the evidence for myocardial infarction associated with the use of rosiglitazone, what should be the way forward? Well, based on all that I have told you in the last five minutes, and erring on the side or precaution, our recommendations going forward are two:

First, continue the ongoing long-term trials and ask their data safety monitoring boards to continue their regular monitoring for signals of cardiovascular mortality and myocardial infarction. Upon completion of these trials, analyze them for cardiac events, cardiac events in general and myocardial infarction in particular, alone or in an integrated analysis, to help reach the statistical power to confirm or refute a hypothetical small increase in myocardial infarction associated with rosiglitazone.

Second, provide additional information for patients and physicians about the cardiovascular safety profile of rosiglitazone by including in the product labeling a description of the cardiovascular data, the data you have seen today.

This concludes our formal presentation, Mr. Chairman. We are now ready to take questions from the members of the committee. To facilitate answering those questions, I would like to invite Dr. David Cocchetto, Vice President of Regulatory Affairs, to the podium.

Clarifying Questions from the Committee

DR. ROSEN: Thank you, Dr. Krall. This discussion is now open for questions from the committee members. Please raise your hand so I can identify you. Dr. Burman?

DR. BURMAN: Good morning. Thank you very much. Rosiglitazone increases LDL and total cholesterol and that wasn't brought up this morning. Do you have any information or new data regarding the increase in LDL and potential cardiovascular adverse effects in the three prospective trials?

DR. COCCHETTO: Yes, Dr. Burman. Let me ask Dr. Stewart to comment on your question.

DR. STEWART: Thank you, Dr. Burman. As you are aware, rosiglitazone does increase LDL.

Pioglitazone also increases LDL by about 3 percent. When you look at the lipid profile for rosiglitazone, we see an increase in LDL cholesterol and an increase in HDL cholesterol, and the total ratio is the same. We don't believe that increase in LDL actually accounts for any increase in cardiovascular events either in the short term or the long term.

To answer the question about the short term, we looked at LDL tertile analysis for changes in LDL with rosiglitazone in ICT and ADOPT data sets. So, what we did isB-and if you would like I can show you that dataB-actually look at the changes in LDL tertiles.

[Slide]

What you can see here is that across the topB-I can't find a pointer but I think you can see rosiglitazone in tertile changes in LDL. If you had expected an increase in LDL rosiglitazone to have had more events, you might have expected a different distribution in the LDL profile. We are actually seeing a similar distribution in the

change in LDL for that. That is for ADOPT. Similar data is seen with ICT.

There are probably two other bits of information I can add. We looked at the effect of LDL with rosiglitazone, and it is modeling work using the UKPDS risk engine. When we did modeling the UKPDS risk engine, we found there was no evidence of an increase in events over four, five or ten years.

So, to answer your question, I don't think LDL does contribute any increase in cardiovascular risk events either in the short term from our tertile analysis or in the long term from our UKPDS risk engine.

DR. ROSEN: Thank you. Dr. Pickering and then Dr. Teerlink.

DR. PICKERING: Thank you. I would like to ask a question about the adjudication by cardiologists of the ICT events. On slide A27, it was shown that the rate of MIs was approximately twice as high in ICT as in RECORD. Yet, on slide 62 the overall death rate was about half what it

was in RECORD and there seems to be a disconnect here, and what we heard was that the adjudication reduced the number of MIs by about half in the ICT database. I would like to ask what sort of data were available for this review and how complete it was. Did you get all the events from the various clinical trials to review?

DR. STEWART: I will ask Milton Packer to come up and explain what happened with the cases of adjudication.

DR. PACKER: I am Milton Packer, and both myself and Peter Kowey were the adjudicators for the ICT and ADOPT study. We set up a set of principles, rules. I actually have a copy of those rules if you would like to see them. We asked to be provided with all of the patient narratives for every single serious adverse event in all of the trials in the ICT analysis and in the ADOPT study. The total number of SAEs was about 2,100 narratives that were reviewed. They represented every single SAE across all the trials in the ICT and ADOPT analysis. Tom, does that answer the

question?

DR. PICKERING: Yes. Can you say something about the ones that you eliminated? You reduced the number in ICT by about half after adjudication. Can you tell us a bit more about that?

DR. PACKER: Yes. Please recall that we defined myocardial infarction in two ways, one definite myocardial infarction when we had evidence for chest pain plus or minus enzymes and ECG changes. There was unconfirmed myocardial infarction where the narrative was very compatible with the course of myocardial infarction and we actually thought myocardial infarction was likely but we just didn't have confirmatory evidence. So, because of the nature of the narrativesB-please recall this was a retrospective review of narratives and some of the events occurred seven, eight years ago-Bwe made sure that we were clear as to the level of evidence that we had to make a diagnosis of myocardial infarction and, therefore, if you wish you can look at the definite plus unconfirmed as being a more comprehensive picture

of myocardial infarction.

DR. ROSEN: Thank you. Dr. Teerlink and then Dr. Fradkin.

DR. TEERLINK: Yes, I have a series of questions just to help clarify some of the things that the sponsor reported. First of all, I find it a bit confusing that Dr. Krall mentioned a number of times and actually emphasized in his closing statements the reassurance that he is getting from DSMBs on these studies. I would just like to emphasize that from my standpoint that is a rather irresponsible comment. If you look at the results just from the RECORD interim analysis, that includes a hazard ratio of 2.4 for the myocardial infarction. So, I think you are placing way more faith in the DSMB's judgment and their duties, in a sense, to put that forward as being reassuring. I am happy to give you an opportunity to comment on that, but otherwise I would like you to kind of retract that as being something that reassures you and reassures against the kind of ratio that is maybe 5 or 10 but I don't think any of us expect

that.

The thing we are concerned about is an increase in cardiovascular events in the 20-40 percent range or the 70-90 percent range, neither of which are going to be picked up by a DSMB on a study. Do you have any comment?

DR. KRALL: I don't want to engage in an argument about how to interpret the findings or the actions of the DSMBs. What I do want to convey is that the DSMBs were provided with the results of the integrated trial analysis. They were made aware of our concerns about the implications of the integrated trial analysis, were they to be true, and asked to make decisions about the continuation of their trials with that knowledge.

DR. TEERLINK: Could I follow-up? I have a series of questions.

DR. ROSEN: Yes.

DR. TEERLINK: The other question is in regards to the ICT definition of myocardial ischemia. There was some mention that confused me, saying that dyspnea and shortness of breath and

heart failure can confound that a bit. I just want to point out that I think specifically dyspnea and shortness of breath and those heart failure-related terms were not included in the myocardial ischemia definition. Is that correct?

DR. COCCHETTO: May I ask Dr. Stewart to address that specifically?

DR. STEWART: There was a long list there. We didn't put down all of them in the list in verbatim terms so things like chest discomfort and dyspnea were included in the list that were looked at for the verbatim terms. I would remind you that when the integrated clinical trial analysis was done, it was done for both myocardial ischemia and congestive heart failure.

DR. TEERLINK: Finally, and this is related to Milton's point that I think, having done these kind of adjudications on post hoc type of analyses myself, the combined confirmed definite and unconfirmed, yet still kind of felt to be significant, was probably the most reliable assessment when you are looking at data where there

wasn't prospective data collection. Of note, on A37 the point estimates don't seem to change much when that adjudication criteria are applied. So, does that seem reasonable and consistent with what you were saying, Milton?

DR. STEWART: I will ask Milton to come up but, yes, I think we would agree with that.

DR. PACKER: John, I agree. It is a retrospective review and we had to make a judgment as to whether the clinical course was compatible. Sometimes we had very little information.

Let me just emphasize that our adjudication, if you include definite and unconfirmed, doesn't really change for ICT but it does actually reduce the point estimates for ADOPT even if you include definite and unconfirmed.

DR. TEERLINK: Right, so with ADOPT it goes from 1.23 to 1.21 and from 1.52 down to 1.20.

DR. PACKER: Right. It goes down a little bit, and please recall that ADOPT was a long-term study.

DR. TEERLINK: Right. Then, finally, on

slide A44, which is in relation to your epidemiological studies, you also mentioned that these studies were done to include revascularization rates as well. I wonder if that analysis has been done for myocardial infarction and revascularization.

DR. COCCHETTO: Yes, the primary endpoint did include revascularization.

DR. TEERLINK: Could we see that data? That would be great.

DR. COCCHETTO: May I ask Dr. Alex Walker to speak to that point?

DR. WALKER: The reports which were submitted through the sponsor to the agency included coronary revascularization and the sum of coronary revascularization and MI. This was both for the Ingenix and for the PharMetrics analyses.

[Slide]

Here we have just the CR, or do you want CR plus MI?

DR. TEERLINK: Yes.

DR. WALKER: CR plus MI? Do we have CR

plus MI together?

[Slide]

There we are, the combined outcome. Here are the results, qualitatively, not substantially different from what you have seen before. These are for the monotherapy groups. Can we go on to the dual therapy?

[Slide]

And finally the insulin?

[Slide]

DR. TEERLINK: Do you have just the final rosiglitazone versus the non-rosiglitazone?

DR. WALKER: Do we have that on these slides? We don't have it on a slide. I can get you the number with a little bit of looking through the papers.

DR. TEERLINK: I would appreciate that.

DR. ROSEN: Dr. Fradkin?

DR. FRADKIN: I just wanted to return to Dr. Burman's question about lipid status. I wondered if there was differential use of statins in the rosiglitazone versus the comparator groups.

