



U.S. Food and Drug Administration

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1 FOOD AND DRUG ADMINISTRATION  
2 CENTER FOR DRUG EVALUATION AND RESEARCH  
3  
4  
5

6 JOINT MEETING OF THE ENDOCRINOLOGIC AND  
7 METABOLIC DRUGS ADVISORY COMMITTEE AND  
8 DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE  
9

10  
11 TUESDAY, JULY 13, 2010

12 7:45 a.m. to 6:30 p.m.  
13  
14  
15

16 Hilton Washington, D.C. North/Gaithersburg

17 620 Perry Parkway

18 Gaithersburg, MD  
19  
20  
21  
22

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10 Clinical Coordinator and Residency Program Director

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12 Saint Luke's Hospital

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3 Pharmaceutical Outcomes & Policy (POP) College of

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7 Director, FDA/CDER Graduate Training Program in POP

8 Research

9 Gainesville, Florida

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11 **GUEST SPEAKERS (*Non-Voting, Limited to Presenting***  
12 ***Only*)**

13 **Maria Mori Brooks, Ph.D.**

14 Associate Professor of Epidemiology and Biostatistics

15 University of Pittsburgh

16 Pittsburgh, Pennsylvania

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19 McMaster University Dept. of Medicine

20 Hamilton, Ontario, Canada

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16 **Steve E. Nissen, M.D.**

17 Medical Director, Cleveland Clinic

18 Cardiovascular Coordinating Center

19 Department of Cardiovascular Medicine

20 Cleveland, Ohio



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**Robert T. O'Neill, Ph.D.**

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1    **John K. Jenkins, M.D.**

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P R O C E E D I N G S

(7:45 a.m.)

DR. BURMAN: Good morning. I'd like to, first, remind everyone present to please silence your cell phones, Blackberries and other devices, if you have not already done so.

I would also like to identify the FDA press contact, Ms. Karen Riley. If you are here present, please stand. Erica Jefferson? They probably are outside.

In the interest of reducing waste, we ask that you hold onto your packet of materials for both days of the meeting.

My name is Kenneth Burman. I am chair of the Endocrine and Metabolic Drugs Advisory Committee. I will now call the meeting to order. We will go around the room, and please introduce yourself. We will start with the FDA, to my left.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs in the Center for Drug Evaluation and Research.

DR. DAL PAN: Good morning. My name is

1 Gerald Dal Pan. I'm the Director of the Office of  
2 Surveillance and Epidemiology at CDER, at FDA.

3 DR. ROSEBRAUGH: Curt Rosebraugh, Director,  
4 Office of Drug Evaluation II.

5 DR. PARKS: Good morning. I'm Mary Parks.  
6 I'm Director in the Division of Metabolism and  
7 Endocrinology Products.

8 DR. O'NEIL: Bob O'Neil, the Director of the  
9 Office of Biostatistics in CDER.

10 DR. WOODS: Mark Woods, Clinical Coordinator  
11 and Residency Program Director at St. Luke's Hospital  
12 in Kansas City, Missouri.

13 DR. KNOWLER: Bill Knowler, from NIDDK in  
14 Phoenix, Arizona.

15 DR. MANN: Howard Mann. I'm a faculty  
16 member at the University of Utah School of Medicine  
17 and a program associate in its Division of Medical  
18 Ethics and Humanities.

19 DR. MOSS: Good morning. I'm Dr. Arthur  
20 Moss, from the University of Rochester Medical Center.  
21 I'm a clinical cardiologist and research cardiologist.

22 DR. KONSTAM: Marv Konstam, Tuft's Medical



1 Center and Tuft's University, cardiology.

2 DR. OAKES: David Oakes, Professor of  
3 Biostatistics, University of Rochester.

4 DR. GELLER: Nancy Geller, NHLBI,  
5 biostatistician.

6 DR. MORRATO: Good morning. I'm Elaine  
7 Morrato, from the University of Colorado-Denver, in  
8 the Department of Health Systems Management and  
9 Policy.

10 DR. VAIDA: Allen Vaida, a pharmacist from  
11 the Institute for Safe Medication Practices.

12 DR. NELSON: Lewis Nelson, emergency  
13 medicine and medical toxicology at New York University  
14 School of Medicine.

15 DR. PLATT: Richard Platt. I'm a  
16 pharmacoepidemiologist at the Harvard Pilgrim Health  
17 Care Institute at Harvard Medical School. FDA has  
18 asked me to mention that I'm the lead investigator for  
19 the FDA's mini-Sentinel program.

20 DR. FELNER: Eric Felner, Associate  
21 Professor of Pediatrics. I'm a pediatric  
22 endocrinologist at Emory University in Atlanta.

1 DR. GOLDFINE: Allison Goldfine, Associate  
2 Professor, Harvard University, and I am the Director  
3 of Clinical Research at the Joslin Diabetes Center,  
4 Boston.

5 DR. PROSCHAN: I'm Michael Proschan. I'm a  
6 statistician at NIAID.

7 DR. BURMAN: Ken Burman. I'm head of  
8 endocrine at the Washington Hospital Center and  
9 Professor of Medicine at Georgetown University.

10 DR. TRAN: I'm Paul Tran. I'm the DFO for  
11 the Endocrinologic and Metabolic Drugs Advisory  
12 Committee.

13 DR. FLEGAL: I'm Katherine Flegal from CDC's  
14 National Center for Health Statistics.

15 DR. THOMAS: Abraham Thomas, Division Head,  
16 Endocrinology, Henry Ford Hospital.

17 DR. ROSEN: Cliff Rose, endocrinologist,  
18 Maine Medical Center.

19 DR. HENDERSON: Jessica Henderson from  
20 Oregon. I'm the consumer representative.

21 DR. WEIDE: Lamont Weide, Chief of  
22 Endocrinology, University of Missouri-Kansas City

1 School of Medicine, and Truman Medical Centers, and  
2 Professor of Medicine.

3 DR. CAPUZZI: David Capuzzi, Professor of  
4 Medicine, Divisions of Endocrinology and Cardiology,  
5 from -- basically, that's it.

6 MS. KILLION: Good morning. Rebecca  
7 Killion. I'm a diabetic. I'm here as the patient  
8 representative.

9 DR. FLEMING: Thomas Fleming, Department of  
10 Biostatistics, University of Washington.

11 DR. VAN BELLE: Gerald van Belle, Department  
12 of Biostatistics, University of Washington.

13 DR. TEERLINK: John Teerlink, University of  
14 California-San Francisco and San Francisco Veterans'  
15 Affairs Medical Center, cardiologist.

16 DR. KAUL: Sanjay Kaul. Good morning.  
17 Cardiologist, Cedars-Sinai Medical Center, Los  
18 Angeles.

19 DR. HAMMERSCHMIDT: Dale Hammerschmidt,  
20 Department of Medicine, University of Minnesota.

21 DR. SAVAGE: Peter Savage, Senior Advisor  
22 for Clinical Studies at NIDDK in Bethesda.

1 DR. SCHAMBELAN: Morrie Schambelan,  
2 Professor of Medicine, Endocrinology, at the  
3 University of California-San Francisco.

4 DR. WINTERSTEIN: Almut Winterstein. I'm a  
5 pharmacoepidemiologist at the College of Pharmacy and  
6 the College of Public Health, University of Florida.

7 DR. HECKBERT: Susan Heckbert, Department of  
8 Epidemiology, University of Washington.

9 DR. DAY: Ruth Day, Duke University,  
10 specialist in medical cognition.

11 DR. FURBERG: Curt Furberg, Professor of  
12 Public Health Sciences at Wake Forest University.

13 DR. BURLINGTON: Bruce Burlington, industry  
14 representative to Drug Safety, retired from FDA and  
15 Wyeth.

16 DR. VELTRI: Ric Veltri, industry  
17 representative for the Endocrine and Metabolic  
18 Advisory Committee. I'm also a cardiologist.

19 DR. BURMAN: Thank you all very much. For  
20 topics such as those being discussed at today's  
21 meeting, there are often a variety of opinions, some  
22 of which are quite strongly held. Our goal is that

1 today's meeting will be a fair and open forum for  
2 discussion of these issues and that individuals cannot  
3 express their views without interruption. Thus, as a  
4 gentle reminder, individuals will be allowed to speak  
5 into the record only if recognized by the chair. We  
6 look forward to a productive meeting.

7 In the spirit of the Federal Advisory  
8 Committee Act and the Government in the Sunshine Act,  
9 we ask that the advisory committee members take care  
10 that their conversations about the topic at hand take  
11 place in the open forum of the meeting.

12 We are aware that members of the media are  
13 anxious to speak with the FDA about these proceedings.  
14 However, FDA will refrain from discussing the details  
15 of the meeting with the media until its conclusion.

16 Also, the committee is reminded to please  
17 refrain from discussing the meeting topic during  
18 breaks and lunch. And I'd also like to note that we  
19 have a busy schedule and we're going to try to keep on  
20 schedule to the extent possible.

21 DR. TRAN: Good morning. The Food and Drug  
22 Administration is convening today's meeting of the

1 Endocrinologic and Metabolic Drugs Advisory Committee  
2 and the Drug Safety and Risk Management Advisory  
3 Committee under the authority of the Federal Advisory  
4 Committee Act of 1972.

5 With the exception of the industry  
6 representatives, all members and temporary voting  
7 members of these committees are special government  
8 employees or regular federal employees from other  
9 agencies and are subject to federal conflict of  
10 interest laws and regulations.

11 The following information on the status of  
12 the committees' compliance with the federal ethics and  
13 conflict of interest laws covered by, but not limited  
14 to, those found in 18 USC Section 208 and Section 712  
15 of the Federal Food, Drug, and Cosmetics Act is being  
16 provided to participants in today's meeting and to the  
17 public.

18 The FDA has determined that the committee  
19 members and temporary voting members are in compliance  
20 with the federal ethics and conflict of interest laws.  
21 Under 18 USC Section 208, Congress has authorized FDA  
22 to grant waivers to special government employees and

1 regular federal employees who have potential financial  
2 conflicts when it is determined that the agency's need  
3 for a particular individual's services outweighs his  
4 or her potential financial conflict.

5 Under Section 712 of the Food, Drug, and  
6 Cosmetics Act, Congress has authorized FDA to grant  
7 waivers to special government employees and regular  
8 federal employees with potential financial conflicts  
9 when necessary to afford the committee essential  
10 expertise.

11 Related to the discussion of today's  
12 meeting, committee members and temporary voting  
13 members have been screened for potential financial  
14 conflicts of interests of their own, as well as those  
15 imputed to them, including those of their spouses or  
16 minor children, and, for the purposes of 18 USC  
17 Section 208, their employers.

18 These interests may include investments,  
19 consulting, expert witness testimony, contracts,  
20 grants, CRADAs, teaching, speaking, writing, patents  
21 and royalties, and primary employment.

22 Today's agenda involves primarily discussion

1 of the cardiovascular safety of GlaxoSmithKline's  
2 Avandia, rosiglitazone, a drug approved for blood  
3 glucose control in adults with Type II diabetes  
4 mellitus.

5 Data specific to rosiglitazone to be  
6 presented will include the results from the  
7 rosiglitazone evaluated for cardiac outcome and  
8 regulation of glycemia and diabetes, the RECORD trial,  
9 observational data, health claims data, and meta-  
10 analysis of controlled clinical trials.

11 In addition, the FDA will present its meta-  
12 analysis of several trials of Takeda Pharmaceuticals'  
13 Actos, pioglitazone, another thiazolidinedione, for  
14 the same indication, in response to the public  
15 documents comparing the safety of rosiglitazone to  
16 pioglitazone based on different meta-analyses  
17 performed on each of these two drugs.

18 This is a particular matters meeting during  
19 which specific matters related to Avandia,  
20 rosiglitazone, and Actos, pioglitazone, will be  
21 discussed.

22 To ensure transparency, we encourage all



1 standing committee members and temporary voting  
2 members to disclose any public statements that they  
3 may have made concerning the products at issue.

4 With respect to the FDA's invited guest  
5 speakers, we would like to disclose that Dr. Ruth  
6 Faden, Steven Goodman, Maria Brooks, and Hertzfel  
7 Gerstein are participating in this meeting as  
8 nonvoting guest speakers. Dr. Brooks is a co-  
9 investigator of the bypass angioplasty  
10 revascularization investigation in the Type II  
11 diabetes trial, which received supplemental funding  
12 from GlaxoSmithKline, the sponsor for Avandia.

13 Currently, Dr. Gerstein is the joint  
14 international principal investigator and chair of the  
15 steering committee of the thiazolidinedione  
16 intervention with vitamin D evaluation, the TIDE  
17 trial, and a co-investigator of the study involving  
18 animal models with rosiglitazone.

19 In the past, Dr. Gerstein was the joint  
20 international principal investigator and joint chair  
21 of the steering committee of the diabetes reduction  
22 assessment ramipril and rosiglitazone medication, the

1 DREAM trial, which is partially funded by  
2 GlaxoSmithKline.

3 Dr. Gerstein was also on the steering  
4 committee of the assessment on the prevention of  
5 progression by rosiglitazone on arteriolosclerosis in  
6 Type II diabetes patients with cardiovascular history,  
7 the APPROACH trial. Lastly, Dr. Gerstein has received  
8 honoraria from GlaxoSmithKline for speaking events and  
9 scientific advisory activities.

10 With respect to the FDA's invited industry  
11 representatives, we would like to disclose that Drs.  
12 Enrico Veltri and Bruce Burlington are participating  
13 in this meeting acting on behalf of regulated  
14 industry. Their role at this meeting is to represent  
15 industry in general and not any particular company.

16 Dr. Veltri is a former employee of Merck and  
17 currently holds Merck stock. Dr. Burlington is an  
18 independent consultant to Pharmaceutical Product  
19 Development and Regulatory Affairs.

20 We would like to remind members and  
21 temporary voting members that if the discussion  
22 involves any other products or firms not already on

1 the agenda for which the FDA participant has a  
2 personal or imputed financial interest, the  
3 participants need to exclude themselves from such  
4 involvement and their exclusion will be noted for the  
5 record.

6 The FDA encourages all other participants to  
7 advise the committee of any financial relationships  
8 that they may have with the firm at issue. Thank you.

9 DR. BURMAN: Thank you. We will now proceed  
10 with the Commissioner of the FDA, Dr. Margaret  
11 Hamburg. On behalf of the committee, we'd like to  
12 cordially welcome her.

13 I would like to remind public observers at  
14 this meeting that while this meeting is open for  
15 public observation, public attendees may not  
16 participate except at the specific request of the  
17 panel.

18 DR. HAMBURG: I really appreciate the  
19 opportunity to address you briefly before the start of  
20 what I know will be a very interesting two days. It  
21 is not typical for an FDA commissioner to address an  
22 advisory committee, though I have done it before, but

1 with the amount of attention that this meeting and  
2 this issue has been receiving, I thought it important  
3 to speak with you for a few minutes as this session  
4 begins.

5           Let me start by expressing my deep  
6 appreciation for the efforts of this advisory  
7 committee. I know that you have given up a great deal  
8 of time to help the FDA think through a series of  
9 important and challenging questions about the safety  
10 of rosiglitazone.

11           You've submitted to a very complex screening  
12 procedure, applicable to all advisory committee  
13 members on all of our advisory committees, and you've  
14 had the pleasure of reading through many hundreds of  
15 pages of background material and some pretty complex  
16 and technical stuff. So I know that you've already  
17 been working very hard.

18           Of course, many of you have traveled far and  
19 wide to be here in lovely Gaithersburg, and all of you  
20 have gotten up bright and early this morning to be  
21 here to start off what will be a very full two days of  
22 meetings and discussions.

1           Today, you'll hear many hours of  
2 presentations from invited speakers and have the  
3 opportunity to ask them questions, and I strongly urge  
4 you to do so.

5           Tomorrow, you'll hear additional  
6 presentations and, also, from the public, and then  
7 you'll have several hours to engage in discussions on  
8 a series of important questions.

9           There's been a lot of back-and-forth in the  
10 public and in the professional media and journals and  
11 meetings on all sides of this issue, but your job is  
12 to try to cut through all of that and to focus on the  
13 evidence. All of your comments, up to and including  
14 your votes, will help FDA as we move forward with our  
15 assessment of this important safety issue.

16           My advice is that you keep an open mind,  
17 apply your sharpest scientific thinking, and bring  
18 your best judgment to the questions facing the agency.  
19 Follow the science where it leads and the rest will  
20 fall into place.

21           Many of you are clinicians and you know how  
22 hard it is when a patient faces a choice of two

1 different pathways for treatment and intervention for  
2 a serious condition, especially when there's some  
3 level of uncertainty about the underlying question.

4 In that situation, you review all the facts,  
5 do your best to think clearly about them, and you give  
6 the best advice that you can. And that's all that  
7 we're asking of you today.

8 Let me make one final comment. For some  
9 advisory committees, all of the FDA opinions line up  
10 nicely with each other. The issues are clear, and all  
11 of the agency scientists are in agreement. And as you  
12 know, that is not the case today.

13 Rather than try to summarize or synthesize  
14 these competing perspectives into a set of bland  
15 documents or presentations, we thought it best for you  
16 to read their words for yourselves, hear from the key  
17 scientists at the agency directly, and factor their  
18 perspectives into your thinking. Doing so is hard  
19 work, I know that, but it will be immensely valuable  
20 to the agency.

21 Everything that you're doing over the next  
22 two days really matters. We wish you the best of luck

1 in your discussions. We really appreciate the time  
2 and effort that you are putting in. The work of these  
3 advisory committees is invaluable to the agency and to  
4 ensuring that we can do our very best in fulfilling  
5 the mission of our agency to promote and protect the  
6 health of the public.

7 So thank you very much, and I will let you  
8 now plunge into the important tasks before you. Thank  
9 you.

10 DR. BURMAN: Thank you, Commissioner. We  
11 will now proceed with the FDA opening remarks from Dr.  
12 Mary Parks. I would like to remind public observers  
13 at this meeting that while the meeting is open for  
14 public observation, public attendees may not  
15 participate except at the specific request of the  
16 panel.

17 Dr. Parks? Dr. Parks, right before we do  
18 that, if I might.

19 Dr. Woodcock and Dr. Temple, would you  
20 please introduce yourselves?

21 DR. TEMPLE: I'm Bob Temple. I'm Deputy  
22 Director for Clinical Science. Thanks.

1 DR. WOODCOCK: I'm Janet Woodcock. I'm the  
2 Director of the Center for Drug Evaluation and  
3 Research at FDA.

4 DR. BURMAN: Thank you both.

5 DR. PARKS: Good morning, Dr. Burman,  
6 members of this joint advisory committee panel. Over  
7 the course of the next two days, you will be hearing  
8 presentations of data that have become available since  
9 July 2007, when the FDA held its first public meeting  
10 to discuss the cardiovascular safety concerns  
11 associated with rosiglitazone, or also known as  
12 Avandia.

13 The objectives of my presentation are to  
14 provide for you the background of this issue and,  
15 also, an overview of the agenda for today's meeting.  
16 Prior to the 2007 advisory committee meeting, there  
17 were several notable events. In December of 2003, the  
18 World Health Organization released its report of a  
19 data mining signal for increased cardiac risk,  
20 including heart failure, for the TZDs.

21 This prompted GSK to perform a series of  
22 meta-analyses of rosiglitazone controlled clinical



1 trials. In August of 2006, the final report, with  
2 datasets, for meta-analysis of 42 controlled clinical  
3 trials was submitted to the agency.

4 While the FDA was reviewing this meta-  
5 analysis, a separate meta-analysis was published in  
6 the New England Journal of Medicine in June of 2007.  
7 These two meta-analyses differed in the following  
8 ways. Clinical trials were different with respect to  
9 which ones were included in the meta-analyses. The  
10 methods for analyzing the data were also different.  
11 Endpoints selected were different, and, finally, the  
12 FDA meta-analysis was the only one that actually  
13 relied on patient level data.

14 Despite those differences, however, these  
15 meta-analyses were viewed as a signal for  
16 cardiovascular risk associated with rosiglitazone, and  
17 it was that signal that led the agency to convene on  
18 July 30th, 2007, the joint advisory committee meeting  
19 on Avandia.

20 At that meeting, FDA focused on the  
21 following items: the meta-analysis of 42 controlled  
22 clinical trials; cardiovascular safety data from long-

1 term controlled clinical trials; cardiovascular safety  
2 data from observational studies comparing rosi to  
3 other anti-diabetic therapies; and, then, finally, the  
4 indirect comparisons between rosiglitazone and  
5 pioglitazone.

6 Due to time constraints, I will not be  
7 discussing the observational studies presented in  
8 2007. However, you will hear about observational  
9 studies since that time later on today.

10 This slide here summarizes for you several  
11 of the characteristics from the 2007 meta-analysis.  
12 It was a large database of over 14,000 patients, all  
13 from randomized double-blind controlled trials.  
14 However, these trials here, the majority of them, were  
15 of six months' duration or less. They were also not  
16 designed to assess cardiovascular risk; so there was  
17 no prospective adjudication of cardiovascular events  
18 by a blinded endpoints committee, except in one study.

19 As a result, those cardiovascular events  
20 were collected by investigators as adverse events  
21 reported on case report forms. These were  
22 subsequently retrospectively analyzed by a blinded

1 endpoints committee and categorized into the  
2 following. Non-serious and serious cardiovascular  
3 events comprised the ischemic heart disease endpoint.  
4 Serious cardiovascular events comprised the ischemic  
5 heart disease component. There was heart failure,  
6 also, adjudicated. And then MACE events, this is the  
7 more conventional endpoint, comprised of  
8 cardiovascular death, nonfatal MI, and nonfatal  
9 stroke. That was also captured later during the  
10 preparation for the previous advisory committee.

11 I want to point out that many of these  
12 adverse event terms considered in the cardiovascular  
13 endpoints were nonspecific for cardiac ischemia. So,  
14 for example, a patient presenting with dyspnea or  
15 shortness of breath could have very well also been  
16 counted as having a cardiovascular event in this meta-  
17 analysis. So this certainly leads to questions of  
18 misclassification and, also, the completeness, whether  
19 or not there was complete ascertainment in the meta-  
20 analysis.

21 This slide here summarizes the results from  
22 the 2007 meta-analysis. On the left-hand column, you

1 have the different components of the endpoints I  
2 talked about earlier, ischemic heart disease, serious  
3 ischemic heart disease, and the MACE endpoint.  
4 Immediately, you would note that the event rates are  
5 actually very low for the two groups, rosiglitazone to  
6 control, and only in the ischemic heart disease  
7 endpoint is the comparison between rosiglitazone and  
8 control statistically significant, with a nominal p-  
9 value of .02. For serious ischemic heart disease,  
10 it's nearly statistically significant, and for MACE it  
11 was not.

12           However, this signal was still of a concern  
13 to the agency, because the risk estimates for all  
14 three categories did not favor rosiglitazone.  
15 However, given the limitations of the meta-analysis  
16 I've outlined in the previous slide and, also, the  
17 fact that the risk estimates were not very robust, the  
18 agency felt that it was important to look more  
19 carefully at this meta-analysis, which was what was  
20 done.

21           This slide here was provided to us by Ms.  
22 Joy Mele. She is the FDA statistician who reviewed

1 this meta-analysis in 2007. And on this slide here,  
2 you see the overall findings, down here in the Forest  
3 plot, and you see it broken population by placebo-  
4 control studies and active-control studies.

5 What you note here in the placebo-control  
6 studies is this is very similar to the overall finding  
7 for the meta-analysis. And this is not surprising,  
8 because 85 percent of the trials making up the meta-  
9 analysis were placebo-control trials.

10 But if you look at the active-control  
11 studies, what you see is that the point estimates for  
12 serious ischemic heart disease and ischemic heart  
13 disease fall along unity. And for the more  
14 conventional endpoint of MACE, what you see is that  
15 the point estimate actually favors rosiglitazone,  
16 although not statistically significant.

17 This led the agency to ask the question:  
18 Does rosiglitazone increase cardiovascular risk  
19 relative to other anti-diabetic therapies? Now,  
20 specifically for the meta-analysis, this would be  
21 metformin and sulfonylurea. They were the only  
22 comparators used in the meta-analysis.

1           In addition to this subgroup here, Ms. Mele  
2   also identified the co-administration of insulin with  
3   rosiglitazone and the baseline use of nitrates as  
4   potential risk factors for excess cardiovascular risk  
5   with rosiglitazone use. I will be talking about those  
6   subgroup analyses a little bit later.

7           Also, in 2007, were data presented from the  
8   long-term controlled trials for rosiglitazone. They  
9   include data from DREAM, ADOPT, and, in 2007, the  
10   interim analysis for RECORD. There is a lot of  
11   information on this slide here, but I only want to  
12   make several key points.

13           For the DREAM trial, this was a 2-by-2  
14   factorial design study not in diabetics, but in pre-  
15   diabetic patients. So this is a low risk patient  
16   population, and you see that there are different  
17   treatment comparisons here, rosiglitazone versus  
18   placebo, rosiglitazone in combination with the ace  
19   inhibitor ramipril versus ramipril alone in  
20   determining whether or not there could be prevention  
21   of Type II diabetes. You'll be seeing data in  
22   subsequent slides presented by those different

1 factorial groups.

2           In addition only one of these three trials  
3 actually had as its primary objective, a  
4 cardiovascular risk evaluation between rosiglitazone  
5 and the comparator. However, both DREAM and RECORD  
6 did have a blinded cardiovascular endpoint committee  
7 adjudicating cardiovascular events in those trials.

8           Combined, all three trials had data in over  
9 14,000 patients, very similar to what was seen in the  
10 meta-analysis. The difference was that a median  
11 duration of follow-up in these trials was 41 months  
12 compared to six months in the meta-analysis. In  
13 addition, if you recall, in the Forest plot that I  
14 showed you earlier with respect to the active-control  
15 trials, the meta-analysis, where we didn't see a  
16 difference between rosiglitazone and the active-  
17 controls, metformin and sulfonylurea, what's  
18 interesting is that the active-controls in these long-  
19 term control trials were also metformin and  
20 sulfonylurea.

21           So this gave the agency at that time a  
22 unique opportunity to look at another database to see

1 if the findings from the meta-analysis could be  
2 confirmed. And over the next three slides, I will  
3 present the cardiovascular findings from the long-term  
4 control trials for rosiglitazone.

5           This slide here is from MACE and if you just  
6 focus on -- these are the overall results. You see  
7 that there's no significant difference between  
8 rosiglitazone and control, the individual trials  
9 contributing to the overall results. As I mentioned  
10 before, the DREAM trial was a 2-by-2 factorial design,  
11 and the data are presented by the factorial groups.  
12 This was not an expected finding, where rosiglitazone  
13 in combination with an ace inhibitor seemed to have a  
14 much greater event rate than the other treatment  
15 groups.

16           I'm not going to delve much further into  
17 that. You will be hearing from other presenters later  
18 on in the day from other databases where this  
19 interaction was explored.

20           This finding is for myocardial infarction,  
21 and you see, once again, for the overall findings,  
22 that there was no significant difference between



1   rosiglitazone and control. The individual trials  
2   contributing to it also carried a similar finding.  
3   Again, DREAM and the factorial treatment groups had  
4   the differences in effect here.

5           I want to point out here that even though  
6   the myocardial infarction finding was not  
7   statistically significant, the point estimate was  
8   still not favoring rosiglitazone across all these  
9   different trials. And while it's not evident on this  
10  scale here, the point estimate, the absolute number  
11  itself, is actually very similar to the point estimate  
12  of a myocardial infarction signal seen in the  
13  published meta-analysis.

14           Finally, this slide here is for the  
15  mortality findings from the three large trials;  
16  overall, no significant difference between  
17  rosiglitazone and control for the individual studies  
18  themselves. Interestingly, for DREAM, there was not  
19  that different effect between the factorial groups for  
20  rosiglitazone versus sulfonylurea. In ADOPT, it was  
21  favoring rosiglitazone, almost reaching statistically  
22  significant, but not so.

1           Unlike the myocardial infarction slide here,  
2   what we're seeing is that the point estimates are  
3   consistently favoring rosiglitazone, again, not  
4   statistically significant.

5           What about the other drug in this class back  
6   in 2007? The other being pioglitazone, or Actos. It  
7   is the only other marketed TCD. Well, there was a  
8   cardiovascular outcomes trial conducted with this  
9   product. It was called the PROactive trial, and this  
10   was presented back in 2007. It enrolled over 5,200  
11   patients with Type II diabetes and macrovascular  
12   disease, randomizing the patients to either  
13   pioglitazone or placebo added on to background  
14   therapy.

15           The primary endpoint was not MACE. It was a  
16   composite of all the endpoints that I have listed up  
17   here, excluding heart failure. There was a late  
18   amendment to the protocol four months after the trial  
19   was stopped, and that was made up of all cause death,  
20   nonfatal MI, and stroke, and this was considered a  
21   major secondary endpoint. However, there were no  
22   provisions to control for Type I error in this

1 analysis.

2 FDA did receive these data. FDA did review  
3 it and in February of 2007, the results from the  
4 PROactive trial were included in the labeling. The  
5 product did not receive a claim of cardiovascular  
6 benefit. However, the information from PROactive was  
7 included under the warnings and precautions section of  
8 labeling.

9 The reason why it went into warnings and  
10 precautions was because in PROactive, the risk of  
11 heart failure was significantly higher with Actos than  
12 to the comparator. However, that was followed with a  
13 statement "no increase in mortality of in total  
14 macrovascular events with Actos."

15 This slide here summarizes some of the  
16 findings from the PROactive trial. For the primary  
17 composite endpoint that I had mentioned earlier, you  
18 see that there is no significant difference between  
19 pioglitazone compared to placebo. For cardiovascular  
20 death, there was no significant difference between  
21 pioglitazone and placebo. And this is the endpoint  
22 that I had mentioned earlier was a late amendment, it

1 suggests that there was a benefit with respect to all  
2 cause mortality, MI and stroke; although, again,  
3 because there was no control for Type I error, the  
4 agency did not believe that this was enough evidence  
5 to support a claim for cardiovascular benefit.

