completed. So, I do have a lot of concerns about that and I am not sure that there is anything necessarily that can be done, but I do think that is going to be a major concern.

DR. ROSEN: Thank you. Dr. Furberg?

DR. FURBERG: As a clinical trialist, I would say that the placebo-controlled trials are clear-cut. They show an excess of cardiac ischemic events. So, I think that is the most important take-home message from those. The active-controlled trials add confusion. It is very difficult to tease out what is the rosiglitazone effect and what is the effect of the other drugs.

In terms of the observational studies, I don't find them helpful at all. When you have placebo-controlled trials you don't need observational studies. There are too many biases. You can't compare users to non-users of a drug. There is no way with all the adjustments in the world you can make groups comparable. So, they are not very useful at all.

In terms of the long-term trials, I think

they are supportive of the meta-analyses and show an excess risk of ischemic events. And, ACCORD and BARI 2D look at very little.

DR. ROSEN: Thank you. Dr. Henderson?

DR. HENDERSON: Thanks. The strengths of the meta-analysis are, of course, they are based on randomized trials so the groups are balanced with regard to the measured and unmeasured factors that can influence the rate of the outcome of interest. Unfortunately, the outcome of interest for these was not ischemic events so it is a meta-analysis, as Dr. Kramer pointed out, of events that weren't the primary outcome, which makes them more difficult to interpret. They certainly raise a very strong signal and perhaps even do more than that.

In terms of the observational cohort studies, I think that using them to compare treated to untreated patients is going to be difficult to interpret in those studies. I agree that the observational comparisons of rosiglitazone versus pioglitazone are less likely to be confounded by

baseline factors, however, those studies that we heard about today have yielded conflicting results. And, I think that knowing that balance is important to the context of making the decision about the ultimate availability of both drugs. I will stop there. Thanks.

DR. ROSEN: Thank you. Dr. Flegal?

DR. FLEGAL: Well, I think the meta-analysis has strengths but it has a lot of limitations as well, and I am concerned about the quality of the data, the low power, lack of adjudication, the statistical issues. We get similar results across three different versions of this with much the same data, which is not too surprising.

But I have concerns about that and also about the degree of inconsistency between the different approaches that we see here. So, I just think that there are really still a lot of issues that these studies don't answer fully.

DR. ROSEN: Thank you. Dr. Kramer?

DR. KRAMER: I think I have already

expressed on the first point on the meta-analysis. For the 42 trials the key limitations have been stated in terms of the short duration of the trials. Primarily, my concern is the source of the data being from adverse events that were not prespecified, standardized and adjudicated in an ongoing way.

Actually, when I think about these three questions together and the conversations that we have had, I sense that the usual tension between our desire to actually pinpoint exactly the effect of the drug, as we like to do in our pre-approval state of looking at drug versus placebo, first is really answering the questions that clinicians need to know. So, what I hear many people saying is, oh well, we shouldn't look at observational data; we shouldn't look at things were there isn't a placebo group. But the real-world questions are no longer placebo versus drug.

So, I would advise that we be careful about discarding studies with a very practical clinical design, like ACCORD. I realize that this

is an open-label trial and, being an equivalence study, that has serious concerns being open-label. However it is a very hard adjudicated endpoint and I think we should look forward to analyzing that carefully.

I was concerned about the fact that not only is DREAM non-diabetic patients but ADOPT itself had 70 percent of patients who had diabetes for a year or less, and I think the risk in those two studies, although they are large, is much different, as I think has been stated by someone else.

In terms of the observational cohort studies, I think we all know the limitations of real-world studies but there are also advantages of real-world studies in terms of capturing what is actually happening in practice and taking a look at it and getting a sense of population risk. I think these were as well done as could be done. I recognize the issue of not being able to capture sudden death, but I do think it contributes to the information and I am glad that it was presented.

DR. ROSEN: Thank you. Dr. Henderson?

DR. HENDERSON: In spite of all the limitations of the data that we have talked extensively about, I feel confident enough in the data that there is a higher risk of CVD with Avandia but I would want more data, especially long-term studies and also within subgroups, particularly the patients on insulin and the older patient.

DR. ROSEN: Dr. Lesar?

DR. LESAR: Yes, I won't pretend to be an epidemiologist, but I am a fairly long-term observer of prescribing practices and therapeutic use of drugs, and my take on this is that the meta-analyses certainly raise a fairly large flag related to cardiovascular toxicity, enough that current prescribing practices certainly need to be reassessed. I believe the observational studies, to me, demonstrate that it is something that you can't really see on observation, and the controlled trials I think simply don't refute the meta-analysis. I know the argument is rather

circular there.

But I think that the big message to me is that there is quite a bit of information to inform the method by which we should be prescribing Avandia, and perhaps pioglitazone as well. So, I don't think you can avoid the discussion of alternative drug therapy. If people aren't going to prescribe Avandia they will prescribe something else, as was said, so if we push people to prescribe something else we certainly need to consider what we are doing if we push them to prescribe something else, and certainly in many cases that will be pioglitazone.

DR. ROSEN: Thank you. Dr. Fradkin?

DR. FRADKIN: So, I would echo Dr. Schade's comments about looking back at what we learned from the CDDT. You know, we are talking here about a long-term disease that people are going to have for decades and I think to really focus on what is happening in these studies that were used in the meta-analysis, which by and large were very short-term studies doesn't really reflect what is

going to be important in the long term for patients. Clearly, in DCCT, you know, you had a lot more hypoglycemia. Patients would have had real harm at the beginning of the study and, yet, in the long term they clearly benefitted from the intervention. We don't know that the mechanisms by which these drugs might affect cardiovascular risk would be the same in the short term versus in the long term, and I think it really is the long term that is going to make the difference for these patients. So, I am just really feeling very uncomfortable by the inadequacy of the data that we have.