DR. COCCHETTO: Again, I would ask Dr. Stewart to comment.

DR. ROSEN: You might as well stay up, Dr. Stewart.

DR. STEWART: I would like to sit down, but, yes, there was differential use of lipids in the longer-term studies. In the short-term studies patients came in on either background therapy and did not change, so in all the short-term studies there really isn't change in the lipid therapies. Within ADOPT and within the RECORD study there was likely to be change in therapy to reach targets.

Something that I didn't say to Dr. Burman is that in both the ADOPT and RECORD long-term studies patients and physicians were encouraged to get people to treat their lipids appropriately with statins. The data that we have in conjunction with statins has shown additional lowering of LDL cholesterol, 30 percent, with further reduction in HDL cholesterol. So, in long-term studies they were allowed to use statins; short-term, statins, no.

DR. FRADKIN: Could you quantitate how much in the long-term studies they used the statins and might that explain some of the differences in terms of the short term versus the longer-term potential differences in CVD?

DR. STEWART: It is difficult because certainly from the RECORD study we don't have that unblinded data because the study is ongoing. But we know they started with baseline use of statins, about 15-20 percent, and it has gone up. In ADOPT there was a slight increase in statin use. When you look at the lipids at the end of the four years in ADOPT, they were about the same and may be accounted for by a slight increase in statin use with rosiglitazone.

DR. FRADKIN: Can I ask one more?

DR. ROSEN: Yes, go ahead.

DR. FRADKIN: I was just wondering if you had done an analysis similar to what you did with regard to the tertile analysis, looking at a different question, which is whether, if there is an increased risk of cardiac events it might be

mediated by fluid retention. So, I wondered if you might have looked at, say, tertiles of weight gain or tertiles of hemoglobin change, or something to see whether there was a relationship.

DR. STEWART: Sure, we did look at that because we did wonder whether there was a relationship with the change in weight with the change in events. What we actually found is that there wasn't a relationship between tertile weight. The highest tertile had people gaining anywhere from 2.7 kgB-and it was interesting that in both the sulfonylurea arms and other arms people were gaining up to 20 kg, yet, when you actually looked at the change in tertiles with change in events there was no relationship.

DR. FRADKIN: The weight might, you know, reflect fat deposition or fluid retention. What about hemoglobin or hematocrit which might be more specific for fluid?

DR. STEWART: Yes, we did some plots as well to see if we could differentiate in terms of hematocrit and I don't think it is sensitive enough

to pick that up. But you are right, most of the weight gain was related to subcutaneous rather than visceral fat.

DR. ROSEN: Dr. Kramer?

DR. KRAMER: I had a question for Dr. Alex Walker about the PharMetrics study. In addition to not being able to capture sudden death because it wasn't captured in the managed care database, am I correct in assuming that MIs that were fatal during hospitalization were not captured since you used discharge diagnoses for MI?

DR. WALKER: But they would be captured. The MIs that aren't captured are MIs that don't result in hospital care.

DR. KRAMER: So, it is non-fatal and fatal but excluding sudden death or not getting to the hospital.

DR. WALKER: Excluding not getting to the hospital in time because, you know, the formal definition of sudden death even includes some people getting to the hospital. It has to do with the interval between onset of symptoms and death.

[Slide]

I think we do have the number of the combined. This is overall in PharMetrics. Taking myocardial infarction and coronary revascularization together, the rosiglitazone versus all others, 1.03 the relative risk, with 95 percent confidence interval of 0.95 to 1.11.

DR. ROSEN: Dr. Hennessy?

DR. HENNESSY: Thank you. This might not be a fair question but I am wondering if you had the opportunity to review the results of the paper that just got accepted for publication in *Pharmacoepidemiology and Drug Safety*, funded by Takeda and performed by Takeda investigators that showed that the rate of myocardial infarction was 22 percent lower in pioglitazone users compared with rosiglitazone users.

DR. COCCHETTO: No, I have not had an opportunity to review that.

DR. ROSEN: I am going to ask Dr. Moss, on the telephone, if he has any questions, or Dr. Oakes. Anything from Rochester? I don't know if

we can hear you. Can you hear us?

DR. OAKES: We can hear you.

DR. ROSEN: Okay. Any comments or questions for the sponsor?

DR. OAKES: I would just wonder if the sponsor has identified any group of patients who might be at higher risk and if they have any suggestions in that regard.

DR. COCCHETTO: Yes, Dr. Moss, subgroups of patients who may be at higher risk, again, let me ask Dr. Stewart to comment.

DR. MOSS: This is Dr. Moss. I do not have any questions at this point.

DR. ROSEN: Thank you.

DR. STEWART: Yes, I think it is important to look at the subgroups to see if there were patients at risk, and I think the category that we saw most at risk was actually from heart failure. So, in the 211 study there were more ischemic events with rosiglitazone as with placebo in patients who had known congestive heart failure. The other group where there were slightly more

events, although I must say the numbers are low, for myocardial ischemia there were 12 versus 4 in the insulin comparison.

DR. ROSEN: Can you clarify for me in the PPR study what percentage were diabetic that were obese?

DR. STEWART: About four percent were diabetic.

DR. ROSEN: Four percent?

DR. STEWART: Yes.

DR. ROSEN: Other questions? If there are no further questionsB-oh, I am sorry.

DR. GELLER: I would like you to comment on your decision to integrate the clinical trials database rather than perform a stratified analysis by trial. It seems to me that that is a very big difference between the other two meta-analyses we have read and yields quite different results, more favorable to you.

DR. COCCHETTO: I will ask Nevine Zariffa to address your question, from our biostatistics group.

DR. ZARIFFA: Thank you, David. I think the question had to do with the choice of methodologies and the modeling exercise that GSK undertook. I will take a stab at it and if there is need for follow-up I will invite Dr. Koch to speak at length.

When trying to combine data from this varied and complex set of sources of the 42 studies, the issue of sparsity was one that was foremost on our mind. Of course, excluding data from studies with zero events was not something that we viewed favorably. So, much like the FDA did, the goal is to provide some stratification, if you will a stratification strategy, that allows for combining data across studies, avoiding zero in any of the strata. We happened to pick one that had to do with comparative groups, seven of them. They are described in the briefing document. The agency chose meta-groups. I actually think the results are quite comparable but others may have a different opinion on that. Is that sufficient?

DR. ROSEN: Pending any further questions,

we would like to thank the sponsor for being on time. We are going to take a ten-minute break, ten minutes only, and during that time I would advise the advisory committee not to speak about this or to the media.

[Brief recess]

DR. ROSEN: We have an invited speaker, Dr. David Gordon. The agenda has been published. I won't go over it again, but we will start with two FDA presentations, Drs. Mele and Mahoney, and the first speaker is Joy Mele and she will be talking about the FDA meta-analysis. Are we ready up front? Not quite yet. While we are waiting, we have some temperature issues, I understand. It is hot in the back and it is cold up here. The panel has priority so we are a little too cold up here. We thought there would be plenty of temperature during the course of the meeting but we are trying to make some minor adjustments to warm things up here, and comments are welcome to warm things up here as well.

FDA Presentations

FDA Meta-Analysis

DR. MELE: Good morning.

[Slide]

My name is Joy Mele and I will be presenting the results of the FDA meta-analysis this morning. Before I begin, I would like to point out that in addition to the copy of my slides you should also have a handout. That handout shows three forest plots illustrating the data for all the studies in the FDA meta-analysis. I think these plots are really important in interpreting the meta-analysis results so I wanted to make sure you have a copy of that.

[Slide]

I am going to begin my presentation with a summary of the motivation for the FDA meta-analysis. Then I will describe the database used by FDA and show how this database differs from the one used to produce the results published in the *New England Journal of Medicine*. After describing the FDA methods I will present the overall results and then show results for subsets of the database. These subsets include the active

control studies, the add-on to insulin studies and the placebo-controlled non-insulin studies. I will show results for subgroups and for the three placebo-controlled trials in special populations. Then I will close my close my presentation with a few summary points.

DR. ROSEN: Dr. Oakes and Dr. Moss, in Rochester, we are getting some feedback, back up north and that is coming back into the committee room. So, if you could mute your part of the telephone connection I think that might solve part of the problem.

DR. MELE: Thank you.

[Slide]

First I would like to point out the reasons why we conducted an FDA meta-analysis in spite of GSK providing FDA with the results of several analyses. GSK provided an overall estimate of risk of 1.3 for non-serious and serious myocardial ischemic events. But it was not clear whether this risk could be generalized to the overall population. Subgroup analyses performed by

GSK and also my early analyses of the pooled data suggested that the effect may be heterogeneous. No results by individual study were shown in the study report provided by GSK so we did not know the weight of individual studies in the overall estimate. The database contained studies with high risk populations and it was important to us to understand the contribution of these studies. Also, GSK's initial model used to produce their overall estimate did not include covariates or study as a stratifier.

[Slide]

Now I will talk about the FDA database. The database used in the FDA meta-analysis was comprised of 42 trials defined by GSK. On some of my slides I abbreviate the database name with ICT for integrated controlled trials. The selection criteria used by Dr. Nissen and Miss Wolski differed by GSK's criteria and, therefore, the databases differed as well. The databases differed on a total of 14 studies. One selection criterion used by GSK was that trials be double-blind so all

42 trials used in the FDA analysis were double-blind compared to 38 in the published database. In both databases the majority of the trials are six-month trials. However, due to the inclusion of the two large long-term studies of DREAM and ADOPT in the published database, the patient exposure in terms of person-years is clearly greater than for the FDA database. In addition to long-term exposure, there are other differences between the long-term studies and the short-term studies that we felt precluded combining these studies. The differences will be explained by Dr. Mahoney.

