in your view, could be anything from Tom's trial all the way to a long-term Phase 3 trial. Correct?

DR. JENKINS: Yes.

DR. ROSEN: Any --

DR. JENKINS: Well, I think Tom Fleming added equivalent evidence. I think we're asking you for -- the question, really, in my mind, comes down to a long-term cardiovascular trial to exclude unacceptable risk at that whatever we decide, 1.33, 1.50, whatever the decision might be for what's unacceptable risk. If you can get equivalent evidence of that, another mechanism, I think that would be acceptable, too. But we're not talking about --

DR. ROSEN: You're exactly right.

DR. JENKINS: We're not talking about the pre-approval screening methodology that leaves us with 1.80 --

DR. ROSEN: That's right.

DR. JENKINS: We're talking about do we need to confirm, either pre-approval or a post-approval, whatever that upper bound is. That's what we're asking.

DR. FLEMING: And so just to

completely agree and to clarify, the long-term trial -- I guess my slide's gone -- the long-term trial were on the left-hand part of my slide. The screening concept is a two-stage process. It's just one version of an approach to getting that kind of evidence. Using the aggregation of the Phase 3 to make up the screening, followed, if necessary, by the confirmatory trial, is another version of getting that evidence. So it seems that the essence of what you're asking for is do you need such evidence from a long-term trial, or from the equivalent sources to that long-term trial.

DR. JENKINS: I think that's correct, with the idea that we're looking for confirmatory evidence, not just the screening evidence. It can be a two-stage process. But we're really asking you, for every drug that we see for diabetes, even if it doesn't have a signal, should we be requiring that they provide us with confirmatory evidence of lack of unacceptable risk?

DR. FLEMING: And that is the intention of the two-stage screening trial, to do exactly what you said.

DR. ROSEN: One final point of clarification. Without a signal means what? In the question. Does it mean 1.0? Does it mean 1.1 in your aggregate data? Does it mean anything -- that you just don't have enough data to make a call on? That it's without a signal?

DR. JENKINS: I think that's, obviously, a judgment call. That we say at the preamble to the question, if we see something we think is a worrisome signal, we're going to require the study anyway. It's a judgment that we haven't seen anything that makes us concerned that there is a cardiovascular signal. And we're asking, in that setting, either pre-approval or post-approval, do we need to require that we get confirmatory evidence to rule out that upper bound of unacceptable risk.

So maybe, I don't know if somebody wants to try to reword that into the

question, but I think you can use long-term cardiovascular trial in the question to really mean confirmation of lack of unacceptable risk at whatever that upper bound might be, 1.33, 1.5, whatever is chosen. That's what we're asking for.

DR. BURMAN: Dr. Fradkin. You had a question.

DR. FRADKIN: So we've heard a lot about the lack of evidence doesn't mean the lack of effective -- so when you're saying a lack of a signal, are you saying that patients are going to -- that you're going to have a sufficient number of patients followed for long enough to actually know that you would have a signal with some? Or, I mean, because, I mean, really the question is, are you going to be doing these expanded Phase 3 studies that we've all been talking about, and are we saying that we should do something over and above that? Or is a yes vote if we think we need these expanded Phase 3 studies to at least give you an ability to find

a signal that would then require a longer one?

DR. JENKINS: It's amazing how often we get into these circles --

DR. PROSCHAN: I think --

DR. JENKINS: In trying to write questions for the Advisory Committee. Yes, I think you should answer the --

DR. PROSCHAN: I mean, just take out the without the signal. I mean, should this be required for every new anti-diabetic drug. I mean, really, that's the question being asked.

DR. TEMPLE: The signal thing was, of course if we see something, we're going to make them do it.

DR. PROSCHAN: Yes, yes.

DR. TEMPLE: Don't worry about that. That's what that was there for.

DR. PROSCHAN: Yes, yes.

DR. TEMPLE: Now we don't see such a signal, should we have to do it. Should it be routine.

DR. BURMAN: Thank you --

DR. JENKINS: I think the other way you can look at that, assume that they've done the best possible Phase 2, Phase 3 development program that you have idealized in your mind, and we're not seeing anything that's worrisome, should they have to do a study to confirm the lack of unacceptable upper bound of risk.