6 Our conclusions were that this was a neutral  
7 study, but reassuring that there was not evidence of  
8 cardiovascular harm.

9 Back in 2007, there were no ongoing or  
10 completed studies, cardiovascular outcome studies,  
11 comparing these two agents. However, Takeda did  
12 submit a meta-analysis of 19 pioglitazone trials to  
13 the agency. This was not reviewed back in 2007, for a  
14 variety of reasons. First, it did not include the  
15 patient level data for these trials. But, also, in  
16 looking at the clinical development program for  
17 pioglitazone and, also, the trial designs of those  
18 trials contributed to the meta-analysis, there were  
19 differences that raised concerns of whether or not it  
20 was appropriate to compare these two products for  
21 cardiovascular safety based on the two meta-analyses.

22 I summarize on the slide here some examples

1 of the differences between the two meta-analyses. For  
2 rosiglitazone, the majority of the trials were of six  
3 months' duration or less. For pioglitazone, half  
4 these studies were of one year duration or more.

5 The comparator was also different. You had  
6 more placebo-controlled trials in the rosiglitazone  
7 meta-analysis versus more active-control trials in the  
8 pioglitazone meta-analysis, particularly of  
9 sulfonylureas.

10 Now, in spite of these differences, it's  
11 natural tendency for us to want to compare these two  
12 drugs, and, indeed, that was what was done in 2007.  
13 This slide was presented before the advisory committee  
14 panel, where the meta-analysis for pioglitazone is  
15 compared to the meta-analysis for rosiglitazone.

16 Not withstanding the limitations in the  
17 different trial designs and the development program I  
18 mentioned in the previous slide, there were also  
19 differences in the endpoints that were evaluated. In  
20 here, it's all deaths, plus nonfatal MI and stroke;  
21 here, it's cardiovascular deaths, MI and stroke.

22 While we may just say, "Well, it's just a

1 difference between all deaths and cardiovascular  
2 death," we need to remember that the concern that was  
3 raised with respect to the rosi meta-analysis on  
4 selection of these endpoints; so nonspecific terms,  
5 concerns for misclassification, incomplete  
6 ascertainment, perhaps even improper adjudication  
7 could very easily apply for both these meta-analyses,  
8 and we don't know how well balanced they were for  
9 that.

10 But if we're going to compare the two drugs  
11 based on meta-analyses, it was also fair to ask,  
12 "Well, why not compare the two drugs based on long-  
13 term controlled clinical trials." And instead of  
14 selecting an endpoint where there's a lot of debate on  
15 whether or not it was appropriately ascertained,  
16 adjudicated and what not, why not pick an endpoint  
17 where there may be less debate over, which is total  
18 mortality, where we do not need a biomarker to  
19 determine if a patient has died or a patient remains  
20 alive in a clinical trial.

21 Now, you'll also hear later on today that  
22 total mortality may also be reflective of

1 cardiovascular risk in the Type II diabetic  
2 population, because the majority of deaths in the Type  
3 II diabetic population are cardiovascular related.

4           So how do these data compare to one another  
5 with respect to rosi and pio? In this slide here, you  
6 have a forest plot of the mortality findings from  
7 three trials for rosiglitazone that I summarized  
8 earlier. And if you look at how pioglitazone, with  
9 total mortality, in the PROactive trial lined up, this  
10 is what you get.

11           Now, this slide is not being presented to  
12 make a conclusion that there is no difference in risk  
13 of mortality between these two drugs based on long-  
14 term control trials. And the reason why that's the  
15 case is that the same limitations that I outlined in  
16 the previous slide for comparing meta-analysis to  
17 meta-analysis applies in this situation, as well.

18           You're talking about very different trial  
19 designs, different patient populations. You have open  
20 label designs, active-control designs, placebo-control  
21 designs, lower risk patient population, high risk  
22 patient population. Those things need to be really

1 considered when you're comparing across trials.

2 But the point that really I'm trying to  
3 emphasize here is that when you choose to make these  
4 types of comparisons, what you choose to compare may  
5 very well give you the answer you want to hear.

6 Indeed, that was -- if you go to the  
7 transcripts from 2007, you'll hear that there was  
8 quite a bit of consternation raised by the panel  
9 members back in 2007 of making such a comparison based  
10 on the two meta-analyses. But despite that, they were  
11 still required to vote on two questions, the first one  
12 being, "Do the available data suggest a conclusion  
13 that Avandia increases cardiac ischemic risk in Type  
14 II diabetes mellitus. The vote was 20-yes and 3-no.

15 I want to point out that this question was  
16 originally written as, "Do the available data support  
17 a conclusion that Avandia increases cardiac ischemic  
18 risk?" And if you go back to the transcripts, you'll  
19 note that advisory committee panel members actually  
20 asked to change -- well, actually, they changed the  
21 question, because there was a lot of concern on voting  
22 on this question in such a definitive fashion based on



1 the clinical evidence that was provided at that time.

2 Now, we do have many of the members from  
3 2007 returning to us today, and certainly this gives  
4 many of you an opportunity to confer with your  
5 colleagues on what was behind their thoughts in making  
6 a change to that question.

7 The second question was, "Does the overall  
8 risk-benefit profile of Avandia support its continued  
9 marketing in the United States?" Twenty-two voted,  
10 yes, that the drug should remain on the market, and  
11 one voted no.

12 Now, you heard from Commissioner Hamburg  
13 earlier that if it wasn't apparent to you coming into  
14 this advisory committee, it will be apparent to you by  
15 the end of today that there are very different  
16 opinions on the findings of cardiovascular risk with  
17 Avandia and, also, what that regulatory action should  
18 be, both internally and externally to the FDA. And  
19 that situation was no different back in 2007.

20 After the 2007 advisory committee meeting,  
21 there was a recommendation from the Office of  
22 Surveillance and Epidemiology, OSE, which was to

1 remove the drug from the market, whereas the Office of  
2 New Drugs, the OND, did not believe there was  
3 sufficient evidence to support its withdrawal.

4           Instead, it was recommended that the company  
5 strengthen the labeling for the product for CV risk  
6 and, also, to conduct a prospective cardiovascular  
7 outcomes trial.

8           Because of the differences in opinion  
9 between two offices from the agency, this then became  
10 a center level decision. So on October 13th, 2007,  
11 that decision was rendered, which is rosiglitazone  
12 would remain on the market, but with stipulations.

13           In a memo dated January 2nd, 2008, the  
14 stipulations were that there would have to be a box  
15 warning to discuss the risk of myocardial ischemia or  
16 infarction; a medication guide was needed; the  
17 warnings section of the labeling needed to discuss  
18 individual risk factors which might contribute to  
19 excess cardiovascular harm with the drug; and,  
20 finally, quote, "The firm would be required to begin  
21 and promptly execute a study comparing their drug to  
22 pioglitazone," end quote.

1           This directive formed the basis for the  
2 required post-marketing trial, thiazolidinedione  
3 intervention in vitamin D evaluation.

4           This slide here summarizes for you the text  
5 from the box warning that was updated in November of  
6 2007. The information in here is what I've already  
7 summarized in previous slides.

8           Now, I mentioned earlier that there were two  
9 subgroups identified by Ms. Joy Mele that were of  
10 concern with respect to increased cardiovascular risk  
11 with rosiglitazone. They were the co-administration  
12 of insulin, along with rosiglitazone, and the co-  
13 administration of nitrates along with rosiglitazone.

14           In determining where these risks needed to  
15 be described in labeling, the agency really had to  
16 explore the signal for these risks. And for the  
17 insulin co-administration with rosiglitazone, that  
18 signal came from clinical trials in which patients had  
19 already been treated with insulin, some for quite a  
20 long time, and then they were randomized to receive  
21 either rosiglitazone or placebo.

22           This is very different from clinical

1 practice. The treatment of a Type II diabetic patient  
2 is often with an oral anti-diabetic agent, often many  
3 oral anti-diabetic, before insulin is actually  
4 initiated. And the patient population that's already  
5 on insulin versus the patient population that is just  
6 on an oral anti-diabetic therapy and just initiating  
7 insulin is very different. The former often has  
8 diabetes for a much longer duration, which means that  
9 they have more risk factors for cardiovascular events  
10 at baseline, and they're also less tolerant of the  
11 fluid-retaining effects of a TZD.

12           So since clinical practice more commonly  
13 uses insulin and rosiglitazone in a manner different  
14 from the studies generating the cardiovascular risk,  
15 it was not deemed appropriate to contraindicate the  
16 co-administration of these two products, but that it  
17 was more appropriate to add this under warnings and  
18 precautions.

19           I do want to point out that the TIDE trial,  
20 that is their post-marketing study that's ongoing  
21 right now, patients who are on insulin at baseline are  
22 excluded from enrolling in this trial. So the use of

1 insulin and rosiglitazone in the trials which detected  
2 this risk is prohibited in the TIDE trial.

3           Now, with the risk of nitrate, that signal  
4 came from a subset of 557 patients out of 14,237  
5 patients in the meta-analysis. Given that this is  
6 such a small number of patients and, as you will hear  
7 from other presenters today, not observed in other  
8 settings, it was also considered not appropriate to  
9 label as a contraindication, and it was placed under  
10 warnings and precautions.

11           I have summarized on this slide here some  
12 excerpts from the section in the Code of Federal  
13 Regulations specific to drug labeling. Events that  
14 should be placed under a contraindication are those  
15 that support the statement the drug should not be used  
16 because the risk of use clearly outweighs any possible  
17 benefit.

18           If these two risk factors were deemed  
19 inappropriate for use under any situation, including a  
20 clinical investigation, the agency would have labeled  
21 it as a contraindication, not a warning and  
22 precaution.

1           This slide here summarizes the sequence of  
2 events following the July 2007 advisory committee up  
3 until today. You've already heard that in October  
4 2007, the center director made the decision that the  
5 drug would remain on the market; however, they would  
6 need to have a medication guide, an update to the  
7 label to describe all the risks that had been  
8 identified from the review of the data back then, and,  
9 also, an update to the box warning. In addition, the  
10 company would also need to perform a large prospective  
11 cardiovascular outcomes trial of rosiglitazone.

12           Now, FDA staff immediately began working to  
13 implement this decision and initiated discussions with  
14 the company about labeling changes and this post-  
15 marketing trial. Indeed, the box warning, I've  
16 already shown you that slide, and the updates to the  
17 label occurred in November of 2007. The medication  
18 guide was approved in February of 2008. So what  
19 remained was that post-marketing trial.

20           Now, in September of 2007, Congress passed  
21 into law the Food and Drug Administration Amendments  
22 Act, also known as FDAAA. Under FDAAA, FDA received

1 new authorities to require that these post-marketing  
2 trials for safety be conducted. And indeed, on May  
3 7th, 2008, FDA informed the company that this post-  
4 marketing trial was going to become a required post-  
5 marketing trial.

6 Specifically, the company was told that this  
7 trial had to evaluate macrovascular events in patients  
8 with Type II diabetes and it had to include the  
9 following three treatment groups: rosiglitazone,  
10 placebo, and pioglitazone.

11 Now, required post-marketing trials under  
12 FDAAA do include timelines that are enforceable by  
13 civil money penalties, and the company met their first  
14 timeline when they submitted the TIDE protocol in July  
15 of 2008. A multidisciplinary team within CDER,  
16 including representatives from OND, OSE, and the  
17 Office of Biostatistics, was assembled to review the  
18 proposed protocol.

19 In October 2008, Drs. Gelperin and Graham  
20 completed a memo in which they reviewed observational  
21 studies for rosiglitazone published in 2007. They  
22 made comparisons between rosi and pioglitazone based

1 on the published observational studies and meta-  
2 analyses of controlled clinical trials of rosi and  
3 pio. They concluded that rosi had cardiovascular  
4 risks not shared by pio and that rosi had no unique  
5 benefit over pio.

6           They further concluded that the TIDE trial  
7 was unethical and that rosi should be withdrawn from  
8 the market. The withdrawal recommendation mirrored  
9 their position from before the 2007 center director  
10 decision following the first advisory committee  
11 meeting.

12           So while awaiting an official position from  
13 the Office of Surveillance and Epidemiology Management  
14 on whether Drs. Gelperin and Graham had raised new  
15 issues that warranted revisiting the center director's  
16 2007 decision on Avandia, the review team continued to  
17 review and discuss the proposed protocol for TIDE.

18           Numerous internal meetings and discussions  
19 with GSK were held to iron out the details of the  
20 protocol, and, in February of 2009, the TIDE trial was  
21 initiated. Also, during this time, the agency  
22 received a citizen petition from Public Citizen



1 requesting that the agency withdraw Avandia from the  
2 market. The agency has not responded to that  
3 petition. We also learned in that very same month  
4 from the company that the RECORD trial was completed.  
5 The last patient last visit was on December 26th,  
6 2008, and the company had plans to submit the results  
7 to the agency in the form of an efficacy supplement to  
8 support labeling changes.

9 That supplement was submitted to the agency  
10 in August 2009. So in addition to the RECORD data and  
11 its complete datasets, there was also an update to the  
12 meta-analysis to include 10 additional studies.

13 Based on these new data, GSK proposed that  
14 the box warning for ischemic cardiovascular events be  
15 removed from the rosiglitazone label. This supplement  
16 is still under review by the FDA, and the proposed  
17 labeling changes are reflected in your questions as  
18 option A under question 7.

19 After receiving the RECORD supplement, the  
20 Office of New Drugs made plans for its review and  
21 presentation before a public advisory committee  
22 meeting in May of 2010. In October of 2009, the OSE

1 director completed a memo in which he reviewed the  
2 recommendations made by Drs. Gelperin and Graham and  
3 restated his view that rosiglitazone should be  
4 withdrawn from the market.

5 On learning of his recommendation, the OND  
6 director wrote a memo to the center director  
7 recommending that given the new data on cardiovascular  
8 risk of rosiglitazone that was currently under review,  
9 that FDA undertake a comprehensive re-review of the  
10 cardiovascular safety of rosiglitazone and discuss the  
11 issue at a public advisory committee meeting before a  
12 regulatory decision is made.

13 Following discussions with the OND and OSE  
14 directors, the center director agreed that was the  
15 appropriate course of action to reach a regulatory  
16 decision. Given the expansion of the review required  
17 to prepare for the advisory committee meeting, the  
18 planned spring advisory committee meeting was delayed  
19 until today to provide time for all necessary review  
20 work to be completed.

21 This is where we are today. How did the  
22 agency plan and prepare for this advisory committee

1 meeting? With respect to the review of RECORD,  
2 comprehensive review of RECORD was undertaken by the  
3 Division of Metabolism and Endocrinology Products,  
4 also, in consultation with the Division of  
5 Cardiovascular and Renal Products, Office of  
6 Biostatistics, and the Division of Scientific  
7 Investigations.

8 In addition, there was also review of  
9 observational studies, an update of new data since  
10 2007, with studies specifically evaluating  
11 rosiglitazone and pioglitazone, and there was a  
12 retrospective cohort study of claims data from the  
13 Center for Medicaid and Medicare Services to compare  
14 rosiglitazone to pioglitazone on selected  
15 cardiovascular endpoints.

16 The meta-analyses of rosiglitazone and  
17 pioglitazone trials were undertaken. For rosi, this  
18 was specifically undertaken to update the 2007 meta-  
19 analysis of rosi, to include those 10 additional  
20 studies submitted under the efficacy supplement. For  
21 pioglitazone, it was to determine whether a comparably  
22 conducted meta-analysis to rosi would enable indirect

1 comparisons of safety between the two drugs.

2 Long-term trials were not included due to  
3 market differences and study designs, and their data  
4 would dominate overall meta-analysis findings.  
5 However, their data were not dismissed. The long-term  
6 trials were reviewed separately. You've already heard  
7 some of those data in my presentation and you will  
8 hear much more about RECORD momentarily.

9 In addition, several guest speakers have  
10 been invited by the agency to enable a comprehensive  
11 view of cardiovascular safety data. The data  
12 presented by several guest speakers have not been  
13 reviewed by the agency.

14 I'd also like to point out that in the  
15 audience, the agency has invited Takeda, the  
16 manufacturers of pioglitazone, or Actos, to be  
17 available if there are questions from the panel  
18 members on their product.

19 In the last couple of slides, I'd like to  
20 introduce the speakers for both days. You will first  
21 hear from GSK, GlaxoSmithKline. Dr. Ian Laws, Dr.  
22 Philip Home, and Dr. Murray Stewart will be speaking

1 on behalf of GSK.

2 Dr. Steven Nissen from the Cleveland Clinic  
3 will be presenting his updated meta-analysis and,  
4 also, his perspectives on rosiglitazone.

5 From FDA, the presentation for RECORD will  
6 come from Dr. Thomas Marciniak, Dr. Ellis Unger, Dr.  
7 Karen Mahoney from the Office of New Drugs, Dr. David  
8 Hoberman from the Office of Biostatistics, and Dr.  
9 Susan Leibenhaut from the Division of Scientific  
10 Investigations.

11 You will also hear from the Office of  
12 Surveillance and Epidemiology. Dr. Kate Gelperin will  
13 be presenting the observational studies that have  
14 published since 2007 comparing specifically rosi to  
15 pioglitazone. Dr. David Graham will be presenting the  
16 retrospective cohort study, utilizing data from CMS.

17 From the Office of Biostatistics, you will  
18 be hearing from Dr. Fiona Callaghan on the meta-  
19 analysis of rosiglitazone trials, and Dr. Brad McEvoy  
20 on the pioglitazone meta-analysis trials, and he will  
21 also sum up the data from both meta-analyses.

22 Wrapping up today will be Dr. Maria Brooks

1 from the University of Pittsburgh. She is a lead  
2 biostatistician for the BARI-2D trial. Then,  
3 following, Mr. Thomas Moritz from the Edward Hines,  
4 Jr. VA Hospital. He is the lead biostatistician for  
5 VADT.

6 For tomorrow, we'll start off with Dr.  
7 Hertzell Gerstein from McMaster University. He is the  
8 principal investigator for the TIDE trial. Following  
9 him will be Dr. Dean Follmann from the NIH. He is a  
10 biostatistician, who will be providing an overview of  
11 the strengths and limitations of the different  
12 clinical data sources you'll be hearing today.

13 Dr. Ruth Faden and Dr. Steven Goodman from  
14 the Institute of Medicine will be presenting the  
15 recently released report from the IOM. There will be  
16 a one-hour public hearing. And after the charge to  
17 the committee given by Dr. Gerald Dal Pan from the  
18 Office of Surveillance and Epidemiology, it will be  
19 opened up to the panel for discussions and responses  
20 to the questions the FDA has posed.

21 On behalf of the FDA, I would like to thank  
22 every member of this panel for your careful

1 consideration of this very complex issue. We look  
2 forward to hearing your deliberations and  
3 recommendations.

4 Thank you.

5 DR. BURMAN: Thank you, Dr. Parks.

6 We will now proceed with the sponsor  
7 presentation. I would like to remind public observers  
8 at this meeting that while this meeting is open for  
9 public observation, public attendees may not  
10 participate except at the specific request of the  
11 panel.

12 Both the FDA and the public believe in a  
13 transparent process for information-gathering and  
14 decision-making. To ensure such transparency at the  
15 advisory committee meeting, FDA believes that it is  
16 important to understand the context of an individual's  
17 presentation.

18 For this reason, FDA encourages all  
19 participants, including the sponsor's nonemployee  
20 presenters, to advise the committee of any financial  
21 relationships that they may have with the firm at  
22 issue, such as consulting fees, travel expenses,

1 honoraria, and interests in the sponsor, including  
2 equity interests and those based upon the outcome of  
3 the meeting.

4           Likewise, FDA encourages you, at the  
5 beginning of your presentation, to advise the  
6 committee if you do not have any such financial  
7 relationships. If you choose not to address the issue  
8 of financial relationships at the beginning of your  
9 presentation, it will not preclude you from speaking.

10           Dr. Laws?

11           DR. LAWS: Thank you.

12           Good morning. My name is Ian Laws and I am  
13 the vice president in GSK's global regulatory  
14 organization, with responsibility for cardiovascular  
15 and metabolic disease.

16           Over the next few minutes, I will provide an  
17 introduction to the sponsor's presentation for  
18 Avandia. That sponsor presentation is comprised of  
19 four sections. Firstly, this initial short  
20 introduction from me, and that introduction will be  
21 followed by an overview of new data available since  
22 the 2007 joint advisory meeting. This overview will



1 be given by Dr. Murray Stewart and will touch on a  
2 variety of data sources.

3 Other speakers later in the day will provide  
4 further detail and insight for some of the studies in  
5 that overview. Then after that review, Dr. Philip  
6 Home, Professor of Diabetes Medicine at Newcastle  
7 University in the U.K., will then present the outcome  
8 of the full RECORD study, and he makes this  
9 presentation in his capacity as chair of the steering  
10 committee for the study.

11 Then, finally, Dr. Stewart will bring all of  
12 the data together in a consideration of the benefits  
13 and risks of the use of rosiglitazone.

14 So before we move to the main discussion,  
15 it's worth pausing, as Dr. Parks has done already, to  
16 briefly look at the previous meeting of this joint  
17 committee, the data that was available, and the  
18 outcome reached.

19 In terms of the data reviewed at the meeting  
20 in 2007, that was in a series of the following areas.  
21 Firstly, there was the integrated clinical trial  
22 analysis from GSK and, indeed, other meta- analyses.

1 Secondly, there was the interim analysis conducted by  
2 the steering committee for the RECORD study; and,  
3 thirdly, there were data from another long-term study  
4 conducted by GSK, the so-called ADOPT study. Finally,  
5 there were data from a limited number of observational  
6 studies.

7 The committee was asked to vote on two  
8 questions, and it reached the following conclusions.  
9 Firstly, the data available at the time suggested a  
10 possible increase in cardiovascular risk; but,  
11 secondly, that rosiglitazone should continue to be  
12 available to patients.

13 Subsequent to the meeting, as Dr. Parks has  
14 described, FDA required the introduction of labeling  
15 for all oral anti-diabetic drugs to reflect the lack  
16 of demonstrated macrovascular benefit. It required  
17 revised labeling for rosiglitazone; and, finally, it  
18 required the conduct of the TIDE study comparing  
19 rosiglitazone, pioglitazone, and placebo.

20 So with that as background, what is  
21 available to us today to instruct on the  
22 cardiovascular profile of rosiglitazone? Described in

1 the briefing document are the data published at the  
2 time, and, in short, they include the following areas.  
3 There is the updated analysis of short-term clinical  
4 trials, with 10 new studies which meet the same  
5 criteria as the original 42 included in the analysis  
6 in 2007.

7           Secondly, there are a greater number of  
8 observational studies of differing sizes. Thirdly,  
9 there are a series of new control clinical trials,  
10 several of which were independently conducted and  
11 studied rosiglitazone in patients with significant  
12 cardiovascular risk, and they are, thus, very relevant  
13 to the discussion today.

14           Finally, we have the completed RECORD study.  
15 This study, you will recall, was a post-approval  
16 commitment in Europe, with the design agreed with the  
17 then EMEA in 2001. The focus at the time was one  
18 around CHF; hence, it's inclusion in the endpoint for  
19 the study.

20           The study is now fully reported, met its  
21 primary endpoint of non-inferiority, and is being  
22 filed to regulatory agencies around the world. The

1 results from the study have recently supported the  
2 renewal of the license for rosiglitazone in Europe,  
3 and, indeed, the data are described in its labeling  
4 there.

5           So against all of that background of data  
6 I've described, what are the questions before us over  
7 the next two days. Firstly, what are the strengths  
8 and weaknesses of the available data when comparing  
9 meta-analyses, observational data, and controlled  
10 clinical trials in understanding whether an increased  
11 risk of cardiovascular events or mortality exists with  
12 the use of rosiglitazone?

13           Next, what do these data indicate for the  
14 benefit-risk profile for rosiglitazone; and, on this  
15 basis, what regulatory actions might be appropriate?  
16 And finally, taking all the discussion into account,  
17 should the ongoing TIDE study be continued?

18           So to begin to share the data to support a  
19 scientific dialogue in response to those questions,  
20 I'd now like to turn the podium over to Dr. Murray  
21 Stewart. Dr. Stewart will briefly review the data  
22 which has become available since 2007.

1 DR. STEWART: Thank you, Dr. Laws.

2 This is an overview of my presentation. I  
3 will present data from three different source; an  
4 update from the integrated clinical trials performed  
5 by GSK; secondly, observational data published since  
6 2007, which provides data on rosiglitazone versus  
7 other oral anti-hyperglycemic medication, including  
8 data versus pioglitazone.

9 I will then concentrate on and present data  
10 from large controlled trials which have completed  
11 since 2007, which, together with RECORD, we believe  
12 provide the most robust and reliable data to assess  
13 the cardiovascular safety of rosiglitazone. This  
14 includes data from independent groups, such as the  
15 VADT and NIH, which conducted both ACCORD and BARI-2D.

16 Finally, I will hand it over to Professor  
17 Home, who, in his capacity as chair of the steering  
18 committee, will present the RECORD study, which was  
19 specifically designed to assess the cardiovascular  
20 safety of rosiglitazone.

21 Given the questions the committee will  
22 consider with regard to serious ischemic events, I

1 will focus on the endpoints of MACE, which stands for  
2 major adverse cardiovascular events; includes CV  
3 death, MI and stroke. This is the main endpoint in CV  
4 outcome studies, and this endpoint chosen by the FDA  
5 and the guidelines for CV safety for assessment of  
6 diabetes drugs.

7 I will not discuss much about CHF. This is  
8 not to diminish the relevance of CHF in overall  
9 cardiovascular safety, but reflects the fact that  
10 fluid effects common to both TZDs, which can  
11 exacerbate heart failure, have been described in the  
12 U.S. label for both TZDs, where physicians are advised  
13 not to prescribe this compound for patients with  
14 symptomatic heart failure.

15 So let's begin with the integrated clinical  
16 trials. As part of GSK's medical governance, it  
17 reviews the safety profile of its compounds in  
18 development and has a diligent pharmacovigilance  
19 program for its marketed products.

20 The cardiovascular safety of rosiglitazone  
21 was and is reviewed on an ongoing basis. Through this  
22 review, GSK identified a potential increase in

1 cardiovascular events, firstly, in its insulin  
2 studies. WHO also identified a potential increase in  
3 cardiac events with both TZDs.

4 GSK, therefore, conducted a retrospective  
5 exploratory analysis in 2005 of its clinical trial  
6 data for the two endpoints, myocardial ischemia and  
7 congestive heart failure. These results were shared  
8 with regulatory agencies.

9 The methods used in the retrospective  
10 analysis in 2005 are described here. Forty-two  
11 studies were included. All studies met the following  
12 inclusion criteria. They were on Type II diabetic  
13 subjects, involved approved doses of 4 and 8  
14 milligrams of rosiglitazone, and the studies were  
15 randomized double-blind.

16 The limitations were that these studies were  
17 not designed to assess cardiovascular effects, and, as  
18 such, no CV events were adjudicated. The studies were  
19 mostly six months duration and, in contrast to the  
20 larger outcome studies, had a low number of CV events.

21 The definition of myocardial ischemia was  
22 broad and included serious adverse events and adverse

1 event terms from nonspecific chest pain due to  
2 myocardial infarction and death. The broad definition  
3 was used to minimize the likelihood of missing  
4 potential signals and maximizing the number of events  
5 to allow modeling assessments.

6 The results of the analysis are shown here,  
7 comparing the events of myocardial ischemia between  
8 patients receiving rosiglitazone and comparator, which  
9 could be an active comparator, such as metformin or  
10 sulfonylurea, or placebo.

11 The total results on the bottom of the table  
12 show, despite the broad definition, the events are  
13 actually less than 2 percent, 1.99 percent for  
14 rosiglitazone and 1.51 percent for the comparator,  
15 which gave a hazard ratio of 1.31 and a p-value of  
16 0.05.

17 When breaking down the trials, the increase  
18 in myocardial ischemia occurred primarily in placebo-  
19 controlled studies and there was no increase in  
20 myocardial ischemia when rosiglitazone was compared to  
21 active comparators, with a hazard ratio of 1.

22 Since the last outcome, we have updated the



1 integrated clinical trials with 10 new additional  
2 studies, which were ongoing in 2007 and have since  
3 completed. We used the same criteria as before and  
4 the studies had the same limitations. We did not  
5 include in these analyses the large outcome studies,  
6 as they would be methodologically inappropriate, as  
7 increased number of events in these large studies  
8 would dominate the analysis and potentially mask a  
9 short-term signal.

10 The endpoint, as before, was myocardial  
11 ischemia. But in addition, given the wider interest  
12 of CV events, we did a MACE analysis using SEA terms.

13 The results shown here are the MACE events  
14 from GSK and FDA's integrated clinical trials. The  
15 FDA analysis is based on the same 52 studies, with  
16 patient level detail. The difference in numbers  
17 reflect the difference in classifications from SAE  
18 terms and different statistical methods used.

19 The data presented here is forest plots,  
20 with point estimates to the right favoring control and  
21 to the left favoring rosiglitazone. The top line of  
22 each group represents the total MACE events, and,

1   beneath, the breakdown of the individual components,  
2   CV death, MI and stroke. Overall the number of events  
3   are low and occur in less than 1 percent of patients  
4   in the studies.

5           The low number of events reflected the wide  
6   confidence intervals and the instability in the point  
7   estimates. However, the pattern in the update  
8   analysis from both GSK and FDA are similar to that  
9   seen in 2007, with an increase in MI, a decrease in  
10   stroke, small numbers of deaths, and the overall MACE  
11   component overlapping 1.

12           The next slide here shows the MACE events  
13   from GSK and FDA's analysis of the updated 52 studies  
14   divided into those studies with rosiglitazone versus  
15   active comparators and rosiglitazone versus placebo,  
16   which includes true placebo and placebo added to  
17   background therapy. The results, as in 2007, show  
18   that there is an increase in MACE events in the  
19   placebo-controlled studies, but not in the active  
20   comparators.