The FDA database is composed completely of patients diagnosed with type 2 diabetes while Dr. Nissen and Miss Wolski included non-diabetic patients. The endpoints for the two analyses were different, with FDA using composite endpoints and Dr. Nissen and Miss Wolski analyzing MI and CV death.

[Slide]

Now I will give you more details about the

FDA database. The FDA database is comprised of trials of rosiglitazone administered as monotherapy or in combination with metformin, sulfonylurea or insulin. In three trials rosiglitazone or placebo was added to background anti-diabetic medication. Background medication refers to the medication the patient was taking at the time of enrollment in the trial. This is similar to PROactive, except that the background medication regimens in these trials were to remain stable.

We did not combine arms of rosiglitazone monotherapy with combination arms within the same study as Dr. Nissen and Miss Wolski did. We did combine doses of 4 mg and 8 mg after seeing no evidence of dose response. Overall, the rosiglitazone database is predominantly composed of placebo-controlled studies, while a similar database for pioglitazone that will be presented by Dr. Graham is predominantly composed of active-control studies. These two databases differed in other ways as well.

[Slide]

Later in my presentation I am going to show results for the three placebo-controlled trials shown here. Based on selection criteria, these patient populations would be considered at high risk for ischemia. Study 352 is a small, short-term study of patients with stable coronary heart disease. Study 211 is a one-year study of patients diagnosed with congestive heart failure. Study 135 is a two-year study in elderly patients. These three studies had the highest rate of ischemia of any of the trials and so may provide some additional insight regarding the risk due to rosiglitazone.

[Slide]

None of the trials in the meta-analysis database were designed to assess ischemia as an endpoint. So, GSK, as they described to you, identified non-serious and serious myocardial ischemic events retrospectively, with adjudication by a blinded committee of physicians. This identification of endpoints retrospectively speaks to one of the shortcomings of the meta-analysis in

that the studies lack a prospectively defined common hypothesis.

A third endpoint, a composite of myocardial infarction, CV death and stroke, was defined by GSK late in the FDA review cycle and so there was no adjudication by GSK and no complete review by FDA. This endpoint, however, is useful for comparing the results of the FDA meta-analysis to the results of the long-term large, prospective studies.

[Slide]

Now I am going to talk about the FDA methods. Because of the heterogeneity that we initially noted, and because we thought it was important to retain the randomized comparisons of the individual studies, we defined meta-groups to which we assigned studies according to design. These are similar to comparison groups that GSK defined, except that we are assigning studies and GSK assigned patients, though for some groups there is no distinction between the two approaches.

The meta-groups used for the analyses by

the FDA were monotherapy rosiglitazone against placebo or an active control; rosiglitazone plus background therapy and this group was not defined as one of GSK's comparison groups; and then four groups of add-on studies, rosiglitazone plus sulfonylurea, plus metformin, plus insulin and plus metformin with sulfonylurea. The number of studies adds up to more than 42 because there are some studies that had more than one possible comparison of rosiglitazone. In those cases, the study was split into two-arm studies duplicating the control arms.

[Slide]

A potential problem in the conduct of a meta-analysis, particularly a meta-analysis of safety data, is how to deal with low event rates. For the GSK and FDA analyses the focus was on composite endpoints. Most trials had events in at least one arm. For example, for serious plus non-serious ischemic events there were four trials that had no events in either arm. If, instead, we looked at the components of the composite endpoints

such as MI or death, there are many trials with no events and results then can vary considerably with an analytical method. For example, with our database I was able to obtain odds ratios for MI ranging from 1.2 to 1.6 and for CV death of 1.0 to 1.8.

Zero events also present problems when trying to create a forest plot, and the forest plot is an important tool in understanding the impact of individual studies. I thought it was important to depict the odds ratios for all the trials so for the forest plots a half was added to each cell for studies with no events in one arm or both arms. This can be seen in the handout that I gave you.

Lastly on this issue of low rates, several meta-analytical approaches drop studies with no events in both arms, as does the exact test that I used. So, it is important to do additional analyses to try to assess the impact of dropping studies and I did several sensitivity analyses.

[Slide]

The first step in the meta-analysis was to

determine whether computing an overall estimate was sensible given the disparate patient populations in the database. So, heterogeneity among studies within each meta-group was assessed and an overall estimate of risk was computed for each of the meta-groups. Based on the results for test of heterogeneity, I redefined the meta-groups creating a separate group for the active control comparisons. We computed overall odds ratios but continued to check for differences among the meta-groups and to examine subgroups. Having access to the patient level data made it possible to conduct analyses accounting for such factors as length of exposure and a wide range of patient characteristics.

[Slide]

Now I will present the results of the FDA meta-analysis.

[Slide]

I will start with a general summary of the FDA findings. FDA computed an overall estimate of the risk of non-serious or serious myocardial

ischemic events associated with rosiglitazone of 1.4. Due to heterogeneity among the meta-groups and potential differences in interpretation of comparisons against placebo versus against an active comparator, we looked at the active-control data and the placebo-control data separately.

For the active-control data there was no evidence of increased risk associated with rosiglitazone compared to metformin or sulfonylurea though the data was limited, so the confidence interval is wide and does not rule out the possibility of a difference either in favor of rosiglitazone or against rosiglitazone. However, I think that these results are supported by the results from ADOPT and RECORD, which is why I will be showing them to you separately. The placebo-controlled data, which comprises more than 80 percent of the database, showed increased risk associated with rosiglitazone compared to placebo, but the results may be considered heterogeneous.

[Slide]

Here are the results for all 42 studies.

The odds ratio for serious and non-serious myocardial ischemic events was 1.4 with a 95 percent confidence interval of 1.1 to 1.8 and a p value of 0.02. The odds ratio for serious ischemic events is consistent with the total results but with half the attributable risk. The event rate for the composite of MI, CV death and stroke is low, at less than 1 percent in each group, and though the estimate is over 1 the confidence interval is wide and the result not significant.

[Slide]

Here is a forest plot with the results ordered by magnitude of the odds ratio in each meta-group. The odds ratios are plotted on an algorithmic scale starting with 0.3 and going to 10. Values to the left of 1 favor rosiglitazone and to the right favor control. Results for all the individual studies that went into the meta-groups are shown in the three forest plots in your handout, as well as in my first review.

At the top of the plot are results for rosiglitazone head-to-head against an active

comparator. The value of 1.1 is obtained from pooling the data for plotting purposes. On your handout you can see that the estimate is 0.99 computed stratifying on study. The remaining groups are all placebo-controlled with odds ratios all greater than 1. The rosiglitazone arms are rosiglitazone plus sulfonylurea, rosiglitazone plus sulfonylurea and metformin and then rosiglitazone as monotherapy, with background medication, with insulin and then with metformin.

The comparison of rosiglitazone added to metformin compared to placebo added to metformin was of concern, with an odds ratio of 3, but difficult to interpret. For example, you can see that the addition of sulfonylurea--this point here--to this combination in a single add-on study yielded an odds ratio of 1.1. Also, the results within the metformin meta-group are heterogeneous with add-on studies showing differing results from the fixed dose combination of Avandamet. Due to my limited time, I would ask you to refer to the handout and the table on page 22 of my first review

for more details on this group. Also, these studies are included in the placebo-controlled studies I will be discussing further.

The insulin group was of interest before looking at the results because of the regulatory history of this combination in both the U.S. and Europe so I will give you a few more details on that group. On the next slide I will show you the active-control data with the placebo-control data for all three composite endpoints.

[Slide]

This illustrates the differences between the active-control data and the placebo-control data. So, the results for the overall database are here, at the bottom; for the placebo-control trials at the top. Active-control trials are shown for the three endpoints in the middle, here.

Since over 85 percent of the database is made up of placebo-control data, the estimates for the full database are essentially the same as for the placebo-control studies. The results for the active-control trials yield estimates of about 1 or

less but the confidence intervals are very wide, speaking to the uncertainty of these estimates.

[Slide]

On this graph the results for MI, CV death and stroke are shown to allow for comparison of the active-control meta-analysis results to the results of the long-term large, prospective active-control studies of ADOPT and RECORD. The active-control results for rosiglitazone against metformin are shown in the top section of this graph, and the results against sulfonylurea are shown in the bottom section. So, I have divided the active-control data. We see that the odds ratios are consistently 1 or close to 1 but, clearly, the meta-analysis results are not alone convincing, with very wide confidence intervals, when looking at these rare events. The upper limits for the confidence intervals for the long-term studies range from 1.4 to 1.9 when comparing against metformin and sulfonylurea separately. Drs. Mahoney and Graham will provide more details on the results of ADOPT and RECORD in their presentations.

[Slide]

For the rest of my presentation I will focus on the placebo-controlled trials, looking first at the add-on insulin trials and then the non-insulin trials.