You know, the screening trial that Tom is describing is not part of Phase 2, Phase 3 development, as the way we look at it today.

DR. BURMAN: Any other --

DR. JENKINS: That's an additional requirement that he's describing.

DR. FRADKIN: If you want that, you should vote yes.

DR. JENKINS: Yes.

DR. BURMAN: Obviously, this is a critical question and time is important, but not as important as resolving everyone's issues before we vote. Does anyone have any other --

DR. KONSTAM: I think -- no, I don't

have -- I'm not sure whether it's resolved or not. I think if we're going to vote, I think we should make sure we've worded it so we know what we're voting on. That's all. Heard things I may understand, may not. But I guess before I vote, if we're going to change the wording, I'd like to change the wording.

DR. JENKINS: Do you have a proposal?

DR. KONSTAM: I was going to ask you.

DR. ROSEN: I think that it was explained pretty appropriately. I'm satisfied. I think I understand what the question is now.

DR. KONSTAM: Okay, do you want to --

DR. ROSEN: And I think more discussion --

DR. KONSTAM: Do you want to word it --

DR. ROSEN: Is going to make -- I think if you take out, without such a signal, as Michael suggested, the question is: if they have no evidence for a risk --

DR. KONSTAM: I got that --

DR. ROSEN: Do you still recommend that they have a longer Phase 3 trial for cardiovascular risk? That's it.

DR. KONSTAM: A single trial --

DR. TEMPLE: Don't call it Phase 3. It could be post-marketing --

DR. ROSEN: That's right. It could be post-approval. It -- a trial.

DR. BURMAN: And Dr. Jenkins, do we stick with a single trial, or?

DR. JENKINS: Again, I think Tom Fleming offered what I thought was a reasonable addition. I think he said for those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or equivalent evidence.

That's why I asked you to suggest what your proposal would be. Or maybe you conduct a long-term cardiovascular trial to confirm lack of adverse outcome, or equivalent evidence from other sources of information.

DR. BURMAN: He's going to try to change that right now. And while he's doing that, any other points of clarification? Comments?

We're going to vote on the -- using the microphones in front of us, either yes, no, and don't forget you can abstain, as well.

Dr. Temple, the --

DR. JENKINS: Let me try to give you wording, here, off the fly. I think trying to edit the slides is going to be challenging. But.

For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term trial, or equivalent evidence from other sources, to rule out an unacceptable cardiovascular risk?

DR. BURMAN: Cicely is saying that we should stick with the original question --

SPEAKER: Take a vote on the modified (inaudible).

DR. BURMAN: Why do we have to do that? Okay, good. I will yield to Dr. Parks. Yes. Dr. Jenkins. Dr. Jenkins and Dr. Parks, are we allowed to change the question?

DR. JENKINS: As far as I'm aware.

DR. BURMAN: Okay.

DR. JENKINS: I don't think I've ever been to an Advisory Committee meeting where you haven't changed the question, so.

DR. BURMAN: What's this you stuff? We -- we've changed it. And what was the suggested wording?

DR. JENKINS: Well, you took down the slide, so I'm going to have to --

DR. BURMAN: Can you put it up --

DR. JENKINS: For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term trial, or other -- or provide other equivalent evidence, to rule out --

DR. BURMAN: Excuse me. Hold on one second.

Please go on. Start again.

DR. JENKINS: A long-term trial, or to provide other equivalent evidence, to rule out an unacceptable cardiovascular risk?

DR. BURMAN: Can you project it at the same time? Okay. So should there be --

SPEAKER: Long-term --

DR. BURMAN: Should there be a requirement to conduct a long-term cardiovascular trial --

DR. JENKINS: Or to provide other equivalent evidence --

DR. BURMAN: Or to provide other equivalent evidence?

DR. JENKINS: To rule out an unacceptable cardiovascular risk?

DR. BURMAN: Other equivalent evidence. That's it? To rule out. What was the last point? An unacceptable cardiovascular risk.

Right. Risk. And then can you show him that?

DR. JENKINS: And Dr. Burman, I think, given the modification of the question, we'd also like that after you get the yes/no vote, that people describe, in the pre-approval, post-approval part of their response, whether they see it as a trial that's conducted completely pre-approval, completely post-approval, or some sort of a hybrid screening confirmatory mix.