In terms of the observational studies, to me, the strongest part of those is potentially the comparison of the rosiglitazone with the pioglitazone, and I think, you know, in both the FDA reviewed studiesB-not the one Dr. Graham cited which wasn't FDA reviewed, but also in the military and the other studies that were presented to us here, I thought we had pretty strong data from that. I think whatever selection bias you might

have, and I think there would be a lot in an observational study looking, say, at different classes of drugs, I don't think you would necessarily have that bias in terms of people choosing rosi versus pio. So, to me, I thought that sort of negated any data, which I thought was pretty weak anyway, from the meta-analysis because I thought the design of the studies that were in the meta-analyses for the two different drugs were pretty different.

I guess all I would say about the randomized study is, you know, how disappointing it really is that we aren't going to have the power to negate what is potentially a significant increase in risk. I mean, clearly a 1.2 hazard ratio would be very significant and we are not going to have the power to exclude that, and that is very disappointing.

DR. ROSEN: Thank you. Ken?

DR. BURMAN: Thank you. We put a lot of emphasis on the meta-analysis and I think, as was even stated in the original article and the

editorial, that is just the first step, really looking more importantly at long-term prospective studies and those, in my mind, don't unequivocally show there is a higher ate of cardiovascular eventsB-better termed uncertain. I think there are certain areas that need further attention--patients taking insulin plus rosiglitazone, those with congestive heart failure and those taking nitrates, as well as the elderly population and certainly high risk patients need to be evaluated more thoroughly. But I tend to put more emphasis on the observational studies and the prospective studies.

DR. ROSEN: Thank you. Dr. Day?

DR. DAY: I appreciate the diversity of types of studies that have been brought before us and the alternative data analyses. I always favor having a multiplicity of types of studies in order to decide questions like this, and for each one I think we have to assess the pros and cons, just as we try to assess the benefits and risks of a drug. But what we need is some model to put together the positives or the substantial conclusions that can

come out of all them to put all the data together in order to have some overall assessment of how to go forward.

But my main concern right now is that by the time we go round the table on this and on the two other questions we will not have addressed the risk management issues. You have about half of the committee here with expertise in that area, and I will just comment briefly that in the sponsor's package the risk management plan was quite underwhelming. I think that there are other suggestions, and I hope that the chair will provide time for comments on that.

DR. ROSEN: Thank you. Dr. Geller?

DR. GELLER: I think the pros and cons of the meta-analysis have been well stated by others as well as myself earlier. I guess I would like to say that I would like to see the FDA have more rigorous requirements for follow-up. Even if they do continue to approve diabetes drugs on the basis of six-month data, that the patients in the trial should continue follow-up and that, of course, all

these adverse events and the multiple adverse events should recorded. I think that would improve our ability to discriminate between the effects of the drugs.

As for the observational cohort studies, I agree that they were well done. I think we have seen way too many times cases where observational studies yield one result and randomized clinical trials yield the opposite. Witness, hormone replacement therapy. I guess I would put a lot less weight on those.

I thought that the three trials mentioned here each had their pros and cons. I think RECORD will not do what Glaxo planned for it to do, and perhaps the FDA should consider asking them to design another study because this one is not going to show what they set out to show.

DR. ROSEN: Thank you. Dr. Goldfine?

DR. GOLDFINE: As we move further around the table it is harder to say something unique. But I think that in the meta-analysis the important points have already been said, that these were

lower risk patients chosen for efficacy, and in a very small number of events over very short duration follow-up, single cases can swap and change our findings in an important way. So, while the signal is very concerning, we are left with how to handle that by very careful analysis of somewhat inadequate information.

I also concur that we are unlikely to get the type and quality of long-term outcome data from the ongoing studies. That leaves us then with looking at the outcomes and observational studies, which I agree are problematic and I think the hormone replacement therapy is an excellent example of them, but these are carefully performed. I think the important thing to consider is what we are actually missing out of those, and those would be the out of hospital event rates. I think if we go back and try to look at those again to try to make sure we are not missing something is also important, although I understand that that would include other sorts of noise. I think that beyond that we get down to registry and reporting to FDA

data to make our decisions because I don't see anything on the highlight.

We are left with a disease where our drug of choice, which is metformin, now is not tolerated from a renal point of view or GI point of view in a considerable number of individuals and then when we got into "what next" we are really left with a question mark that is very important for us to try to handle in an informative way for the clinicians and the patients. And, I think while we are talking about comparative, while many good issues have been raised about the pioglitazone, I think that the with incretin pathway-altering drugs we have even less long-term information on, and I think that if we have people lumping pio and rosi that is currently our alternative.

DR. ROSEN: Thank you. Miss Killion?

MS. KILLION: I want to thank the panel for their very distinguished analysis here today. It has been very informative to me. I have one singular concern that affects all the data that I have heard today, and it is very clear to me that I

am not a statistician but I am a diabetic and I think that is important.

My primary concern is that my feeling is that we are being asked today to take a very draconian action based on studies that have significant weaknesses and are sort of inadequate for us to make that kind of decision. That is just my general observation for all these studies.

DR. ROSEN: Thank you. Dr. Holmboe?

DR. HOLMBOE: I really don't have a whole lot more to add, other than just to emphasize the importance that we are not comparing this drug to placebo. Diabetics have to take something, just to reemphasize that point.