[Slide]

This graph shows the incidence rates for the placebo-controlled trials on the X axis and the rosiglitazone on the Y axis. Each dot represents a single placebo-controlled study. These are the results for serious and non-serious myocardial ischemia. I want to point out that the points that are above the line favor the control, while points below the line favor rosiglitazone. These three studies that I mentioned earlier are clearly outliers. Study 211 was that study in CHF patients and study 135 was that study in elderly patients. Study 352 is the study in CHD patients. I have highlighted the results for the insulin trials with pink squares. Notice that the control rates for four of the insulin studies are consistent with the other studies, while the rosiglitazone rates are

higher than most studies.

[Slide]

The results for the five insulin studies are depicted in the forest plot on this slide and also in your handout where you can actually see the patient numbers. These five six-month studies of rosiglitazone add-on to insulin enrolled about 1,400 patients. The average time since diagnosis of diabetes in these patients was 13 years, about double what was seen in the overall database. Otherwise, these patients had similar baseline characteristics to the overall population. Across all three endpoints approximately a doubling of risk is seen, with borderline significant results. CHF results also showed a doubling of risk for this group.

[Slide]

Assuming that the risk seen in the insulin group is clinically important, I chose to look at the non-insulin, placebo-controlled studies to see if these studies, without the five insulin studies, independently provided evidence of increased risk.

So, the results shown here are for the placebo-controlled non-insulin studies. Both the active-control data and the insulin data are excluded. Nevertheless, the sample size is still large, with almost 11,000 patients. These results are nearly identical to the results I showed you earlier for the overall database, with estimates greater than 1 and borderline significant results for myocardial ischemia. Again, the non-adjudicated endpoint of MI, CV death and stroke showed no statistically significant treatment difference.

[Slide]

Looking still at the placebo-controlled, non-insulin studies, the results for several subgroups are depicted in this graph. I have put a line above 1 and 1.4 which was the overall estimate of risk. The subgroups were chosen based on exploratory analyses by both GSK and by FDA. The baseline characteristics that defined these subgroups are age, cardiovascular risk factors, number of cardiovascular medications taken at

baseline and history of diabetes medications, history of coronary heart disease, use of ACE inhibitors or nitrates at baseline.

Most of the results appear to be consistent with the overall results. Note that the ACE inhibitor users and the nitrate users and the patients over 65 all show a significant doubling of risk or more. On the next few slides I will show additional data regarding these subgroups.

[Slide]

Study 135 was a two-year study in elderly patients, the longest study in the meta-analysis base. Patients in this study were put on glipazide during a run-in period and then randomized to rosiglitazone or placebo.

This is a Kaplan-Meier curve of time to first myocardial ischemic event. The X starts at 0.8 and the event rate in this trial is approximately 9 percent. There is clearly no difference between rosiglitazone and placebo and no evidence of increased risk in an elderly population, contrary to what was suggested by the

subgroup analysis. Also, for this study I saw no subgroup differences with nitrates or ACE inhibitors. In the next few slides I will show you data for nitrate users.

[Slide]

A significant interaction with nitrates was seen in spite of the very low nitrate use overall in the database. These Kaplan-Meier curves illustrate the interaction. On the left are the results for over 10,000 patients who were not using nitrates at baseline. On the right are the results for the nitrate users, about 400 patients.

Weighting on study, the risk difference for patients not taking nitrates at baseline is 0.3 percent, with a p value of 0.2 compared to a statistically significant difference of 8 percent for those patients taking nitrates at baseline. It is interesting to note how quickly events occur and continue for the full six months, to here. This pattern of response was unique to this endpoint and to this nitrate subgroup.

[Slide]

I think it is important to look for confirmation of the nitrate interaction in individual trials. The use of nitrates in the large, prospective trials of DREAM and ADOPT was very low so that data is not helpful for testing this hypothesis. RECORD is an ongoing study so there are no subgroup results available for that study. The highest nitrate use in the 42 studies was seen in studies 211 and 352, as would be expected since these trials were conducted in CHF and CHD patients.

About a third of the patients in 211 and about half of the patients in 352 were taking nitrates at baseline. The odds ratios for these studies with high risk patients are greater than 1 but, clearly, the confidence intervals are very wide and the results are not significant. This is the p value for the interaction of nitrates. These results we can consider borderline significant, with a p value of 0.11. The interaction for nitrate use then in 211 is borderline. Looking at the results by nitrate use in study 211 appears to

show a treatment difference for nitrate users but not for patients not taking nitrates, although the number of events is clearly very small in all the groups, with only 3 here and only 11 in total here.

[Slide]

This slide shows the results for the three composite variables. The nitrate users are at the top and patients not taking nitrates at baseline at the bottom. A significant interaction was only seen for serious plus non-serious ischemia, represented here by the estimates at the bottom of each grouping. No interactions were seen for the other two endpoints. Note that only the serious plus non-serious ischemic results for nitrate users are statistically significant but all the estimates are greater than 1.

[Slide]

With this last slide of results I am showing results for the composite of MI, CV death and stroke by ACE inhibitor use in the placebo-controlled trials for the meta-analysis database and in DREAM. DREAM is a

placebo-controlled factorial study with ramipril and rosiglitazone. In DREAM patients were randomized to an ACE inhibitor, while for the ICT ACE inhibitor use was defined by use at time of enrollment in the trial. The interaction depicted here is not statistically significant. However, the interactions for serious myocardial ischemic events in the meta-analysis and for MI in DREAM were significant at p values less than 0.1. Note that DREAM has not been reviewed by FDA so I would consider these results as preliminary.

[Slide]

In summary, I have shown you the results of a meta-analysis of 42 studies. These trials were not designed to assess myocardial ischemic risk and not conducted under a common protocol. So, the results from these trials taken together should not be characterized as if they come from a large randomized clinical trial.

The design and conduct of a single clinical trial provides a statistical framework for the computation of a p value. This rigorous

framework is lacking in the meta-analysis.

With these shortcomings in mind, we find the increased risk of myocardial ischemia associated with rosiglitazone compared to placebo as nominally statistically significant at the 5 percent significance level when including the insulin trials. The results are borderline significant excluding the insulin trials. The most convincing results were for add-on rosiglitazone to insulin which consistently showed a doubling of risk associated with rosiglitazone treatment.

The results for combination with metformin, however, are difficult to interpret due to significant heterogeneity within the meta-group. Differential risk was also observed in subgroups of patients defined by baseline use of nitrates or ACE inhibitors. The interpretation of these results is complicated, however, by results varying depending on the endpoints measured. I don't know if the risk observed in these subgroups reflects an effect shared by the general population of patients taking rosiglitazone or whether the risk is

specific to these subgroups. Data outside the meta-analysis database is needed to understand these interactions. The active-control data, though limited in the meta-analysis database, appear to provide results consistent with the results seen in ADOPT and RECORD.

[Slide]

The subgroup results of the meta-analysis have generated hypotheses that could be examined further with a formal FDA review of DREAM and subgroup analyses of RECORD.

[Slide]

Lastly, I would like to thank the FDA staff of OSE and DMEP and especially my statistical colleagues for their help and support in many ways during the review of this application. Thank you for your attention. The next speaker will be Dr. Karen Mahoney.

Overview of Large, Long-Term, Prospective Trials of Thiazolidinediones

DR. MAHONEY: Good morning, Mr. Chairman, ladies and gentlemen.

[Slide]

My name is Karen Mahoney and I am an endocrinologist in the Division of Metabolism and Endocrinology Products. You have heard about FDA's meta-analysis in shorter-term trials with rosiglitazone. I will be presenting an overview of some other larger, longer-term trials of thiazolidinediones. I must apologize in advance for talking fast.

[Slide]

I will present overviews of study characteristics and myocardial infarction safety data for these trials, the acronyms for which are ADOPT, DREAM, RECORD and PROactive. The FDA has received the full study reports for ADOPT and PROactive and these trials can be presented in more detail than can DREAM and RECORD for which little data beyond published results are available. I will present some common cardiovascular endpoints across these data sources and end with a brief summary.

[Slide]

You just heard that the FDA meta-analysis is consistent with increased myocardial ischemic event risk for rosiglitazone, with some questions about whether some baseline factors are contributing significantly to the signal. After a meta-analysis it is common to look at other data sources to assess the consistency of the finding. While meta-analyses can be extremely useful, they have some limitations. These include problems with heterogeneity among included trials in terms of patient populations, background and control medications, baseline cardiovascular risk factors, variable follow-up, lack of original adjudication and other concerns.

In a large trial the single randomization and uniform inclusion and exclusion criteria do largely overcome this heterogeneity problem. Of course, even large prospective, randomized trials are not perfect. All data sources have limitations. [Slide]

A few important points about the characteristics of these data sources, only RECORD

and PROactive were specifically designed to examine cardiovascular outcomes. ADOPT compared durability of monotherapeutic efficacy of rosiglitazone to sulfonylurea or metformin. DREAM examined the effect of rosiglitazone on progression from impaired glucose tolerance to overt diabetes mellitus. The studies in the FDA meta-analysis were diabetes treatment trials aimed at glycemic control.

These four trials were large and of long duration while the meta-analysis had a mean duration of study of about six months. The rosiglitazone exposure by patient-year in these three trials alone is over five times that in the entire group of 42 trials included in the FDA meta-analysis.

[Slide]

Patient populations, controls and endpoints varied considerably across trials. ADOPT and most of the original trials in the meta-analysis did not have preplanned adjudication of cardiovascular events but the other large trials

did. Since GSK has already presented the design of the rosiglitazone trials, I will not be representing those designs in detail.