DR. BURMAN: Absolutely.

DR. JENKINS: Maybe you can do that as you go around the table.

DR. BURMAN: Absolutely. And the question now is being projected. Thank very much, Cicely.

It is as follows. It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a

long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk.

Vote yes or no.

MR. TRAN: For our voting members, please enter yes, no, or you can have abstain from the vote as your third choice.

DR. BURMAN: But before we vote, any other comments?

Just want to give full disclosure. Full. Okay. Then I think we're ready.

MR. TRAN: Please enter your choice.

Yes, you can change your mind. Just hit yes, no, or abstain, and -- we will know. We will know. All right. So now I'll give you 10 more seconds to change your mind.

I just want to read this into record. There are 14 yes, 2 no, and 0 abstain.

DR. BURMAN: Thank you very much. And this now gives us an opportunity for everyone to go around and give their reasons. And I just

want to give you an overview: this is -- it's 3:20, in terms of time, and we have to leave by 4:30 and we still have the fourth question, which, I think, will not be that long of discussion. So we do want to hear what you say, succinctly, in your vote. And maybe we should start on this side.

Yes. Dr. Holmboe.

DR. HOLMBOE: The reason I voted yes was for all the conversations we just had. I mean, I think that the current pre-approval process isn't sufficient to rule out cardiovascular risk in a disease where cardiovascular morbidity, mortality is so prevalent.

And so it just makes good clinical sense that you would want to do this, because if it causes harm, that could definitely change the risk/benefit ratio from a patient's perspective. So really, thinking it from that point of view.

I'm in favor of some sort of

pre-approval process, either the screening trial that Tom described or Marv's, kind of, integrated approach. And then if that still shows some worrisome signal, then there should still be a post-marketing study performed, depending on what that level of risk is. If it's, obviously, unacceptably high, you end there. If it's turned out not to show something, even a long-term post-trial, I would still be in favor of some sort of prospective surveillance.

DR. KONSTAM: Yes, I mean thinking about this, I think this is sort of a no brainer, in the sense that I believe that on some level, the FDA believes that they're doing something along these lines now. I mean, there is some conceptual level of risk that is just intolerable. I mean, I don't think you could approve a drug that is beyond some conceptual boundary of what the cardiovascular risk is. I think that you're just, sort of, not stating what you think it is, and you're just making

some assumptions, and you're not requiring rigorous statistical documentation of that.

And I guess we're saying well, it's important, you know? It's important to be within certain boundary of cardiovascular risk. Now, that's all we've said. We've said that you need to do that, that it requires evidence, that there ought to be a program of evidence, perhaps a single trial or multiple trials. I would just, sort of, add to me, I think it is a clinical boundary. I don't think it is a specific, upper-statistical boundary. I think there ought to be statistical upper boundaries, but I think that at the end of the day, I don't think you can go away with long-term exposure to the population when there is any serious possibly that there is, say, above a 30 percent excess in cardiovascular risk. Somehow or other, at the end of the day, I think you've got to get there. And if you can argue you can get there through priors,

including other information that you can bring to bear, so be it. But I think you have to get there.

DR. LESAR: Yes, I think that it was clear from the discussion that some improvements in the screening of these agents are needed. And secondly, I think, the discussion also revealed the fact that this can be done in a fairly efficient manner, without undue burden to the sponsors. And also without causing undue delay in the marketing of these agents, if they do prove to be safe. So I think it strikes the right balance and it is, certainly, a necessity for patient safety.

DR. PROSCHAN: Yes, I think it's absolutely necessary before approving the drug to have some long-term safety data. I would prefer that that be a single trial. I could see pooling different trials if they're like Tom said, 2-1/2 years of duration. But I would be reluctant to be pooling trials of three months and other trials of 2-1/2 years. So I think

that other equivalent evidence really would have to be from pooling of clinical trials, not observational evidence. And I think those trials would have to be long-term trials, and conducted in a similar way.

Could I -- I'm sorry. And I already mentioned how I thought would be a good way to do it, in terms of pre-approval or post-approval. You know, start a big trial, perhaps give approval on the basis of the interim results, and then finish that trial.