The second is that if the randomized, controlled trials are not going to give us the answer, then we really are left with observational studies, for better or worse, and we need to do those better and I think, again, a registry is an approach where we could capture those out of hospital events by using that technique, and I hope the FDA will consider that.

DR. ROSEN: I will weigh in on the evidence, and I think it is low to moderate and I think that would go along with what the *Annals* and Cochran database is talking about. We do have some evidence we have a strong signal I think in cardiovascular risk from three independent investigative groups, the sponsor, Dr. Nissen and also from FDA. So, it does suggest that there is an increased risk. There are some issues related to trial duration which are a problem.

In terms of observational data, I think we do have to be extremely cautious about these kind of data sets. We have been misled several times on that front. It is not the strongest piece of evidence, yet, there are numbers to suggest that the risk may be less than we appreciate. But I think there are a number of complicating factors. We are having a hard enough time controlling for factors in randomized, placebo-controlled trials so when you think about observational data, it is complicated tenfold.

I am extremely disappointed, and I think

this is really important, that we are not going to get any really greater insights on this question from the randomized, placebo-controlled trials. I think that that point has been fairly well established, that we are not going to get the outcomes we expect based on the data sets that will be coming from several of the other trials.

So, I think there is a signal. I think I am quite concerned about that signal, and I think the meta-analyses do provide some level of concern for us as a committee. Dr. Pickering?

DR. PICKERING: Thank you. I will limit my comments to the meta-analysis. I am a bit concerned that there is an attempt to make a silk purse out of a sow's ear. If you look at the largest analysis, which was the Nissen paper, out of 27,000 patients there were 86 MIs in the rosiglitazone group and I think 72 in the control groups. So, there is a difference of 14 and these were not adjudicated events. So, a lot depends on this very small number of events to make the difference.

I am also concerned, we have heard that diabetes is a very high risk condition for deaths from myocardial infarction. We also heard that rosiglitazone increases the risk of heart failure, which is another highly lethal condition and, yet, nobody, so far as I am aware, has provided any significant findings that there are increased deaths from patients taking rosiglitazone, and one of the advantages of death is that, as has been said, it is one of the endpoints about which there isn't a whole lot of argument.

If you look at the FDA analysis, their strongest case, as has been pointed out, is the placebo-controlled trials with ischemic heart disease events where there does seem to be a significant effect, but there is absolutely nothing in the active-control trials, and when you look at the placebo-controlled trials that include myocardial infarction, cardiovascular deaths and stroke as the outcome the point estimate is still there but the confidence intervals now overlap unity so this adds to my reservations about the

robustness of the meta-analysis. So, my conclusion is that it is suggestive but by no means conclusive.

DR. ROSEN: Dr. Savage?

DR. SAVAGE: Just a couple of quick points, although I certainly agree with the concerns about looking at epidemiologic data, I think that there have been a lot of cases where epidemiologic data has turned out to be a good indication of what actually was going on when trials were done. So, that needs to be remembered.

I also think that I would like to second the comment that I think the data that looks at the differences between the two TZDs in the epidemiologic data struck me as indicating that the difference may not be as great as some of the claims, and things, that have been made. I came into this whole process thinking that rosiglitazone might have higher rates of cardiovascular disease. So, I think that may be real. There is no reason to think there would be bias in the way people would choose to use those drugs the way they would

be about choosing to use insulin.

The last statement I would like to make, which no one has said and I think it is sort of disappointing, is that although it wasn't involved in the justification for approving these drugs, I think there was a feeling out in the research community that they might provide a major reduction in cardiovascular disease by reducing insulin resistance which had been hypothesized as an underlying factor contributing to these complications. We have really seen nothing that would suggest that the TZDs are going to provide that benefit.

DR. ROSEN: Thank you. Dr. Schade?

DR. SCHADE: Yes, I just have a couple of comments. First, I think if I were a betting person I would probably vote for a cardiovascular risk for rosiglitazone. I am not a betting person and, therefore, I think the amount I would bet on it certainly wouldn't be my house; it would be more likely my lunch. But the point I want to make really is that I am a clinician. I have been in

diabetes for 30 years. I have seen things come and go, and I actually was the principal investigator in the DCCT at which time triglitazone was taken off the market.

Now to address for a second Dr. Graham's point that we ought to be dealing with populations and treatment of populations, not individuals, I would agree 100 percent. But the point I want to make is that we absolutely, as diabetologists, need to have a TZD on the market and if we remove rosiglitazone for what I consider a borderline indication, or borderline data indication, and in one or two years we find out that pioglitazone causes bladder cancer or something else and we then have to take it off, with no choice, we are all going to look back and say, gee, why did we do this? So, I am very concerned, and I agree with the point made down the table, that to perform a draconian type of operation on this medication would probably not be advised in the long run.

DR. ROSEN: Thank you, Dr. Schade. Dr. Nelson?

DR. NELSON: I, like Dr. Pickering and several others, feel a little bit concerned about the low number of events that we have actually seen, and I am a little bit concerned about the focus on relative as opposed to absolute risk, and I think that that is something that we need to really get through to our constituencies and our patients as we try to describe the risk associated with this drug and other drugs like it. I think that we sometimes may be overstating the risk when we use relative risk and this really just needs to be framed properly.

I am also concerned about something I mentioned before, which is biologic plausibility and we haven't really discussed that. I am not sure that is necessarily the point of this meeting, but when you start to try to put together the pathophysiology or mechanism as to why things happen it is always more satisfying when you can explain it. Given that we have seen a lot of data that goes in multiple different directions, I think that if we try to come up with some understanding

of why this might be we would feel perhaps more comfortable with making a recommendation, at least I would. That is what I have to say.