[Slide]

A few basics about ADOPT, it was designed to examine time to monotherapy failure and to examine general safety. It was not a specific cardiovascular outcome study and did not have preplanned adjudication of cardiovascular events. It had a high and differential withdrawal rate. Patient-year exposure in the sulfonylurea group was lower. Time to event and exposure analyses were used to evaluate adverse event data.

[Slide]

This graph illustrates the pattern of withdrawal in ADOPT. The X axis is time in months and the Y axis is the portion of patients on study. The two upper lines which are red and green are for rosiglitazone and metformin and they follow a highly similar pattern, while the sulfonylurea group, the black line, has a lower proportion of patients on study beginning fairly early. The

difference in rates was related to withdrawals due to hypoglycemia in the sulfonylurea group.

[Slide]

Deaths and other adverse events were routinely captured until 30 days after cessation of study medication. Beyond 30 days capture may not be complete because it was dependent on volunteer reporting.

In this table the first row includes deaths which occurred during the treatment or within 30 days of treatment. For these deaths rates were numerically highest in the sulfonylurea group, followed by metformin and rosiglitazone groups. In the second row, for total reported deaths the rates were similar for all three treatments.

[Slide]

This is a busy slide and I have included it so that the committee members can get an idea of the ways that we have looked at the cardiovascular event data. There is considerably more detail in the briefing document and in some backup slides.

Two independent FDA reviews were done, one by an endocrinologist and one by a cardiologist. We have looked at data by system organ class, by individual event terms, by new analyses using GSK's myocardial ischemia event groupings, and in a blinded fashion by multiple FDA event groupings.

The bottom line is this, to date we have not found a difference between rosiglitazone and sulfonylurea or metformin for total myocardial ischemic events and various composites of events. I will say, however, that out of 104 observed individual serious cardiovascular event terms, the single term myocardial infarction occurs with slightly greater numerical frequency per 100 patient-years for rosiglitazone than for comparator.

[Slide]

Time to event analyses can be helpful in the setting of a high and/or differential withdrawal rate. In these analyses the number of patients at risk at any given time point is taken into account. In these Kaplan-Meier curves the X

axis is time in months and the Y axis is the proportion of patients surviving and without an event.

Please note the compressed scale of the Y axis which only includes the range from 0.7 to 1. Even with this compressed scale, there is no significant separation between plots over time, with rosiglitazone, the red line here, ending up in the middle.

[Slide]

There are some limitations to the usefulness of ADOPT for assessing the cardiovascular safety of rosiglitazone. It was not designed or powered as a cardiovascular outcome trial. It had a high and differential withdrawal rate. It had an active comparator design. If either of the comparators carries an increased risk of cardiovascular events, one might not detect increased risk with rosiglitazone. Small numbers of cardiovascular events increase the uncertainty of estimates. A few events added to one group or another could alter the estimates of relative risk

considerably. Of course, many of these limitations also apply to the pool of studies included in the meta-analysis.

[Slide]

ADOPT has some strengths as well. It was large and of long duration, and treatment groups were well matched at baseline. I have used multiple methods to search for problems with event ascertainment and coding, the details of which are in a Division memo and some backup slides. Companies have to make choices about how to identify events for analyses, and every time I review any drug I find a few terms that I might have handled differently. However, for ADOPT I have not found evidence of systematic problems with ascertainment or coding.

While the previous slide discussed the drawback of active-control design, it is also more akin to real-world treatment decisions than is a placebo-control design. In clinical practice one does not make a treatment decision between adding a given diabetes drug or adding no drug at all. One

makes a choice between adding one diabetes drug or another diabetes drug.

[Slide]

How might ADOPT contribute to the evaluation of myocardial ischemic risk for rosiglitazone? It has large patient-year exposure. It addresses the hypothesis created by the FDA meta-analysis at this time in an early diabetic population and it addresses risk relative to the two most-commonly prescribed diabetes drug classes.

[Slide]

I will now speak very briefly about the DREAM trial. The FDA has not received the full study report and data sets for DREAM and, therefore, it does not have much information beyond that which has been published.

[Slide]

All I want to say here is that DREAM's 2X2 factorial design was intended to evaluate the effect of rosiglitazone and separately of ramipril on progression to overt diabetes.

I want to spend a little time on this

slide which was not in the DREAM publication. After the publication an unexpected finding arose in the form of an apparent interaction between rosiglitazone and ramipril for risk of cardiovascular events. Because this was a 2X2 factorial design there were actually four treatment groups, placebo, rosiglitazone alone, ramipril alone and combined rosiglitazone and ramipril. As a reminder, ramipril is an ACE inhibitor. It has an approved indication for reduction of cardiovascular risk in patients who have elevated baseline risk.

[Slide]

When comparing rosiglitazone alone to placebo alone there was little difference between groups for the cardiovascular events composite and most of its components. However, when comparing the combination of rosiglitazone and ramipril to any of the individual treatments there was a higher rate for the combination group. Interestingly, if you look at the bottom row, this finding applies not only to macrovascular events but also to heart

failure events, resulting in little difference between rosiglitazone alone and placebo alone but higher rates with the combination of rosiglitazone and ramipril.

This raises the question of a similar mechanism contributing to increased risk for both macrovascular and heart failure events. The ACE inhibitor observation is hypothesis generating only but we could not dismiss it and it warrants further evaluation. It also appeared in the meta-analysis but not in ADOPT or PROactive. Data were not available for RECORD to assess for this.

[Slide]

What might DREAM contribute? It has large patient-year exposure. It looks at risk in a pre-diabetic population. This population is not the same, however, as a non-diabetic population in terms of cardiovascular risk. At the time of diagnosis of diabetes many patients already have established cardiovascular disease. It looks at risk relative to placebo and it raises the question of a possible contribution of an interaction

between rosiglitazone and an ACE inhibitor for cardiovascular risk.

[Slide]

RECORD is an ongoing cardiovascular outcome study for which an interim analysis was recently published.

[Slide]

I won't repeat its design.

[Slide]

This slide was updated on the separate handout.

[Slide]

This table includes some of the interim results from RECORD and I only want to make two points on it. The components of the primary endpoints suggested that heart failure was contributory to the hazard ratio. In the first row, here, with heart failure events the hazard ratio was 1.08. In the second row, here, without the contribution of heart failure events the hazard ratio was 1.01. The 95 percent confidence intervals overlap. One might also note that even

though the event rate had been lower than expected, the upper limits of the 95 percent confidence intervals are fairly tight for interim data.

[Slide]

As mentioned earlier, the lower than expected event rate in RECORD has affected the planned statistical power of the study which was 99 percent on the primary endpoint. Dr. John Lawrence, an FDA statistician, performed conditional power analyses using the published interim data. What is conditional power? When evaluating interim trial data, conditional power is the probability that the trial will demonstrate statistical significance for an endpoint at the end of the trial, conditional on the data observed in the trial thus far. These calculations are dependent on what one has already seen in the trial and also on what one might reasonably expect to see for the rest of the data to come.

[Slide]

Each of these columns presents the power to exclude a given hazard ratio. This left-hand

column includes assumed future hazard ratios, the original of 1.0 and those observed in interim. If one wishes to exclude a difference between groups with a hazard ratio of 1.2, which was the original non-inferiority margin, one can see that the lower event rate has resulted in lower predicted power. For either of these assumed future hazard ratios, if one wants to exclude a difference between rosiglitazone and comparator, along the lines of what was seen in the FDA meta-analysis which had a point estimate of 1.4, the power to detect that is still quite high, 97-99 percent as you can see in this right-hand column. These calculations use the lower expected total number of primary events from the interim publication, not that from the original protocol.

[Slide]

What might RECORD add? It is a cardiovascular outcome study with predefined adjudication. It already has large patient-year exposure. Despite concerns about its low event rate to date, it should be noted that the trial

already has more cardiovascular events across its treatment groups than does the entire group of trials in the meta-analysis. Its estimates are less apt to be swayed by an event or two here and there compared to the events in the meta-analysis. It looks at risk for add-on rosiglitazone relative to another add-on oral hyperglycemic agent. The choice regarding which agent to add to a failing oral regimen is a common clinical scenario. And, using standard conditional power calculation methods RECORD has high conditional power to exclude a hazard ratio of 1.4, which is similar to the point estimate in the meta-analysis, or a hazard ratio of 1.3, but lower power to exclude a smaller difference between rosiglitazone and comparator.

[Slide]

The PROactive trial involved the other approved thiazolidinedione, pioglitazone.

[Slide]

It is the only completed cardiovascular outcome study for a TZD. Pioglitazone or placebo

were added to underlying diabetes medications. All patients had a history of macrovascular disease. Heart failure and insulin monotherapy were exclusion criteria. Medications, including diabetes meds, were to be added or titrated in both groups to achieve international diabetes federation goals for A1c, blood pressure and lipids. However, control at endpoint favored pioglitazone and this was not ideal because it raised questions about whether effects were due to differential risk factor management or to pioglitazone.

[Slide]

The primary endpoint was a composite of these seven components, which I won't read. Neither the primary endpoint nor any of the other efficacy endpoints included heart failure. Recall that the composite endpoint of DREAM and RECORD did include heart failure which increased the hazard ratios in those studies.