DR. FLEGAL: Well, I think we need this information, and I think we all agree we have to find the best way to get it, and it can be done. I actually agree with Michael's suggestions, too, about how to start the trial, and have an intermediate look, and then continue it or not, as necessary. So I think this is a plan that gives people the data we're going to need.

DR. BERSOT: I think that the evidence

could be trial or other evidence, but with the caveat that there is the duration of treatment that goes beyond two to three years, as we discussed previously. And given what was said, I think by Dr. Nissen yesterday, about the suggestion from the FDA that post-approval trials be conducted and the lack of follow through on that, that these studies should be required to be initiated before approval.

DR. HENDERSON: I voted yes, because I think this is the way we get the sufficient evidence that we need. Also as the consumer representative, I am concerned with the burden on the patient or consumer, and having sufficient evidence is the least burdensome for the consumer. I also support the mixture, hybrid screening.

DR. BURMAN: Thank you. My thoughts are that diabetes is a complex disorder with multiple variable factors indicating an increased risk of microvascular complications, MI, stroke, and death.

The medications used to treat diabetes confound the issue and may have adverse effects, in and of themselves. Diabetes is, as we've talked about, is a progressive disorder, and the patients who live longer due to treatment of their microvascular disease will have greater exposure to macrovascular events.

Our major objective, and my major focus, is to be patient-centric, not glucose- or cardiac-centric. And it's difficult, however, to interpret the absolute and relative risk of a slight change in the beneficial fashion in cardiovascular events from -- in microvascular events, and have a slight worsening of cardiovascular events. We have to evaluate that.

Taking positions into consideration, I think we should continue to focus on hemoglobin A1c for approval, but we absolutely need other specific parameters and long-term studies, such as we're talking

about, to look at cardiovascular events and other events, as well. I, personally, think this should be in a post-approval market.

DR. GOLDFINE: That was an eloquent discussion that I will have very little to add to. But I did vote yes, we should be requiring an additional trial. I believe that cardiovascular disease is the major morbidity and mortality for our patients, and that not to understand the safety here is an inexcusable event to be in.

I think that the timing of pre-approval to post-approval has to be adjusted based on what you find in your preliminary trial development. Because as you outline, you want to be looking at patients who are drug naïve, on monotherapies with others, these are earlier patients. And it is possible, especially as we drive down the cholesterols and blood pressures with our other medications, that the event rates could leave you with sparse data, and we have all

wrestled with how to deal with sparse data.

So if you have a sufficient event rate in the pre-clinical -- in the pre-approval processes that are so sparse, then this may need to actually be added in. If, on the other hand, in the pre-approval, or at least begun pre-approval with an early look. If, on the other hand, there are sufficient events in those that one can judge there is reasonable evidence of neutrality or potential benefit, then, I think, beginning these coincident with approval is an acceptable thing. But it is based on how much you actually have already occurring in the portfolio when they're actually considering it.

DR. FLEMING: I voted yes to Question 3, because I think it is extremely important to be able to have adequate clinical trials to address cardiovascular safety risks, in order to be able to provide an informed choice to caregivers and patients. But this

data is also necessary to allow timely and reliable identification of unacceptable safety risks.

My concern is if this were done entirely in a post-marketing setting, it would take seven years, maybe longer, in order to be able to get this trial, long-term trial, with an average of five years of follow-up. Having been on data monitoring committees for a number of such studies, there's no question that the sponsor's sense of urgency in such studies done purely in a post-marketing setting doesn't match the sense of urgency that exists when it's a requirement in a pre-marketing setting. Therefore, my preference would be to have this study done in a pre-marketing setting.

However, I think the concept of the screening trial provides a rational middle ground that allows us to at least provide a screening assessment in a shorter time frame, to allow the pre-marketing setting to be done

without substantial delays, and then a confirmatory trial done after. So in order to ensure that this is done in an adequately timely and reliable way, either I'd like to see this done pre-marketing, or it would be acceptable in a middle ground to have the screening assessment done pre-marketing and then the confirmatory trial done after, as post-marketing.