21           In considering data from integrated clinical  
22   trials, the following factors need to be taken into

1 account. These are primarily from short-term trials.  
2 They were not designed to assess cardiovascular  
3 endpoints, and the data, therefore, is based on  
4 investigated-reported SAEs and not adjudicated events.  
5 And probably most importantly, there are only a small  
6 number of MACE events in the total ICT-52 studies,  
7 just over 100.

8           This is contrast to large outcome studies,  
9 where events are respectively adjudicated, the number  
10 of events are far higher. In RECORD, there were over  
11 300 adjudicated MACE events; and patients with  
12 established coronary artery disease and, therefore, at  
13 high risk of cardiovascular disease had over 450  
14 adjudicated MACE events in the BARI-2D study.

15           Therefore, rather than rely on integrated  
16 clinical trials and other similar meta-analysis, a  
17 more definitive assessment requires focus on long-term  
18 outcome studies.

19           I will now discuss the data from the  
20 published observational studies. Observational  
21 studies are important, as they can represent the drug  
22 used in a real world setting. Generally, they include

1 data from a larger, more diverse patient population  
2 that may not be recruited into clinical trials. They  
3 can also provide useful comparative data across agents  
4 in the same class.

5           However, there are limitations. There are  
6 several sources of potential bias that are important  
7 in Type II diabetes. Type II diabetes, as you know,  
8 is a progressive disease, and you could be comparing  
9 patients at different stages of the disease.

10 Databases don't readily capture the duration of  
11 therapy, including concomitant medication or the  
12 different doses of therapies.

13           There's also lack of information on the key  
14 and most important risk factors that actually  
15 determine CV outcome, such as weight, glucose, lipid  
16 control, smoking status, duration of diabetes.

17 Furthermore, there is often incomplete and lack of  
18 validation of diagnosis, including death, which is  
19 often not captured.

20           I will present data comparing rosiglitazone,  
21 firstly, against other anti-hyperglycemic agents,  
22 including metformin, sulfonylurea, and insulin, for

1 the endpoint of nonfatal MI. The biases important to  
2 consider when comparing rosiglitazone versus other  
3 agents reflects disease progression and the  
4 positioning of rosiglitazone in the treatment  
5 paradigm.

6           Currently, diabetes guidelines and  
7 reimbursement criteria could result in those patients  
8 receiving therapy being at very different background  
9 cardiovascular risk. An example; your newly diagnosed  
10 patient with low CV risk receives metformin, the first  
11 line, and in the database, they are then compared to  
12 patients receiving rosiglitazone, who, according to  
13 the guidelines, will only be given this when other  
14 therapies have failed and at late stage of the disease  
15 with high CV risk. Therefore, it may be the  
16 difference in background risk that drives the apparent  
17 difference in CV outcome, including myocardial  
18 infarction.

19           Here are the results, which are presented as  
20 relative risk estimates and 95 percent confidence  
21 intervals for each of the studies on a log scale and  
22 arranged in dissenting order of variance of the risk

1 ratios from left to right.

2           The log scale was used in order to show  
3 accurately the difference in precision amongst the  
4 various studies. As can be seen, in general, the  
5 studies with the lower variance of estimates and  
6 tighter confidence intervals, which are the more  
7 robust studies, have risk ratios that are very close  
8 to 1, indicating no or minimal difference in the risk  
9 of myocardial infarction between rosiglitazone and  
10 other anti-hyperglycemic agents.

11           Given some of the limitations here of  
12 comparing rosiglitazone with metformin and  
13 sulfonylurea, where use of the agents may differ  
14 according to guidelines, it is often easier to compare  
15 agents within the same class, where use might be  
16 expected to be similar.

17           The next slide shows the data comparing  
18 rosiglitazone and pioglitazone for the same risk of  
19 nonfatal MI. The studies are ordered, again, in  
20 descending order of variance, with the more robust  
21 studies to the right, and indicating no or minimal  
22 difference in the risk of MI between rosiglitazone and

1     pioglitazone.

2             One potential confounder to consider relates  
3     to the differential use of these agents since 2007.  
4     Given concerns with rosiglitazone, most users are  
5     repeat prescriptions rather than new patients; and,  
6     therefore, in a database, you'll be comparing  
7     rosiglitazone patients with longer duration of  
8     diabetes and higher CV risk compared to pioglitazone  
9     patients with lower CV risk.

10            So in considering observational studies,  
11     it's important to take into account the following: the  
12     varied study designs; the difficulty in confirming  
13     diagnosis; the capture of treatment duration and  
14     exposure; the varied statistical methods performed;  
15     and, finally, two sources of bias that may impact the  
16     results, use of the drugs at different stages of the  
17     disease and differential use of rosiglitazone and  
18     pioglitazone since 2007.

19            If the estimated relative risks are small,  
20     as in the studies I've shown you, selection bias and  
21     confounding may explain the association seen in  
22     observational studies, and, therefore, it's

1 appropriate to focus on long-term controlled clinical  
2 trials, which may give a more definitive assessment of  
3 the cardiovascular safety of rosiglitazone.

4 I'd now like to discuss the data from  
5 controlled clinical trials, in which the studies were  
6 in patients at high risk of CV events, where the  
7 events were adjudicated by independent committees, and  
8 many of the studies were run independent of GSK.

9 The APPROACH study was conducted by GSK, but  
10 it had independent safety monitoring and clinical  
11 endpoint committees. The aim of the study was to  
12 examine the effect of rosiglitazone on progression of  
13 atheroma. Assessment of atheroma was determined using  
14 IVUS. The study population was in patients with Type  
15 II diabetes and background cardiovascular disease.

16 The active comparator was a commonly used  
17 sulfonylurea, glipizide, and the primary endpoint was  
18 percentage change in atheromatous volume. The results  
19 of the study are shown here, and show no progression  
20 of atheroma and no difference between sulfonylurea.  
21 Cardiovascular events were adjudicated in the study.  
22 The event rate was over 11 percent in both groups,



1 reflecting the high risk patients.

2           Although the absolute event count is not  
3 high and the study was not powered for CV events,  
4 there was no difference between rosiglitazone and  
5 sulfonylurea for the composite or the individual  
6 components.

7           The ACCORD study is an NIH-run study. The  
8 aim of the study was to determine the effect of three  
9 different strategies on cardiovascular events:  
10 intensive glycemic control versus conventional  
11 control, intensive blood pressure control versus less  
12 tight control, and effective lipid control with  
13 fibrates versus placebo on top of statins.

14           The population was patients with Type II  
15 diabetes with background CV disease. There were over  
16 10,000 patients randomized and approximately 7,000  
17 patients were taking rosiglitazone. The  
18 cardiovascular events were adjudicated, and the  
19 primary endpoint was the composite MACE.

20           The intensive glycemic arm of the study was  
21 stopped early due to concerns about increased  
22 mortality, and the authors reviewed the data with

1 regards to the medication used in the study.

2           The results were presented at the ADA in  
3 2008 and showed that for mortality, the hazard ratio  
4 for rosiglitazone is less than 1, and the authors  
5 concluded that rosiglitazone is not associated with an  
6 increase in mortality.

7           These are the results from post-hoc analysis  
8 of the VADT study, of which you will hear more later.  
9 This study was conducted independent of GSK in  
10 patients with Type II diabetes at high risk of  
11 cardiovascular disease.

12           The events in the study were adjudicated and  
13 although the study was set up to examine strategies of  
14 tight versus less tight glycemic control, they have  
15 analyzed the data to determine the effect of  
16 rosiglitazone use on time to first myocardial event.

17           The data shown here demonstrate no increase  
18 in time to MI with rosiglitazone, and the MACE results  
19 were consistent with these findings and will be  
20 described later.

21           The authors' conclusion was that based on  
22 the results of the VADT study, there is no evidence to

1 suggest that use of rosiglitazone increased the risk  
2 of cardiovascular morbidity or mortality in patients  
3 with Type II diabetes.

4 In addition to VADT, here are the results  
5 from the BARI-2D study. This was a study in patients  
6 with Type II diabetes, all with established coronary  
7 artery disease, and, therefore, at high risk of CV  
8 events. The trial design and full results will be  
9 presented later.

10 In the sub-analysis of rosiglitazone versus  
11 no TZD use in this high risk population, the point  
12 estimate on the forest plots were to the left of 1,  
13 poising rosiglitazone for the endpoints of death, MI  
14 and MACE.

15 The authors concluded our observations from  
16 BARI-2D do not suggest a significant cardiovascular  
17 hazard and may suggest a potential beneficial effect  
18 on ischemic cardiovascular events associated with  
19 treatment with rosiglitazone among patients with Type  
20 II diabetes and established coronary artery disease,  
21 like those in the trial.

22 I would now like to hand over to Professor

1 Home to describe the RECORD study and its results.

2 DR. HOME: Thank you very much. And it's my  
3 pleasure to attempt to help the committee with its  
4 deliberations today by discussing the RECORD study.  
5 I'm a clinical researcher and, indeed, a practicing  
6 physician in Newcastle upon Tyne. I'm chairman of the  
7 RECORD steering committee.

8 It may help you to know I'm also a member of  
9 steering committees and, indeed, chair two DSMBs of  
10 five other outcome studies in diabetes, none of those  
11 connected with GSK.

12 Mr. Chairman, yes, I do have dualities of  
13 interest. You asked for a declaration. I do not take  
14 fees personally from GSK. I have no financial  
15 interest in the company. But GSK does fund  
16 institutions from which I'm concerned for my advisory  
17 research and educational activities, including my  
18 appearance here today. I have similar dualities of  
19 interests with other pharmaceutical manufacturers,  
20 including products used in the RECORD study.

21 The RECORD study was supervised by a  
22 steering committee under my chairmanship. The names

1 are given there and you can see they included two  
2 representatives from GSK, as well as international  
3 diabetes authorities from around Europe, including two  
4 cardiologists and a prominent professor of  
5 biostatistics.

6 We also had an independent data safety  
7 monitoring board, chaired by a diabetologist,  
8 Professor Ian Campbell, and, again, including a senior  
9 clinical trial statistician and a cardiologist, as  
10 well as endocrinologists.

11 Now, sadly, the integrity of the DSMB has  
12 been challenged in an editorial in the New England  
13 Journal currently. I have to take the opportunity to  
14 declare the information in that editorial is false and  
15 the DSMB were not approached or compromised by GSK in  
16 2007.

17 So what about the RECORD study?  
18 Importantly, this is an active comparator study of  
19 rosiglitazone versus metformin and sulfonylurea, and  
20 both arms were in combination with metformin or  
21 sulfonylurea.

22 The primary endpoint was the time to first

1 occurrence of any CV death or CV hospitalization.  
2 This was a randomized study. It was open label,  
3 because we had asymmetric rescue medication involving  
4 transfer to insulin therapy.

5 The endpoint was non-inferiority, with an  
6 upper bound set conservatively of 1.20 for the upper  
7 confidence limit. There was blind adjudication of  
8 endpoints by an independent endpoint committee, which  
9 I will come to.

10 We attempted to recruit a fairly typical  
11 population of people with Type II diabetes, the  
12 limitations for age, HbA<sub>1c</sub>, and body mass index.  
13 There, you will see trying to target people with  
14 typical Type II diabetes for second line therapy. And  
15 as such, they already had to be to be on maximum of  
16 maximum tolerated doses of either metformin or a  
17 sulfonylurea at recruitment. The sole sponsor was  
18 GlaxoSmithKline.

19 The primary outcome was rosiglitazone versus  
20 active-control, and the events were time to first CV  
21 hospitalization or CV death. Why CV hospitalization?  
22 Well, we were trying to ensure the quality of the

1 endpoint data and did not wish to take endpoint data  
2 which, in a non-inferiority study, because of noise,  
3 can result in false non-inferiority being generated  
4 towards the end.

5           As has already been noted, this study was  
6 set up because of concerns over heart failure with  
7 thiazolidinediones, and you'll note that heart failure  
8 was part of the primary endpoint both in regard of  
9 hospitalization and death.

10           You'll also notice that we had quite a wide  
11 CV endpoint here. Towards the bottom, you'll notice  
12 inclusion of unplanned revascularization, amputation  
13 of extremities, and any other definite cardiovascular  
14 reason, and you will see how we coped with that issue  
15 later.

16           As I've said, there was blinded adjudication  
17 by a clinical endpoints committee; broadly, what  
18 investigators thought was an endpoint or reported as  
19 an SAE, and, of course, hospitalizations, or SMEs,  
20 were referred for adjudication. Data was handled by  
21 an independent clinical trials organization,  
22 Quintiles. Very careful attention was taken to

1 removing any reference to study drugs from the  
2 material presented.

3           Two individuals of the clinical endpoints  
4 committee are listed here, and adjudicators, and if  
5 they agreed, fine; if they disagreed, it went to the  
6 whole committee. The committee is basically composed  
7 of cardiologists, with one diabetologist and one  
8 stroke doctor.

9           They used strict definitions formulated for  
10 other purposes by the European Cardiology Society,  
11 indeed, the American equivalent. So this was strict  
12 adjudication to avoid problems of misjudgment at the  
13 end of non-inferiority.

14           So we took people on monotherapy, either  
15 metformin or sulfonylurea. We randomly allocated them  
16 to rosiglitazone or the other agent, so that the  
17 primary comparison at the end becomes rosiglitazone  
18 either added to metformin or to sulfonylurea against  
19 metformin and sulfonylurea in combination.

20           As I said, there was also provision for  
21 rescue therapy, as the blood glucose control  
22 deteriorated with time, as, of course, it does in Type



1    II diabetes.

2               This is the trial profile. We aimed to  
3   recruit 4,000 and went somewhat beyond that. You will  
4   see that nearly half-and-half background metformin or  
5   sulfonylurea; randomized them then into the two  
6   groups, as specified. And you will notice, towards  
7   the bottom, that we lost, in the 5.5 years, about 3  
8   percent of the population to follow-up.

9               Some 1,950 or more in each group completed  
10   the study for a CV endpoint or for last visit or died,  
11   and a small proportion, around 7-8 percent, we were  
12   able to ascertain vital status, but did not have a  
13   final visit.

14              Here are the baseline characteristics. You  
15   will see that fairly typical for a Type II diabetes  
16   population entering a diabetes study, with a mean age  
17   of around 60; a BMI which varied slightly between the  
18   two groups, being higher in the metformin background  
19   group; and, an HbA<sub>1c</sub>, determined somewhat by the entry  
20   criteria of around 7.9 percent.

21              Of note here, on the bottom three lines, you  
22   will see that this is a typical diabetes population,

1 not enriched for cardiovascular disease. So that only  
2 5 percent have had experience of a prior myocardial  
3 infarction, and around 25 percent had any prior  
4 cardiovascular disease. This is very different, of  
5 course, from ACCORD, PROactive, and other studies.

6 This then is the headline result, the  
7 primary endpoint, CV hospitalization or CV death. The  
8 solid vertical line is unity equivalence between the  
9 two drugs. The non-inferiority margin is marked by  
10 the dotted vertical line. You can see there were 321  
11 events on rosiglitazone and 323 on control  
12 metformin/sulfonylurea, a reasonable number of events.

13 With the hazard ratio then coming in as .99,  
14 the confidence interval gives an upper bound, in  
15 green, of 1.16 and meets the non-inferiority margin,  
16 thus being statistically significant, if you like,  
17 non-inferiority.

18 This is the Kaplan-Meier curve. It broadly  
19 says nothing more to you than the previous slide,  
20 except, of course, that the outcome events accumulated  
21 entirely consistently over the 5.5 years of the study.  
22 You'll see there's no suggestion of variation towards

1 the beginning, the middle or the end. The data  
2 consistently accumulated in both arms.

3 We did some sensitivity analyses. Some  
4 statisticians prefer per protocol analysis for non-  
5 inferiority study. There is the per protocol data on  
6 the second line; hazard ratio very similar to that for  
7 the primary ITT analysis; of course, the confidence  
8 interval slightly wider, because there are smaller  
9 numbers of people in the per protocol analysis.

10 Per protocol analysis was done on randomized  
11 dual therapy only and for 30 days thereafter. Because  
12 the broad primary endpoint, the steering committee was  
13 concerned that it might give non-inferiority for  
14 events which rosiglitazone couldn't be expected to  
15 affect, so we also looked at atherosclerotic events  
16 only and you will see that gives a hazard of .97. The  
17 confidence interval is quite tight and would, again,  
18 meet our non-inferiority criterion for rosiglitazone  
19 against metformin/sulfonylurea.

20 As part of the sensitivity analysis, we also  
21 looked at the two strata on background metformin,  
22 background sulfonylurea, and you can see that

1   rosiglitazone versus sulfonylurea or rosiglitazone  
2   versus metformin gave identical, in statistical terms  
3   anyway, identical hazard ratios, very close to unity.  
4   Of course, again, the confidence intervals are  
5   slightly wider, because there are only half the events  
6   in either group as in the primary analysis.

7           So the sensitivity analysis, very much  
8   suggesting there was nothing untoward or unusual about  
9   the primary analysis in showing non-inferiority.

10           Some issues relate to CV medications. In  
11   each of these histogram bars, the left-hand two lines  
12   in yellow and blue are baseline and the two bars to  
13   the right in mauve and green are at five years. And  
14   you can see, not surprisingly, in a CV study in which  
15   investigators were encouraged to follow local  
16   guidelines, use of cardiovascular medications  
17   increased with time in nearly all groups.

18           On the left, we have the data for statins  
19   rising from some 20 percent to some 50 percent, and  
20   you will notice here there is an imbalance between use  
21   of statins in the rosiglitazone compared to the  
22   control group; and it is, therefore, appropriate to

1 ask whether that might have influenced the primary  
2 endpoint.

3           It can be calculated from the statin outcome  
4 studies that such an influence might be as great as  
5 .02 on the hazard ratio; i.e., it would not have  
6 materially affected our conclusions. And I see from  
7 the briefing document the FDA reached an identical  
8 conclusion.

9           There was also a small difference in use of  
10 loop diuretics, consistent with more edema on  
11 rosiglitazone. I have no idea how that might  
12 influence the outcome data.

13           What about secondary endpoints? I ask you  
14 to remember that RECORD was never powered to look at  
15 secondary endpoints. However, all cause death on  
16 rosiglitazone was 21, numerically lower on  
17 rosiglitazone than metformin/sulfonylurea; hazard  
18 ratio then down at .86; and, you will see, again, the  
19 confidence intervals very comfortably confirming non-  
20 inferiority.

21           Cardiovascular deaths of all kinds were 11  
22 lower on rosiglitazone compared to control, giving

1 similar hazard ratios, though, with slightly wider  
2 confidence intervals, because the numbers are much  
3 smaller.

4           Statistically, one should conclude that  
5 there is no evidence that rosiglitazone is inferior to  
6 metformin and sulfonylurea in regard of either all  
7 cause or cardiovascular deaths. But some people have  
8 suggested that rosiglitazone increases death rates in  
9 people with diabetes. And if you take the attitude  
10 that that's the case, then the probability of a  
11 decrease as against an increase is enormously in favor  
12 of rosiglitazone lowering deaths rather than  
13 increasing them.

14           This is the Kaplan-Meier curves, and, again,  
15 this contains the same data I've shown you, but  
16 against time. And, again, I only put them up to show  
17 you that the data we presented was consistent  
18 throughout the trial; that is, numerically, the  
19 rosiglitazone for all cause mortality ran below the  
20 metformin/sulfonylurea curves, but no suggestion of  
21 any difference with time.

22           The same is true, again, for the

1 cardiovascular data. Broadly speaking, a smaller  
2 number of events; therefore, rather more erratic  
3 curves, but, again, there is no suggestion that  
4 anything untoward is happening in any particular year,  
5 for example, which might be influencing the results.

6           We've also broken down the death results,  
7 because these are important. There, again, is the top  
8 line, 11 numerically less on rosiglitazone. If you  
9 scan down, you will see that there is no real  
10 suggestion that any group is increased on  
11 rosiglitazone. With the exception of heart failure,  
12 there, there are numerically 8 more on rosiglitazone  
13 compared to control, but that is balanced out by  
14 slightly smaller numbers in other areas and a largish  
15 difference in regard of stroke.

16           At the bottom, there are the non-CV deaths,  
17 and, of course, arithmetically, that adds up to the  
18 results I gave you earlier; so 10 less non-CV deaths  
19 on rosiglitazone.

20           Further secondary endpoints, heart failure,  
21 of course, was the intention of the study. It was no  
22 surprise it was increased. We knew this anyway from

1 the interim analysis. Basically, 30 different events  
2 between the two groups, with much worse on  
3 rosiglitazone, giving a hazard ratio of about doubling  
4 and an absolute risk of an increase of about 1 per 400  
5 patient years, highly statistically significant.

6 Again, I ask you to remember that this data  
7 is included within the primary endpoint and I would  
8 point out to you this includes fatal and nonfatal  
9 events.

10 The MACE endpoint there also is less in the  
11 rosiglitazone group than in the control group, giving  
12 a hazard ratio of .93, and, again, quite tight  
13 confidence intervals, with an upper bound of 1.15,  
14 comfortably suggesting non-inferiority.

15 For myocardial infarction, there were 8 more  
16 events on rosiglitazone than in the control group,  
17 giving a hazard of 1.14 and quite wide confidence  
18 intervals, as you can see, whereas for stroke, the  
19 data are very much the other way around, with some 17  
20 less events on rosiglitazone than control, a hazard  
21 ratio of .72.

22 You may remember that the ICT-42, two years



1 ago, showed statistical reduction in stroke on  
2 rosiglitazone and the hazard ratio in ADOPT was .77.  
3 So this finding is consistent with other data.

4 Obviously, myocardial infarction is of  
5 interest to us and, therefore, we have looked at the  
6 myocardial infarction data in further detail. This is  
7 the Kaplan-Meier curve, and, again, you will see it  
8 tracking. In fact, if you look, the lines are  
9 parallel apart from years 2 to 3, which is where most  
10 of the excess of 8 events comes from.

11 Myocardial infarction, as I said, was very  
12 tightly and correctly adjudicated in RECORD to ensure  
13 that less strong data did not give false non-  
14 inferiority. And for that reason, some of the events  
15 which, say, in ACCORD, might be called MI will appear  
16 in RECORD as unstable angina or angina.

17 So let us look at that data. Here, acute  
18 coronary syndrome then includes the MI data, plus  
19 unstable angina, 50 percent more events. The  
20 confidence intervals close and the hazard ratio is now  
21 1.05. If we add in hospitalization for angina, the  
22 event rate goes up another 42. The hazard ratio is

1 now .96, and the upper confidence interval is now  
2 1.25.

3 In the modern world, of course, some  
4 patients end up with revascularization before they can  
5 meet tight criteria for adjudication of MI. So  
6 including the revascularization data, we now have  
7 double the number of acute coronary events; hazard  
8 ratio almost exactly on 1.99, with a top interval of  
9 1.27.

10 In looking at these data, the steering  
11 committee finds it very difficult to conclude that  
12 rosiglitazone increases acute coronary events in  
13 people with diabetes compared to  
14 metformin/sulfonylurea.

15 A further issue, of course, is what happens  
16 after the first event. Here, again, is the 8  
17 difference, 64 versus 56. I had not yet pointed out  
18 to you that the small number of deaths in both groups  
19 contributing to those data is the same at 4, while 60  
20 and 52 go on towards the end of the study.

21 What happened in them while in the  
22 rosiglitazone, group 7 had a further MI; in the

1 metformin-sulfonylurea, 11 had a further MI. Adding  
2 in the other categories of acute coronary syndrome,  
3 you can see there were 14 on rosiglitazone and 13 on  
4 metformin/sulfonylurea.

5 If we look at deaths in this group, there  
6 are 7 cardiovascular deaths on rosiglitazone versus 10  
7 on metformin/sulfonylurea, and 11 and 12 any cause.

8 It seems, then, that there is no signal in  
9 this small dataset to suggest that anyone having a  
10 first MI on rosiglitazone does any worse than  
11 metformin/sulfonylurea.

12 So in summary, the primary endpoint in non-  
13 inferiority was satisfied for rosi versus the two  
14 other drugs. Sensitivity analysis were very much in  
15 line with the primary analysis, with the per protocol  
16 atherosclerotic events all within strata.

17 The secondary endpoints confirm a  
18 significant increase in heart failure, but show  
19 numerically less CV death, all cause death and stroke,  
20 and acute coronary event analysis is indistinguishable  
21 from metformin/sulfonylurea; also, indistinguishable  
22 with the recurrent events in those having an on-study

1 myocardial infarction.

2 I'm not going to show you other data,  
3 because I'm asked to present here on cardiovascular  
4 events. But just to note -- and we do have backup  
5 slides -- that durability of blood glucose control was  
6 better in RECORD than for sulfonylurea and metformin,  
7 P less than 0001 at 5 years of being a reduction of  
8 HbA<sub>1c</sub> of .2 to .3 against sulfonylurea -- sorry --  
9 against metformin or sulfonylurea.

10 I also am happy not to present you with  
11 other safety data, but I will just remark now that we  
12 confirmed that the distal fracture rate is markedly  
13 increased in women, around double, and our data show  
14 some uncertainty as to whether an increase occurs in  
15 men. But we have no useful data for or against hip or  
16 spinal fractures. This is, however, an issue. The  
17 excess fracture rate is about 1 per 100 patient years  
18 in women.

19 So what about some of the challenges in a  
20 study like RECORD and, indeed, to RECORD from those  
21 outside it? Challenges include excessive loss to  
22 follow-up and could this result in some bias.

1           Here is the follow-up data. The people  
2 completely lost to follow-up are the people in gray  
3 along the top. You'll see the curve rises to 100  
4 percent at the end of randomization and then continues  
5 up to the first close of study visits in September  
6 2008.

7           The yellow are the people who died during  
8 the study and could not be followed up. The orange  
9 are those -- the 7-8 percent in vital status, the only  
10 follow-up which we worked very hard to make sure that  
11 data was complete.

12           The result of that was that we lost to  
13 follow-up for primary endpoint 7.2 percent; under  
14 vital status, 2.0 percent, and we think that not  
15 unreasonable in a study of this duration.  
16 Furthermore, it was balanced between the treatment  
17 groups.

18           Low number of people on randomized therapy  
19 at endpoint. This is a red herring. It's not  
20 relevant. At the end of a study, the proportion of  
21 people on a drug is important, of course, if you're  
22 making a measurement at that time, say, what is the

1 blood pressure control after 5 years; but it's  
2 actually exposure during the study that matters to a  
3 safety analysis, where you're accumulating events  
4 throughout the study.

5 Exposure to randomized treatments was good,  
6 rather better in the rosiglitazone group than in the  
7 metformin/sulfonylurea group, to some extent, an  
8 artifact of the rescue therapy algorithm.

9 Here is the data for the rosiglitazone  
10 group. Cardiovascular follow-up, we have over 12,000  
11 patient years; on treatment, about 10,800 patient  
12 years; follow-up on treatment, 88 percent. That 88  
13 percent has been challenged in the literature as being  
14 inconsistent with interim analysis data. The  
15 challenge is due to a miscalculation based on that  
16 interim data. This figure is correct. We have looked  
17 at it in all directions. In the other group, it was  
18 83 percent.

19 So what about event rate? The event rate  
20 was unreliably low, some say, and, as a result, the  
21 study was underpowered. Well, as is pointed out,  
22 again, in some of the FDA's analysis, it had enough

1 power that 640-odd events to show non-inferiority at  
2 endpoint.

3 Furthermore, the rate of events in RECORD is  
4 actually in line with other diabetes outcome studies.  
5 I'll show you a slide shortly, but just to note, also,  
6 that the sensitivity analyses do not show erratic  
7 changes in hazard ratio between different analyses, as  
8 can sometimes occur in underpowered studies.

9 This poster appeared at the ADA recently in  
10 Orlando, and I have to say it comes from GSK. What  
11 the authors have done here is to take the UKPDS risk  
12 engine, they have put in a factor to correct for prior  
13 CV disease, because UKPDS was a primary prevention  
14 risk engine, and plotted the various studies that are  
15 in the literature.

16 First, note that the horizontal axis has  
17 twice the number of events predicted from the model as  
18 the observed diabetes outcome studies, and now giving  
19 half the number of events you would expect from UKPDS  
20 data, consistent with our better therapies.

21 But you will see from ADOPT, in the left-  
22 hand corner, a monotherapy study up to BARI-2D, at the

1 right-hand top study, in which everyone had known  
2 coronary artery disease. All the studies lie on the  
3 same line for predicted events -- for observed events  
4 compared to predicted events, once you correct for  
5 prior CV events at entry.

6 RECORD, as I pointed out, was a typical  
7 unselected population, low risk. It's down there to  
8 the bottom left in green, and you will see it sits  
9 exactly on the line, possibly slightly above it.

10 Lest you think this is a biased analysis for  
11 GSK, I ask you to refer to the identical conclusions  
12 reached by the FDA in your briefing document, with a  
13 similar kind of graph. I think it's page 260.

14 So other issues. The progressive nature of  
15 diabetes resulted in algorithms to use insulin, yes,  
16 inevitable; less a problem in the rosiglitazone group,  
17 partly due to the protocol, partly because of better  
18 durability.

19 Open label, yes, because of the issue over  
20 insulin therapy and the fact we couldn't use it with  
21 the rosiglitazone; and, therefore, intensive local  
22 monitoring for event CRAs went into all the



1 investigator centers all the time, checking of SAEs  
2 for admissions against investigator reports of  
3 endpoints, and entirely blinded, independent  
4 adjudication by experts.

5           Tight adjudication, yes, because a rigorous  
6 approach is desirable in a non-inferiority study.  
7 Gaining events by looking at silent MIs and the like  
8 is a wonderful way of proving non-inferiority when  
9 it's           not there.