[Slide]

Statistical significance was not met for the primary endpoint, therefore, the secondary

endpoints would generally be considered exploratory. But in looking at them, there was no difference for the predefined endpoint of cardiovascular mortality. After the last trial visit, the applicant added a new endpoint of all-cause mortality, non-fatal myocardial infarction, excluding silent MI, and stroke. For this later secondary composite there were fewer events in the pioglitazone group, with a p value of 0.028 without adjustment for multiple comparisons.

[Slide]

You may recall that the rosiglitazone meta-analysis raised questions about risk differences with co-administration of other diabetes drugs and differences between placebo and active control. Here are the results of that secondary endpoint by baseline oral diabetes therapy.

For metformin only or sulfonylurea only, the pioglitazone group patients did not have increased risk. Among patients who were taking neither metformin nor sulfonylurea at baseline, the

hazard ratio exceeded 1 not favoring pioglitazone, with a confidence interval including 1. At baseline this small group came close to being a true placebo group for PROactive, but recall that addition and titration of underlying diabetes medications occurred. An add-on trial with titration of underlying diabetes medications is not quite the same as a traditional placebo-controlled trial where other glycemic control interventions are held stable.

[Slide]

You may hear a reference to an analysis by Takeda regarding pioglitazone. It can be very confusing to hear of so many different meta-analyses performed in different ways. The FDA has not yet received the meta-analysis for pioglitazone that looks similar to that for rosiglitazone. During the review of PROactive, Takeda did submit an analysis using a pooled clinical trials database of their later favorable secondary endpoint. The overall estimate for this included a hazard ratio of 0.78 and the p value was

0.12. Data sets were not submitted, nor were analyses by treatment comparator such as versus placebo or versus sulfonylurea, etc. Takeda has agreed to perform a meta-analysis of its clinical trial database that will be similar to that done for rosiglitazone and to submit it and data sets to the FDA.

[Slide]

The FDA and Takeda have been working to develop a meta-analysis approach that will allow something of an apples to apples comparison to the rosiglitazone meta-analysis. Apples to apples won't work very well, however, if one just lumps all the pioglitazone trials together and compares them to all the rosiglitazone trials together. That is because the two drug study pools differ in some important ways. For example, the rosiglitazone trials were about 85 percent placebo-controlled which, you have heard, was associated with a higher hazard ratio than active control. In contrast, about 20 percent of the pioglitazone database was placebo-controlled.

About 15 percent of the rosiglitazone database was head-to-head against sulfonylurea which, you have heard, was associated with a lower hazard ratio. In contrast, about 62 percent of the pioglitazone database was head-to-head against sulfonylurea. Therefore, a comparison of overall estimates might not be informative since the compositions of the trial databases differ. However, analyses using treatment comparison meta-groups could be of interest.

[Slide]

The long-term nature of PROactive may have been important. In this Kaplan-Meier plot of the primary endpoint the X axis is time in days and the Y axis is the event rate. Pioglitazone is the solid line and placebo is the dotted line. Early on event rates did not favor pioglitazone. After about 400 days though the curves cross and begin to favor pioglitazone with a statistically neutral and numerically favorable result at endpoint. A similar time pattern was seen for myocardial infarction, stroke and acute coronary syndrome.

This may serve to illustrate that clinically meaningful analyses of cardiovascular outcomes typically require long-term follow-up and accumulation of a minimum number of events. To date, clinical trials have not demonstrated significant reduction of macrovascular risk for any diabetes drug. In the DCCT, aggressive insulin treatment in type 1 diabetes was associated with initial worsening of the macrovascular complication of retinopathy, followed by a long-term reduction in progression. This microvascular benefit of hemoglobin A1c lowering took time to declare itself.

[Slide]

What might PROactive add? It is the only completed cardiovascular outcome study of a TZD. It had a statistically neutral and numerically favorable outcome for pioglitazone. It's endpoints didn't include heart failure which occurred with significantly greater frequency among pioglitazone patients. Recall that heart failure was included in the composites for DREAM and RECORD. Duration

of study may have been important. The study had a favorable secondary endpoint. When that same endpoint was applied across the pioglitazone pooled studies database that result was also favorable. There are substantial differences between the databases for rosiglitazone and pioglitazone. Takeda is working with the FDA to perform a pooled studies meta-analysis comparable to that done for rosiglitazone.

[Slide]

Across these data sources a variety of endpoints have been used. Biometricians both inside and outside of FDA have suggested that the use of a common composite endpoint could allow for a better perspective on the risk information.

[Slide]

There are many endpoints which could be used but the common one is the composite of cardiovascular death, myocardial infarction and stroke, which is sometimes referred to as the MACE endpoint for major adverse cardiovascular events. I refer you to page 100 of the DMEP briefing

document for much more information, including a discussion of the limitations of this endpoint across data sources.

This slide includes this endpoint for the pooled shorter-term diabetes studies and for ADOPT and for DREAM. The next slide includes RECORD and PROactive. This third column includes values for the composite, while columns four through six include the components. In each of these cells the top number is a hazard ratio or odds ratio. The middle includes the 95 percent confidence interval and the bottom of the cell has the p value.

Some observations include that for the DREAM trial an ACE inhibitor interaction is again suggested, as evidenced by higher hazard ratios in this bottom row where the combination is compared with ramipril alone, and in the row above it where rosiglitazone alone is compared to placebo alone. Across these data sources for the composite and for myocardial infarction hazard ratios are generally greater than 1, with confidence intervals spanning 1 except in the case of the apparent ramipril

interaction for MI. For cardiovascular mortality and stoke some hazard ratios are greater than 1 and some are less than 1.

[Slide]

Looking at MACE for the two cardiovascular outcome studies, RECORD for rosiglitazone and PROactive for pioglitazone, hazard ratios are less than 1 for the composite and for cardiovascular mortality, with overlapping confidence intervals. The hazard ratio for MI exceeded 1 for the RECORD interim data, with the confidence interval including 1. NP here indicates unavailable data.

One note, although I have sometimes presented statistical significance information, I want to emphasize that the agency does not make safety decisions based on statistical significance, rather, significance is presented to give some sense of the strength of a finding.

[Slide]

Summarizing some similarities and differences between the group of trials in the FDA meta-analysis and the large long-term trials of

rosiglitazone, the two data sources had similar sample sizes and were randomized and controlled.

A couple of points about differences, heterogeneity in the meta-analysis has been discussed. There are about 4,000 total patient-years in the meta-analysis and about 20,000 in the large trials to date. The FDA meta-analysis was consistent with a significantly increased risk of total myocardial ischemic events for rosiglitazone versus comparator. The individual large trials did not demonstrate an increased risk for total myocardial ischemic events. However, for myocardial infarction terms per se several hazard ratios exceeded 1.

[Slide]

As I have stated earlier, no anti-diabetic agent has been established to reduce the risk of cardiovascular disease through controlled clinical trials. As with other anti-diabetic agents, we have no definitive evidence of cardiovascular benefit associated with rosiglitazone. We have been learning something about cardiovascular risk

however, and I think the next two slides are representative of what we can say at this time.

This slide presents the interim results of RECORD graphically. All these events were adjudicated by a blinded endpoint committee. For all these measures of cardiovascular risk, except for heart failure which is a known adverse effect of the TZDs, the point estimates are consistently close to 1 and the upper bounds of the 95 percent confidence intervals are generally not high. The point estimates for cardiovascular death and all-cause mortality favor rosiglitazone but the confidence interval does not exclude 1.

[Slide]

This slide summarizes all-cause mortality from the three large, long-term rosiglitazone studies. With death, adjudication is generally not an issue. In all three studies the point estimate for all-cause mortality favors rosiglitazone compared to control but the 95 percent confidence intervals include 1.

[Slide]

One final thing, I am an endocrinologist and I have been dealing with diabetes and diabetes drugs for many years. I care about patients with diabetes. As an FDA reviewer, the best thing I can do for patients is to make sure that I conduct a comprehensive, scientifically rigorous and unbiased review of data. The hundred pages of the Division briefing document are a fraction of what I have written on this topic so far. So far, I have reviewed over 100,000 pages of submitted materials regarding TZD cardiovascular safety, innumerable literature references and data sets so large that computer upgrades were required. Up to the last minute, more data have been coming in from multiple sources. Others may present some of these data which have not received in-depth review. In science it is important not only to see the numbers but also to understand the methods that led to those numbers. This has been an extraordinarily complex review and I would like to acknowledge my colleagues on this slide.

I thank the advisory committee and I look

forward to your discussion and advice. Next, Dr. Gordon will present an overview of the design of the ongoing BARI 2D trial.

Dr. Rosen: Thank you, Karen. Dr. David Gordon is next. Dr. Gordon comes to us from NHLBI, and he is going to talk about the BARI 2D trial.

Use of Rosiglitazone in the Bypass Angioplasty Revascularization Investigation (BARI) 2 Diabetes Trial

DR. GORDON: Thank you very much for inviting me to present the BARI 2D trial.

[Slide]

I am going to talk fast but I am not going to apologize because I only have ten minutes. I will say a couple of things just as prefatory remarks. First of all, I am the executive secretary and former project officer of the BARI 2D DSMB trial so although I have no financial conflict of interest in terms of, you know, GlaxoSmithKline, I do have a professional interest in the successful completion of the BARI 2D study. The second thing I want to say right off the bat is that BARI 2D is

an ongoing trial. I am not going to present any interim outcome data for this trial.