DR. FELNER: I voted no. And I think, as I had spoke before, that this is a progressive disease. I do not think that in 2-1/2 years, as some have suggested, maybe even up to three to five years, that you will actually determine if there are cardiovascular effects from the drug.

With that being said, I would like to believe that the Committee that's involved in approving the drugs is good at what they do, as what -- some of the questions, I think, that were brought up, that took so long to get to this point, were really

focusing on was what your cut point should be, or how many events you should have.

And so I think that if you wait this amount of time, whether it be 2-1/2 years or three to five years, you're going to be preventing certain drugs from getting out there, or new drugs, that may be more beneficial than what we have.

And of course, the post-marketing studies should be done. But I think that you won't learn much, from a cardiovascular standpoint, in this short time. But you still will be able to learn by continuing to follow the patients, with the added benefit that you'll have a new drug there that may be better than what's out there.

DR. DAY: I voted yes, for the reasons already given, and favor straddling the pre-approval and post-approval periods for such study. And I think some criteria are going to have to be set as to what is adequate in the pre-approval stage, because this started

yesterday with the suggestion that enrollment had already taken place or enrollment was underway. And I think there are going to have to be some clear criteria as to the nature of the data that must already be collected at the time of potential approval.

DR. ROSEN: I voted yes, because I think this is the only way to at least partially address this issue of long-term safety. And I endorse the idea of a mixed hybrid screen where you might have some compromise with an interim analysis included, so that the speed of entry into the market may not be compromised as much as we might think.

And I'd like to mention that I'd like to applaud the FDA for being open about this process and, also about listening to what we've had to say, because I think this is a very difficult question, it affects a lot of people. And I think their response in this hearing for the two days has been emblematic of their openness in this respect.

So.

I voted yes.

DR. KILLION: Based on my somewhat mercurial understanding of the question, I, like Dr. Felner, voted no to the question, because as I read the Phase 2/3 development portion of the question, and I understood it to be that these would be Phase 2 and 3 that would be enhanced to look, specifically, for a signal, a cardiovascular signal.

So on the basis of that enhanced review failing to produce a signal, I thought it unnecessary to make a requirement, and I focused on the word requirement, for a long-term study when there was no signal being given.

Now, my preference, of course, would be that there was this, but perhaps not that there be a regulatory requirement for the same course. Having said that, the more information that can be gathered, the better. But, I didn't want to overburden the process

and, perhaps, as Dr. Felner pointed out, delay or prevent drugs from getting to the market that would be helpful to diabetics in the process.

DR. SAVAGE: I voted yes because I thought that a more structured system is the only way we're going to really get the type of information we need to be sure we don't, at some time in the future, make a serious mistake and let something slide through.

I think there's one relatively unique thing in the cardiovascular field right now, which is that because of the introduction of the statins and other effective therapies, there's a considerable improvement, ongoing, in terms of cardiovascular mortality. And if a drug was introduced into the diabetic community that produced a 20 percent increase problem and was given to several million people, but not all the diabetics, the overall rate in the diabetic community might still drop and the

slope just change a little bit. And if all we had was the type of information we have on rosiglitazone, even today, given the follow-up to last year, we wouldn't necessarily recognize such a thing happening.

So that's why I thought that we had to vote yes, to put more structure into the system.

DR. FRADKIN: I voted yes because while I think that A1c is the proper basis for approval for efficacy, I think that the current trials to develop that efficacy information don't give us sufficient duration of follow-up or sufficient numbers of patients for the FDA, really, to know whether there is or there is not a cardiovascular safety signal.

So I would like to see a pre-marketing study. Hopefully that could be an extension of some of the Phase 3 studies, to have more patients and longer follow-up, so that we would really be able to more closely define what the signal is.

And then I really have a lot of confidence in the wisdom of the FDA. And I think that depending on what you see with a relatively well defined signal, it might be that an additional study would need to be done pre-marketing to better define it. It might even be that if you exclude maybe a 1.2 or a 1.25 in your confidence interval, then maybe a post-marketing study wouldn't need to be done.

But I think we need more information, prior to the approval, to, sort of, decide that.

DR. BURMAN: Thank you all very much. To summarize, the vote was 14 yes, 2 no, 0 abstentions.