10           Changing use of other non-glucose therapies,  
11 like the statins, inevitable, but we used local  
12 guidelines to avoid any risk of sponsor or study bias.  
13 It's true that some of the end follow-up, a very small  
14 percentage was by telephone, was by vital status, and  
15 was by lots of other means. We have done sensitivity  
16 analysis just recently to show that if you exclude  
17 telephone follow-ups, which occurred towards the end,  
18 there is no material effect on the conclusions.

19           The database was latterly held and analyzed  
20 by the sponsor, yes, indeed, but both the interim and  
21 currently we performed an independent check in  
22 Professor Carol Cox's laboratory in London University,

1 without finding any suggestion of deviation from the  
2 analysis results which I have presented to you.

3           So overall conclusions. In a typical Type  
4 II diabetes population, when compared to  
5 metformin/sulfonylurea and in combination,  
6 rosiglitazone is non-inferior for cardiovascular  
7 events, does not increase death, either CV or all  
8 cause or stroke, with some probability in the opposite  
9 direction; gives similar rates of acute coronary  
10 events; does not increase the risk of recurrent events  
11 in those having an MI, but does increase the risk of  
12 heart failure.

13           It also increases the risk of distal  
14 fractures, particularly in women and possibly also in  
15 men, and the data I haven't shown you, but was a  
16 statistically significant improvement in durability of  
17 glucose control.

18           I thank you for your attention. I'm now  
19 going to hand back to Murray Stewart, who is going to  
20 discuss benefit-risk.

21           DR. STEWART: Thank you, Professor Home. I  
22 will now present the benefit-risk on rosiglitazone.

1 This is an overview of my presentation. I'd like to  
2 remind everyone of the high unmet need in treating  
3 patients with Type II diabetes. Following this, I  
4 will present data on the benefits of rosiglitazone  
5 lowering glucose in the short and long term, and how  
6 that results in reduced macrovascular events in the  
7 RECORD study.

8 I will then summarize the data on  
9 rosiglitazone's effects on macrovascular events from  
10 controlled clinical trials. I will also describe the  
11 efficacy, safety and tolerability profile of  
12 rosiglitazone in the context of other oral  
13 antihyperglycemic agents, including comparison of  
14 rosiglitazone with pioglitazone. Finally, I will  
15 conclude the overall risk-benefit profile of  
16 rosiglitazone.

17 Type II diabetes is a serious disease with  
18 devastating consequences. There are over 17 million  
19 people with diabetes in the USA, and I'd like to  
20 comment on some key issues.

21 There are two main complications with  
22 diabetes, macrovascular complications, which includes

1 the MACE components death, MI and stroke, and  
2 microvascular complications, which includes  
3 retinopathy, eye disease, which can lead to blindness,  
4 nephropathy, kidney disease, which leads to dialysis,  
5 and foot problems, which can lead to amputations.

6           Although we've heard about the macrovascular  
7 complications, the microvascular complications have  
8 significant effect on morbidity, with 24,000 cases of  
9 blindness every year, 44,000 patients starting  
10 dialysis, and over 70,000 amputations.

11           A key challenge in diabetes was highlighted  
12 in the UKPDS study, which showed the progressive  
13 nature of diabetes, requiring multiple therapies to  
14 lower and maintain glucose over time. Importantly,  
15 the study demonstrated that improving glucose control  
16 reduced microvascular complications.

17           Now, rosiglitazone has been shown to lower  
18 HbA<sub>1c</sub> to 1.5 percent in short-term studies, whether  
19 used as monotherapy or in combination with metformin  
20 or sulfonylurea or insulin. I will show you some of  
21 the long-term data on glycemic effect from ADOPT and  
22 RECORD before showing the effects on microvascular

1 events collected in the RECORD study.

2           This is the data from the ADOPT study, which  
3 looked at the long-term glycemic control of  
4 rosiglitazone compared to metformin or sulfonylurea in  
5 newly diagnosed patients. The graph shows the data on  
6 each agent for time to monotherapy failure, defined as  
7 an increase in fasting plasma glucose up to 180  
8 milligrams per deciliter.

9           As expected, glycemic control was not  
10 maintained with sulfonylurea or metformin, consistent  
11 with the UKPDS study. The data on rosiglitazone  
12 demonstrates that it's better than metformin or  
13 sulfonylurea in maintaining glycemic control, and, to  
14 me, it reflects the key benefit of rosiglitazone,  
15 which is long-term durable control.

16           The ADOPT data was in monotherapy. The  
17 durable effect of rosiglitazone has been consistently  
18 reproduced in the RECORD study, which was in dual  
19 therapy. On the left, the rise in HbA<sub>1c</sub> with  
20 sulfonylurea, in blue, added to metformin compared to  
21 rosiglitazone added to metformin.

22           On the right, the rise in HbA<sub>1c</sub> with

1 metformin, in green, added to sulfonylurea compared to  
2 rosiglitazone added to sulfonylurea. I'll now  
3 superimpose the pattern and dashed lines from the  
4 ADOPT study, which was used in monotherapy, and  
5 together this confirms the highly consistent effect of  
6 rosiglitazone in maintaining durable glycemic control.

7           Now, this improved glycemic control was  
8 accompanied by improvements in microalbuminuria, as  
9 shown in the ADOPT study here. The albumin creatinine  
10 ratios reduced with rosiglitazone compared to  
11 metformin and sulfonylurea. This ratio is a reliable  
12 surrogate for progression to diabetic nephropathy.

13           This reduction in microalbuminuria is  
14 reproduced in RECORD in patients with more advanced  
15 disease and is also seen in the DREAM study in pre-  
16 diabetic subjects.

17           This is a Kaplan-Meier cumulative instance  
18 curve for time to first microvascular event from the  
19 RECORD study. The long-term improved glycemic control  
20 with rosiglitazone has resulted in similar  
21 microvascular events as compared to metformin and  
22 sulfonylurea. These agents, remember, already

1 demonstrated benefit in reductions in microvascular  
2 events in the UKPDS study.

3           This table breaks down the microvascular  
4 events and amputations from the RECORD study comparing  
5 rosiglitazone versus other active comparators,  
6 metformin and sulfonylurea. The table lists the  
7 number of events and shows less events with  
8 rosiglitazone; less requirements for laser therapy;  
9 less cataract extraction; less foot complications;  
10 and, less amputations.

11           Now, what about the macrovascular on  
12 rosiglitazone? Rosiglitazone affects several  
13 cardiovascular responders. LDL was increased; weight  
14 is increased; blood pressure is decreased. So in  
15 order to determine the impact and relevance of these  
16 risk factors, it is important to look at the data of  
17 surrogates and outcome studies.

18           From a mechanistic point of view,  
19 rosiglitazone does not result in progression of  
20 atheroma, which has been studied in several carotid  
21 IMT studies and coronary IVUS studies. When you look  
22 at the data from large, independent clinical trials,

1 with adjudicated events in high risk patients, you get  
2 a consistent picture.

3 ACCORD decreased mortality. VADT decreased  
4 mortality, MI and MACE. BARI-2D decreased mortality,  
5 MI and MACE. And, finally, importantly, the study set  
6 up to look at CV safety with rosiglitazone, the RECORD  
7 study, as you've heard, has not shown an increase in  
8 MACE events or an increase in the primary endpoint of  
9 CV death or hospitalization compared to standard of  
10 care, the most commonly used agents, metformin and  
11 sulfonylurea.

12 Now, when considering the overall efficacy  
13 and benefit of rosiglitazone, this is best done by  
14 comparing the data with other diabetes agents. Let's  
15 begin with sulfonylurea. Sulfonylurea is a good drug.  
16 It lowers glucose in the short term, but this is not  
17 maintained in the long term. The UKPDS demonstrated  
18 benefit on microvascular endpoints. With regard to  
19 macrovascular endpoints, the data on benefit is not  
20 proven.

21 Initially, there were concerns raised with  
22 the older sulfonylureas from the UDDP study, but the



1 long-term follow-up from UKPDS-80 actually suggests  
2 some benefit.

3           What about metformin? Metformin lowers  
4 glucose in the short term. The ADOPT study showed it  
5 was better than SU in maintaining control in the long  
6 term. The UKPDS suggested benefit on microvascular  
7 endpoints. And although not definitively proven,  
8 many diabetologists believe the data from the obese  
9 sub-study of UKPDS, which demonstrated reduction in  
10 macrovascular events.

11           Rosiglitazone lowers glucose in the short  
12 term. Both ADOPT and RECORD show long-term durable  
13 glycemic control compared to metformin or  
14 sulfonylurea. RECORD demonstrates similar  
15 microvascular events to metformin and sulfonylurea.  
16 And with regard to macrovascular benefit, RECORD has  
17 demonstrated no difference with rosi between met and  
18 SU.

19           I will expand on the comparison between  
20 rosiglitazone and pioglitazone in the next slide. But  
21 in terms of efficacy data, let's look at pioglitazone.  
22 Pioglitazone lowers glucose in the short term,

1 probably in the long term. There is two-year data  
2 showing pio was superior to sulfonylurea for glycemic  
3 control.

4 Part of the three-year study and due to the  
5 relatively short duration of the study, there is no  
6 long-term data on microvascular events, but there is  
7 some short-term data on microalbuminuria.

8 Although, as with all other diabetes agents,  
9 the macrovascular benefit is not proven, the proactive  
10 study suggested possible benefit on macrovascular  
11 events when compared to placebo.

12 Now, DPPIVs have recently been approved.  
13 They have a more modest effect on glycemic control in  
14 the short term. There is no long-term comparative  
15 durable control. There is no microvascular data and  
16 although the short-term data did not suggest any  
17 increase in macrovascular events, there is, at  
18 present, no long-term CV outcome study with the  
19 DPPIVs.

20 Now, what about rosiglitazone compared to  
21 pioglitazone? Overall, there are many similarities  
22 between rosiglitazone and pioglitazone, and I will

1 describe these first and then discuss potential  
2 differences.

3           With regards to glycemic efficacy, it's  
4 similar short-term effects. Both TZDs have the  
5 advantage compared to other agents that they don't  
6 cause hyperglycemia or GI disturbance.

7           With regards to safety, both TZDs cause  
8 weight gain. They both cause fluid retention, which  
9 appears dose-related, and, in susceptible individuals,  
10 can lead to or exacerbate congestive heart failure.

11           Given our understanding of TZDs and fluid  
12 retention, U.S. prescribing information appropriately  
13 does not recommend the use of TZDs in patients with  
14 symptomatic heart failure.

15           The second concern is fractures, as  
16 Professor Home mentioned. Both TZDs have been  
17 associated with increased fractures, first identified  
18 in the longer-term study, ADOPT. And information  
19 about the risk of fractures is contained in the  
20 warning and precautions and the U.S. prescribing  
21 information for both TZDs.

22           The rare similar CV effects on risk markers,

1 such as blood pressure, HDL, and inflammatory markers.  
2 There are, however, three differences. Firstly, there  
3 is more long-term durable glycemic control with  
4 rosiglitazone up to six years compared to pio with  
5 three years in PROactive.

6 Secondly, a difference in potential risk of  
7 malignancy with pioglitazone compared to  
8 rosiglitazone. The label describes the P-per-alpha  
9 effect with pioglitazone on malignancy in animal  
10 models. Whether this translates to man is not known.

11 There was a small numerical increase in  
12 blood cancer in the PROactive study with pio, but I  
13 think the short duration of the study and this normal  
14 number of events leads the conclusion uncertain.  
15 Long-term data will be needed to answer this question.

16 Rosiglitazone is shown in a recent  
17 publication from the long-term ADOPT and RECORD study  
18 to be no different with regards to malignancy than  
19 metformin, which is thought to have a beneficial  
20 effect.

21 Thirdly, the small alpha effect may also  
22 explain the small differences in LDL effects between

1 the agents. The label describes that rosiglitazone  
2 increases LDL by about 10 to 15 percent, and the pio  
3 label is neutral for LDL.

4 In a short-term head-to-head study by  
5 Goldberg, where patients were not permitted to use  
6 statins, both agents increased LDL, but to a greater  
7 extent with rosiglitazone, 23 percent, versus 16  
8 percent with pioglitazone, giving a difference of 7  
9 percent in LDL between the agents.

10 The clinical impact of the small difference  
11 is not known. However, when mechanistically looking  
12 at progression of atheroma, the agents are similar  
13 from IVUS and IMT studies, with neither agent causing  
14 progression of atheroma.

15 So with regards to looking at CV outcomes  
16 between the two agents, it's worth looking at  
17 PROactive and RECORD. Unfortunately, there are too  
18 many differences to reach firm conclusions. The  
19 populations studied are very different.

20 RECORD was in a broad range of patients.  
21 The background CV events was less than 20 percent, on  
22 contrast to the PROactive population, where 100

1 percent of patients had CV risk factors.

2           The study design and goals were different.  
3 RECORD, as you've heard, was a non-inferiority study  
4 against an active comparator, which has shown benefit.  
5 PROactive was a placebo-controlled study. The  
6 endpoints were different in the two studies. Heart  
7 failure was adjudicated and included in the primary  
8 endpoint of RECORD. Heart failure was not adjudicated  
9 and not included in the endpoint of PROactive.

10           So, therefore, it's very difficult to  
11 compare CV events between rosiglitazone and  
12 pioglitazone. This is primarily and importantly,  
13 because at present, there is no completed large head-  
14 to-head controlled trial comparing rosiglitazone and  
15 pioglitazone.

16           There are more similarities than differences  
17 between the agents. The observational data are  
18 confounded. The trial data available are from  
19 different populations. Thus, the statement shown  
20 here. The AHA/ACCF recently concluded that you cannot  
21 choose one agent over the other.

22           In order to establish if there is a

1 difference between the two agents and demonstrate that  
2 both TZDs might or might not have beneficial effects  
3 compared to placebo provides strong rationale from the  
4 TIDE study, which will be discussed tomorrow by Dr.  
5 Gerstein.

6 I would like to finish with my final overall  
7 conclusions. Type II diabetes is a progressive  
8 disease and it's difficult to maintain glycemic  
9 control. Therefore, we need agents like  
10 rosiglitazone, which have good long-term durable  
11 control.

12 Rosiglitazone has been extensively studied  
13 in long-term clinical trials. In the RECORD study,  
14 rosiglitazone has demonstrated the benefit in lowering  
15 glucose over five years, with reductions in  
16 microvascular events.

17 With regards to macrovascular events, all  
18 the long-term controlled adjudicated clinical trials  
19 sponsored by GSK, NIH or VA, which includes APPROACH,  
20 ACCORD, VADT, BARI-2D and RECORD, consistently show  
21 reductions in mortality and MACE events and support  
22 the overall cardiovascular safety of rosiglitazone.

1 Overall, when used appropriately,  
2 rosiglitazone has a positive benefit-risk profile and  
3 should remain a treatment option for patients with  
4 Type II diabetes.

5 That concludes my presentation. I'd like to  
6 hand it back to the chair, and both Professor Home and  
7 I will be available for questions.

8 DR. BURMAN: Thank you very much, and thank  
9 you for keeping on time. We'd like to open the floor  
10 up for clarifying questions to the sponsor from the  
11 committee, but the way we would like to do this is we  
12 have about 10 minutes -- it's 9:55 and we're going to  
13 go to 10:05 before our break, given the large number  
14 of people on the committee, please raise your hand and  
15 Paul will write the names down and we will go through.

16 I will remind you that we will have time  
17 tomorrow for further questions to the sponsor. I'd  
18 like to open the floor up.

19 Dr. Kaul?

20 DR. KAUL: Thank you, Dr. Burman. I have  
21 two quick questions. One is a general question  
22 regarding the ACCORD trial. The ICH-10 guidance



1 recommends that the non-inferiority margin should be  
2 based on statistical reasoning and clinical judgment  
3 and be suitably conservative.

4           While I agree that a non-inferiority margin  
5 of a hazard ratio of 1.2, using RECORD, is suitably  
6 conservative, could you elaborate on the statistical  
7 reasoning and clinical judgment?

8           In other words, what was the quantitative  
9 estimate of the cardiovascular benefit of active  
10 control compared to placebo and what proportional loss  
11 of this putative benefit were you willing to accept,  
12 given the ancillary advantages of the experimental  
13 therapy? Then I have a follow-up question to that.

14           DR. HOME: Thank you. I could take that  
15 one. In 2000, when we were setting about designing  
16 the study, we had, of course, enormous problems in  
17 trying to understand whether placebo and active  
18 control would give differences in cardiovascular  
19 outcomes.

20           We already had some data from the UKPDS  
21 suggesting a quite marked effect from metformin,  
22 statistically significant reductions of the order of

1 30-40 percent, which, frankly, we didn't care to  
2 believe in designing the study. We had that problem  
3 with insulin-sulfonylurea in the same study, which was  
4 the only evidence of a p-value of 0.052 for the around  
5 15 percent reduction.

6           So our best guess was that the active  
7 comparators would be giving us a 15 percent reduction  
8 over placebo, if, by placebo, you mean doing nothing  
9 for 5.5 years. But, of course, you can't do nothing  
10 for 5.5 years. So what happens is you get  
11 investigators titrating up other glucose-lowering  
12 therapies and get a bit of a mess as to what placebo  
13 is from about two years onwards.

14           So coming back to your statistical point,  
15 .then, I have to say, based on the surrogate data for  
16 rosiglitazone relating to insulin sensitivity, blood  
17 pressure, microalbuminuria, cardiovascular risk  
18 factors, we were hopeful that we might see some  
19 reduction over the active comparators, which, in  
20 themselves, one might hope would be active over  
21 placebo.

22           But choosing 1.20, with the numbers we

1 intended to recruit, and, at that time, a much higher  
2 anticipated event rate, we were very adequately  
3 powered to do a non-inferiority test based on the data  
4 we had; and, in fact, we were adequately powered for  
5 the two strata individually.

6 One also -- you are right, of course --  
7 should base these things on clinically acceptable  
8 levels of differences in risk, and there I can only  
9 note the FDA itself has chosen more recently to use  
10 1.30, i.e., less conservative than our 1.20.

11 DR. BURMAN: Thank you. Dr. Kaul, do you  
12 have a very quick follow-up question? Because we only  
13 have a couple of minutes and couple more questions.

14 DR. KAUL: In the concluding slides, Dr.  
15 Stewart said that the macrovascular benefits of both  
16 of the active control components remain unproven.

17 So if the cardiovascular benefits of active  
18 control are not proven, then is it possible to  
19 reliably estimate the efficacy or safety of  
20 rosiglitazone compared with placebo?

21 DR. STEWART: I think I put definitively  
22 unproven. And as I mentioned in the discussion on

1 metformin, some people would suggest that metformin  
2 does have benefit, and I think that's clearly a  
3 discussion point for many of the diabetologists.

4 DR. BURMAN: Thank you. Dr. Thomas?

5 DR. THOMAS: Two quick questions. One is  
6 there was a comment by Dr. Stewart that the  
7 observational studies, there may be a change in the  
8 prescription pattern, that younger patients, in terms  
9 of duration or diabetes, may be getting prescriptions  
10 of pioglitazone.

11 Is there any data to support that? Because  
12 you could also make the opposite conclusion that  
13 people are being switched from rosiglitazone to  
14 pioglitazone, which would not change their duration or  
15 diabetes or underlying disease. And I have one more  
16 question after that.

17 DR. STEWART: So we do have some data that  
18 most of the patients receiving rosiglitazone now are  
19 repeat prescriptions rather than new cases, and I  
20 think that reflects the decrease in use of  
21 rosiglitazone. Switching could go in both directions,  
22 as you say. I think it just highlights the difficulty

1 sometimes with confounding factors of duration and  
2 dosage of the drugs.

3 DR. THOMAS: And the second question is, I  
4 know that you are supposed to use years of exposure  
5 for safety studies. But out of curiosity, in the  
6 RECORD study, how many subjects were actually on the  
7 active agent for either rosi or the comparator at the  
8 end of the study and what were the reasons for  
9 dropout?

10 DR. HOME: I'd like to take issue, if I may,  
11 with your word "dropout." A large percentage of the  
12 randomized population who came off therapy were  
13 protocol-driven; i.e., this was rescue therapy coming  
14 into play.

15 Of course, the other group of significant  
16 size were the deaths. By endpoint, then, it was on  
17 the slide, in the rosiglitazone group, 60 percent was  
18 still taking therapy at endpoint.

19 Yes, if I could have the slide, please. You  
20 can draw a line across from the bottom of the orange  
21 on the right to 60 and you will see it's very close,  
22 61 percent; and, in the comparator group, because of

1 differences in the algorithm for rescue therapy, it  
2 was 50 percent.

3 As I pointed out, however, in the safety  
4 study, it's not the endpoint numbers that matter.

5 DR. BURMAN: Thank you. We have two to  
6 three minutes. Dr. Winterstein will be the last one.  
7 Dr. Konstam, I apologize, we'll get to you tomorrow or  
8 later in the day.

9 DR. WINTERSTEIN: Professor Home alluded to  
10 the fact that proper ascertainment of outcomes is very  
11 important in non-inferiority studies. At the same  
12 token, he didn't talk about proper selection of  
13 outcomes that measure the construct of interest, in  
14 this case, cardiovascular morbidity and mortality.

15 I would like to know how -- there are a few  
16 outcomes in the portfolio that are quite unusual, like  
17 unplanned cardiovascular events, any other definite  
18 cardiovascular reasons, and then most curious to me is  
19 amputation, which I don't think has a cardiovascular  
20 etiology typically.

21 So I'm just curious, if my math is correct,  
22 that those types of outcomes should make about 40

1 percent of the entire primary composite. And I'm  
2 curious how they were selected, because they could  
3 potentially water down the difference between those  
4 two drugs quite extensively, and with this, of course,  
5 affect power.

6 DR. HOME: Yes. As I said, the steering  
7 committee shared your concerns and thought about this  
8 and discussed it on more than one occasion.

9 When we set up the study, basically, we  
10 thought to ourselves that the most robust way of  
11 handling the data would be to choose CV  
12 hospitalization as the key thing alone CV death, of  
13 course, to get good quality data.

14 But when we thought about it a bit more, we  
15 did realize, like your good self, that inclusion of  
16 some CV events, which one might think as non-  
17 atherosclerotic, I gave the example of a mini-  
18 embolism, might then dilute the appropriate test for  
19 non-inferiority.

20 That is why we pre-specified the  
21 atherosclerotic sensitivity analysis, which you  
22 remember gave identical results, and excluded what you

1 might call as junk CV events. And it's also why, I  
2 think, in retrospect, it's important to look at that  
3 MACE endpoint, which you call just MI, stroke and CV  
4 death, which was, again, a hazard ratio very close to  
5 1, in fact, below 1.93, again, with an upper  
6 confidence level of 1.2.

7 So we accept your criticism, but we think  
8 we've dealt with it by those two sensitivity analyses,  
9 which used more conventional cardiovascular endpoints.

10 DR. BURMAN: Thank you very much. And I'd  
11 like to thank the sponsor for the morning's  
12 presentation, as well as the FDA.

13 We will now take a 15-minute break. Panel  
14 members, please remember that there should be no  
15 discussion of the meeting topic during the break  
16 amongst yourselves or with any member of the audience.  
17 We will resume promptly at 10:20.

18 [Whereupon, a recess was taken.]

19 DR. BURMAN: Please take your seats. We  
20 will now proceed with our presentation from the first  
21 guest speaker, Dr. Steven Nissen.

22 I would like to remind public observers at



1    this meeting that while this meeting is open for  
2    public observation, public attendees may not  
3    participate except at the specific request of the  
4    panel.

5                If you could, could you please close the  
6    door outside, as well?

7                Dr. Nissen?

8                DR. NISSEN: Thank you. First of all, I  
9    want to make a couple of housekeeping announcements.  
10   It's great to see all of you. I've served with many  
11   of you on other panels, and welcome you back here to  
12   the lovely Gaithersburg Hilton Resort and Spa, where  
13   we have these gatherings.

14               I wonder if we could maybe shut the door so  
15   we can all hear?

16               I also want to make some disclosures. First  
17   of all, although I am an SGE, I'm not appearing here  
18   as a special government employee. I am here as an  
19   independent academic. The data that I present is data  
20   that we have developed. It's not FDA data, although  
21   I'm going to show you some FDA data.

22               This is my disclosure slide. I do consult

1 for many pharmaceutical companies. Our clinical trial  
2 center has done studies on behalf of these sponsors.  
3 Please note that they include Takeda, maker of  
4 pioglitazone, and Roche, that has another PPAR in  
5 development. However, companies are directed to pay  
6 any honoraria, speaking or consulting fees directly to  
7 charities, so that neither income nor a tax deduction  
8 is received. That allows me to maintain my  
9 independence.

10 I want to take you back for a minute and  
11 tell you how we got where we are. Let's go back to  
12 May of 1999, and there was one TZD, troglitazone, and  
13 concerns had emerged about hepatic toxicity. And the  
14 FDA was eager to approve a safer alternative, and both  
15 rosiglitazone and pioglitazone appeared free of liver  
16 toxicity.

17 The registration package for rosiglitazone  
18 was five trials, primarily, 2,900 patients, mostly  
19 short term, and the drug was presented and approved on  
20 May 22nd, 1999.

21 Now, I went back and looked at the approval  
22 package and I want you to see what was there. There

1 were ischemic events in 1.24 percent of the  
2 rosiglitazone patients and .69 percent of the  
3 comparators, and that was, obviously, a pretty high  
4 relative risk. So the FDA reviewer did an adjustment  
5 for time on drug and some other maneuvers and got it  
6 down to a relative risk of 1.1.

7           What I'm going to show you is that that  
8 elevated point estimate for relative risk of ischemic  
9 events never goes away. It just gets stronger and  
10 stronger over time, and that is the fundamental  
11 problem we must deal with.

12           The other thing that happened in the  
13 approval package that I believe was sufficient not to  
14 approve this drug in 1999 were its lipid effects.  
15 These are the three pivotal studies, showing LDL-C  
16 increases of 24, 20 and 13 percent, and the FDA, in  
17 the approval package insert, put in an 18.6 percent  
18 increase for patients with a mean baseline LDL of 125.

19           Now, I know you all know this, but the one  
20 thing that we don't want to do in diabetic patients is  
21 increase LDL cholesterol. In fact, to a greater  
22 extent than blood sugar, LDL cholesterol tracks with

1 adverse cardiovascular outcomes.

2           In fact, you could model this, as I have  
3 done, from the cholesterol-lowering trialist  
4 collaborative, who looked at 18,000 diabetic patients  
5 treated with LDL-lowering therapies, and here is what  
6 they reported; that for every 1 millimole difference  
7 in LDL-C, the hazard ratio is .78.

8           The 18.6 percent is .6 millimoles for an LDL  
9 baseline of 125. You do a little bit of a back-of-  
10 the-envelope calculation and you would estimate the  
11 effect on the hazard ratio for major adverse  
12 cardiovascular events based upon the LDL-C effects  
13 alone to be 1.17.

14           So I want to point out to you that several  
15 years after rosiglitazone was approved, ezetimibe was  
16 approved in 2002 on the basis of a 15 to 18 percent  
17 reduction in LDL-C, because that magnitude of LDL  
18 reduction is presumed by regulatory policy to confer  
19 cardiovascular benefits.

20           What should we presume about a drug that  
21 increases LDL-C by a similar amount? The mistake that  
22 was made here was that we had a drug that modestly

1 lowered blood sugar, but modestly increased LDL-C; two  
2 biomarkers.

3 Looking at this in retrospect, I suspect  
4 that almost everybody on this panel would agree that  
5 in such a situation, you have to have clinical outcome  
6 data to decide whether such a drug is beneficial or  
7 harmful. But in the haste to replace troglitazone,  
8 the mistake got made, the genie got out of the bottle,  
9 and we've been trying to put the genie back in ever  
10 since.

11 This was confirmed in a head-to-head study,  
12 that the other TZD that was approved in 1999 had a  
13 different lipid profile. This is the head-to-head  
14 study of Goldberg in *Diabetes Care* in 2005.  
15 Triglycerides with rosiglitazone went up 14.9 percent,  
16 and they went down 12 percent, a difference of  
17 approximately 25 percent in triglycerides and,  
18 obviously, an important difference. And if you want  
19 to factor HDL cholesterol into this equation, then you  
20 should use non-HDL.

21 Non-HDL in this study went up 18.6 percent  
22 with rosiglitazone and 3 percent with pioglitazone.

1 And so there was, in fact, a profound difference in  
2 lipid effects and that difference is, in my view, very  
3 likely clinically significant.

4 Then the next step occurs. The World Health  
5 Organization runs the Upsala drug monitoring group and  
6 they were receiving spontaneous reports of heart  
7 failure and ischemia with rosiglitazone. And so they  
8 alerted the company and asked them to investigate.

9 GSK, in conjunction with its drug safety  
10 board, decided to do a comprehensive analysis of  
11 rosiglitazone and the risk of ischemic events, which  
12 they refer to as their integrated clinical trial.

13 Now, while I don't agree with the methods  
14 they use, and neither did the FDA, because they're  
15 very conservative at minimizing hazard, nonetheless,  
16 this is what they found. This is now five years ago.

17 Overall hazard for ischemic events was 1.29  
18 and the confidence interval just barely escaped  
19 statistical significance. In those patients with  
20 preexisting coronary heart disease on nitrates, the  
21 relative risk or the hazard ratio was 2.45.

22 Now, why should it be so much worse? Well

1 this is not rocket science. Patients that have heart  
2 disease that take nitrates have angina. That's why  
3 they're taking nitrates. These are people that are at  
4 higher cardiovascular risk. And the thing that really  
5 looks worrisome here is that the people at the higher  
6 risk are showing the greatest hazard.

7           Here, the lower confidence interval is 1.34.  
8 And so in 2005, this drug is in big trouble. So the  
9 data were submitted to the FDA and in an unfortunate  
10 mistake, neither GSK nor the FDA made any public  
11 statement warning physicians or patients of the  
12 finding. We didn't know.