[Slide]

What I would really like to do is describe the trial. I am going to describe the monitoring of this trial. I am going to tell you the sorts of things generically that our data and safety monitoring board looked at last month when it reviewed the Avandia data from this trial and then I am going to present their conclusions.

First of all, the BARI 2D trial is run out of the University of Pittsburgh. It is a multicenter trial. The study chair is Robert Frye and the co-chair is Saul Genuth. It has financial support primarily from the NHLBI but also contributions from NIDDK and from GlaxoSmithKline and there are many in-kind contributors, too long a list to summarize here.

[Slide]

The BARI 2D trial is a multicenter 2X2 factorial, randomized, controlled trial. It is not blinded. The two interventions that are being

looked at, the two hypotheses, are, one, comparing elective revascularization plus medical treatment versus medical treatment only. The second one, which is the one of interest to this group, is the insulin sensitization versus insulin provision. BARI 2D has 2,368 patients randomized. They all have type 2 diabetes, mostly long-standing, and stable coronary artery disease, proven by angiography. They have to be candidates for revascularization. Five years mean follow-up is planned. The study is expected to be completed at the end of 2008.

All patients are titrated to a goal of less than 7 percent for hemoglobin A1c. And, the primary endpoint of the study is all-cause mortality. It was calculated at the beginning of the study that we would have about 300 deaths over the course of the study. There is what our data and safety monitoring board calls a principal secondary endpoint which is the composite of all-cause mortality, non-fatal MI and stroke. I will mention that the reason for all-cause

mortality is that this is not a blinded study, though I will mention that the causes of death, the non-fatal MI and stroke are all adjudicated.

[Slide]

I want to emphasize that this is a trial of treatment strategies in diabetes. It is not a trial of any one drug per se. So, in the insulin sensitizer group about 70 percent of the patients were on a TZD at year one and, in this case, it is mostly rosiglitazone. About 80 percent of the insulin sensitizing group were on metformin, whereas the use of those in the insulin providing group is very small. On the other hand, sulfonylureas and insulin are much more commonly used in the insulin providing group. But you will notice in particular that about 24 percent of the insulin sensitizing patients are also on insulin which reflects in large part the fact that they were on insulin when they entered the study and have hemoglobin A1c's that can't be brought under control without also having insulin. So, again, it is not a pure rosiglitazone study.

[Slide]

Another thing that I want to point out is that this study features very rigorous control of cardiovascular risk factors, active and rigorous. The hemoglobin A1c, which I mentioned before, the mean is 7.1 percent. The mean LDL cholesterol is 83 mg/dL and over 90 percent of the patients in this study are on statins, many of them were at baseline as well. Mean triglyceride, 151; mean blood pressure, 127/72, a lot of blood pressure drug use; smoking, 10 percent, current smoking. The only risk factor that we have been unable to make much headway on is body mass index.

[Slide]

I want to mention, just to summarize before I get to the DSMB, the main differences between the BARI 2D trial and especially the smaller trials in the 42 trial meta-analysis. First of all, we are talking about people who have been diabetic for a long time. Second, we are talking about long-term follow-up. We are talking about strategies, not drugs. We are dealing with a

high risk population and we have this program of control of other risk factors.

BARI 2D is monitored by a data and safety monitoring board that is appointed by and advisory to the director of the NHLBI. The NHLBI appoints an executive secretary, in this case me, who is separate from the project officer and is sort of an intermediary between the DSMB and the director in terms of formulating and conveying the recommendations.

The DSMB meets at least twice a year. Its charge is to monitor the safety of participants, but also the integrity of data collection and evidence for differential efficacy of the strategies. I should emphasize that it includes looking at external data, such as the data from GlaxoSmithKline and from the Nissen meta-analysis, and so on. That is part of the charge, to look at the data in context of external data. There are no formal stopping rules for futility, although there are for efficacy.

[Slide]

The board has expertise in the relevant disciplines, in this case cardiology and diabetes. We have a cardiothoracic surgeon. We have a biostatistician. We have a clinical trials expert. We have a bioethicist on the board. This is sort of typical.

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I will also mention that the DSMB first had the rosiglitazone safety issue drawn to its attention by data that was provided unsolicited to me by GlaxoSmithKline, and was reviewed in January of 2006. At that time, the board authorized or recommended that a letter be sent to the BARI 2D investigators alerting them to the heart failure risk of rosiglitazone even without insulin being given. They asked for various improvements of the monitoring for heart failure in BARI 2D. They also asked for additional analyses of existing BARI 2D data. This was an ad hoc meeting. At the regularly scheduled DSMB meeting in March, two months later, they asked for a disclosure statement of heart failure and risk or rosiglitazone to be

presented to and signed by participants at their next BARI 2D visit.

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On October 23rd there was additional encouragement of BARI 2D patients to have a yearly ophthalmologic examination, and to add a question to the data form about macular edema. In January of 2007, there was an additional ad hoc conference call to discuss the recently published fracture data from the ADOPT trial.

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For this particular DSMB review of the possible adverse effects of rosiglitazone on myocardial ischemic events, the BARI 2D data can draw from the following kinds of analyses. One is the comparison of the insulin sensitizing versus insulin providing group. This has the advantage of being a randomized, intention-to-treat comparison. It has the disadvantage of the fact that rosiglitazone use is confounded with metformin use and confounded with lesser use of sulfonylureas and insulin.

However, there were additional analyses that were not done by intention-to-treat where they actually looked at rosiglitazone use per se as a predictor of future events. One was just looking at people taking rosiglitazone at year one and looking at that as a predictor of cardiovascular events and death in subsequent years. There were also time-dependent proportional hazards models done that looked at recent rosiglitazone use, proximate rosiglitazone use as a predictor of cardiovascular events and death. These proportional hazards models were controlled for baseline cardiovascular risk factor levels, control for baseline insulin use levels, control for use of other diabetes drugs during the trial and, finally, and this last one was done after the May 30th data and safety monitoring board meeting but as a result of questions asked, there was also an analysis that controlled for hemoglobin A1c levels and other cardiovascular risk factor levels during the trial.

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In addition, they also looked at the data

in context of published meta-analysis data. The RECORD data came out a little bit later than their actual meeting but this information was provided to them later. I wanted to point out on this slide that BARI 2D by the end of the trial expects to have 180 cardiovascular deaths. Currently, they are about 60 percent of the way through follow-up so already there are more cardiovascular deaths, approximately as many or more cardiovascular deaths in the BARI 2D trial than in the entire 42 trial meta-analysis.

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In addition, they looked an analysis of myocardial infarction as an endpoint and, again, we expect about 270, roughly, MIs by the end of the study. The current number of MIs is comparable to the number of MIs in the entire 42 trial meta-analysis. They actually looked at the odds ratio and so on but that I can't show you.

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Here are their conclusions after looking at all of those data. The first one is just a

statement of what I have already said. They thoroughly reviewed both the published data on heart attacks and deaths in patients receiving rosiglitazone.

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In the research setting of BARI 2D, the board made no observations that would justify a recommendation to terminate treatment with rosiglitazone. These are all taken verbatim from a statement prepared by the DSMB.

The board was satisfied, very satisfied with the coordinated care of BARI 2D patients. The trial participants are strongly encouraged to adhere to their recommended treatments for diabetes, hypertension and dyslipidemia.

Then the last one, which I think is an important caveat, the board is not in a position to comment on the use of rosiglitazone in routine clinical practice because, as I said, there are many differences between this trial and clinical practice and some of the other data that they are looking at.

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Finally, I would want to refer you to the NHLBI public website for more detailed statements by the NHLBI which build on these recommendations and the recommendations of the data safety monitoring board for the ACCORD trial, and that is right there.

DR. ROSEN: Thank you, Dr. Gordon. We will return to the FDA for their presentations, and the first speaker is Dr. Gelperin, who will talk about the role of observational studies in the use of evaluation of cardiovascular morbidity.

FDA Presentations Continued

Observational Studies: Effect of Anti-Diabetic Agent Choice on Cardiovascular Morbidity and Mortality in Type 2 Diabetes Mellitus

DR. GELPERIN: Good morning.

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During the next ten minutes I will talk about observational studies of cardiovascular outcomes in type 2 diabetes. Last year my division was consulted to review pooled analyses of

randomized, controlled trials as an observational study, both of which explored the question of cardiovascular risk with Avandia. Our review was completed in February and made recommendations based on information available at that time. Since then results of additional studies have become available, including two new observational studies from GSK and a new study from Takeda that have not been formally reviewed by FDA.

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I will start by describing two published population-based studies that illustrate approaches to some of the challenges inherent in studying outcomes in diabetes. I will then present FDA's perspective on observational studies commissioned by GSK that you heard about earlier today, as well as a study from Takeda. Two of the GSK studies, as well as the Takeda study were not received in time to complete formal review and are not included in the FDA background package.

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The question I will address is whether

these observational studies can provide sufficiently robust evidence to refute the safety signal identified in the meta-analysis of randomized, controlled trials with rosiglitazone.

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A key challenge in studying cardiovascular outcomes is the ascertainment of out of hospital cardiovascular deaths. A large proportion of heart attacks manifest as sudden cardiac deaths that typically don't result in a hospital claim because death occurs before reaching the hospital or in the hospital emergency room. Exposure misclassification is also a challenge. In a disease like diabetes where poor adherence, as we heard from Dr. Ratner, switching and adding drug therapies is the norm. Finally, unmeasured confounding and other sources of potential bias can be difficult to overcome.