And we have on record everyone's thoughts about pre- versus post-marketing, and I think that gives the FDA leeway.

I would like to ask if the FDA has any other comments or wants clarification on this one issue before we move to issue 4.

Anybody? Yes.

DR. PARKS: We just wanted some clarification. It wasn't clear, Dr. Konstam and Dr. Lesar, if your recommendations were pre or post.

DR. KONSTAM: Yes, I'm sorry. The simple answer, I think, the straddle comment that others have made would be fine. And I think you could have one reasonable pre-approval target, and then an ultimate target, so to speak, which you might or might not hit pre-approval. But if you didn't hit it pre-approval, you'd need to hit it post-approval.

DR. LESAR: Very much the same comments, that certainly, pre-approval could be designed to answer those questions or a large percentage. And if needed, then a post-approval to, sort of, confirm it, would be fine.

DR. BURMAN: Dr. Parks, is that adequate? You want any further definition of those comments of pre-approval? You want an

informal vote? You want a -- are you okay with everything?

You're okay.

Good. Then let's move -- again, at 3:40. Let's move to the last question, which in and of itself, of course, could be a very difficult question, as well. But we -- I think we'll open this for discussion for the group, to give the FDA some advice.

And the question is: as no currently marketed anti-diabetic therapy has established evidence of macrovascular benefit and most have not been tested for lack of cardiovascular harm, please discuss how any suggestion for a requirement for a long-term cardiovascular trial in Question 3 above for drugs or biologics seeking an indication for the treatment of type 2 diabetes mellitus should be applied to existing anti-diabetic therapies.

In other words, what do we do now that we've voted yes that there should be a

requirement for new drugs, what should be the advice given to the FDA regarding the drugs that are already on the market, of which don't have any of the material that we may be asking for.

So I'd like to open this up for discussion and interaction.

DR. FLEMING: I think it would be inconsistent to not want to have an adequate level of reassurance of cardiovascular safety for agents that are in use. There are, already, adequate evidence in some cases. So some of these agents already have, in essence, satisfied the hurdle that we're talking about. Some have not, and the Agency's already made a declaration of the need for such a study.

So now we're talking about the rest. And from a practical perspective, I think it does make a difference whether you're talking about a long-term generic or a more recently approved agent. But Dr. Nissen was talking yesterday about, I think it was

sitagliptin, as an agent that was -- had a substantial increase in use after the rosiglitazone evidence emerged. And yet I think the number of cardiovascular deaths, strokes, and MIs in that application for that program was relatively small, two to three dozen. And so it would seem logically inconsistent that an agent such as that, or exenatide, or other recently approved agents wouldn't be expected to have the same type of assessment.

For the longer-term generics, it would be, certainly, more problematic. I guess it would have to be, my sense is, from a practical perspective, in certain cases would NIH or government be interested in studying such. But I would expect that that would be unlikely.

But for more recently approved agents, it certainly would seem illogical to not want to have this same level of insight. And in some cases, it's already been

determined that that should be provided or the agents have already satisfied that hurdle.

DR. KONSTAM: I actually want to make a comment and then get into the specifics of this. But I just want to say that, personally, I'm -- how humbled I am by Rebecca's comments from earlier. And I just was, sort of, can't get them out of my head.

So I just want to say something that -- you know, I think that she's really addressing all of the same questions that we've been addressing, but with a perspective that most of us around the table just don't have, about what actually is important to the patient. And I don't want to put words in her mouth, but what I hear her saying is that we need to take a step back and think about what is really important because I'm not sure that what has been very important to the rest of us is quite as important to her, and I think she's prioritized it differently. And

I think that is a critical perspective that I just wanted to comment on. And how important it is to have her here, and maybe we need to have more of her in these panels. So I just want to reflect on that.

And so I guess I'll use that as a segue into this. I mean, I think that somehow, I don't know how, but what -- I mean, none of the discussions that we've been having up to this point are against placebo long-term placebo controlled trial. They're against other standard therapy. We're not going to sit around with hemoglobin A1cs off the map. So how in the world would we go back over each of the existing therapies and test that? Against what would we be testing it? I have no idea.