13           The company came back and in the next year,  
14 2006, they updated now with 42 clinical trials. They  
15 now get 1.31 using very conservative methods. The  
16 lower confidence interval is now statistically  
17 significant, above 1, and with nitrates in heart  
18 disease patients, they get 2.14, and it is highly  
19 significant.

20           They again submit the data to the FDA and,  
21 again, neither GSK nor the agency made any public  
22 statement warning physicians or patients of the

1 findings. No one was aware, but then there was a  
2 trigger.

3 First of all, let me take a diversion and  
4 tell you why I believe the agency failed to act. GSK  
5 supplied FDA with a quickly commissioned observational  
6 study performed by a commercial vendor and that was  
7 submitted along with their integrated analysis. So  
8 they did an observational study, and this was called  
9 the Ingenix Research Database study, and it showed no  
10 hazard for rosiglitazone compared with other diabetes  
11 therapy or placebo.

12 But there was a major issue. The study  
13 included all data on all major comparator drugs except  
14 for pioglitazone. We don't know why the pioglitazone  
15 data was missing from the study that was submitted to  
16 FDA. You can draw your own conclusions. But I will  
17 show you what the missing data actually showed,  
18 because it later emerged, and here it is.

19 This was the observational study that was  
20 submitted that allowed the drug to continue to be  
21 marketed in 2006. Now, .admittedly, this was  
22 sponsored by Takeda. They went back to the same



1 database and they said, "Show us the rosiglitazone  
2 versus pioglitazone data," and this is what it showed.  
3 A hazard ratio of .78; you can see the Kaplan-Meier  
4 curves steadily separating over time, and it was  
5 published, unfortunately, after the FDA advisory board  
6 meeting in 2007. And so those of you that served on  
7 that panel were unaware of the observational data.  
8 But here it is for your consideration. Consider that  
9 it's sponsored by their competitor. All those things  
10 have to be factored in, but this wasn't in the  
11 submission.

12           So in 2006, rosiglitazone survived the  
13 emergence of strong evidence of a cardiovascular  
14 hazard after the company submitted an observational  
15 study that was carefully constructed to avoid  
16 comparing rosiglitazone and pioglitazone.

17           I believe if the agency had access to the  
18 rosi versus pio data, they may have acted decisively  
19 to warn physicians and patients. Instead, by the end  
20 of 2006, rosiglitazone became the largest selling  
21 diabetes drug in the world. No one knew, we didn't  
22 know, and people continued to increase their

1    prescriptions of this agent.

2               Then came a signal, and we owe Dr. Hertzl  
3   Gerstein a debt of gratitude for providing us with  
4   these data. The group at McMaster is very independent  
5   and although this study was sponsored by GSK, I have  
6   absolutely no doubts about the integrity of the data.

7               This was the diabetes prevention trial,  
8   known as DREAM, you've already heard about. But I  
9   want you to see what happened -- what really happened  
10  in the DREAM trial. This is taken directly from *The*  
11  *Lancet* these data. MI, 15 to 9; stroke, 7 to 5; CV  
12  death, 12 to 10; adjudicated heart failure, 14 to 2;  
13  new angina, 24 to 20; revascularization, 35 to 27;  
14  and, the composite isn't quite statistically  
15  significant, but it's getting close.

16              I saw this, wrote a letter to the editor, to  
17  *The Lancet*, and I said to myself, "Gee, if you're  
18  reducing new onset of diabetes, which this drug did,  
19  why are the most important complications of diabetes  
20  all going in the wrong direction."

21              I became worried and I sought to find the  
22  truth. I requested patient level data from the

1 company and over three or four months, communications  
2 went back and forth; and, when it was clear that I  
3 wasn't going to get access, I sought to do my own  
4 analysis.

5           So I got very fortunate here. Serendipity  
6 intervened. It turned out that as a result of a court  
7 settlement with the State of New York, GSK is required  
8 to post results of all of its clinical trials.

9           The State of New York had sued the company  
10 because the company had not published results of  
11 studies with their antidepressant, Paxil, that had  
12 showed increased suicidal thinking in children.

13           It made the attorney general of the state  
14 very angry. He sued the company. And instead of  
15 asking for a monetary settlement, he required TSK to  
16 create a Website where they posted all their clinical  
17 trials data. We located that Website and obtained  
18 data from 42 clinical trials, 35 of which were  
19 unpublished.

20           We took it to the *New England Journal of*  
21 *Medicine* and published it. I will tell you, we knew  
22 it would be controversial. We recognized that study

1 level data is not as good as patient level data. But  
2 we felt that this belonged in the public domain, that  
3 you, as physicians, and the public had a right to know  
4 that there was a major concern about this drug. And  
5 I, to this day, do not regret getting this out into  
6 the public domain.

7 We did not have a significant hazard on  
8 cardiovascular death, but it was certainly trending in  
9 the wrong direction.

10 The FDA then convened that panel in 2007 and  
11 they replicated our findings, although they used  
12 different endpoints. Their primary outcome measure  
13 was serious ischemic myocardial events. An FDA  
14 analysis got 1.4, lower confidence interval of 1.1,  
15 with a p-value of .02. You know what the advisory  
16 committee voted, but there was little or no  
17 pioglitazone data presented to the advisory committee.

18 I disagree with Dr. Parks. Some of you  
19 served on it and you may recall the information, but I  
20 felt it was not completely presented.

21 Later, a non-public internal FDA safety  
22 board voted 8-7 to allow continuing marketing of the

1 drug. So the internal decision at the FDA was very,  
2 very close. You've heard about this dispute within  
3 the FDA. I could tell you more about it. I will not,  
4 but just say that this was a very close call back in  
5 2007.

6           What have we learned since 2007? Well,  
7 we've got observational studies. You will hear about  
8 those from the Office of Surveillance and  
9 Epidemiology. Some fine epidemiologists will present  
10 the data. I cannot review it for you in the time  
11 allotted to me.

12           But what they generally show is that younger  
13 patients have excess myocardial infarctions and older  
14 patients show an increase in cardiovascular death.

15           Why is that? It's simply that each decade  
16 that goes by, the older you get, the more the ratio of  
17 sudden death is. That is, out of hospital death to  
18 nonfatal MI. And so when you deal with people in  
19 their 50s, they have infarctions and they survive and  
20 you don't get a death. But when you deal with people  
21 in their 70s, as you will see when you look at the  
22 Medicare data a little later, presented by Dr. Graham,

1     you'll see that the excess is in cardiovascular death.

2     It's a perfectly understandable phenomenon.

3             This is the large Medicare study published

4     two weeks ago in JAMA that will be presented to you.

5     By 2009, the American Diabetes Association and the

6     European Association for the Study of Diabetes had had

7     enough, and they published this consensus algorithm.

8             This is the group, some of the most

9     prominent diabetologists in the world. And their

10    consensus was the consensus group members unanimously

11    advise against using rosiglitazone.

12            Then comes RECORD. Now, I was going to

13    present RECORD in some detail and after reading Dr.

14    Marciniak's review, I don't think I need to, but I

15    want to say a few things about it.

16            As you heard, it was an unblinded study.

17    Patients and physicians knew who was taking

18    rosiglitazone. But this just wasn't unblinded the way

19    we ordinarily do a probe design. This was a study

20    where there was unrestricted availability of treatment

21    codes to quintiles in GSK from the beginning of the

22    study. That's what's in Dr. Marciniak's review.

1           We have some very experienced clinical  
2   trialists around the room. I see Marvin Konstam. I  
3   see people like Sanjay Kaul. Anybody here ever see a  
4   study presented to this committee where the company  
5   and its CRO had access to the treatment codes from the  
6   start of the study?

7           If somebody came in here to an advisory  
8   panel for a drug approval with an unblinded study,  
9   where they had open access to who was getting what and  
10   who was having what events, would you even vote?

11          So just from the very beginning, this study  
12   was unacceptable in quality. It's also clear that a  
13   decision was made to remove silent MIs from the  
14   endpoint. According to Dr. Marciniak's review, that  
15   was done with knowledge of data coming into the trial.  
16   That's not acceptable in clinical trial design. They  
17   split 10 to 5, rosiglitazone versus control, 10 more  
18   MIs than rosiglitazone.

19          Now,. what about silent MIs? Dr Holmes said  
20   that they're noise. So I went and did a little  
21   research on my own. In diabetic patients, the  
22   prognosis for a silent MI is every bit as bad or worse

1     than it is for a painful MI.

2             Why is that? Because these people do not  
3     have an intact warning system and when they have an  
4     infarct, they go on to have heart failure and  
5     ultimately death. It was not acceptable to remove  
6     these events. And when you find out that they break  
7     10 to 5 against rosiglitazone, it changes the  
8     interpretation of the study.

9             The decision to publish the interim  
10    analysis, according to Dr. Marciniak's review,  
11    violated the charter of the DSNB and the steering  
12    committee.

13            Despite these flaws, they get a hazard ratio  
14    for MI, as you heard, of 1.14, with an upper  
15    confidence interval of 1.63. Okay. Dr. Marciniak  
16    then comes along, does a source document review,  
17    recalculates everything, and gets 1.38, and it's  
18    almost significant.

19            If you add the 1.38 to the meta-analyses  
20    that we've had to date and add RECORD now to  
21    everything else we know, it doesn't refute a hazard,  
22    it strengthens the association. It's right along the



1 lines of what we saw in our 2007 publication and what  
2 the FDA found in their own meta-analysis.

3 Now, I'm going to show you the latest  
4 versions of the meta-analyses. And I want to tell you  
5 that we did this differently from FDA and I want you  
6 to understand why. FDA, in the briefing document,  
7 removed all trials of greater than two years, which  
8 eliminates the majority of mortal and morbid events.

9 So the FDA analyses in your briefing  
10 document are all on data of less than two years  
11 duration. We chose to include all randomized control  
12 trials to provide a comprehensive assessment with the  
13 narrowest possible confidence intervals. And by the  
14 way, this is not a criticism of the FDA statisticians.  
15 I fully understand why they did what they did. They  
16 wanted to compare short term for rosiglitazone and  
17 short term for pioglitazone, and I appreciate what  
18 they were doing.

19 But I also thought you should see  
20 everything, and so we did that. And here is what we  
21 find, published two weeks ago in the *Archives of*  
22 *Internal Medicine*. And for MI, we have 56 studies,

1 enrolling 35,531 patients; for MI with RECORD we get  
2 1.28, and it's significant.

3 Even if you assume RECORD is correctly  
4 reported, you still have a 28 percent approximate  
5 increase in myocardial infarction. If you take RECORD  
6 out, which I think is a more reasonable thing to do,  
7 you've got 55 trials and you get 1.39.

8 Cardiovascular death, RECORD makes a huge  
9 difference. It's whether it's 1.46 or 1.03. You can  
10 decide for yourselves whether or not RECORD should be  
11 included.

12 Now, Dr. Mahoney and Dr. Unger believe that  
13 in spite of what would happen in the conduct of this  
14 trial, that it could still be used for regulatory  
15 purposes. I must respectfully disagree. Clinical  
16 trial conduct has to count for something. For those  
17 of you around this table who I know, I see John  
18 Teerlink, I see other people who have done trials, we  
19 work very hard to maintain blinding, to do the things  
20 we need to do to make certain that trials are not  
21 biased.

22 We cannot and we should not allow data of

1 this quality to influenced a decision that affects the  
2 lives of so many hundreds of thousands of people.  
3 This trial was not properly handled and it cannot be  
4 used for regulatory purposes.

5 We were criticized in 2007 for our analysis  
6 not including zero event trials. So we did it again  
7 in 2010 and this is with the zero event trials. So  
8 this is absolutely everything, all 56 trials. Again,  
9 we get 1.28 for MI, excluding RECORD, 1.38. For  
10 cardiovascular death, it looks neutral. If you  
11 exclude RECORD, it looks like it's 1.36, not  
12 statistically significant.

13 Well, what does this yield us? What is the  
14 cost if these point estimates are correct? If, in  
15 fact, there is a 28 to 39 percent increase in  
16 myocardial infarction, what does it mean for patients?  
17 It means that the number needed to harm, including  
18 RECORD, is 52 and the number needed to harm, excluding  
19 RECORD, is 37.

20 We have few therapies in cardiovascular  
21 medicine with numbers needed to treat this favorable.  
22 Number needed to harm of this magnitude is enormous

1 and that is the burden that you carry in making this  
2 decision, and it's not an easy burden to carry,  
3 because it means a lot of people are going to be put  
4 at risk here.

5           What about pioglitazone? Well, we asked the  
6 manufacturer for all of their data and they agreed, in  
7 2007 and again in 2010. This is the same dataset  
8 supplied to the FDA, although, again, the FDA have not  
9 reviewed our analyses and you have to take that into  
10 account. It's a matter of trust. If you trust Kathy  
11 Wolski and I to do this correctly, we certainly tried  
12 to be as careful as we could.

13           Mike Linkoff, in 2007, took all the pio data  
14 and this is now MACE. Death, MI or stroke. I would  
15 consider this to be the most relevant endpoint for our  
16 consideration. What he got was a hazard ratio of .82,  
17 with a p-value of .005, these are the Kaplan-Meier  
18 curves. This is everything we had on pioglitazone as  
19 of 2007.

20           The point estimate and the confidence  
21 intervals are clearly on the protective side.  
22 Remember, however, that this drug has much more

1 favorable effects on lipids and there are other  
2 differences I will show you.

3 In 2010, and we have not had a chance to  
4 publish this yet. And I'd like to have published data  
5 to show you, but this is our most recent analysis.  
6 And we had 746 events in 22,131 patients. The hazard  
7 ratio is now .8. This is death, CV death, MI or  
8 stroke. P-value was .003. There is the Kaplan-Meier  
9 curve. Clearly, reinforcing the evidence This is now  
10 trials, the entire clinical trial, relevant clinical  
11 trial dataset for pioglitazone the opposite effect of  
12 what you see with rosiglitazone.

13 I want to compare and contrast what we see  
14 from what the FDA has for you in your briefing  
15 document. So you can see that in the FDA analysis for  
16 pioglitazone, there's a lot of instability in the  
17 point estimates or the hazard ratio, but look at the  
18 number of events that they have and I will drill down  
19 on this in a minute.

20 Using the totality of all the trials, both  
21 short and long term, we have many more events, and I  
22 want you to see the hazard ratios. MACE is .8. CV

1 death .89; MI .79; stroke .8; all cause mortality .9;  
2 total ischemia .82; and, heart failure is the only  
3 thing that goes In the wrong direction at 1.33.

4           Those shown in gold are independently  
5 statistically significant, so that includes MACE, MI,  
6 and total ischemia. Here is the rosiglitazone data  
7 per FDA and per myself and Kathy Wolski. And again,  
8 the number of events in the FDA analysis is very  
9 limited.

10           You can see that in the FDA analysis, the  
11 hazard ratios and the confidence intervals show harm.  
12 The FDA gets 1.44 for MACE, but it's not quite  
13 significant. For MI, it is significant at 1.8. FDA  
14 gets 1.46 for serious ischemia, 1.34 for total  
15 ischemia, and 1.93.

16           We get a lower MI hazard using everything.  
17 This is now without RECORD and I will show you in a  
18 minute with RECORD, and we get the same hazard for CV  
19 death. With RECORD, it's now 1.28.

20           Now, let me show you some forest plots so  
21 that you can really understand the precision involved  
22 in these measurements, in these calculations.

1           So here is our pioglitazone analysis of all  
2   35 trials, 746 events. And what you see is we get a  
3   hazard ratio of .8, with clear confidence intervals  
4   below 1.0. In the briefing document, the FDA reduced  
5   this to 29 trials of less than two years. They get  
6   almost exactly the same point estimate, but their  
7   confidence intervals extend above 1.

8           The FDA, using 52 trials with rosiglitazone  
9   gets 1.44, not quite statistically significant. Now,  
10   I think you can see, no matter whose data you want to  
11   use, that the pio data is to the left of 1 and the  
12   rosiglitazone data is to the right of 1, and that's  
13   true virtually across the board.

14          What about MI? Clearly, a relevant  
15   consideration. We had 306 events. the FDA only had  
16   64 events, because they lose those six long-term  
17   trials. They get .91, to the left of 1, but very wide  
18   confidence intervals. We get .79, extending up to  
19   .99. It's statistically significant for MI.

20          The FDA, for MI, with 52 rosiglitazone  
21   trials, gets 1.8, and it's statistically significant.  
22   We get 1.28 or 1.39, depending on whether you use the

1 RECORD data or not. It doesn't matter whose analyses  
2 you use, you get a hazard for rosiglitazone and you  
3 either get neutrality or a protective effect for  
4 pioglitazone.

5           What about myocardial ischemia? Well, we've  
6 got 1,275 events and .82, with very tight confidence  
7 intervals. The FDA is close, they're .86, but they've  
8 only got 305 events. And so the confidence intervals  
9 cross 1. The FDA for rosiglitazone gets 1.34 and it's  
10 statistically significant.

11           We don't have the long-term data from the  
12 FDA and since we don't have access to patient level  
13 data, we couldn't make these calculations, so we can't  
14 give them to you.

15           What about CV death? Well, it's much less  
16 clear. The FDA has only got 40 events here and 26  
17 events here. So these are not stable estimates. We  
18 have, for all 35 pio trials, we've got 323 events, and  
19 we get .89 for cardiovascular death.

20           If you really want to look more closely,  
21 let's ignore RECORD, since, again, you may not want to  
22 do this, but I choose to believe that it's not a



1 regulatory quality trial. For 55 trials with  
2 rosiglitazone, we get 1.46. The FDA, with only 26  
3 events, gets 1.46, with wide confidence intervals, and  
4 you compare that to pioglitazone. It's not nearly as  
5 clear and, frankly, it's always less clear for death.  
6 The reason it's less clear is there's just always less  
7 deaths to look at. I mean, it was hard. We went on  
8 for years unable to show whether statins actually  
9 reduced cardiovascular death. We knew they reduced  
10 myocardial infarctions, but you need a lot more data  
11 to be able to know what's going on with cardiovascular  
12 death.

13 DR. BURMAN: Dr. Nissen, I apologize for  
14 interrupting. It's 10:50. So we do want to keep on  
15 time, if you would --

16 DR. NISSEN: I'll accelerate here. I got  
17 the most important thing I wanted to give you. Let me  
18 quickly say, why are these drugs different. They are  
19 different, in fact, because they have a different gene  
20 profile. They turn on and off completely different  
21 genes. This is not a class of drugs. Each of these  
22 drugs has a unique nuclear profile.

1           Let me just say that there are no benefits  
2 known for rosiglitazone that are not produced by the  
3 companion drug, pioglitazone. We have 13 classes of  
4 drugs to reduce blood sugar and we have a safe  
5 alternative in the same class.

6           Let me just mention the TIDE trial. I've  
7 calculated, based upon the current enrollment, that it  
8 will take at least another eight years to complete,  
9 and we will not have final data before 2020. And so  
10 given the current usage, are we willing to wait that  
11 long with a drug with this hazard to wait for the  
12 completion of the trial? This trial could have been  
13 done in 2001. It can't be done in 2010.

14           Let me just make one more quick point and I  
15 will wind up in a second and say that here is the MI  
16 data; .79 for pio, 1.8 or 1.39 for rosi. Now, what  
17 has happened is they've gone now to the third world to  
18 get this trial done. And are you willing to expose  
19 economically vulnerable third world patients to a  
20 trial that U.S. physicians won't enroll in? I don't  
21 think it's acceptable.

22           I'm going to jump forward to conclusions,

1 since I've been asked to conclude. I had more I  
2 wanted to say to you, but I will leave it for another  
3 time. Rosiglitazone increases the risk of ischemic  
4 myocardial events in a highly vulnerable population,  
5 70 percent of whom will eventually die of  
6 cardiovascular disease.

7 With an alternative in the same class with a  
8 favorable effect on CV outcomes, continued marketing  
9 of rosiglitazone cannot get medically or ethically  
10 justified.

11 Thank you very much for your attention.

12 DR. BURMAN: Thank you, Dr. Nissen, and  
13 thank you for keeping on time. We're going to have  
14 clarifying questions from the committee. If you'd  
15 raise your hand, Paul will get you.

16 I would like to take the prerogative of the  
17 chair. And you had one slide that mentioned that the  
18 ADA had an official statement on this topic. And they  
19 have given an update on June 30th, which says "The  
20 American Diabetes Association does not have an  
21 official position favoring or recommending against  
22 specific drugs that were approved by the FDA to lower

1 glucose. The 2009 consensus statement on medical  
2 management of hyperglycemia in Type II diabetes does  
3 not reflect the official position of the ADA, but  
4 rather the expert opinion of the authors of the paper.

5 DR. NISSEN: Thank you.

6 DR. BURMAN: Thank you. Dr. Konstam?

7 DR. KONSTAM: Thanks. Steve, first, I just  
8 want to thank you for all your hard work on this  
9 topic. Looking at the FDA version of the meta-  
10 analysis, they divide by placebo controlled versus  
11 active controlled and it looks like most of the signal  
12 is driven by placebo controlled. There doesn't seem  
13 to be a signal with non-pio active control, and I  
14 think that's consistent with the observational data,  
15 too.

16 So I guess I'd ask you, do you agree with  
17 that, number one? If you do, reflect how that impacts  
18 on our ability to compare the rosi versus the pio  
19 databases. And three, are you concerned about  
20 sulfonylureas and metformin, that they're just as bad?

21 DR. NISSEN: Well, I don't have analyses of  
22 sulfonylureas and metformin. That's a great question,

1 Marvin. Look, when you start to parse the data and  
2 you start to divide it up into subgroups, you lose so  
3 much power that if you did any statistical test for  
4 heterogeneity, I don't think you would even come  
5 close.

6 So all you can look at for those comparisons  
7 are what are the confidence intervals, and the  
8 confidence intervals clearly overlap.

9 So we have not proven that there is  
10 heterogeneity between the different groups. I hear  
11 what you're saying, but the bottom line is I actually  
12 consider the placebo controlled trials to be purist  
13 experiment and ask the question, "Is this a harmful  
14 drug or is it not?" And if it's worse than placebo,  
15 then it's a harmful drug, and that's really where the  
16 action is.

17 DR. BURMAN: Thank you. Dr. Weide?

18 DR. WEIDE: Thank you. I had actually three  
19 questions, but Marvin asked one of them. So I  
20 appreciate that.

21 In your meta-analysis that you just did, you  
22 actually made some comments and broke down the

1 differences between the trials that were less than 12  
2 months or longer than 12 months and gave both with and  
3 without RECORD. But for CV mortality, the trials less  
4 than 12 months had an odds ratio of 2.32, which sounds  
5 very high. But longer than 12 months, that  
6 observational dropped to 0.94.

7 DR. NISSEN: I'm sorry. For what endpoint?

8 DR. WEIDE: For cardiovascular mortality.

9 DR. NISSEN: That was not my analysis.  
10 Sorry.

11 DR. WEIDE: If you need to refer to your  
12 paper.

13 DR. NISSEN: Okay. Which one?

14 DR. WEIDE: The one that just came up. Page  
15 E-4.

16 DR. NISSEN: Can I see? Because I think we  
17 have a misunderstanding here. I see. You're talking  
18 about splitting out the trials by duration.

19 DR. WEIDE: Yes.

20 DR. NISSEN: I'm sorry. What was your  
21 question about that?

22 DR. WEIDE: You did that with less than 12

1 months or greater than 12 months.

2 DR. NISSEN: Yes.

3 DR. WEIDE: And for CV mortality, you  
4 commented that the odds ratio for less than 12 months  
5 was 2.32; greater than 12 months, 0.94. So there's  
6 quite a disparity and it looks like that perhaps in  
7 those short trials, there may have been some  
8 predisposition in some of those patients that skewed  
9 the data.

10 Then when you put that all together, you  
11 have the skew, because your odds ratio for everything  
12 was 1.46. I know it's a complicated question, but  
13 could you comment on that?

14 DR. NISSEN: I understand your question. I  
15 would be terribly cautious of subgroup analyses here.  
16 We put those in in the interest of completeness. But  
17 it's so, so difficult, because if you start to parse  
18 the data by different comparator drugs, by different  
19 duration, you get much smaller numbers of events. You  
20 get a lot of skewing of the data, and I can't  
21 interpret the findings as accurately.

22 I hear what you're saying. Keep in mind

1   that the long-term data is very heavily influenced by  
2   RECORD and you have to decide whether you are going to  
3   use the RECORD data or not, and, again, I have  
4   concerns about it.

5               DR. WEIDE:   I would also ask you --

6               DR. BURMAN:   Dr. Weide, please, keep it very  
7   brief.

8               DR. WEIDE:   The hazard ratios and odds  
9   ratios tend to exacerbate differences, whereas  
10   absolute risk and relative risk perhaps do not.

11              In your initial analysis in 2007, you got a  
12   positive difference.   But if you look at the absolute  
13   risk of being on rosiglitazone, of having an MI, it  
14   was 0.6 percent and in the non-rosi group, it was 0.6  
15   percent.

16              If you look at cardiovascular death in the  
17   same groups, it was 0.37 for rosiglitazone and 0.24  
18   percent with non-rosiglitazone groups.

19              DR. NISSEN:   Let me tell you what the  
20   difference is.   Those analyses do not look at  
21   different randomization ratios for the studies, and so  
22   they are not a valid way to look at the data.   Tom



1 Fleming could probably comment better for you about  
2 that.

3 But fundamentally, it's just not a  
4 meaningful analysis. The odds ratios are calculated  
5 keeping in mind the randomization ratios of the trial.  
6 So those raw absolute numbers, you can't calculate a  
7 hazard based upon them, statistically.

8 DR. BURMAN: Thank you. And for  
9 clarification, you're referring to Dr. Nissen's recent  
10 2010 *Archives of Internal Medicine* article.

11 DR. WEIDE: For the first question, yes.  
12 For the second question, with those numbers, it was  
13 the 2007 meta-analysis.

14 DR. BURMAN: Thank you. And one last quick  
15 question, Dr. Rosen.

16 DR. ROSEN: Steve, you predicate a lot of  
17 your argument on the difference between pioglitazone  
18 and rosiglitazone and you didn't have a chance, maybe  
19 because time truncated it. But can you give us a very  
20 brief overview of where you think the difference lies  
21 etiologically, because I think this is actually very  
22 critical?

1           In the past, we've considered these class  
2 agents and, obviously, they're not. And we know from  
3 what we do in the lab that PPAR is regulated  
4 differentially.

5           So is it more than just lipids?

6           DR. NISSEN: Yes, it is, I think. Again, I  
7 had to rush, because I wanted to respect the chair's  
8 request to stay on time. But if you look at those  
9 Venn diagrams for the genes that are upregulated and  
10 downregulated, there is only partial overlap.

11           Something that the committee should be aware  
12 of that probably many of you are not is since  
13 rosiglitazone and pioglitazone were approved, at least  
14 50 PPARs have been developed, all of which failed  
15 during clinical development and many of them for  
16 cardiovascular toxicity.

17           So this isn't a unique problem to  
18 rosiglitazone. If you turn on and off the wrong genes  
19 with a PPAR, you're going to get a hazard, and that  
20 seems to be what happened.

21           There was a paper in *PLoS Medicine* that  
22 showed that rosiglitazone upregulates matrix metallo-

1    proteinase-3, which is an enzyme that's active in  
2    plaque rupture, and that's not upregulated by  
3    pioglitazone.

4            There are many other differences that have  
5    been shown. And so let me be as clear as I can and  
6    answer your question. This is not a class of drugs.  
7    Every PPAR is targeting a different genetic profile  
8    and that's why these drugs are probably so different.

9            DR. BURMAN: Dr. Nissen, thank you very  
10   much, and thank you very much for keeping on time. I  
11   would remind everyone that the guest speakers will be  
12   available tomorrow and there will be more time for  
13   discussion.

14           DR. PARKS: Dr. Burman?

15           DR. BURMAN: Yes, of course.

16           DR. PARKS: I apologize for interrupting.

17           DR. BURMAN: Thank you.

18           DR. PARKS: I just want to make a  
19   clarification about PPARs in development. Yes, there  
20   have been quite a few PPARs that have been  
21   discontinued in development, but the majority of them  
22   have been discontinued not because of cardiovascular,

1 but because of malignancies.

2           So from non-clinical studies, all these  
3 drugs are actually placed on a partial clinical old  
4 for six months' duration until these studies are  
5 actually completed. As a result of many of these non-  
6 clinical studies showing cancer in multiple species  
7 and multiple types of cancers, they have been  
8 discontinued.

9           However, there have been some, but they have  
10 not made up the majority with respect to  
11 discontinuation due to cardiovascular concerns.

12           DR. BURMAN: Thank you, Dr. Parks. We will  
13 now proceed with our presentation from the FDA  
14 presenter, Dr. Tom Marciniak.

15           I'd like to remind public observers at this  
16 meeting that while the meeting is open for public  
17 observation, public attendees may not participate  
18 except at the specific request of the panel.

19           DR. MARCINIAK: Good morning. As the first  
20 FDA speaker, I'd like to say that like all of Gaul is  
21 divided into three parts, regarding this topic, the  
22 FDA is divided into three factions, actually.

1           You have the faction that was involved with  
2 the approval of this drug, continuing to be used since  
3 2007, and it's probably not surprising they might have  
4 a bias towards not reversing themselves.

5           You also have the other faction, the one  
6 that has been saying since 2007 that this is a  
7 dangerous drug and that it should be removed from the  
8 market, and the same thing there. They are probably  
9 reluctant to say that, "No, it doesn't look that bad  
10 and it should stay on the market."

11           Then I think you have me. I had not been  
12 involved with rosiglitazone prior to fall of last  
13 year. I have a clean slate there. So I think what I  
14 amount to, I think, is the tiebreaker in terms of  
15 whether this is a good or bad drug.