DR. ROSEN: Thank you. Dr. Van Belle?

DR. VAN BELLE: One thing that I was struck by when I reviewed the data was how similar the analyses were by the sponsor, by the FDA and by Nissen. So, I didn't think there was much to argue in terms of the meta-analysis method as such. The actual use of the method can be discussed more intensely I suppose.

What also struck me was the additional analysis done by the FDA in terms of the interactions. That, to my mind, is the way to go in terms of trying to determine what could be the possible group of patients or treatments that might not benefit the patients. Then, going along with Dr. Nelson's point, this is where some speculation as to mechanism of the interaction would be very helpful and would maybe give some biological sense to these data.

To my mind, what this exercise has

suggested to me is that one size doesn't fit all and that when this particular drug is used some care has to be taken in who gets it, what circumstances, what age, and so on and so forth, and then the absolute risk is relatively small, as was pointed out by the sponsor as well, although on balance I think there is a blip and we need to take that into account.

DR. ROSEN: Thank you. Dr. Levin?

DR. LEVIN: I am a generalist so I can't speak to a lot of the detail of the statistical analysis and the epidemiological analysis. But at the end of the day I, like others, believe that when three different meta-analyses reach about the same conclusion, that says to me there is a signal, although there are obviously differences of opinion around the table as to how strong that signal is.

As a consumer advocate, I guess I believe in the precautionary principle which sort of turns on its tail and says really when you have indications of a problem you have to have evidence that that problem isn't there to decide what to do,

rather than the converse, which is the certainty that the problem does exist as sort of a threshold for decision-making.

I, like everyone else, am frustrated by the lack of clarity and confidence in the data we have, which I think speaks to some real structural issues about how we approve drugs and how we monitor them in the postmarket period that those of us who sat through this frustrating experience before really need to push. Because I have been in this position too many times of being at a table where everybody is expressing frustration about having to make a difficult decision based on either poor quality, poor quantity or inadequate quantity of evidence, I think, you know, we all should sort of try to assure that in the future we are not in the same position again.

DR. ROSEN: Thank you, Dr. Levin. Dr. Schambelan?

DR. SCHAMBELAN: Well, one of the advantages of being toward the end is that most of the points you want to make have already been made.

I think there has been excellent discussion.

I would agree with you that there is a signal from the meta-analyses. I think the data could be more robust than they are, and we are sort of left with what is there. I would agree with Judith that these are short-term data, not long-term data and that concerns me. Also, it struck me that we have nice placebo-controlled data looking at rosiglitazone. I wish we had the same for sulfonylureas and metformin analyzed as robustly as these have been analyzed, and we already know that sulfonylureas had this specter placed on it before. So, we are not really able to compare the drugs that are in the armamentarium.

I am concerned about the long-term studies going forward being under-powered and at the end of the day not answering the questions that we hope they will answer so we are going to be left in a bit of a quandary.

I just want to make the point that I think the thiazolidinediones are more useful than simple patient testimony. I think that those of us

practicing endocrinology have clearly seen the benefit for certain groups of patients. There are robust effects. And, I am very concerned about being asked, in a sense, to throw out a class of drugs or, as an alternative, to accept data about another in that class that hadn't been reviewed as carefully as the rosiglitazone data. So, I am going to be thinking about that as I vote for what to do because the TZDs I think are very valuable drugs in treating type 2 diabetes.

DR. ROSEN: Dr. Teerlink?

DR. TEERLINK: So, I, like many of my colleagues here, have been struggling through this data and I think a couple of guiding principles for me in approaching this are that there is no such thing as a perfectly safe drug, and that any time we evaluate these it needs to be clearly within a context. Given that, there need to be different levels of evidence for safety than approval. This applies not only to the types of trials but also to how you interpret subgroup analyses and other observations of smaller groups.

So, with regard to the specific question on the meta-analysis, I think the meta-analyses have the advantage, actually almost by accident, of including a broad base of patients, many of whom were at higher risk than any of the patients that we see anywhere else in the studies in the data package. We have three trials that have been pointed out to actually drive the results. Patients who have heart failure, patients who are older and patients who had preexisting coronary disease all did worse within that context. So, I think we actually see an overall signal for increased cardiovascular risk and actually may have some information in terms of who these patients are based on, you know, incomplete data, not perfectly collected, but still I think we have a lot of information. There is other information within there saying that sicker patients have a higher risk in this group, not only from those three trials but also from the subgroup of patients on nitrates that do worse; patients on insulin do worse. So, patients who seem to be sicker patients

have this signal.

The challenge is that when we look at the observational database we aren't going to be able to pick that up from the observational data. So, while I won't go nearly as far as my colleagues here to say observational studies are not worth anything, I would say that in this particular case the observational studies don't inform my decision a whole lot.

Then we have the randomized, controlled trials which are the gold standard and hands-down the way normally we should evaluate studies. The problem for me in this setting is that none of the randomized, controlled trials study the patients that I am interested in. They all actively excluded the patients who we are concerned about. So, I would admit I don't see a signal for bad outcomes in most of the large randomized, controlled trials but I don't think that necessarily informs my decision about what to do about the drug as a whole. That is I think the sum of my comments on that.

DR. ROSEN: Thank you very much. We are going to ask the two people on the phone. Dr. Oakes first, any comments about the design, trials randomized versus observational versus the meta-analysis?

DR. OAKES: Well, I do think the limitations of the meta-analysis are, obviously, the issues of the data on which it is based, particularly the short-term nature of the studies, so any conclusion we make is a conclusion about short-term risk essentially and that needs to be borne in mind in terms of any action that is taken.