To illustrate this point consider the current approved labeling for metformin that includes a contraindication for patients with renal dysfunction suggested by serum creatinine levels

greater than the upper limit of normal. It is not known whether prescribers adhere to this restriction. Information about renal status and serum creatinine is typically not available in claims data so any effect of this metformin contraindication on prescribing practices remains unmeasured in the observational studies you are hearing about today.

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For a background perspective, I would like to tell you now about two diabetes outcome studies that draw from regions in Saskatchewan, Canada and Tayside, Scotland with publicly funded health systems. Both of these populations-based studies utilize linked health services and vital statistics data that include coded cause of death. Because of this unique patient level data linkage, the study outcome includes out of hospital deaths.

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This graph from the Saskatchewan paper shows time to a composite outcome of non-fatal cardiovascular hospitalizations or cardiovascular

death in a retrospective cohort analysis. The blue line is metformin monotherapy and the red line represents sulfonylureas. The study used propensity scores to adjust for potential confounding and concluded that new users of metformin monotherapy had a lower risk of non-fatal cardiovascular hospitalizations, as well as all-cause and cardiovascular mortality, compared with new users of sulfonylurea monotherapy.

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From the Scottish cohort study, this graph shows the cumulative cardiovascular mortality rates over eight years of follow-up. The blue line is the metformin group and the red line represents sulfonylurea users. New users of metformin or sulfonylureas were identified from the diabetes audit and research in Tayside, Scotland. Mortality was ascertained from a validated national database. The study showed a decreased risk of total mortality and cardiovascular mortality for new users of metformin monotherapy compared with sulfonylurea monotherapy. Relative risk was

smaller after adjustment for differences between groups, but remains statistically significant with an adjusted risk ratio for sulfonylurea of 1.7 compared to metformin.

The authors pointed out that the cardiovascular mortality rates they found for new users of sulfonylurea were consistent with expected rates in a diabetic population, and support the theory that metformin is cardioprotective rather than sulfonylureas being cardiotoxic. However, they felt that they could not rule out residual confounding or unknown differences in the groups at baseline, and concluded that their results do not form a definitive basis for treatment decisions but do warrant further investigation.

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Now I will turn to the three observational studies commissioned by GSK. The first study is a propensity score matched cohort study, conducted by the I3 Drug Safety Division of Ingenix. The study made use of claims data from enrollees of United Health Care. The outcome for this study was

limited to new cases of myocardial infarction or coronary revascularization and did not include out of hospital deaths.

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This figure shows the proportion of patients in each of the grous who remained event-free of the composite outcome, MI or revascularization. The blue line is the metformin group, the red line is the sulfonylureas and the grey line represents rosiglitazone as monotherapy. The study found increased risk for new users of sulfonylurea compared to metformin monotherapy. However, the risk for new users of rosiglitazone was not significantly different from either of the other two groups.

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The second study from GSK is a cohort study that was also conducted by I3 Drug Safety but uses claims data from a different data source, PharMetrics. This study is much larger than study number 1. It included a pioglitazone group and shows overall results generally similar to study

number 1 with the same definition of outcome.

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However, both the Ingenix and the PharMetrics databases are limited by poor representation of patients older than age 65. Older patients represent a higher risk group for potential drug-induced cardiovascular toxicity and also a substantial proportion of patients in the U.S. who are prescribed rosiglitazone therapy.

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A major limitation for each of these studies is the definition of outcome that was not sufficiently inclusive to capture the adjudicated events that comprised the cardiovascular signal in the pooled analysis of randomized, controlled trials.

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As can be seen in this table, of the 22 adjudicated cardiovascular deaths identified by GSK, over half occurred out of the hospital and would not have resulted in a hospital claim.

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Of the total number of adjudicated serious myocardial ischemia events in the rosiglitazone pooled trials, roughly 10 percent would be missed in hospital claims data.

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With regard to study exposure in the cohort studies a new user was defined by non-use of the study drug in the preceding six months. FDA reviewers were concerned that six months may not be long enough to reliably characterize and capture true new users in claims data. Unknown compliance, poor adherence and switching among study cohorts can lead to misclassification bias.

[Slide]

Questions remain on unmeasured confounding. FDA reviewers were concerned that the six months was not long enough in claims data to capture information about confounders. Some major risk factors, such as smoking and aspirin use were not captured in claims data.

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The third study from GSK is a nested case

control study which compared patients' TZD therapies to a reference group of patients on non-TZD therapies including insulin. Since the oral therapy and insulin therapy patients would be expected to have very different risk profiles, the introduction of bias is likely. The design of this study was considered by FDA reviewers to be seriously flawed.

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Two observational cohort studies include direct comparisons of rosiglitazone and pioglitazone. Neither of these studies has been formally reviewed by FDA but they are mentioned here for completeness. The definitions of outcome for each include MI and revascularization. The PharMetrics study from GSK showed no difference in risk for the two drugs. The hazard ratio of less than 1 would favor rosiglitazone. The Takeda study showed a decreased risk of MI or the composite of MI plus revascularization in the pioglitazone group. These two studies have difference results.

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This figure is taken from the analysis performed by Takeda staff, which will be published next week in a peer reviewed journal and is used here with permission. The adjusted hazard ratio for MI for pioglitazone versus rosiglitazone is 0.78. Note that the Y axis starts at 0.978 and is compressed.

The Takeda study has limitations similar to the GSK cohort studies. For instance, with regard to exposure misclassification, FDA reviewers were concerned that there may be an issue. The unidirectional time-varying covariate approach used by Takeda may add unpredictable amounts of misclassified exposure time to the denominators of both groups.

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To summarize, despite large numbers of exposed patients in what has been called today a real-world setting, the limitation of these studies include the following: A definition of outcome that does not fully address the cardiovascular signal from the pooled clinical trials, in large part due

to missing out of hospital cardiovascular deaths. Other unresolved issues include a potential exposure-related misclassification of unmeasured confounding and unmeasured confounding due to incomplete ascertainment of baseline risk factors.

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Because of the limitations in these observational studies of myocardial ischemia, we cannot conclude that they provide adequate evidence to refute the signal identified in the meta-analysis of randomized, controlled trials for rosiglitazone.

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I would like to thank my colleagues in the Division of Metabolic and Endocrine Products in the Office of Biostatistics, and particularly the FDA observational data review team.

Now I would like to introduce Dr. David Graham, the Associate Director for Science and Medicine in the Office of Surveillance and Epidemiology.

Assessment of Cardiovascular Risks and

Health Benefits for Rosiglitazone

DR. GRAHAM: Good morning, or maybe it is just about afternoon now.

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In the next few minutes I will be presenting an assessment of cardiovascular risks and health benefits of rosiglitazone. I hope the advisory committee recognized that in all materials they received there is really no discussion of what are the population risks and population benefits and integrating the two and putting them together, and that is the purpose of my talk.

What I present now represents in a sense my own view, but I am authorized to say the following, my Office Director, Dr. Gerald Dal Pan, worked closely with me in all of the analyses that we will be showing here and he helped me in putting the talk together, and he fully endorses, supports and agrees with the methods that we have used, the analyses that I will be presenting and, ultimately, with the recommendations and conclusions that I present, but he prefers not to have that represent

an Office position because he hasn't consulted with everyone who is on our team. But I just want you to understand that this just isn't David Graham, FDA whistle-blower and health advocate talking about a drug safety problems. This has the scrutiny of my office director and he concurs with what I am about to present.

Now, 70 percent of patients with type 2 diabetes die of coronary heart disease. So, coronary heart disease is the leading killer of patients with diabetes. The main reason for treating diabetic patients really is the hope of reducing coronary heart disease occurrence and deaths. At the end of the day that is the Holy Grail. That is what we are seeking to accomplish. Any drug used for the treatment of diabetes that increases the incidence or severity of coronary heart disease in patients with diabetes is unacceptable. It makes no medical sense and it violates the basic principle taught to all of us in medical school of *primum non nocere*, or *primum non nocere* if you prefer the classical versus the

church pronunciation. That is, first do no harm.

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So, when we looked at this question we thought there are really three questions that are very important. First, does rosiglitazone itself intrinsically increase the risk of cardiovascular events, most importantly cardiac death, MI and stroke?

A second question, of almost equal importance but not quite, is how does rosiglitazone compare with pioglitazone?

Then, third and less important than the first two questions, does the cardiovascular risk with rosiglitazone differ from that of other oral anti-diabetic agents, most particularly metformin and sulfonylurea?

Now, if the answer to any of these questions is yes, then it is imperative that we ask the following question, are there documented health benefits with rosiglitazone to justify its cardiovascular risks? If there aren't, then you understand where we are going.

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This slide summarizes the data that in most part has been discussed already by other speakers, both from the company and from the FDA. The comparison groups used, and the particular questions the Office of Surveillance and Epidemiology we posed, so you can see from ADOPT down to rosiglitazone meta-analysis that would be the integrated clinical trials meta-analysis, to use Dr. Mele's nomenclature, and the particular control groups, and then the question from my previous slide that the particular study is relevant to. The reason why we have question marks next to ADOPT, BARI 2D and RECORD, all relating to question three, is, as you will see later, the issue of study power and the possibility of a false-negative finding.

[Slide]

So, we are now going to go through each of the questions and talk about what the evidence is from our perspective. Does rosiglitazone use increase the risk of cardiac death, MI and stroke?