16           Now, that's not to say that I don't have  
17 biases. So I think I should explain to you what I  
18 think my biases were at that time. I'm an Office of  
19 New Drug reviewer. I review new drugs. And like it  
20 or not, I actually think that does mean I have a  
21 slight bias in favor of the drug, and it's for two  
22 reasons. There's a natural human tendency to want to

1 be involved with the positive, to be involved with  
2 getting that new product on the market that I helped  
3 with. So the bias is a little bit towards approval,  
4 if there's any doubt.

5           There's another simpler problem that I think  
6 I'm a little bit resistant to; that is, if I approve a  
7 drug, my bosses all say "good job." My work is done.  
8 If I say a drug is bad, there are endless meetings and  
9 hours of additional work. So it also biases that  
10 direction.

11           I'm also affected by a second bias, which is  
12 this has got a lot of almost a circus atmosphere, and,  
13 in fact, actually, the speaker you just heard, Dr.  
14 Steve Nissen, was once a respected member of the  
15 cardiovascular or cardio-renal advisory panel, and we  
16 thought we had a good working relationship with him.  
17 In fact, at least some of the, I think, senior members  
18 of the FDA believe we were a little bit blinded in  
19 2007 by that meta-analysis.

20           I believe that some people would really  
21 think that they would really appreciate if I could  
22 show definitively that Steve Nissen was absolutely

1 wrong.

2           So those are two of my biases. I do have a  
3 third bias, not really a bias. I don't believe you  
4 can find truth from these studies by superficially  
5 looking at the top level data without checking it  
6 thoroughly, without understanding it and coming to any  
7 sort of truth.

8           So basically, that's what I did and that's  
9 what I'd like to tell you about. Now, before I do  
10 that, RECORD is a very complex and confusing study.  
11 I'm a numbers man, so I actually picked out three  
12 numbers that characterize not the results, but the  
13 challenges of dealing with RECORD; 25,000, roughly,  
14 1,400, 15, and 811.

15           Now, what are these numbers? The 25,839.4  
16 should be the easy one. That's the total person years  
17 of exposure of both arms in RECORD, and it looks  
18 impressive; or 4,500 patients, or whatever it is, 5.6  
19 median years on therapy, et cetera; looks like a very  
20 robust CV outcomes trial.

21           If you look at the second number, it sounds  
22 even more impressive, 1,438. That is the number of

1 pages in the CRS for just one of the RECORD patients,  
2 329 megabytes. Multiply that by 4,500, or multiply a  
3 couple hundred by 4,500. This is the challenge of a  
4 reviewer in trying to deal with the studies. That's  
5 kind of why I like it.

6           They're paying me to solve this gigantic  
7 puzzle, which not only are they paying me reasonably  
8 well for, but, in fact, I think I actually benefit  
9 public health doing it. But it is a huge challenge to  
10 try to find those few needles in the haystack.

11           Fifteen, what number is that? We have this  
12 huge, robust CV outcomes trial. For MIs, you only  
13 have to, in fact sloppily or otherwise, change about  
14 15 events and , in fact, now you've made RECORD  
15 statistically significant with regard to the MI  
16 results.

17           Same thing for death, same thing for any  
18 other endpoint. It is not vast amounts of cases that  
19 have to accidentally be changed. They are in the low  
20 teens.

21           Eight-eleven. This is the FDA toll-free  
22 emergency number for you. It is the sum of the number



1 of pages in the documents at least that we initially  
2 sent out from the FDA and the sponsors. So I can  
3 appreciate that while 1,438 is a big problem for me,  
4 81 is a big problem for you, and really appreciate it.

5 So I believe in getting down and dirty. So  
6 that's the way we're going to start out. We will look  
7 at some of the actual case report forms from RECORD,  
8 what I believe is the real RECORD. We'll then discuss  
9 some of the study conduct issues briefly, study design  
10 issues, my study results, and then, finally, of  
11 course, my conclusions.

12 So we'll start with case A. It seems pretty  
13 straightforward. On page 125, the investigator  
14 reports a typical myocardial infarction, life-  
15 threatening, hospital prolonged, in November '05. But  
16 this is crossed out. Why? Because 15 months later,  
17 for undisclosed reasons, the investigator suddenly has  
18 a change of heart and he deletes the serious adverse  
19 event.

20 This was after that patient, in fact, had  
21 gone on to have a PTCA, also not adjudicated, and died  
22 from heart failure, which was adjudicated before this

1 event was deleted. This makes no sense.

2 I have seen this sort of pattern and changes  
3 I adverse events in only two other of the 70 or so  
4 submissions I have done. In each case, there were  
5 multiple problems. In each case, we disapproved those  
6 and, in fact, there are some parallels to here I'd  
7 love to discuss, but I don't have time.

8 But there's another point. When I say this  
9 vanished, I mean it vanished in particular from the  
10 datasets that everybody uses within the FDA. Steve  
11 Nissen, you name it, to try to understand what's  
12 happening in the studies. If it's gone, you cannot  
13 tell it's not there.

14 If someone says that the London School of  
15 Hygiene and tropical medicine looked at the datasets  
16 and confirmed the analyses are right, they didn't know  
17 about this case. It was not there.

18 Lastly was something -- my one political  
19 announcement. There was something called the CDISC  
20 SDTM, an industry-developed standard which the FDA is  
21 using, which, in fact, is putting this problem into  
22 concrete.

1           Let's consider case B now, another case  
2 report form. This lady presented with pulmonary  
3 edema, improved with furosemide at admission. But she  
4 has a rocky course and 46 days later, she dies of  
5 pneumonia. This brief note here is all we know about  
6 this 46-day hospitalization. There were no CV events  
7 adjudicated for this patient. The pulmonary edema  
8 apparently was ignored.

9           Now, you might be sympathetic in the  
10 Ukraine, where you might have problems with  
11 communication. But this was actually less than a 3-  
12 hour drive from a CRO, and, of course, it was just a  
13 short phone call away.

14           I think this type of handling of event sis  
15 completely unacceptable and, in my view, there are at  
16 least two additional ones that, in fact, I think are  
17 equally of problem.

18           What I usually do with a review is I start  
19 looking at things. Usually, you don't find much  
20 problems. You kind of go through a few and then you  
21 stop. I didn't have much choice here. I had to keep  
22 on going.

1           So what I ended up with is actually  
2 reviewing 549 CRFs, roughly balanced between the two  
3 groups.

4           I did focus on problems or area where I  
5 thought there might be problems. For example, did the  
6 initial adjudicators disagree? Were there lots of  
7 unstable angina admissions, but no MI? Was there  
8 acute heart failure admission, but no MI?

9           So I tended to look at things like that,  
10 concentration, concentrating on the MACE events.  
11 Initially, I actually found about one in four records  
12 to have some major problem. Towards the end, I only  
13 found one in 10, and, in fact, the one in 10 were  
14 largely in this other cardiovascular hospitalization  
15 endpoint and not in the primary MACE.

16           What I end up concluding is that about 13  
17 percent of these reviewed cases had endpoint problems  
18 and they were greater than four to one favoring  
19 rosiglitazone.

20           Now, to try to, in fact, give a statistical  
21 estimate, I did do a random sample of 100 cases, 50 in  
22 each of the two major arms, if you like. For these,

1 about 9 percent had endpoint problems, two to one  
2 favoring rosiglitazone, still suggesting we've got a  
3 problem; and, hence, from the ones I sampled, the ones  
4 submitted, which is about, I think, 78 percent of all  
5 patients, you'd expect 310 problems. Remember, at  
6 this point in time, I found about 70 problems.

7 Well, what's the nature of the problems?  
8 They were fairly wide range. You've heard about the  
9 unacceptable case handling in four. There were  
10 another eight that were failures to refer for  
11 adjudication, all in the relationship group.

12 What I've tried to indicate in the right-  
13 hand column here are what actually I judge the bias to  
14 be. And if you will notice, many are biased in favor  
15 of rosiglitazone. The no bias is not without its  
16 problem. This is a non-inferiority study. Biasing  
17 towards the no will also get you non-inferiority. So  
18 there aren't any problems here that don't create  
19 problems for interpretation of the study.

20 There are also some that I called neutral.  
21 The neutral ones, in fact, are also not without  
22 concern. For example, number 11, the endpoint case

1 report forms, the ones where the investigator was  
2 supposed to describe the detail on the MI, on the  
3 stroke, on the death, were, quote, "not databased."  
4 They were not even submitted with the initial  
5 submission of CRFs, as was required by our  
6 regulations.

7           What I think all of this suggests is that  
8 from the study conduct biases, that any CV estimates  
9 of risk you get from RECORD should not be viewed as  
10 precise statistical estimates, but as lower bounds.  
11 It's likely to be higher.

12           Well, some of this you could have actually  
13 predicted if you had really looked very closely at the  
14 study design. Here, the biases are theoretical, what  
15 you might predict them to be.

16           What I've tried to shade in the center  
17 column is -- in fact, the ones shaded in red are the  
18 issues that I consider to be the key issues. I think  
19 the open label nature of this did lead to problems.

20           Yes, supposedly, the adjudication was  
21 biased, but if you don't refer the cases for  
22 adjudication, the committee is not going to be able to

1 judge them.

2           The active control, we just heard a  
3 discussion on that, about whether, in fact,  
4 sulfonylurea and metformin, in fact, increase CV risk.  
5 Well, the control included both of them. Why hedge  
6 your bets? Make sure you get in both.

7           CV hospitalizations in the primary endpoint.  
8 Why did we think that a drug can affect anything from  
9 Gautier (ph) disease, to pulmonary embolism, to  
10 peripheral vascular disease, to arrhythmias, you name  
11 it. You didn't have to do that here.

12           You may have some belief of doing it early,  
13 but I think midway through the study, you could have  
14 decided that what's really been shown in terms of your  
15 meta-analyses is an effect upon MIs, potentially an  
16 effect upon MACE, and focused on that.

17           Analysis populations, because of the  
18 problems with crossovers, with discontinuing  
19 treatments, and I'll talk a little bit more about  
20 those in a second, we would not pick as the primary  
21 analysis population something for the entire duration  
22 of a study from an ITT approach.

1           Last, but not least, on this, handling of  
2   withdrawals, it is actually the looming problem I am  
3   seeing. This is true not only of RECORD, but  
4   virtually every recent outcome trial I've seen. What  
5   I mean by that is all an investigator has to do is  
6   check a box on a form that the patient has withdrawn  
7   consent. There doesn't have to be any documentation  
8   on it. He could have had a severe chest pain the day  
9   before and that's why he's withdrawing consent, and  
10   that patient is taken out of the running and, in fact,  
11   these patients tend not to be followed-up on very  
12   well.

13           So I will say, if I had been consulted in  
14   advance, I would have rejected this study design as  
15   completely inappropriate and biased.

16           What's interesting is, to show you how  
17   complex it is, we will actually get to a sixth major  
18   study design, which I had missed, in fact, all my  
19   colleagues had missed, and we'll talk about that in a  
20   second.

21           So far, I've talked largely about endpoints.  
22   I got down to a month before I was supposed to have my



1 view done, when normally what I do is I pull out the  
2 censoring dates, run my analyses, write up my paper,  
3 and then I'm done. And then I hit this.

4 Right now, nobody knows what the last study  
5 contacts are in RECORD to this day, and this is the  
6 example. You had to fill out a visit form. And this  
7 investigator nicely filled out a visit form on the  
8 13th of January '09, explaining, as he had in previous  
9 CRFs, that he had lost the patient in November of '07.

10 GSK used this date as the date of good  
11 follow-up. So when they say they've got good follow-  
12 up, remember, you don't even know when the dates of  
13 last follow-up are. And this, clearly, for this  
14 patient, is the wrong date for cardiovascular follow-  
15 up. You last really talked to him in detail back in  
16 2007.

17 Well, what I didn't realize, actually, when  
18 I picked this slide and to show you I've tried not to  
19 be biased, this is actually a control patient. This  
20 problem is just sloppiness.

21 DR. BURMAN: Dr. Marciniak, sorry to  
22 interrupt. It's 11:18. You have a few more minutes,

1 but I did want to give you enough time, because I see  
2 you have some more slides, and want to make sure you  
3 get the points you want to get to in the next minute  
4 or two.

5 DR. MARCINIAK: Okay. Thank you. The last  
6 study date was 24 December 2008. It is questionable  
7 whether this should even be used. It was long after  
8 you said you were going to finish follow-up on these  
9 patients.

10 The third problem, the study report we have  
11 says that there was only one patient in cardiovascular  
12 follow-up that, in fact, was after that 24 December  
13 2008 date, on 26 December. There are at least two  
14 more in the cardiovascular group. There are 38 more  
15 in the vital sign follow-up, with dates of follow-up  
16 as late as March of 2009.

17 Every time you look at the study more  
18 closely, you find not fewer problems, but more  
19 problems. So, in fact, I'll look at my random sample.  
20 There are actually -- I have in the review 7 percent.  
21 Since looking at vital signs follow-up, I found an  
22 eighth. So there's 8 percent errors in the random

1 sample of 100 CRFs, 95 percent confidence limits up to  
2 15 percent errors that I'm estimating. Half of the  
3 errors were substantial, minus 24 months, 20 months,  
4 14, 8 months, and then 4, 2, 1, 1, and 1.

5 If you can't even decide when you last saw  
6 the patient, what confidence should you have in  
7 complex determinations such as MI or CV  
8 hospitalizations?

9 So actually, what I said is because this is  
10 a non-inferiority study, if you've got missing data,  
11 it will bias towards the null; that, in fact, what I  
12 need to do is somewhat arbitrarily cut it off at a  
13 point in time.

14 This shows the CV follow-up by year. At 3.5  
15 years, you drop below 90 percent follow-up. And this  
16 is what I said I would use and this is what I will  
17 present to you. We certainly can do sensitivity  
18 analyses of 95, which actually is about here or 80  
19 percent.

20 Follow-up is not only a problem, of course.  
21 Not using drug is a problem. This shows the  
22 rosiglitazone use by year. Actually, it ends up being

1 very similar. I said I'd pick 80 percent for  
2 rosiglitazone use, and that actually occurs at about  
3 3.6 years. So these are what I incorporate into my  
4 analyses.

5 Now, one of the issues that's been raised  
6 is, well, yes, the study has its problems, but  
7 mortality should be good. I already talked about we  
8 don't even know when the patients were last seen. So  
9 you've got to wonder about how much you know about  
10 mortality.

11 This is the worst case I had come across. I  
12 have not exhaustively tried to look at all 4,500 cases  
13 or even all deaths or non-deaths. In 2002, a patient  
14 is reported as died and the investigator says he  
15 doesn't even know the year. No one checks up on this.  
16 This is all we know about this patient.

17 So what do I know about vital status follow-  
18 up?

19 DR. BURMAN: Dr. Marciniak, I apologize.  
20 You have 15 more slides and really we're over time  
21 already. So please point out your most poignant  
22 slides, so we can have questions for you.

1 DR. MARCINIAK: For vital signs, then, we  
2 really don't know. If you notice, median missing  
3 vital status follow-up on at least 3 or 4 percent,  
4 using the dates we know are erroneous, is 4.9 years.

5 When to believe all cause mortality. We  
6 really don't depend on it typically in CV studies.  
7 This, of course, is RECORD. This happens to be TRITON  
8 study, primary analysis group for prasugrel, where, in  
9 fact, prasugrel is the one with the worst mortality;  
10 kind of not accepted, because what we really think,  
11 we've got to look at the whole pattern of things, not  
12 just the one isolated statistic, even if it is all  
13 cause mortality.

14 So can any information be salvaged from  
15 RECORD? I believe so, and I believe so because I  
16 think, actually, the investigators were, in general,  
17 honest. So if you go back to their records, you can,  
18 in fact, find close to the truth.

19 I have nothing to hide in my review. I've  
20 got more examples of the CRFs with real problems. I  
21 have all of the cases, summaries of them, where I  
22 differ from GSK's determinations.

1           So what did I find? Very simple. I found  
2 patterns. MI, diverges after about a year, clearly  
3 divergent. We'll see this analysis, at least to here,  
4 is not statistically significant, but clearly  
5 suggesting its diverging.

6           Time to first stroke, dead on, no change  
7 there. Time to CV death, also virtually identical. So  
8 not surprisingly, MACE will show a slight difference,  
9 but a lesser difference than what you saw for MI.

10           The hazard ratios. This is actually the  
11 ITT, I should have said, to 90 percent follow-up.  
12 Randomized treatment phase is per protocol on  
13 treatment. I think you can't use that, because this  
14 is what I missed in terms of a study design flaw.

15           Rosiglitazone patient develops heart  
16 failure. What should you do? You should remove him  
17 from the randomized treatment phase. Those are the  
18 patients that are more likely to go on and develop  
19 events. and I actually have a backup slide that will  
20 show you that's exactly what happened.

21           So you can't use these. You may have some  
22 differing opinion about exactly what to use, but by my

1 calculations, you've got upper 95 percent confidence  
2 limits far exceeding 1.3. But you're right, shouldn't  
3 look at the only study, should incorporate these into  
4 a meta-analysis, and it's very clear, if you do that,  
5 you will have very negative hazard ratios.

6 Now, what about MIs and silent MIs? The  
7 correct statement is originally the steering committee  
8 considered whether they should be included. They went  
9 through the process. They said they were going to go  
10 off and look at some data and then, all of a sudden,  
11 they dropped them.

12 Silent MIs, by my count, yes, there are  
13 problems with ascertainment, are 10 to 5 against  
14 rosiglitazone. If you incorporate them, by my  
15 analysis, as Dr. Nissen quoted, 1.5. Actually, what  
16 you should do, if you incorporate them, is you should  
17 use GSK's analysis that they said was primary, the one  
18 to the end of the study.

19 If you do that, the p-value for the  
20 difference in most failure curves is 0.034. So if  
21 you're a slave to p-values, by the primary MI analysis  
22 of GSK's, p-equals 0.034, and I can show you the

1 complete statistics on that.

2 Possible MIs also that I thought were  
3 actually 16 to 6 against rosiglitazone. So the  
4 sensitivity on MI analyses suggest there is a problem.

5 DR. BURMAN: Dr. Marciniak, excuse me,  
6 please wrap up.

7 DR. MARCINIAK: I'll try to wrap up.

8 DR. BURMAN: Well, not just try. Please do.

9 DR. MARCINIAK: Heart failure, twice as  
10 much, does not diverge early. Time to heart failure  
11 death, only occurs delayed and then goes up fairly  
12 dramatically. Atrial fibrillation, interesting story  
13 about this, but, in fact, it looks like it does  
14 diverge, and, in fact, atrial fibrillation is more  
15 associated with rosiglitazone and heart failure and  
16 with MI than you would expect.

17 I think this says something about the  
18 mechanism. I have a backup slide on that. The  
19 tantalizer there is what about muraglitazar. How do  
20 you explain that?

21 What my conclusions basically are is that  
22 RECORD was inadequately designed. You really can't



1 depend upon it for safety. You can view it as being a  
2 lower bound. It does confirm the problems of heart  
3 failure and extends them regarding heart failure  
4 deaths, and, in fact, RECORD does suggest that  
5 rosiglitazone increases the risk for MI.

6 Thank you.

7 DR. BURMAN: Thank you. We'll open the  
8 floor up for clarifying questions for a couple of  
9 minutes. Thank you, Dr. Marciniak.

10 Dr. Capuzzi?

11 DR. CAPUZZI: My question is this. Of the  
12 entire dataset that you looked at and evaluated, how  
13 many of the patients that were enrolled in the placebo  
14 group and in the drug treated group did you evaluate?  
15 And the second question is, what is the -- how many  
16 sites were involved in this kind of shoddy behavior?  
17 Was it mostly one or two or three sites or all across  
18 the board?

19 DR. MARCINIAK: Here are the cases reviewed  
20 again, about one-eighth of the cases. I said 100  
21 randomly sampled, the rest selected for some cause,  
22 particularly related to MACE, not related to which arm

1 they were on.

2 The number of sites, actually, it usually  
3 ended up that there were a few sites that had more  
4 than one case. With only reviewing 70, you might  
5 suspect them having, what is it, several hundred  
6 sites. Usually, there was only one case per site that  
7 I considered to be bad.

8 DR. CAPUZZI: How many sites had the problem  
9 and what is the number of sites versus the total  
10 number of sites involved in the study?

11 DR. MARCINIAK: I would have to run those  
12 numbers for you.

13 DR. CAPUZZI: It's an important question.

14 DR. MARCINIAK: It's somewhere just under  
15 70. As I said, there were very few duplicates. And  
16 perhaps GSK could say how many sites there were in the  
17 RECORD.

18 DR. BURMAN: We can follow-up on that and  
19 maybe you can get specific information for that  
20 important question and come back to us on that.

21 We'll take one more question from Dr.  
22 Fleming.

1 DR. FLEMING: So many issues that you've  
2 raised, I wish we had a lot more time. It was  
3 intriguing to me, when I looked at your summaries,  
4 that cases that had insufficient information that  
5 weren't included were in excess in rosiglitazone 16 to  
6 6.

7 Cases where there was failure to submit for  
8 adjudicating, 8 to zero. Interestingly, in an open  
9 label trial, could that, in fact, have not been a non-  
10 chance event?

11 There were also decisions made seemingly  
12 late in the process to exclude the silent MIs, as  
13 you've noted, and Dr. Nissen, that are 10 to 5 in  
14 excess against GSK. And to call as events not just  
15 sudden unknown deaths, but all unknown deaths as  
16 events that are 5 to 10 against the control.

17 Those latter two decisions, I understand,  
18 were made late in the process. Is it correct that  
19 after 2003, the sponsor had access to information on  
20 code and is there any concern that these late  
21 decisions to exclude the silent MIs that were going  
22 against rosiglitazone and to include all deaths, all

1 unknown deaths were decisions that were made knowing  
2 what the impact would be on the analysis?

3 DR. MARCINIAK: I guess all I can do is  
4 repeat what I understand to be the facts as given to  
5 me by GSK. The quote I gave you on the unrestricted  
6 availability of study code is from their steering  
7 committee minutes. It seems fairly clear to interpret  
8 that.

9 There are various dates when things were  
10 done, also, documented in the various documents. I  
11 don't know.

12 DR. BURMAN: Thank you. Does GSK have a  
13 quick point of clarification?

14 DR. STEWART: Yes. I have some clarifying  
15 points. There were over 360 sites, to that  
16 gentleman's point.

17 I think I also want to show one of the  
18 backup slides regarding distribution of SAEs and which  
19 buckets they go into. So if you wanted to know what  
20 happened in terms of going to higher levels, so you  
21 say, well, were some events not sent for adjudication,  
22 let's look at the number of SAEs reported by the

1 investigators for the endpoint of myocardial  
2 infarction, that you can see on the top.

3           You can see the number of SAEs reported were  
4 equally distributed, 93 versus 88. Now, of those MIs  
5 that were sent for adjudication, you can see in the  
6 far length, 116 of those were adjudicated as an MI.  
7 Some of those were not adjudicated as an MI. So what  
8 was the balance in those not adjudicated? 40 to 21  
9 versus 21.

10           What about those that were adjudicated  
11 either through an investigator MI, but the  
12 adjudication said it was something else? Well, they  
13 were balanced 10 to 8 for a non-CV.

14           What also occurred is the endpoint  
15 committee, when they were reviewing dossiers, if they  
16 saw something that wasn't an SAE of an MI, but another  
17 SAE, that was also adjudicated. You can see,  
18 generally, the balance is the same.

19           Now, some of the MIs were not sent for  
20 adjudication and the reason they were not sent for  
21 adjudication is they did to meet the criteria.

22           What's important to know is we did not

1 include myocardial infarction as an endpoint. And I  
2 just want to correct a misperception that was said  
3 after the event. That was in the predefined endpoint.  
4 So the actually definition of MI agreed by the  
5 committee was agreed before. So they sometimes were  
6 not included.

7 We have other data, if you go to the next  
8 backup slide.

9 DR. BURMAN: Please.

10 DR. STEWART: Of those not sent for  
11 adjudication, and you can see splits. So some of the  
12 things Dr. Marciniak has pointed out, I think, as GSK,  
13 we would actually disagree with.

14 DR. BURMAN: Thank you. Thank you to both.  
15 And thank you, Dr. Marciniak. We will have much more  
16 time tomorrow to discuss these issues.

17 In fact, those two slides that you just  
18 showed, would it be possible to hand them out after  
19 lunch to the committee? The FDA could help you do  
20 that. Thank you.

21 We will now proceed with our presentation  
22 from the FDA presenter, Dr. Ellis Unger.

1           I would like to remind public observers at  
2   this meeting that while this meeting is open for  
3   public observation, public attendees may not  
4   participate, except at the specific request of the  
5   panel.

6           DR. UNGER:   Good morning, ladies and  
7   gentlemen.   I'm Ellis Unger.   I'm Deputy Director of  
8   the Office of Drug Evaluation I within the Office of  
9   New Drugs.   And I've been asked to provide some of my  
10   perspectives on RECORD.

11           But before I begin, I need to make a few  
12   remarks.   First, as asked, I receive no compensation  
13   from the pharmaceutical industry and donate none of it  
14   to charity.

15           [Laughter.]

16           DR. UNGER:   I needed at least one joke.  
17   It's very serious here.   I think I could retitile my  
18   talk, Bias and Truth, and, in fact, I think in view of  
19   the last three or four talks, I am going to kind of  
20   redesign my talk a little bit here.   So you'll have to  
21   bear with me.

22           In the Office of New Drugs, we encourage our

1 review staff to probe the quality of the sponsor's  
2 data, to consider it critically from an unbiased  
3 perspective, and, when seemingly useful, to conduct  
4 alternative sensitivity and exploratory analyses to  
5 try to gain additional insights from trial data.

6 My office, the Office of Drug Evaluation I,  
7 has oversight for the Division of Cardiovascular and  
8 Renal Products, where Dr. Marciniak is the senior  
9 medical officer and team leader. And as you've seen,  
10 he is one tenacious reviewer. He is extremely  
11 competent. He doesn't generally depend on  
12 biostatistics support, because he's fully capable of  
13 statistical analyses. He is great.

14 My belief is that everyone in CDER is  
15 passionate about public health, but as you see, we  
16 consider some pretty complicated issues and we don't  
17 always agree on things. And when management disagrees  
18 with a reviewer's specific results or conclusions, we  
19 debate the facts on scientific principals, but we work  
20 hard to make sure that all voices are heard.

21 So I'd like to provide just a little bit of  
22 our perspective on Dr. Marciniak's review from Office



1 of Drug Evaluation I. As you've seen, Dr. Marciniak  
2 worked painstakingly for six months or more to assess  
3 the quality of the RECORD data and he carefully  
4 examined case report forms, focusing on MACE events,  
5 and where suspicions of errors or underreporting.

6 As he told you, he examined one-eighth of  
7 the case report forms, one-eighth in both groups, and  
8 he uncovered a number of important concerns about the  
9 conduct of the trial and data quality, and we take  
10 these concerns very seriously.

11 Whether or not particular adverse events  
12 were forwarded for adjudication, whether there was  
13 bias, uncertainty regarding dates, these are all  
14 important issues, and the issue here is really truth.

15 I've read, honestly, Dr. Marciniak's review  
16 two or three times and I think you could sum it up in  
17 one word, and the word is truth. Can we trust the  
18 sponsor with the results of RECORD, and I think that's  
19 something the committee is going to need to think  
20 about here as we go on today and tomorrow.

21 But I'll try to provide an interpretation  
22 based on what we know and what we fear that we don't

1 know. There is one approach, however, that Dr.  
2 Marciniak took with the data with which we don't  
3 agree, and that's basically that he reinterpreted the  
4 information, as you saw, adding and subtracting actual  
5 endpoint events. In other words, he conducted his own  
6 independent re-adjudication of RECORD. Then having  
7 changed some of the data, he provides analyses and  
8 comments. And we don't agree with this approach in  
9 the Office of New Drugs.

10 You see that his results -- actually, he  
11 went through them very quickly, but they're not that  
12 different from the sponsor's, but we don't think that  
13 they can be viewed as anything other than exploratory.

14 The policy in OND is basically that  
15 adjudication of endpoints in a clinical trial is really  
16 the responsibility of the sponsor. If we find  
17 problems with an adjudication and we have questions  
18 about it, we refer it back to the sponsor and, in rare  
19 cases, unusual cases, when we think that a new  
20 adjudication is needed, then we have standard  
21 operating procedures.

22 We would have a panel of people. We would

1 agree in advance on those operating procedures, and it  
2 would be adjudicated blindly by a panel of people who  
3 had no knowledge of the trial or the data.

4 In this case, the individual who had the  
5 concerns actually conducted the analysis himself, and  
6 we don't agree with that. He also did, as the sponsor  
7 pointed out, changed the definition of acute MI. The  
8 sponsor used, I think, the 2000 definition of acute  
9 MI. Dr. Marciniak applied a 2007 definition.

10 Maybe that's better, but you have to kind of  
11 go with the prospectively agreed upon endpoint here.  
12 And if you don't, it's fine, but that's an exploratory  
13 analysis and that's, I think, how you have to view Dr.  
14 Marciniak's conclusions.

15 So now I'll actually give a talk. And this  
16 is the outline of the presentation.

17 Most of the RECORD key features you've heard  
18 and I'm going to go through them very quickly. Dr.  
19 Nissen presented the results of his meta-analysis from  
20 2007. That is the reason why we're here.

21 The results, the primary results are in this  
22 table. The point estimate for the odds ratio of acute

1 MI was 1.43, with a p-value of .03.

2 Maybe of more concern to us was deaths from  
3 cardiovascular causes, the point estimate being -- the  
4 point estimate 1.64, with a p-value of .06. And here,  
5 we're talking about death, so that's a concern.

6 Well, every meta-analysis has limitations  
7 and, actually, Dr. Parks went through these, I think,  
8 very well in terms of the Nissen-Wolski meta-analysis.  
9 I would like to underscore one concern that I have,  
10 which is the concern about patient level source data.

11 I think if an author or authors go through  
12 the back tables in a publication and they think  
13 they're looking at acute MI or heart failure or new  
14 cancers and they haven't looked at the patient level  
15 data, that they really don't have a clue what they're  
16 actually counting.