I do think that the ongoing RECORD study may provide some useful supplementary information. They may not achieve the state of objectives in terms of non-inferiority but we will accumulate more events in both arms of the study that will inform decision-making.

The observational studies, I think, yes, it is a good point that they may exclude a lot of the people we are really interested in. I think they would have the potential to detect or exclude

very large effects but may not be able to address the sort of more moderate side effects we are talking about here.

It does seem to be clear that the evidence of cardiac ischemia due to rosiglitazone is stronger in the placebo-controlled studies than in the active-controlled studies so logically that would suggest that the active comparators may not themselves be entirely without risk and that needs to be borne in mind also. And, I do think it is important that the data for pioglitazone needs to be examined at least as thoroughly as that that we have seen here.

DR. ROSEN: Thank you. Dr. Moss?

DR. MOSS: Well, with regard to the meta-analysis, I think it makes limited contribution due to the limited number of events, short follow-up and analytic problems that have been discussed.

As far as the observational cohort studies, they provide some incomplete information and are limited to a degree, but it would be

difficult to base a decision on those studies.

With regard to the large randomized, controlled trials, I am intrigued that everybody seems to comment that they are not going to show anything. It seems to me that the FDA can place much greater demand on gathering much more complete information, particularly if one wants to collect multiple endpoints, and really get an answer to this. It seems to me that the FDA is in a very powerful position in making a considerably greater demand on the RECORD trial in particular in terms of accumulating more endpoints and maybe even expanding the numbers of patients.

Then, I would have to say that FDA has to take some responsibility for the dilemma in which we find ourselves for approving less than optimally designed trials in the past. It just surprises me that one has allowed these trials that are clearly not definitive to have sort of usurped the trial demand. It is my understanding that any company doing any trial has to get FDA approval for the trial that they are conducting. So, I do think

that there is a problem and that, hopefully, this can be rectified in the future.

Questions to the Committee and Vote

DR. ROSEN: Thank you, Dr. Moss. We are moving to the voting stage and I am going to explain the process. There has been a modification in how we are going to vote. First of all, you have three options. You can vote yes, no or abstain. In regards to the new rules, I am going to ask people the first question, which is question number four, and ask for a show of hands for those individuals who would vote yes. This will be a simultaneous show of hands. You have to keep your hand up during the time that I query you individually. So, be prepared for a little isometric exercise because you are going to have to keep your hand up until I get to you to ask for your vote. They will be recorded and repeated so that everybody knows how you vote. After the yes votes are completed and tallied, the no votes will be asked and they will be tallied as well, and they will be queried individually. You will have to

state your name when I ask for your vote, your name and your vote. At the end of the no votes, the abstentions will be counted in the same manner, after which the entire vote tally will be repeated so that all interested observers will know what the response is.

In regards to the sub-questions, there are some comments that can be made with respect to voting yes for each of question four and five. Now, I have sensed a little bit of uneasiness about sub-question four and, because of that, I will query you if you do answer yes to see if you are willing to make any comments about what the evidence is in regard to the comparison of the drug Avandia with other available drugs. So, you can respond however comfortably you feel about it as a panel member after hearing the evidence. If you don't want to comment, if you say yes and you don't want to comment, that is fine. If you say no you don't have to do anything so you are relieved of that responsibility.

Are there any questions before we start?

Yes, Dr. Kramer?

DR. KRAMER: Could you clarify, if you think that there is a suggestion of a risk that should be followed or perhaps requires a warning but it is not definitive, should that be an abstention or a yes with a qualification?

DR. ROSEN: I would say that that should be a yes with a qualification, and that will come in, in question five. Dr. Fradkin?

DR. FRADKIN: I assume that the first question in four is, is there an increase in risk compared to placebo, not compared to comparators. Is that right?

DR. ROSEN: I am going to ask for a clarification from the FDA because I didn't write these questions. That is a great question for a question.

DR. MEYER: We actually didn't explicitly consider that. So, I think it is a clinical call, does it support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus in a clinically important way? So, if you consider

that with regard to placebo, fine. If you consider that with regard--

DR. ROSEN: I think, Judith, you can qualify your statement. If you say yes you can qualify your statement when I query you.

DR. MEYER: Clearly, the way the question is structured, it at least implies that there is a separation between the relative and the absolute. So, if you feel more comfortable answering in an absolute sense, that is fine.

DR. ROSEN: Yes, Dr. Geller?

DR. GELLER: I wonder how the FDA would feel about dividing that question, one part comparing to placebo and the other part--

DR. MEYER: We really discourage modifying the questions. I would much prefer you caveat your answer.

DR. ROSEN: And I think it is built in that we can caveat our answer when we query. This is your last chance to ask, or yell, or do anything before we get to the question and answer period.

DR. OAKES: How are you going to handle the

telephone in this?

DR. ROSEN: You know, that is another great question. Aren't you holding the phone? If you are, your hand is up. We will query you individually. So, you will have to simultaneously hold your answer while we talk to the other people.

So, this is question number four, and the question is do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes? All those who feel that it does increase the risk, raise your hand. How about on the phone? Dr. Oakes or Dr. Moss, do you vote yes or no?

DR. OAKES: I vote yes but I will qualify it.

DR. ROSEN: Okay.

DR. MOSS: I vote no.

DR. ROSEN: Okay, one yes and one no. We are going to start with Dr. Teerlink and we will move around the table to the right because he is tired already with his hand up. Okay, John?

DR. TEERLINK: Yes, but with no real

qualifications.

DR. ROSEN: Dr. Schambelan?

DR. SCHAMBELAN: Yes.