So the reality is, and I'm I don't think that would be doing the patients a particularly good service. So I just don't think we're going to be able to -- now, certainly, if there are signals that exist

now, that's another story. I mean, I think where there are specific drugs that have a particularly concerning signal against existing therapy, I think that really requires additional consideration. But I just wouldn't go back and retest every drug. I don't think it could be done.

DR. BURMAN: Thank you. Other comments? Dr. Goldfine first.

DR. GOLDFINE: Start with one very obvious comment, but I think it should be made. And it's that not all diabetes is the same, there are multiple types. And that, absolutely, for patients with type 1 diabetes, insulin is lifesaving. And therefore, we can't hold it to the same regard. So I think that we need to just comment that we're focusing on type 2 diabetes here, and luckily, the DCCT extension EDIC trial has suggested the cardiovascular benefit in that condition.

I think beyond that, one looks at, we have very old drugs. We have a couple

that are generic and are effective at lowering blood sugars, that have been around for the longest interval of time. And then we have, really, a new rash approved, of which one of them has shown that it is either neutral to beneficial, and that one of them has some question, both within the TZD class of risk. And I think that the FDA has already suggested that the one with the question of risk have more rigorous testing.

So I think that leaves us, then, with really fresh drugs, of which some of them, as Dr. Fleming just also suggested, have been used more heavily recently, with very little data. And I think we do need to suggest that those will go through more rigorous and formal testing.

So when you then figure out how we will actually design the trials, if these are then done, since we all now agree that we can't do the placebo trial, if the trials are designed against our oldest or more generic

drugs, then we will begin to be able to see are these in a position better than what we actually have available. Are they equivalent to what we have available. And therefore, we will then know whether -- how they stand. And I think this will fall out when we actually request these trials.

DR. BURMAN: If I can ask you, how would you categorize, in your mind, newer drugs versus older drugs? Is it by category? Is it by year when they were approved?

DR. GOLDFINE: So I think that we can't go back and test every derivative of every sulfonylurea that we have available. We can't test every -- I -- you know, I think that we're, sort of, lucky in that for metformin we have one of that class, which is probably neutral to beneficial, which is used, really, very commonly as frontline agent. And I think then what do you do as an add-on when that fails. And I think that that's where there gets to be much more debate in clinical practice about what to

add. And I think that one could then pick I certainly don't think anybody would go back to the first generation SUs (?), but we've got second to third. And I think then if we begin to class them, the problems begin when we get into the -- some of the derivatives of the (inaudible) that are intermediate in their derivative --

DR. BURMAN: And if I can just ask one more question on this for more detail. What about an agent that doesn't get absorbed? And it's taken orally, but may have some benefit on glucose. Would you require that to have further studies?

DR. GOLDFINE: Well, I think they've actually -- I think that we're talking about apropos here, and I think that they've actually gone through in a stop mitim (?) trial and tried to show, really, even in the long-term study in the early population, that they're actually beneficial to (inaudible) there's a little bit of question, but they're neutral to beneficial,

once again. And I think, again there are some questions on the interpretation of that data, but I think they've actually already provided this to us, to a way -- that when we compare against these, we know that -- where we stand.

DR. BURMAN: But, of course, if there's a newer agent to prove next year -- and I don't know if there is; I'm just speculating, just theoretically -- that is similar to that, but is newly approved, but is in a class that doesn't get absorbed, do you think that ought to be studied?

DR. GOLDFINE: I think it's going to depend on how similar or dissimilar its mechanism is, and if we really believe just because it's not absorbed, if it's acting through the same, what we believe is the same, molecular pathway, and it's some modification for e-pharmaco (?) for uptake or whatever longer duration, slower pass through the gut or something, then the question is different than if it's really a different non-absorbed target

on a different enzyme --

DR. BURMAN: Thank you. Dr. Genuth.

DR. GENUTH: I think the first phrase in the question isn't exactly correct. I think the UKPDS has provided us with randomized clinical trial evidence, in a placebo-controlled randomized clinical trial, that metformin does have cardiovascular disease benefit, both in the reduction of myocardial infarction and in total mortality. I think I'm right about total mortality.

So I think that's the only drug that has given us positive evidence, and so I would suggest that when we test new drugs, that metformin is the logical comparative drug to use.

DR. BURMAN: Dr. Fradkin.