17 I would take that a step further and I would  
18 say having, in my travels at FDA, personally,  
19 classified about a half a million adverse events,  
20 categorizing them for various and sundry trials, if  
21 you don't look at the verbatim term, what the  
22 investigator actually said, you can be badly misled.

1           So if you don't have patient level source  
2 data, you have an extremely concerning limitation.

3           I'm going to move on to RECORD. I think  
4 after 800-and-some pages, most of you probably have  
5 these features memorized. And I won't go through the  
6 points, except the last two.

7           The adjudication of potential endpoint  
8 events was by the clinical endpoint committee, and  
9 they were blinded to treatment assignment. But you  
10 have this potential for ascertainment bias, and I'd  
11 like to focus on that a bit.

12           So the protocol directed that all  
13 cardiovascular hospitalizations and cardiovascular  
14 death endpoints will be reported in the CRF.  
15 Reporting or non-reporting of potential endpoint  
16 events was at the discretion of the clinical  
17 investigator. Bu the investigator, of course, knew  
18 what the treatment assignment was.

19           Now, adverse events that were not considered  
20 potential endpoint events, and "potential" is in  
21 quotes, because that is a key word, in the  
22 investigator's opinion, would not be reported to the

1 CEC. So the CEC's primary charge was really just to  
2 downgrade events that the investigator deemed to be  
3 potential endpoints; in essence, to overrule the  
4 clinical investigator.

5 So by design, there was limited provision to  
6 search for events that investigators deemed not to e  
7 endpoint events and then have the CEC upgrade them. I  
8 think that was a mistake, in retrospect, but I wasn't  
9 around when the trial was planned.

10 So consider a patient hospitalized with  
11 pneumonia and a touch of failure. Clinicians in the  
12 audience have seen these patients. So the clinical  
13 investigator had to judge whether this was a potential  
14 endpoint event.

15 In other words, was that a cardiovascular  
16 hospitalization or was that pneumonia? So if  
17 operational, ascertainment bias could have affected  
18 all the endpoints, with the probable exception of all  
19 cause mortality. That is pretty hard to bias.

20 So what I would like, in retrospect, or  
21 would have liked is for the protocol to have cast a  
22 wide net. It could have set a low threshold for

1 referral of adverse events for blinded adjudication to  
2 help ensure that all endpoint events were captured,  
3 but, again, that's not how the study was conducted or  
4 designed.

5 Here are eight hospitalizations that are  
6 highlighted by Dr. Marciniak on page 95 of his review  
7 as adverse events that should have been referred for  
8 adjudication, but were not.

9 Again, realize that hospitalizations only  
10 countered towards the primary endpoint if they were  
11 cardiovascular hospitalizations, and there is some  
12 subjectivity there. No one is saying that these eight  
13 cases constitute trial misconduct. The investigators  
14 just were following the protocol. Their opinion was  
15 that the cases were not potential cardiovascular  
16 hospitalizations.

17 Our Division of Scientific Investigations  
18 inspected the sites, the records of these patients.  
19 They found no evidence of serious deviations from the  
20 study protocol or procedures.

21 But reasonable people could debate whether  
22 or not these hospitalizations had a cardiovascular

1 basis, and, in retrospect, I think it would have been  
2 desirable to have these kinds of events adjudicated.  
3 But again, that's not how the protocol was designed.

4           So let me emphasize that these  
5 hospitalizations are not examples of problems with  
6 study conduct, data quality issues, and they're not  
7 extreme mishandling. They exist simply because the  
8 trial did not require investigators to report these  
9 things.

10           But there's a problem, there's a "however."  
11 It's the eight versus zero. All of these were in the  
12 rosiglitazone group, and, again, Dr. Marciniak looked  
13 at both groups with the same scrutiny. So this  
14 suggests ascertainment bias, the selective  
15 underreporting of potential cardiovascular endpoints  
16 in the rosiglitazone arm. And again, the protocol  
17 didn't protect against this. You can see how three  
18 factors could conspire to produce misleading results  
19 -- the open label design, no plan to cast a wide net  
20 in search of endpoints, and possible ascertainment  
21 bias.

22           So the eight-to-zero ratio is the issue and



1 if it's actually representative of the whole trial,  
2 then strong ascertainment bias seems likely and  
3 results couldn't be trusted.

4 But if one looked harder and were able to  
5 find events in the control group,. And, in fact, they  
6 were fairly evenly divided, then I think that would  
7 assuage our concerns.

8 There are actually two pieces of information  
9 that seem to refute the possibility of ascertainment  
10 bias. So here is the other side of the argument.

11 Here are the fractions of total deaths  
12 seemed to be cardiovascular deaths? So the red bars  
13 are the ones that count as endpoints. The percentages  
14 are dependent on two things. The clinical  
15 investigator had to categorize a death as a  
16 cardiovascular death and the CEC had to agree with  
17 their assessment.

18 If there had been some bias or motivation by  
19 the clinical investigators or CEC to categorize fewer  
20 deaths as cardiovascular in the rosi group, the net  
21 effect would have been to decrease the fraction in  
22 that group; but, in fact, they're the same.

1           Second, there's a backup slide I have, but  
2   there's an analysis that was done by Division of  
3   Scientific Investigations that I think Dr. Leibenhaut  
4   may show this afternoon, and it was requested from the  
5   sponsor to show when the CEC agrees and disagreed with  
6   the decision of the clinical investigator on the  
7   cardiovascular endpoints.

8           It turns out that the CEC agreed with the  
9   investigator in 70 percent of cases, and that was true  
10   in both treatment arms. So, again, that kind of rules  
11   against ascertainment bias and it flies in the face of  
12   the eight to zero that Dr. Marciniak found.

13          So is there unequivocal evidence of  
14   ascertainment bias? Absolutely not, but we can't rule  
15   it out. Could one find then un-adjudicated events in  
16   the con arm? Dr. Marciniak didn't, but they may be  
17   there. But to verify the extreme kind of ascertain  
18   bias, as suggested by Dr. Marciniak's review, one  
19   would actually have to audit the entire trial, which  
20   is doable, I think.

21          So my interpretation of findings. With the  
22   open label design, the possibility of ascertainment

1 bias confounds interpretation of the primary endpoint,  
2 as well as MACE.

3 I don't want to spend a lot of time on these  
4 results. They have been shown by others. But the GSK  
5 MACE estimate was .91. You see the confidence  
6 intervals .73 to 1.13 Dr. Marciniak's analysis is  
7 somewhat different, but, again, we view it as  
8 exploratory.

9 Acute MI and RECORD, GSK's findings you've  
10 seen, 2.9 versus 2.5 percent. Dr. Marciniak, again,  
11 worked independently, changed the definition and had  
12 some different results. So both analyses show an  
13 unfavorable trend in RECORD. GSK has a slight trend,  
14 Dr. Marciniak a strong trend, but the results were not  
15 statistically significant for either of the GSK  
16 analyses or for Dr. Marciniak's post-hoc re-  
17 adjudication and analysis.

18 So I would say the findings on MI seem  
19 inconclusive. Viewed in isolation, the results are  
20 not particularly reassuring, but they don't  
21 substantiate the meta-analysis of Nissen-Wolski on  
22 excess MIs.

1           For the record, there were about two-thirds  
2   as many MIs in RECORD as there were in the 42 trials  
3   in the original Nissen-Wolski meta-analysis, and that  
4   occurred in about one-fifth of the patients, the  
5   number of patients, because of so many small trials in  
6   the meta-analysis.

7           Re-adjudication of MIs in RECORD, it could  
8   be discussed. It could be an audit or a re-  
9   adjudication, or both, to try to get a better number.  
10   I'm not sure if that's the way to go, but it's  
11   plausible.

12           On all cause mortality, that's the hard  
13   endpoint here. It's objective. It's insensitive to  
14   bias. You don't need to adjudicate it. You can  
15   verify it with public records, and it's particularly  
16   germane because of the findings in the Nissen-Wolski  
17   meta-analysis, although I recognize that the findings  
18   in that meta-analysis were cardiovascular mortality.  
19   I'm talking about all cause mortality, which I like  
20   better, because it doesn't need to be adjudicated and  
21   not susceptible to bias.

22           GSK did two analyses, which they presented,

1 but I'd like to present a third analysis, and I'll  
2 show you why. This scheme was showed by GSK and the  
3 concern is here are the deaths, 6.1 versus 7.0, about  
4 2.7 to 3 percent loss to follow-up.

5 But here, down here in blue, if you can see  
6 it, you've got about 8 or 9 percent where there was no  
7 final visit, but they were said to be known alive at  
8 study end. The real question is, do you believe that.  
9 That's what the sponsor says, do you believe it or  
10 not.

11 Dr. Marciniak says, "I don't know if I  
12 believe it." It's a lot of people. It's 9 percent  
13 here, plus 3 here. It's 12 percent of people. I'm  
14 just not quite sure about the follow-up. He said the  
15 dates in the case report forms were sometimes wrong or  
16 they used the wrong date. So I'm not sure I should  
17 trust it. And that's a reasonable question.

18 But I question the reasonableness of the  
19 analyses that were shown, because they were all  
20 basically the ITT analysis. And I don't really care  
21 what happens to a patient two years after they stop a  
22 drug, unless you think a drug has some permanent

1 effect on the cardiovascular system, if it causes a  
2 valvulopathy or something, okay, then we care way down  
3 the road.

4 But otherwise, when you follow patients  
5 after they're off a drug, there's a bias towards a  
6 nil, which is not what we want. It confounds a non-  
7 inferiority study. So this is an all of all cause  
8 mortality and it's the randomized treatment phase plus  
9 30 days, and there's a pretty strong trend -- you see  
10 the log rank here -- pretty strong trend in terms of  
11 rosiglitazone preventing or not increasing all cause  
12 mortality.

13 Again, there shouldn't be any bias here.  
14 Dr. Marciniak's legitimate concern about the follow-up  
15 is negated here completely, because all these patients  
16 were known to be alive and taking the drug 30 days  
17 before the cutoff.

18 I would say there are a couple limitations  
19 of things. You lose patients in the rosiglitazone  
20 arm, not surprisingly, for a couple reasons. One,  
21 when they switch to insulin, they come off treatment;  
22 and, the other point that Dr. Marciniak made is that

1 if they develop heart failure, they may well come off  
2 treatment.

3 But within the first year or two, there's  
4 very good retention in both the rosiglitazone and  
5 control arms, and there's pretty good separation here.  
6 And compare this to the Nissen meta-analysis, where  
7 the median length of the trial was half of a year or  
8 so, this is pretty strong evidence of no adverse  
9 effect on mortality.

10 So the all cause mortality is probably the  
11 most interpretable endpoint in RECORD. The GSK  
12 analysis is very reassuring, a favorable trend on all  
13 cause mortality.

14 Dr. Marciniak's uncertainty because of  
15 patients lost to follow-up, questions about the  
16 censoring data. he questions about the censoring data  
17 censoring data, actually, have no effect or minimal  
18 effect on the results, whereas the errors in the vital  
19 status are critical. But the veracity could be  
20 checked for subjects where there is uncertainty.

21 The analysis of the randomized treatment  
22 phase I just showed you, plus 30 days, it's highly

1 interpretable, largely eliminating the concern  
2 regarding missing data. I find the results pretty  
3 reassuring.

4 Now, a key point here is if you view the  
5 almost statistically significant excess in death from  
6 cardiovascular causes reported in the Nissen-Wolski  
7 meta analysis as a hypothesis for future study, that  
8 hypothesis substantiated by the results of RECORD.

9 For regulatory purposes, RECORD is viewed as  
10 a means to test two hypotheses generated by the meta-  
11 analysis in Nissen and Wolski, the increased risk of  
12 MI, the increased cardiovascular mortality.

13 There are some questions on the validity of  
14 the MI results because of possible ascertainment bias,  
15 but no analysis of RECORD is showing us statistically  
16 significant increase in MIs. GSK's results on  
17 cardiovascular mortality favor rosiglitazone, but  
18 interpretation is in question because of possible  
19 ascertainment bias. Results for all cause mortality  
20 are largely free of bias and are reassuring.

21 RECORD's results are not as definitive as  
22 they might have been, because of a key design issue,



1 obviously, the open label design, but not casting a  
2 wide net to ascertain endpoint events possible  
3 ascertainment bias by investigators; questions  
4 regarding the mortality follow-up. But nevertheless,  
5 the results of RECORD do not substantiate the findings  
6 from the Nissen-Wolski meta-analysis on myocardial  
7 infarction and cardiovascular death.

8 I thank you for your attention.

9 DR. BURMAN: Thank you, Dr. Unger, for  
10 staying on time. We have about seven minutes for  
11 questions, if you would raise your hand.

12 Dr. Veltri?

13 DR. VELTRI: Thank you, Dr. Unger. My  
14 question relates to the fact that you feel pretty  
15 comfortable based on the total mortality and CV death,  
16 in particular. So my question is, do you find it a  
17 little unusual in a Type II diabetes population  
18 followed for, let's say, 5.5 year, that most of the  
19 deaths are non-cardiovascular?

20 Then if you look at the adjudication, about  
21 half of them seem to be unspecified etiology. And  
22 does that all sway you one way or the other on the

1 reliability? That's assuming that patients who were  
2 alive were alive, and patients who were dead were not  
3 resuscitated.

4 DR. UNGER: Well, here is the number.  
5 Forty-five percent were deemed to be cardiovascular  
6 deaths. How accurate is that? I'm not sure. It could  
7 be higher. I don't know. Does it seem surprising?  
8 Forty-five percent doesn't seem surprising.

9 I might expect it to be a bit higher, but  
10 this is a clinical trial and there is some  
11 subjectivity here in deciding it was cardiovascular or  
12 not.

13 DR. BURMAN: Dr. Proschan?

14 DR. PROSCHAN: It's actually related to that  
15 slide. So my understanding is that if you didn't  
16 know, if it was unknown cause of death, it was  
17 automatically classified as cardiovascular. And isn't  
18 that one of the problems? With so many unknown deaths  
19 that are going to be classified as cardiovascular,  
20 then it would not be surprising that you'd see this  
21 similarity in the proportions of cardiovascular deaths  
22 in the two groups.

1 DR. UNGER: Well, I agree with Dr.  
2 Marciniak. I don't like cardiovascular deaths in a  
3 trial that's open label, because there is some  
4 subjectivity. Sometimes you have to do that. But for  
5 BARI-2D, they used all cause mortality. It was an  
6 open label study. That's another approach. That  
7 wasn't the approach that was used here.

8 But, yes, you can always raise questions  
9 about the criteria that were used to call a death  
10 cardiovascular or not. But, hopefully, those are  
11 debated when the trial is planned and reasonable  
12 people agree and then you stick with the criteria.

13 DR. PROSCHAN: Could I just add one quick  
14 thing? I don't consider a p-value of .22 to be close  
15 to being significant. You sort of made a big deal out  
16 of that in the briefing material and in this slide, p-  
17 value of .22, I think it was. That doesn't seem all  
18 that close to .05.

19 DR. UNGER: This is not a big deal, I will  
20 say it. These are exploratory analyses, and so I  
21 don't care what the p-value is. It's exploratory.

22 DR. BURMAN: Dr. Nelson, did you have a

1 question?

2 DR. NELSON: No. Thank you.

3 DR. BURMAN: Anybody else? Dr. Geller?

4 DR. GELLER: I'd like to know if the other  
5 trials we're looking at today have been scrutinized to  
6 the same extent as RECORD.

7 DR. UNGER: Dr. Marciniak, did you look at  
8 the other trials? No. I really don't --

9 DR. GELLER: I don't mean necessarily by Dr.  
10 Marciniak, but by the FDA in general.

11 DR. UNGER: I'm being a little silly here.  
12 I don't think that we can really say. But Dr.  
13 Marciniak really takes an intense look at trials, and  
14 he didn't look at the diabetes trials. He's looked at  
15 many cardiovascular trials, however.

16 DR. GELLER: I'm just concerned about data  
17 quality overall.

18 DR. UNGER: I think we all are or we should  
19 be. But that's where the all cause mortality comes  
20 in.

21 That's pretty difficult to fudge.

22 DR. GELLER: Not if you report the wrong

1 follow-up date and not if you withdraw patients from  
2 the trial just prior to their death.

3 DR. UNGER: Fair enough.

4 DR. BURMAN: Dr. Moss?

5 DR. MOSS: Although there are always some  
6 errors in ascertainment and categorization for any of  
7 a variety of reasons, specifically when you have so  
8 many sites, over 360 sites, and so many centers. But  
9 with the fact that the hospitalizations were not  
10 adjudicated, it seems to me that that reduces any  
11 ability to interpret that information.

12 So in trying to separate the forest from the  
13 trees, it seems to me that the only possibility is to  
14 look at all cause mortality. And if there is some  
15 minor error in that, that can probably be handled.

16 But the only information that, it seems to  
17 me, is going to be useful for the decision-making will  
18 be all cause mortality.

19 So just any particular points that you want  
20 to further emphasize on that?

21 DR. UNGER: No. I think you said it well.

22 DR. BURMAN: Dr. Konstam?

1           DR. KONSTAM: I just want to, Ellis, come  
2 back to your conclusion about RECORD not  
3 substantiating the Nissen meta-analysis. I guess  
4 you'd say the same thing about the FDA meta-analysis.

5           But I just keep coming back to the fact that  
6 those meta-analyses are so strongly driven by placebo-  
7 controlled trials that they don't show a signal, to  
8 me, at least, from what I've seen, show a signal with  
9 reference to non-pioglitazone active control trials,  
10 which is exactly what RECORD was showing.

11           I think later on, I think we should really  
12 get into what the implication of that is vis-a-vis  
13 drugs that are currently on the market for management  
14 of diabetes, like metformin and sulfonylureas.

15           But I just sort of want to get your comment  
16 about that, because those meta-analyses are so  
17 strongly driven by placebo-controlled trials.

18           DR. UNGER: Right. Like Dr. Marciniak, I  
19 really haven't had much involvement with this. But I  
20 did have some involvement in 2007, when I was deputy  
21 office director of Office of Surveillance and  
22 Epidemiology.

1           I looked at the meta-analysis terms and I  
2   made a comment that some of the terms were so  
3   nonspecific that they were useless, terms like "chest  
4   pain," comma, "non-cardiac," "bundle branch block."

5           So I have problems with those meta-analyses  
6   on the basis of garbage in-garbage out, and the FDA  
7   used the same terms as the sponsor. And so I have  
8   some problems with them.

9           DR. BURMAN: Any other questions? One last  
10   question.

11          DR. VAN BELLE: Maybe this is a good last  
12   question. What do we know in 2010 that we did not  
13   know in 2007?

14          DR. UNGER: I'm not sure I'm the right  
15   person to answer that question. In fact, I'm sure  
16   that I'm not.

17          You have the RECORD trial. It was eagerly  
18   anticipated. It's a large outcome trial. It's not  
19   huge. You have issues of ascertainment bias. It's an  
20   open label study.

21          So what do you trust? Maybe you trust all  
22   cause mortality. Dr. Geller raises some concerns

1 about that, informative censoring. There's no clear  
2 picture here. If there were, then you guys would be  
3 back at home. So that's why you're here, to sort out  
4 all this stuff and read 1,000 pages and figure it out.

5 DR. BURMAN: Thank you. And Dr. Parks' and  
6 other information did compare 2007 to 2010, and we can  
7 talk more about that tomorrow, as well.

8 That was a good last question, but there is  
9 one other last question from Dr. Kaul.

10 DR. KAUL: Thank you, Dr. Burman. I have  
11 one comment and a quick question. That Dr. Marciniak  
12 found ascertainment and other biases should hardly  
13 come as a surprise in an open label, non-inferiority  
14 trial.

15 The key question is whether his review  
16 unearthed a deliberate attempt to stack the results in  
17 favor of rosiglitazone. In other words, was there any  
18 evidence of malfeasance involved?

19 Identifying biases is one thing, but  
20 implying malfeasance is quite different, especially  
21 when you're only sampling about 12 percent of the CRF.

22 The key question I have for Dr. Unger is



1 that DR. Marciniak's post-hoc adjudication assigned 19  
2 extra MIs to rosi and 3 to control. How many of these  
3 MIs were strictly defined by elevated biomarker  
4 criteria alone? And what was the threshold that was  
5 used and what was the clinical context? Were there  
6 spontaneous biomarker elevations or were they post-  
7 CABG and post-PCI? Because these two different types  
8 of biomarker elevations in two different settings have  
9 different clinical implications.

10 DR. UNGER: I can't tell you the details of  
11 the MIs that Dr. Marciniak added. I guess if it's  
12 important, you could pose the question to him.

13 But I agree with your question and I agree  
14 with your comment about the ascertainment bias. The  
15 question is, is there a malfeasance here. Can we  
16 trust the results or not? And maybe the only way is  
17 to audit the whole trial. I don't know. Unless you  
18 want to depend on all cause mortality, in which case,  
19 you might be able to trust what you see.

20 DR. BURMAN: Thank you. Dr. Marciniak, did  
21 you want to respond to that question?

22 DR. MARCINIAK: Well, again, all the cases

1 where I differed are in -- I believe for MIs, it's my  
2 appendix 6. So you can look through them and make an  
3 initial impression. Those are my summaries.

4 I have also offered to provide the copies of  
5 the actual CRFs that correspond to any of those  
6 decisions.

7 DR. BURMAN: That's a very good and complete  
8 answer. Thank you very much. We will now break for  
9 lunch. We will reconvene again in this room one hour  
10 from now at 1:00. Please take any personal belongings  
11 with you. The ballroom will be secured by FDA staff  
12 during the lunch break.

13 Panel members, please remember, there should  
14 be no discussion of the meeting during lunch among  
15 yourselves or other members.

16 [Whereupon, at 12:04 p.m., a lunch recess  
17 was taken.]

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A F T E R N O O N S E S S I O N

[1:01 p.m.]

DR. BURMAN: Good afternoon. We will now proceed with our presentation from the FDA presenters, Dr. Karen Mahoney and Dr. David Hoberman.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Mahoney?

DR. MAHONEY: Good afternoon, Mr. Chairman, members of the committee, ladies and gentlemen. At the time of the 2007 advisory committee meeting, questions arose regarding whether RECORD would be an interpretable trial.

Concerns were expressed regarding the lower than expected event rate at interim and some felt that the trial would be uninterpretable. Once the final study report was submitted, a primary focus of the DMEP review for the briefing document was to provide information which would allow the committee to discuss

1 whether the results of the trial are, in fact,  
2 interpretable.

3           In this talk, I will discuss some of the  
4 concerns which have been raised in the public press  
5 and identified by FDA reviewers and analyses related  
6 to these concerns. I'll discuss several topics,  
7 including trial design issues; the higher rate of  
8 statin initiation among patients in the rosiglitazone  
9 group; a subgroup analysis of patients with a baseline  
10 history of ischemic heart disease; the issue of actual  
11 time on randomized therapy and its effect on outcomes  
12 of analyses; the possibility of an effect of negative  
13 publicity in the 2007 interim analysis on trial  
14 outcomes; the rate of myocardial infarction;  
15 mortality; and, finally, what RECORD can and cannot  
16 address regarding the cardiovascular safety of  
17 rosiglitazone.

18           Much discussion has occurred regarding  
19 design limitations in RECORD; for example, the fact  
20 that it was a non-inferiority design, was open label,  
21 and used active comparators. Understanding why the  
22 trial had these design elements boils down to this.

1 It was a trial for the European Agency for the  
2 Evaluation of Medicinal Products, or EMEA, and it was  
3 not conducted under a U.S. investigational new drug  
4 application.

5 It was intended to evaluate the  
6 cardiovascular safety of rosiglitazone under the  
7 conditions of use that were approved in Europe at the  
8 time. At that time, rosiglitazone could be used in  
9 combination with metformin or sulfonylurea, which  
10 constituted essentially all non-thiazolidinedione  
11 anti-diabetic drug use in Europe.

12 At that time, concomitant use of  
13 rosiglitazone and insulin was not approved in EMEA  
14 countries. European regulators wanted to know that  
15 rosiglitazone didn't carry an unacceptably higher  
16 cardiovascular risk than metformin or sulfonylurea.

17 The resultant EMEA approved trial design was  
18 complex. On this slide, I want to point out one trial  
19 design issue that is a recurring theme, and that is  
20 the asymmetry in the trial design regarding addition  
21 of a third agent for diabetes control.

22 Patients started out on either metformin or

1    sulfonylurea monotherapy. Patients on background  
2    metformin were randomized to the addition of  
3    rosiglitazone or sulfonylurea, and patients on  
4    background sulfonylurea were randomized to the  
5    addition of either rosiglitazone or metformin.

6           Once patients progressed to the need for a  
7    third agent for control, however, patients in the  
8    rosiglitazone group couldn't get insulin and patients  
9    in the comparator group couldn't get a TZD.  
10   Therefore, rosiglitazone group patients got the other  
11   non-background oral agent and comparator group  
12   patients got insulin. Insulin was a fourth agent for  
13   the rosiglitazone group.

14           This asymmetry complicated interpretation  
15   after addition of a third agent, but the use of  
16   analyses that included only dual oral therapy avoided  
17   this issue.

18           Non-inferiority trials have limitations.  
19   Ideally, one would compare the drug to another agent,  
20   which is considered to be the gold standard for the  
21   endpoint in question; in this case, cardiovascular  
22   events. However, when the trial was initiated in 2001

1 and continuing to this day, no anti-diabetic drug has  
2 been definitively shown to decrease major  
3 cardiovascular events.

4           The non-inferiority margin must be carefully  
5 pre-specified. In RECORD, the 95 percent confidence  
6 interval upper bound of 1.2 which was selected was  
7 considered conservative for the time.

8           Multiple other factors can reduce assay  
9 sensitivity. Certain design features can ameliorate  
10 these problems somewhat, and RECORD did include  
11 blinded adjudication and pre-specified endpoint  
12 definitions.

13           There has been discussion regarding which  
14 analysis method might have been best to use, with some  
15 favoring analysis using an as treated population  
16 rather than an intention to treat population. The  
17 agency's 2010 guidance on non-inferiority trials  
18 recommends analyses using both approaches and both  
19 were performed for RECORD.

20           An open label design does introduce a  
21 potential for investigator bias in event reporting or  
22 other aspects of the trial. In the case of RECORD,



1 blinding would have been very difficult, because the  
2 EMEA approved trial design had a complex study  
3 medication algorithm. It included medications which  
4 are given with different frequency and different  
5 numbers of pills, and with dose titration. If  
6 blinding had occurred, patients would have had to take  
7 multiple pills and placebos multiple times per day;  
8 and, in order to blind insulin administration,  
9 patients potentially would have had to take dummy  
10 injections for five to seven years.

11           Also, the common occurrence of edema with  
12 TZDs may unmask treatment assignment to investigators  
13 and patients even in blinded TZD trials. Open label  
14 trials were common at the time RECORD began.

15           In trials where the treatments are open  
16 label, it is important that certain entities in the  
17 trial be blinded to treatment, such as the  
18 adjudication committee and the statistics and  
19 programming groups, and this occurred in RECORD.  
20 Overall, however, one would not be able to exclude  
21 some potential for bias in an open label trial.

22           The EMEA approved design specified a primary

1 endpoint of cardiovascular death or cardiovascular  
2 hospitalization. I believe its limitations have been  
3 thoroughly discussed and I won't reiterate. For  
4 better or worse, it was the primary endpoint. A more  
5 typical endpoint that is in use now for cardiovascular  
6 outcomes trials is the MACE, or Major Adverse  
7 Cardiovascular Events endpoint, which is a composite  
8 of cardiovascular death, myocardial infarction or  
9 stroke. That endpoint was also evaluated for RECORD.

10           Concerns have been expressed that the  
11 comparator in RECORD was an active anti-diabetic drug  
12 rather than a placebo. Recall that the EMEA wanted to  
13 know whether rosiglitazone had a different  
14 cardiovascular safety profile from the other available  
15 agents, which, at that time, were metformin and  
16 sulfonylurea.

17           From a practical standpoint, in clinical  
18 practice, when a patient is failing monotherapy, one  
19 can't add a placebo. One has to add an active drug,  
20 and, thus, this design mimicked the conditions of use  
21 in EMEA countries at the time.

22           Also, concerns about an active comparator

1 are perhaps more of a concern if the comparator is  
2 known to have an effect on the outcome of interest,  
3 and that's not the case with either metformin or  
4 sulfonylurea.

5           From this point forward, I will be  
6 presenting several slides which summarize  
7 cardiovascular events in RECORD and analyses done to  
8 address concerns regarding these outcomes.

9           The presentations from our review division  
10 and from the Office of Biostatistics used the event  
11 rates in the application and not those of Dr.  
12 Marciniak's unblinded post-hoc re-adjudication.

13           We concur with some of Dr. Marciniak's  
14 concerns about the design of the trial, but we have  
15 not been able to replicate the results of his re-  
16 adjudications. The division received his consult on  
17 the last day prior to the due date for briefing  
18 documents, and the consult's unclear case selection  
19 methods and frequent lack of source citations have  
20 been impediments to peer review.

21           Many of the cases about which he had  
22 concerns were the subject of source document reviews

1 in the audits conducted at the study sites and study  
2 coordinating centers by the Division of Scientific  
3 Investigations.

4 All of the cases which he cites in his  
5 review as examples of referral bias were inspected,  
6 and only one case was cited by the cardio-renal  
7 auditor as a case that should have been referred for  
8 adjudication.

9 Our analyses are based on event rates from  
10 contemporaneous review by a blinded, independent  
11 adjudication committee comprised of five  
12 cardiologists, a diabetologist, and a neurologist,  
13 with blinded review of each potential cardiovascular  
14 event by multiple committee members.

15 Moving on, as a basis for further  
16 discussion, I wanted to briefly review the results of  
17 the applicant's main analyses of the trial. This  
18 table presents the major endpoints in the trial and  
19 includes both the ITT analyses and the analyses done  
20 using only time on dual oral therapy.