DR. ROSEN: Any qualifications?

DR. SCHAMBELAN: [Off microphone]...complete placebo-controlled trials. I don't know what it does in comparison to the other comparators.

DR. ROSEN: Did you forget to say something, John, about the comparators? No?

DR. TEERLINK: No, I was just confused about whether I have to keep my hand up.

DR. ROSEN: You can put your hand down. Dr. Levin?

DR. LEVIN: Yes, no qualifications.

DR. ROSEN: Dr. Van Belle?

DR. VAN BELLE: Yes, with some effect in some subgroups.

DR. ROSEN: Dr. Nelson?

DR. NELSON: Yes, no qualifications.

DR. ROSEN: Dr. Savage?

DR. SAVAGE: Yes, with stronger evidence in

the placebo control.

DR. ROSEN: Myself, yes, with definite evidence in the placebo. I am not sure about the comparators. Dr. Holmboe?

DR. HOLMBOE: Yes, with also some concern about certain combinations that appear to be at greater risk.

DR. ROSEN: Miss Killion?

MS. KILLION: Yes, with some qualification with respect to certain subgroups.

DR. ROSEN: Dr. Goldfine?

DR. GOLDFINE: Yes, with some qualifications about the subgroups and also a clarification that the conclusion is a serious concern.

DR. ROSEN: Dr. Geller?

DR. GELLER: I think there is some evidence for the placebo-controlled trials. I think the signal is not there for SU and the active comparator trials.

DR. ROSEN: So, yes with qualifications?

DR. GELLER: With qualifications, yes.

DR. ROSEN: Dr. Day?

DR. DAY: Yes, with the qualifications already mentioned around the table about the different types of trials.

DR. ROSEN: Dr. Burman?

DR. BURMAN: Yes, with qualifications as noted, and also that I would prefer "suggests a conclusion" rather than "supports."

DR. ROSEN: Dr. Fradkin?

DR. FRADKIN: Same, I will go for "suggests" and that it is particularly in the placebo.

DR. ROSEN: Dr. Lesar?

DR. LESAR: Yes, with some qualifications related to subgroups and combinations.

DR. ROSEN: Dr. Henderson?

DR. HENDERSON: Yes, particularly in subgroups.

DR. ROSEN: Dr. Kramer?

DR. KRAMER: Yes, with qualifications and I think we should note the insulin observation that the statistician noted, and concern about the risk

of other therapies like sulfonylurea.

DR. ROSEN: Dr. Flegal?

DR. FLEGAL: Yes, with qualifications. I would prefer to say "suggests" and under some circumstances.

DR. ROSEN: Dr. Hennessy?

DR. HENNESSY: Yes. I like "suggests" as well, versus placebo, and I am also puzzled by the lack of a dose-response relationship.

DR. ROSEN: I will get to the nos in a second, but we will talk about "suggest" in the caveats since we can't change the actual question itself, but we can recommend that it be "suggest." Dr. Oakes I think said yes. Correct?

DR. OAKES: Yes, and my two qualifications are, one, the issue about the difference between comparison and placebo and not just comparatives but also the short-term nature of the studies and that we are talking about a short-term risk.

DR. ROSEN: Thank you. Now we are going to go to the nos and I will start with Dr. Moss. Are you a no, out in Rochester?

DR. MOSS: No.

DR. ROSEN: Yes or no for an answer?

DR. MOSS: Oh, I vote no.

DR. ROSEN: You vote no. All right, we don't need to ask you anything else. Down the line, Dr. Pickering?

DR. PICKERING: I vote no on the grounds that the patient is presumed innocent if guilt is not proven, on the British justice basis, and I consider the overall body of data is not convincing.

DR. ROSEN: Dr. Schade?

DR. SCHADE: Yes, I vote no because I am not convinced either.

DR. ROSEN: So, the final tallyB-I am sorry, abstentions? There are none in Rochester, I know that. There are no abstentions around the room that I can see, and you can't change your vote. So, the final tally for question number four is 20 yes and 3 no.

I am trying to decide whether we need to debate the issue of other therapies, and I think

that this is a methodological question. I can go around the room and ask the yes people if they are convinced but I think there are enough caveats about other therapies that I don't think I need to do that. Unless the committee feels otherwise, I would say that we have enough caveats to say that we have some concerns about the other therapies. Are we okay? Everybody okay?

Let's move on to question number five then. This is also difficult and there are caveats involved if you say yes. Does the overall risk/benefit profile of Avandia support its continued marketing in the U.S.? If you vote yes, what should the FDA do to maximize the risk/benefit considerations? The question really is should it continue to be marketed, and if you vote yes then I will ask you to elaborate on what you would recommend the FDA consider doing considering your concerns in question four.

Is everybody clear about the statement of how the question is read? It is for continued marketing. Does the overall risk/benefit profile

support continued marketing? Is everybody ready to vote?

DR. OAKES: Could I just ask, this would not preclude the FDA taking some later action at some point in the future?

DR. ROSEN: Absolutely, this does not preclude them from taking action in the future, absolutely correct. Of course, we are just advisory people so they make the final decisions. Any other questions before this vote is taken? I don't see any objections.

So, does the overall risk/benefit profile support its continued marketing in the U.S.? Raise your hand if you say yes. I am going to go around the room and I think I will start with Dr. Hennessy because Dr. Teerlink gives me a bad look when I call on him first. Dr. Hennessy votes yes.

DR. HENNESSY: Yes, are we doing our qualifications?

DR. ROSEN: Yes, you can do your qualifications now. If you vote yes you have to sort of say what you think the FDA should do.