DR. FRADKIN: I would just add to that that the Diabetes Prevention Program, which may or may not ever have enough cardiac events to give an answer, will give even more data looking at people who started out with pre-diabetes,

many of whom now have diabetes, and are continuing to receive placebo -- well, not placebo, but to receive nothing or metformin, now, in an open label, but according to the original randomization. So there will be even more data forthcoming with regard to metformin.

DR. BURMAN: Thank you. Other people's comments on this topic? Dr. Lesar.

DR. LESAR: I'd just like to bring up one thing that is rolling around in my mind, but it hasn't really come up, and that's -- because, actually, I'd, sort of, dismissed it because the complexity of the situation, and that has to do with pharmacovigilance. I think everybody's heard of the complexity of care and (inaudible) confounders, and so I kind of thought that it just wouldn't work. But if you actually think about the way we do trials, there's almost as many confounders in these controlled trials as there is in a pharmacovigilance study, given all of its -- their weaknesses.

But I kept wondering about some

modification of the methodology used in pharmacovigilance to look over time -- over a much longer period of time, and whether we shouldn't be starting now to do that. It is, kind of, like jumping on a moving train, I agree. But I was wondering if there was any comment related to utilizing ongoing pharmacovigilance as perhaps picking up some other safety signals we're concerned about.

DR. BURMAN: That's a good point.

Dr. Day.

DR. DAY: I was going to raise this same question and ask the Panel what types of data like that would be acceptable. Are there some, I mean, it'll depend on the situation, but there's a variety of evidence from insurance databases, and all kinds of places, the AERS database, and so on. Does the Panel have any rank ordering of those types of information?

DR. PROSCHAN: In trying to discuss this question, it seems that from a legal standpoint, can the FDA really withdraw approval

without having a reason? I mean, in other words, for drugs that haven't been shown to have a cardiovascular harm, can you say, we changed our mind, now we're withdrawing your approval. I'm just wondering whether this question might be a moot point if it's -- if they don't have the authority to do that.

DR. JENKINS: Okay, I'll wade into that a little bit. We do have new authorities, under the FDA Amendments Act of 2007 that went into effect in March of this year, to require certain post-marketing clinical trials to address a serious safety issue.

So that's -- the statute as it's defined for a post-marketing setting, primarily, I think, envisions an identification of a new, serious safety issue. So we would have to decide whether that statutory provision would apply to a currently marketed diabetes drug for the concern about cardiovascular risk, to determine whether we could trigger that

statutory requirement to require a study. There are penalties for failure to complete those required studies.

So that, in a very high-level nutshell, just to say we do have new authority to require studies. They have to be safety studies to address a serious safety concern. But I don't think I want to get in any deeper about whether the hypothetical you're posing would apply. That would require a lot of internal review.

DR. BURMAN: Thank you. I was just going to mention, my opinion is the same. And depending on the agent, class, and year of approval, I do think some post-market analysis of some type should be performed on drugs or agents that are already on the market, as has been discussed already.

Anybody have any other comments on this issue? Is now -- does the FDA have any other comments they want to make before we adjourn?

DR. PARKS: No additional comments, other than to really thank this Panel for a really thoughtful discussion, deliberation. We know that this has been a very difficult issue. I recall, about a year ago, one of the Panel members looked over at the FDA and said, I don't envy your position.

I think today, I look at you and I say I don't envy your position.

Although now, with all your advice, we have quite a bit of work to do, but we certainly appreciate the sage advice and information provided to us today. Thank you.

DR. BURMAN: Thank you. And speaking, I'm sure, for myself and for the whole Committee, I want to publicly thank the FDA. In all of my dealings, both personal -- before the meeting and publicly, here, you've been excellent, really been a model of how -- a prototype of how institutions should work.

So thank you very much. I echo the comments that were made earlier, specifically

to Dr. Parks, and to all the others that we interacted with the most.

I also want to thank the Panel members for their time and really thoughtful considerations. The speakers and the visitors for persevering.

Paul, do you have any other final comments?

Then, if everyone agrees, I will adjourn the meeting. Thank you very much.

(Whereupon, at approximately 3:54 p.m., the MEETING was adjourned.)

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