DR. HENNESSY: So, I will say yes. Given that we have spent absolutely zero time on what a risk management program for this would look like, I don't want to go off half-cocked so I am not going to say anything.

DR. ROSEN: Dr. Flegal?

DR. FLEGAL: I would say yes and I feel the weakness of the evidence really needs to be analyzed more carefully. As to who should be warned and exactly what, I don't really have a recommendation at this point.

DR. ROSEN: You do not have a recommendation. And, Dr. Hennessy, you did not have a recommendation at this stage. Dr. Kramer?

DR. KRAMER: I think it should stay on the market. I know it hasn't been the subject of our discussion but clearly the heart failure should at least be a boxed warning, if not a contraindication. There should be a definite warning about the risk of ischemic disease with information, specifically with the information on the subgroups, insulin patients receiving

concomitant insulin. Also, I think certainly there was a weight of evidence for patients with established coronary disease, patients on nitrates, etc., that might suggest that people would take extra caution and consider possibly not using them in that subset of patients.

DR. ROSEN: Thank you. Dr. Henderson?

DR. HENDERSON: I agree, and I think that it should at least have a warning, particularly with the subgroups that we have identified today, and the warning could also say that there is still ongoing research, that we haven't reached a conclusion yet.

DR. ROSEN: I would like to go back to Dr. Hennessy. I am sorry to bother you, but would you agree with a warning or not? It would be nice to specify what you would recommend the FDA do, if possible.

DR. HENNESSY: A warning and additional research at a minimum.

DR. ROSEN: Dr. Flegal?

DR. FLEGAL: I can agree with a warning and

additional research.

DR. ROSEN: Thank you. Dr. Lesar?

DR. LESAR: Yes, at this time, based on the weakness of the data, however, also issues related to the other potential options related to therapy, and that labeling should be changed addressing patient choice, sequenced combinations, monitoring, patient education, use with other anti-anginal and potentially ARVs, also mandatory collection of data related to both the macrovascular and microvascular benefits or problems, and duration of therapy.

DR. ROSEN: Thank you. Dr. Fradkin? Yes?

DR. FRADKIN: Yes. So, I would suggest considering not having an indication for use together with insulin, both because I think the risks may be higher in people with insulinB-I mean, it may add more risk to the people on insulin, but also I think you don't have the benefit of the comparator issue because there wouldn't really be any reason to be on the other oral agents in particular if you were on insulin so you wouldn't gain that part of the benefit.

DR. ROSEN: Are you saying a warning for insulin?

DR. FRADKIN: Well, I am not sure what the best way is. I am not sure if it is a warning or that there should just not be an indication. I mean, I would have to ask the FDA what is better to say.

DR. MEYER: We were just about to query you whether you are suggesting a contraindication for use with insulin or removal of the current indication that it can be used with insulin.

DR. FRADKIN: I am not sure that I really understand the consequences of the difference, but I guess what I would be thinking is that there shouldn't be an indication for the use. Maybe there shouldn't be an indication and there should be a warning.

DR. MEYER: Just to be clear, in fact there was a mention about this in the open public hearing. In Europe a contraindication sort of means you really shouldn't do this. In the United States a contraindication means you mustn't do

this. You must never do this.

DR. FRADKIN: I wouldn't make it a contraindication. I think I would probably have no indication and a warning.

DR. ROSEN: I think that is clear. I think. Dr. Burman?

DR. BURMAN: I agree, a warning about possible--

DR. ROSEN: I am sorry, can you just say yes, I vote yes?

DR. BURMAN: I vote yes. Thank you. And a black box warning for certain conditions, including insulin, severe congestive heart failure, severe arteriosclerotic heart disease and use of nitrates.

DR. ROSEN: Thank you. Dr. Day, I think you raised your hand, didn't you? I would like you to discuss the risk management.

DR. DAY: Yes, I had my hand partially up. It is a fence-sitting hand here. We really need to have better data, and I fear the only way really to get it is to consider very seriously something like a registry. I do know that that places a

great burden on the sponsor. There are other programs out there so there are established methods for doing that. But I think those would be the best data that we could have in order to understand what is going on in this interim period.

DR. ROSEN: Thank you. Dr. Geller?

DR. GELLER: I vote yes, with a black box warning. I think in the public session one speaker did put up the U.K. warning and I certainly think that is a good starting point.

DR. ROSEN: Great, thank you. Dr. Goldfine?

DR. GOLDFINE: I also vote yes. I also agree that there should be labeling. I think there should probably be the removal of the indication because it is hard to have it as an approved indication with a black box warning, but I don't think that we can quite go to the point of saying it is contraindicated, especially for patients with very profound insulin resistance who are requiring many units who have benefitted. I think that we can do the careful review of the complementary

therapies and reconvene and discuss when we actually have that data available to us. I think that is a very important piece of missing information from this vote. And, I think that education to care providers and distributing that this black box warning has happened will be an important additional step.

DR. ROSEN: Thank you. Miss Killion?

MS. KILLION: I vote yes and I agree with Dr. Goldfine, with special emphasis on education to providers and to patients so they can make proper choices.

DR. ROSEN: Dr. Holmboe?

DR. HOLMBOE: I vote yes, and given the lack of efficacy, a black box warning and other things, I agree with Dr. Day that it should be restricted to those patients who are on a registry at this point.

DR. ROSEN: I vote yes, and I agree with a warning, and I think the concerns, particularly for individuals with severe atherosclerosis on nitrates and insulin should be considered. Dr. Pickering?

DR. PICKERING: I also vote yes, and I am puzzled by how people can vote yes for both questions, but that is beside the point. I don't have any specific recommendations about warnings but I am very anxious to see, for example, that the RECORD and ACCORD trials are continued and the FDA does an appropriate analysis with pioglitazone.

DR. ROSEN: Thank you. Dr. Savage?

DR. SAVAGE: I vote yes. I also think there needs to be a stiffening of the warnings. Since we didn't get a chance to discuss that issue in any great detail, I don't really feel that I can be too specific. Certainly the signal with insulin seemed to be the most worrisome, and the nitrate issue. There are several things that are identified. The other things is that I would urge the FDA to consider the absolute risk as well as the relative risk when you are trying to balance the potential benefit versus harm.

DR. ROSEN: Dr. Schade?

DR. SCHADE: Yes, I vote yes. I would be against a black box warning but I think there

should be a warning in the text indicating that this drug may cause the myocardial infarction, etc. type of issues. I would be against being specific about subgroups because there is data in the literature that these drugs with insulin can be beneficial in very obese patients, and when you are giving a patient 500 units a day and it causes all the problems that that much insulin does, these drugs can be very beneficial for reducing insulin resistance. So, without the data I am very hesitant to start naming subgroups in which this drug should not be used in combination with.

DR. ROSEN: Thank you. Dr. Nelson?

DR. NELSON: I vote yes as well. I agree with the idea of putting a boxed warning on. I like the idea of a registry. I just think it is just such an overwhelming task to undergo and it is essentially going to eliminate the drug from any real widespread use. But maybe there is something in the middle. I am not sure what the options really are that the FDA has, but I know in terms of mandating a certain degree of data collection, you

know, or some more pharmacovigilance than we probably currently have and, you know, allowing the company to run on its own perhaps may not be the best option, but a little more oversight. Something along those lines would be more satisfactory I think.

DR. ROSEN: Thank you. Dr. Van Belle?

DR. VAN BELLE: I vote yes and I would recommend something like the labeling that was agreed to with the European medical agency.

DR. ROSEN: Dr. Schambelan?

DR. SCHAMBELAN: I vote yes, and would agree with the suggestions for a black box warning, particularly with respect to insulin, although I wouldn't make it contraindicated. I agree with Dr. Schade, there probably are some patients for whom this drug could be useful in conjunction with insulin but it certainly shouldn't be routine practice in my opinion.

I would also like to just endorse what Dr. Hellman listed before as some recommendations for the agency, the NIH, and other bodies going forward

to get us out of this hole that we are in with trying to analyze the kind of data we have been asked to analyze today. As much effort as went into it, there were still a lot of deficiencies in the data and they could be improved if we had a different way of developing drugs.

DR. ROSEN: Dr. Teerlink? I see your hand wasn't still up. Can you raise it again!

DR. TEERLINK: Thank you. So, I vote yes and suggest that we remove the indication for insulin; that we put a black box warning that includes the issue of heart failure, patients on insulin, as well as symptomatic coronary artery disease patients requiring nitrates. I add the latter with a bit of reticence but see that as the strongest signal. I am actually comfortable with the insulin issue because that was the one result that was relatively homogeneous.

DR. ROSEN: Thank you. I am going to query people for a no voteB-oh, I am sorry, Dr. Moss and Dr. Oakes. Dr. Oakes?

DR. OAKES: I vote yes, continue marketing

with, I think, the same kind of comments other people have made about strengthening the warnings and undertaking more research.

DR. ROSEN: Great. And Dr. Moss?

DR. MOSS: I vote yes and I would encourage putting pressure on the company to do a more extensive job on endpoints and to accumulate the endpoints that may have already accumulated, particularly the multiple endpoints, and I would add ask GlaxoSmithKline for quarterly reports of events so that the FDA would be immediately abreast of what is going on.

DR. ROSEN: Thank you. I am going to ask for no votes. Dr. Levin? And you don't need to explain but if you want to make a comment--

DR. LEVIN: No, I will make a comment. Again, it seems to me that given the evidence of a strong safety signal, given the fact that there are around this table and FDA some doubts about the ability of ongoing clinical trials to answer definitively the question about the cardiovascular safety of the drug, and given the enormity of the

potential public health risk by allowing this drug to continue to be marketed and used by millions of people for the rest of their lives, I logically can't find any way to justify leaving this drug on the market.

DR. ROSEN: Thank you very much. We have a comment from Dr. Day about management which is apropos to the final vote. So.

DR. DAY: It is very easy to say that we will then have patient and physician education. I must report to you that after the last "Dear Healthcare Professional" letter came out, or one of them for this drug, I did test physicians who reported regularly prescribing this drug. First of all I asked them if they were aware there had been a "Dear Healthcare Professional" letter recently, and there was only one person in a large room who said yes. When I asked him what the warning was about, he did not know. That was for macular edema.

In addition, I then tested their knowledge of possible side effects for this drug. I didn't

test their memory. I gave the information to them and that information was from the company website from the patient information section, the easy part, and there were 26 potential side effects. They studied them and then I asked for their knowledge. They were just as bad as the lay persons. They got less than a third of them.

So, let's not assume that, yes, we will do all our usual education things. We have to provide a better way for showing that information. When we showed that information in a new display, designed to enhance the cognitive accessibility of the information, improvement went up by 100 percent. So, it is not just what we tell them, it is how we tell them.

DR. ROSEN: Thank you. Unless there are any further comments, the vote was 22 in favor of continuing on the market and 1 opposed; no abstentions.

Unless there are any comments, I think I have the power to adjourn this meeting. Thanks to everybody on the committee for some very hard work.

[Whereupon, at 5:45 p.m., the proceedings were adjourned.]

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