21 As mentioned earlier, there has been  
22 discussion about whether one should use an ITT

1 approach of an on treatment approach. Use of the dual  
2 oral therapy population provides an on treatment  
3 analysis and it also avoids the issue of the  
4 asymmetric study design regarding addition of a third  
5 agent, which I just presented.

6 Perhaps of most note in the table is the  
7 next to the bottom row, in yellow, for heart failure,  
8 which occurred statistically significantly more  
9 commonly among rosiglitazone group patients than among  
10 comparator group patients.

11 This is a known effect of the  
12 thiazolidinediones and is included in a boxed warning  
13 in the labels of both rosiglitazone and pioglitazone.  
14 For other endpoints, most estimates were near or below  
15 1, including that for total mortality, in the bottom  
16 row, which had point estimates of 0.79 and 0.69 for  
17 the ITT and dual therapy populations, respectively.

18 The component of myocardial infarction had  
19 point estimates of 1.14 and 1.18 for the ITT and dual  
20 therapy populations, respectively, but neither the MI  
21 results nor any other non-heart failure endpoint  
22 results were statistically significant.

1           The upper bound for the MACE endpoint, in  
2   the second row from the top, was less than 1.2 for  
3   both analyses. And under the agency's recent  
4   cardiovascular guidance for diabetes drugs, an upper  
5   bound of less than 1.3 would meet the standard for  
6   demonstration that a drug is not associated with an  
7   unacceptably increased risk of major adverse  
8   cardiovascular events.

9           I'm going to skip this slide. It's just  
10   there to illustrate that the study design and event  
11   reporting process were complex.

12           [Laughter.]

13           DR. MAHONEY: One concern that has been  
14   expressed was that a provision in the protocol which  
15   allowed for the initiation of insulin in patients with  
16   very high hemoglobin A1Cs could have meant that some  
17   patients remained on randomized treatment for only a  
18   very short period of time, but were still counted in  
19   the ITT population.

20           You may recall that in either group, once  
21   patients started insulin, per protocol, they were no  
22   longer considered to be on randomized treatment.

1 While early initiation of insulin was a theoretical  
2 concern, it does not appear to have occurred very  
3 often.

4 This slide presents cumulative events of  
5 initiation of insulin through the trial. The X-axis  
6 displays months of study and the Y-axis depicts the  
7 cumulative percentage of patients on insulin by that  
8 point. At each time point, the yellow bar on the left  
9 is for the rosiglitazone group and the red bar to its  
10 right is for the comparator group.

11 If you look at the really short bars on the  
12 far left for all time up to six months, you'll see  
13 that only 0.4 percent of patients initiated insulin  
14 before six months of study. This was a total of 17  
15 patients across both groups. You can also see that  
16 you have to go beyond three years of study before you  
17 even begin to have 10 percent of comparator patients  
18 on insulin and beyond five years before you begin to  
19 have 10 percent of rosiglitazone patients on insulin.

20 Overall, although early insulin initiation  
21 was identified as a potential concern, further review  
22 of actual data does not suggest that it would have had

1 much effect on cardiovascular outcomes analyses.

2           One of the issues that has been most  
3 discussed is the observation that the rate of  
4 initiation of statins was higher for the rosiglitazone  
5 group patients than for the comparator group. The  
6 thiazolidinediones are known to raise LDL and statin  
7 use could be appropriate if a patient reached a  
8 threshold LDL level.

9           By the end of cardiovascular follow-up in  
10 RECORD, 50.7 percent of rosiglitazone group patients  
11 were taking statins, while 42.2 percent of comparator  
12 group patients were.

13           This difference was apparent at year 1 and  
14 from year 2 on, the difference between groups was  
15 stable, with an approximately 7 to 9 percent  
16 difference between treatment groups at each time  
17 point.

18           You've seen analyses that have shown that  
19 even if the statins convey their full expected event  
20 reduction effect, it would only have altered the point  
21 estimate for the primary endpoint by 0.02. Of note is  
22 the fact that the differential statin use did not



1 convey an LDL advantage for rosiglitazone group  
2 patients, as demonstrated in the following slides.

3           The next two slides display mean LDL over  
4 time, first, with a background metformin stratum and  
5 then for the background sulfonylurea stratum. The  
6 rosiglitazone line is red and solid, and the  
7 comparator line is blue and hashed.

8           Looking at the upper red line, you can see  
9 the typical thiazolidinedione effect of an early  
10 increase in LDL, while the comparator group is perhaps  
11 declining slightly. After about six months, LDLs are  
12 declining in both groups, but the rosiglitazone group  
13 never catches up to the comparator group. From year 2  
14 on, the difference between groups is stable and  
15 remains there throughout the study.

16           If the statin use had somehow lowered the  
17 rosiglitazone group LDL below that of the comparator  
18 group, there would have been more of a concern.  
19 However, that did not happen. The same pattern of LDL  
20 in the other stratum, with the rosiglitazone group  
21 never getting to an LDL advantage.

22           Another question that arose was whether

1 patients in the rosiglitazone group might have been  
2 getting more potent statins or higher doses of  
3 statins. Investigators were to follow their local  
4 countries' consensus guidelines regarding lipid  
5 management, and the protocol did not specify which  
6 statins or which statin doses to use.

7           In this graph, there is a bar assigned for  
8 each of the major statins and, on the far left, for  
9 the use of any statin, each at the end of year 5 of  
10 study. Bars for individual statins are ordered by  
11 LDL-lowering potency from left to right. Each bar  
12 represents a ratio of the percentage of patients in  
13 the rosiglitazone group taking that statin versus the  
14 percentage of patients in the comparator group taking  
15 that statin.

16           As you can see, the overall ratio was a  
17 little less than 1.2 for the use of any statin. Among  
18 statins, the most potent are rosuvastatin and  
19 atorvastatin, in the second and third bars. As you  
20 can see, the ratio of use for these more potent  
21 statins was essentially exactly reflective of the  
22 overall imbalance in statin initiation.

1           The bars that do show some differential use  
2   are for fluvastatin, which is a considerably less  
3   potent statin, and lovastatin, which is the oldest  
4   available statin and, also, one of the less potent.

5           Overall, it appears that investigators were  
6   not preferentially choosing the most potent statins  
7   for rosiglitazone patients.

8           The question was also examined regarding  
9   whether patients in the rosiglitazone group were  
10   getting a higher dose of statins and, in particular,  
11   of the more potent statins, than were patients in the  
12   comparator group.

13          In this graph, each bar shows the ratio of  
14   mean dose of the specified statin for patients in the  
15   rosiglitazone who were taking that statin to patients  
16   in the comparator group who were taking that statin at  
17   year 5. If you look at the far left column, for any  
18   statin, you see that the ratio of mean doses was about  
19   1.2 overall. If you look at the potent statins, you  
20   see that for rosuvastatin, it was a little above this,  
21   and for atorvastatin, it was a little below this, and  
22   there was no overall pattern across the potency range.

1           It should be noted that mean doses of any of  
2   these statins were nowhere near the maximum approved  
3   dose. For example, for rosuvastatin, for which the  
4   maximum approved dose is 40 milligrams, the mean doses  
5   were 14 and 11 milligrams for the rosiglitazone and  
6   comparator groups, respectively.

7           For atorvastatin, with a maximum approved  
8   dose of 80 milligrams, the mean doses were only 21 and  
9   19 milligrams, respectively. Therefore, the average  
10   patient who was getting a statin in the rosiglitazone  
11   group wasn't getting anywhere near the maximum  
12   approved dose of the statin.

13          Multiple baseline subgroups were examined  
14   and, for most, there was no evidence of a statistical  
15   interaction by baseline characteristic. One concern  
16   arose for patients with a prior history of ischemic  
17   heart disease. There was an interaction p-value of  
18   0.06 for this subgroup for the primary endpoint.

19          In this slide, you can see that for the  
20   primary endpoint, the point estimate among patients  
21   with a prior history of ischemic heart disease was  
22   1.26, while for those without prior IHD, it was 0.91.

1 The next logical concern would be what kind of events  
2 were occurring more commonly among patients with prior  
3 IHD.

4 Myocardial infarction was examined and it  
5 did not display a statistical interaction by baseline  
6 history of IHD, with a slightly lower point estimate  
7 among patients with prior IHD and an interaction p-  
8 value of 0.82.

9 So what kinds of events did appear to be  
10 occurring more commonly among patients with prior IHD?  
11 This table displays the numbers for the primary  
12 endpoint in multiple components, including all first  
13 events for each component.

14 Looking for where the differences like  
15 between patients with prior IHD and those without,  
16 look at the bottom two event rows. It looks as if the  
17 difference lies in heart failure events and perhaps in  
18 hospitalizations for unstable angina.

19 You can see that for heart failure, the gap  
20 between rosiglitazone and comparator widens among  
21 patients with a prior history of IHD compared to those  
22 without IHD. And below that, for prior IHD patients,

1 hospitalizations for unstable angina were more common  
2 among RSG patients than among comparator patients,  
3 while for patients without prior IHD, they were equal  
4 to slightly favoring rosiglitazone.

5           There did not appear to be much of a  
6 difference between patients with and without prior IHD  
7 for the endpoints of myocardial infarction, stroke,  
8 cardiovascular death, or all cause death.

9           There has been a lot of discussion about  
10 patient follow-up in RECORD. Regulatory agencies  
11 encourage multiple efforts to capture outcome  
12 information in clinical trials, and RECORD had  
13 multiple mechanisms. In addition to the methods  
14 used in the original main protocol, there was  
15 also a tracking sub-study to try to reenroll and  
16 capture event data from prior withdrawals, and an  
17 event sweep to encourage capture and submission  
18 of all events.

19           Also, patients who withdrew were asked  
20 to consent to checks on their survival status.  
21 For patients who didn't agree to this, attempts  
22 were made to determine vital status using public

1 records of death, which are more readily  
2 available in many European countries than in the  
3 U.S.

4 It's also important to distinguish between  
5 true dropouts and protocol-specified movement out  
6 of randomized therapy after initiation of  
7 insulin. These patients continue to have follow-  
8 up for cardiovascular events, but publicity  
9 surrounding the trial has confused this issue and  
10 perhaps made it appear that more patients were  
11 dropping out than actually did.

12 So what were the actual numbers? A total of  
13 86 percent of patients completed study to the  
14 final visit in the main study, not including the  
15 tracking sub-study, or they died. Therefore, one  
16 could say that for about 86 percent of patients,  
17 there was full cardiovascular follow-up for all  
18 endpoints.

19 When one adds patients who had a primary  
20 endpoint event before withdrawal, you get up to  
21 87 percent. With the tracking sub-study, you get  
22 up to 89 percent. When you add survival status

1 participants and vital status checks, you get up  
2 to 97 percent of patients for whom you have  
3 mortality data. There is a backup slide that  
4 displays these numbers by treatment group.

5 There's been a lot of discussion about the  
6 percentage of patients who were not taking dual  
7 oral therapy at the end of study. It's important  
8 to note that Type II diabetes is a progressive  
9 disorder and it is the norm for patients to  
10 require the addition of other medications over  
11 time and eventually to require insulin. The  
12 protocol provided for this expected requirement  
13 for additional medications.

14 Recall the asymmetry in design regarding  
15 third diabetes medications, oral for  
16 rosiglitazone, insulin for comparator, and the  
17 fact that once a patient required insulin, the  
18 protocol specified that the patient was no longer  
19 considered to be on randomized therapy, even  
20 though they continued to be followed for  
21 cardiovascular events.

22 However, the majority of cardiovascular



1 follow-up did occur on randomized therapy, 88  
2 percent for rosiglitazone, with 75 percent as  
3 dual oral therapy, and 13 percent as triple oral  
4 therapy, and 83 percent for the comparator group,  
5 which was all dual oral therapy per protocol.

6 So what did happen to patients who moved out  
7 of protocol-defined randomized treatment? As I  
8 mentioned earlier, moving out of randomized  
9 therapy didn't usually mean drop out from study.  
10 As the right-hand column shows here, 60 percent  
11 of patients completed the study to final visit or  
12 died; 31 percent of patients moved out of  
13 randomized therapy, but entered the post-  
14 randomized treatment phase and continued to have  
15 cardiovascular event follow-up, which I  
16 abbreviate here as PRT/CVO.

17 Looking at the rest of the patients who  
18 never entered the PRT/CVO phase, the question  
19 arises as to why they didn't; 4 percent had  
20 withdrawn at their own request; 2 percent had  
21 elected to move to the survival status only  
22 group, where they only agreed to contacts with

1       them or a designated representative regarding  
2       whether the patient was dead or alive; 1 percent  
3       withdrew due to adverse events; and, 1 percent  
4       was lost to follow-up at that juncture.

5               Therefore, the majority of patients who  
6       moved out of protocol-defined randomized  
7       treatment continued to have cardiovascular  
8       follow-up for events and were not true dropouts.

9               This slide is perhaps the most telling of  
10      all in the debate over the number of patients  
11      remaining on dual oral therapy and the question  
12      of which analysis population was the most  
13      appropriate to use in a non-inferiority setting.

14              These two forest plots are for the ITT  
15      population and the dual oral therapy population,  
16      which is abbreviated here as PP for per protocol,  
17      which was the sponsor's term for the dual oral  
18      therapy patient time population.

19              On the far left are the various endpoints.  
20      What's striking about these two forest plots is  
21      their marked similarity in pattern. Since the  
22      per protocol population included only time on

1 dual therapy, it had someone less time for events  
2 to accrue and, therefore, somewhat wider  
3 confidence intervals.

4 However, it should be noted that 76 percent  
5 of all primary endpoint events and 76 percent of  
6 all myocardial infarctions occurred during the  
7 period of dual oral therapy. Now, if you focus  
8 your eyes on the point estimates in the two  
9 forest plots, the pattern is indistinguishable  
10 between the two populations.

11 Although there's been a lot of debate about  
12 multiple issues related to this, in the end, the  
13 results look essentially the same.

14 An assertion has been made in a published  
15 commentary that it is mathematically implausible  
16 that rosiglitazone could have been administered  
17 during 88 percent of person years of follow-up  
18 when, at end of study, 40 percent of patients  
19 were no longer taking rosiglitazone.

20 From calculations performed by Dr. Hoberman,  
21 one can conclude that this commentary was not  
22 correct in this regard. First, for the

1 percentage of patients who were no longer taking  
2 rosiglitazone at end of follow-up, look at the  
3 top of the columns, under the words "no" and  
4 "yes." You can see that 876 out of a total of  
5 2,220 comes out to 40 percent.

6 Now, looking at the percentage of time spent  
7 on rosiglitazone, you total the bottom row, which  
8 shows the total follow-up time on rosiglitazone  
9 and you divide that by the total of the top row,  
10 which is the total of all follow-up time. Do the  
11 math, and you get 88 percent.

12 In May 2007, a highly publicized study level  
13 meta-analysis suggested a increased risk of  
14 myocardial infarction and cardiovascular death  
15 with rosiglitazone. The publication received a  
16 large amount of attention in the media and from  
17 Congress. Because of this, the RECORD  
18 investigators published an interim analysis,  
19 which did not demonstrate a significant  
20 difference between rosiglitazone and comparator  
21 at that point.

22 Questions have arisen regarding whether

1 investigator or patient behavior might have  
2 changed, either intentionally or unintentionally,  
3 after the negative publicity and interim  
4 analysis. While one can't rule this out, one can  
5 make a few observations.

6 First of all, the previously mentioned  
7 statin use difference was well established before  
8 this and the difference in treatment groups did  
9 not change after May 2007. Also, the firewall  
10 procedures for the interim analysis are described  
11 in the briefing document.

12 A separate statistics and programming team  
13 which had not previously worked on RECORD did the  
14 analysis behind an electronic firewall that was  
15 maintained for the duration of the study. The  
16 specified plans for when to end the study did not  
17 change after May 2007. Stopping criteria were in  
18 the data safety monitoring board charter and did  
19 not change after study initiation. And despite  
20 extensive negative publicity, patients did not  
21 leave the trial in large numbers.

22 There was an assertion in a published

1 commentary that the pattern of event rates  
2 reversed after the interim publication from not  
3 favoring rosiglitazone to favoring rosiglitazone.  
4 Dr. Hoberman examined event rates before and  
5 after the interim analysis.

6 This table looks at myocardial infarction  
7 rates. For both arms, the rate of onset of MI  
8 declined somewhat after the interim analysis.  
9 However, it declined to approximately the same  
10 degree in both groups and there was not a  
11 reversal in rates. That is, the rate of  
12 myocardial infarction remained numerically  
13 somewhat higher in the rosiglitazone arm than in  
14 the comparator arm.

15 There have also been concerns that the rate  
16 of myocardial infarction in RECORD was relatively  
17 low and that this might reflect under-  
18 ascertainment of MI. This is possible, but  
19 another contributing factor might be the low  
20 baseline cardiovascular risk of the population.

21 To assess this, we examined multiple trials  
22 that were conducted in patients with Type II

1 diabetes. Some trials included only patients  
2 with diabetes and some had a large subset of  
3 patients with diabetes to carve out and examine.

4 We documented multiple baseline  
5 cardiovascular risk factors in these trials to  
6 see where RECORD stood in terms of baseline risk.  
7 You have an expanded version of this table in  
8 your briefing document, which includes multiple  
9 other baseline risk factors.

10 On this slide, the left column of numbers  
11 displays the rate of myocardial infarction that  
12 occurred among patients with diabetes in these  
13 studies. And the three columns to the right  
14 display the prevalence of three major baseline  
15 characteristics which are predictive of  
16 myocardial infarction risk; prior macrovascular  
17 event or known coronary artery disease; prior  
18 history of myocardial infarction; and, history of  
19 diabetes for at least 10 years at study entry.

20 The table is ordered by the percentage of  
21 patients with a prior macrovascular event  
22 history, and you can see that RECORD falls third

1 from the bottom in a cluster of studies with  
2 similar on study MI rates.

3 You can also see that RECORD falls on the  
4 low risk in for the columns for prior MI and  
5 longstanding diabetes. Dr. Hoberman performed  
6 analyses for the rate of myocardial infarction  
7 observed in these studies versus baseline risk  
8 characteristics. Pearson correlation  
9 coefficients confirmed a strong relationship  
10 between prior macrovascular event or myocardial  
11 infarction history and study myocardial  
12 infarction rates, with correlation coefficients  
13 of greater than 0.8.

14 This scattergram illustrates this  
15 relationship. The vertical axis is the study  
16 myocardial infarction rate and the horizontal  
17 axis depicts the percentage of patients with a  
18 prior history of macrovascular or known coronary  
19 artery disease. The correlation is evident with  
20 a Pearson correlation coefficient of 0.843.

21 I've labeled the point for RECORD; thus, it  
22 appears that at least, in part, the rate of MI in



1       RECORD was reflective of the fact that it  
2       enrolled a low risk population.

3             This is an added slide, but it's not a new  
4       figure. It's from page 93 of the DMEP briefing  
5       document. I thought you might like to see the  
6       results for baseline myocardial infarction risk  
7       versus study myocardial infarction, and here is  
8       basically the same observation.

9             Another possible contributor to a low rate  
10      of myocardial infarction could be a restrictive  
11      definition of MI. RECORD utilized the MI  
12      definition that was in effect at the time from  
13      the joint European and American Cardiology  
14      Societies. That definition required elevation of  
15      cardiac biomarkers, plus either typical symptoms  
16      of cardiac ischemia or new ECG findings, which  
17      were defined.

18            The question arises regarding whether some  
19      patients who did not have biomarker results could  
20      have, in fact, had an MI if they had typical  
21      symptoms and ECG findings.

22            To look for this, all cases which had been

1       referred as potential MIs were examined and out  
2       of these, there was one case where biomarkers  
3       were missing and the patient might have had an  
4       MI.

5             This case initially had a split adjudication  
6       decision, and it's described further in the  
7       briefing document. It did not appear that lack  
8       of biomarkers frequently led to events that  
9       otherwise looked like myocardial infarctions  
10      being adjudicated as non-MIs.

11            Concern has been expressed that even though  
12      it did not appear that lack of biomarker results  
13      was a common reason for an event to be  
14      adjudicated as not an MI, there could have been  
15      other circumstances in which this could have  
16      occurred. For example, if the patients MI was  
17      fatal, then biomarkers were not obtained. If the  
18      patient died out of hospital or if MI was noted  
19      only at autopsy.

20            We do have one way of looking at these  
21      concerns, because these circumstances all have  
22      something in common. In each theoretical case,

1       there was a death. And we do know that  
2       rosiglitazone did not have a higher rate of  
3       mortality than comparator.

4           As you can see in these Kaplan-Meier curves,  
5       total mortality favored rosiglitazone throughout  
6       the study. Total mortality is useful endpoint,  
7       because ascertainment was good in RECORD, with  
8       verification of vital status for 97 percent of  
9       patients, and mortality usually does not require  
10      adjudication.

11          As you see for this ITT analysis, the point  
12      estimate was 0.79 favoring rosiglitazone, and you  
13      may recall that for the dual therapy only  
14      population, it was 0.69, with both 95 percent  
15      confidence intervals including 1.

16          To summarize some of the limitations I have  
17      discussed, RECORD had some trial design issues,  
18      which do complicate interpretation. Some design  
19      concerns, but not all, are ameliorated by the use  
20      of blinded adjudication, predefined major CV  
21      endpoints, and analyses using only the time on  
22      dual oral therapy.

1           Statin initiation was more common among  
2           rosiglitazone-treated patients, but this would  
3           probably not have much effect on analysis  
4           results.

5           Concern has been expressed regarding the  
6           relatively low rate of myocardial infarction.  
7           However, it would appear that the rate was  
8           comparable to that in studies that enrolled  
9           subjects of similar cardiovascular risk.

10          Regarding the percentage of patients who  
11          were not taking randomized therapy at end of  
12          study, this was related more to the effect of  
13          diabetes progression and initiation of insulin,  
14          which, per protocol, moved patients out of  
15          randomized treatment due to the EMEA proscription  
16          against co-administration of TZDs with insulin  
17          than it was to actual dropouts.

18          Analyses using time on dual oral therapy  
19          avoid this problem and had highly similar  
20          results. There was a large amount of negative  
21          publicity about rosiglitazone in 2007 and one  
22          cannot entirely rule out an effect on

1 investigator or patient behavior after that.

2       However, the previously mentioned statin use  
3 differences were established well before 2007.  
4 There was no reversal in event rates, and patient  
5 retention was reasonable.

6       These limitations are important, but RECORD  
7 might also have some usefulness, particularly in  
8 comparison to some other data sources. It is the  
9 only source we have of new randomized controlled  
10 cardiovascular outcomes data since the 2007  
11 advisory committee meeting.

12       It had a largest patient year exposure, over  
13 24,000 patient years, with threefold greater  
14 rosiglitazone exposure than all trials in the  
15 2007 meta-analysis combined.

16       Since it was a single trial, randomization  
17 was preserved and RECORD did not have some of the  
18 issues which limit other data sources; for  
19 example, statistical heterogeneity among trials  
20 included in the meta-analysis and unmeasured  
21 confounders for observational studies.

22       It used blinded adjudication and included

1       hard cardiovascular endpoints. Its use of an  
2       active comparator, while also discussed as a  
3       limitation, mimics a common real world clinical  
4       choice. Subgroup analyses were generally  
5       consistent with the overall analysis. Analyses  
6       including only time on dual oral therapy avoided  
7       many of the concerns regarding trial design and  
8       were highly consistent with the ITT analyses.

9               For the MACE endpoint, the upper bound of  
10       the 95 percent confidence intervals would have  
11       met the agency's standard for demonstration that  
12       a diabetes drug is not associated with an  
13       unacceptable increased risk of major adverse  
14       cardiovascular events.

15              I'd also like to point out that Dr. Nissen's  
16       earlier statement that the original registration  
17       trials showed an increased risk of cardiovascular  
18       events for rosiglitazone is incorrect. The  
19       hazard ratio actually for MACE was 0.92, and I  
20       can download a slide that shows a forest plot for  
21       all the registration trials, if the committee is  
22       interested.

1           Finally, total mortality, which generally  
2           does not require adjudication and is associated  
3           with fewer problems with ascertainment, favored  
4           rosiglitazone throughout the study.

5           I think most scientists involved with the  
6           review of RECORD would agree that it cannot  
7           answer every single question one might have about  
8           the cardiovascular safety of rosiglitazone. It  
9           perhaps did further address the observation from  
10          the 2007 meta-analysis that rosiglitazone did not  
11          appear to exhibit a higher risk of myocardial  
12          ischemic events than did other popular and  
13          commonly used anti-diabetic medications.

14          The controls used in the meta-analysis  
15          studies were the same as those in RECORD; namely,  
16          metformin and sulfonylurea. RECORD is probably a  
17          reasonably good source of information regarding  
18          total mortality risk of rosiglitazone, which, as  
19          others have mentioned, correlates with  
20          cardiovascular events in patients with diabetes.

21          Most people consider total mortality to be a  
22          very important endpoint, which is objective, with

1 little potential for bias and particularly useful  
2 in open label trials. RECORD cannot answer the  
3 question about whether there is a real difference  
4 between rosiglitazone and pioglitazone, because  
5 pioglitazone was not a comparator.

6 This is an added slide, but it's not a new  
7 figure. It is from page 19 of Dr. Graham's  
8 briefing document. It's been suggested that  
9 perhaps a randomized control cardiovascular  
10 outcomes trial was not necessary to address the  
11 question of cardiovascular safety of  
12 rosiglitazone and that perhaps new observational  
13 studies could suffice.

14 However, the ability to obtain interpretable  
15 new information from observational studies has a  
16 major limitation that is illustrated in this  
17 figure. This slide presents the entry of  
18 patients into the cohorts for the Medicare study.  
19 The X-axis is the time period of study from July  
20 2006 to May 2009. The Y-axis is the number of  
21 patients that are entering each cohort.

22 You can see that from July 2006 until May



1       2007, patients are initiating pioglitazone and  
2       rosiglitazone at essentially exactly the same  
3       rate. In May 2007, after that large amount of  
4       negative publicity regarding rosiglitazone, a  
5       dramatic change occurs in this pattern. New  
6       patient initiation in the pioglitazone group  
7       continues at essentially the same rate.

8             The rate of increase in patients in the  
9       rosiglitazone group essentially stops completely.  
10      Now, the pioglitazone group is being continually  
11      refreshed with patients who are at an entry level  
12      of cardiovascular risk. But the rosiglitazone is  
13      not being refreshed.

14            The rosiglitazone patients are continuing to  
15      age and their diabetes is continuing to progress;  
16      and, along with progression of diabetes comes a  
17      natural accrual of cardiovascular risk.

18            In a sense, after May 2007, the pioglitazone  
19      group remains forever young in terms of  
20      cardiovascular risk, but the rosiglitazone group  
21      continues to age.

22            Another possible analogy would be that up

1       until May 2007, both groups were running a relay  
2       race, with new, fresh runners continually taking  
3       up the baton. After May 2007, the pioglitazone  
4       group gets to keep on running it as a relay race,  
5       but the rosiglitazone group doesn't get to. The  
6       same tired runners have to go the distance from  
7       that point on.

8               A difference between rosiglitazone and  
9       pioglitazone for cardiovascular outcomes could be  
10      a result of different cardiovascular risk over  
11      time in the compared populations.

12             Many people contributed to the review of  
13      RECORD, but I would particularly like to  
14      acknowledge the individuals on this slide.

15             I'd also like to thank the committee, and I  
16      look forward to your discussions. Dr. Hoberman  
17      of Biostatistics will now present, and we will  
18      then take questions together.

19             DR. HOBERMAN: Good afternoon. I'm going to  
20      just make two brief comments about the trial's  
21      capacity to reach two statistical benchmarks.

22             The first is the power of RECORD, and the

1 second is the trial's capacity to show  
2 statistically significant difference between the  
3 control and Avandia groups, showing that Avandia  
4 is actually worse; that is, the capacity to show  
5 that the lower bound of a 95 percent confidence  
6 interval actually excludes the number 1.0.

7 First, RECORD's power. It was planned for a  
8 99 percent chance of ruling out a hazard ratio of  
9 1.2, if the true hazard ratio was equal to 1.  
10 This assumed an 11 percent yearly rate of primary  
11 composite endpoint.

12 For example, the expected number of events  
13 around 2,000 after five years of follow-up on  
14 each subject would yield roughly 98 percent  
15 power. Those are my calculations, not the  
16 sponsor's.

17 Now, the power falls to about 60 percent to  
18 rule out 1.2 due to the roughly 3 percent yearly  
19 rate that actually occurred that yielded 644  
20 events. This is not the standard of 80 percent  
21 usually found in clinical trials, but it's also  
22 not reflective of recent years' predictions of

1 the trial's failure.

2 Also, the 644 events provides a 90 percent  
3 chance to rule out 1.3, the current U.S. non-  
4 inferiority margin in the diabetes guideline.

5 All told, despite the initial overestimates  
6 of events, the trial had substantial power to  
7 reach its stated goal.

8 Now, for the second topic involving MIs, we  
9 could have a big discussion of possible powers.  
10 I want to sidestep powers, because they involve  
11 discussions of possible states of nature; that  
12 is, true hazard ratios, and I've tried to short-  
13 circuit that by comparing the RECORD trial to a  
14 database that, in fact, did produce a lower bound  
15 greater than 1.0, and that is Dr. Nissen's  
16 original 2007 meta-analysis.

17 Now, in this slide, what I've done is state  
18 the number of MIs that occurred in that meta-  
19 analysis, 158, with a hazard ratio of 1.43. And  
20 one can use a simple formula involving the  
21 observed hazard ratio and the number of events to  
22 construct the entire family of possible 95

1       percent confidence intervals.

2               So, for instance, in the meta-analysis, the  
3       confidence interval can be expressed as -- the  
4       lower bound would be the observed hazard ratio  
5       times .73, and the upper bound of the hazard  
6       ratio times 1.38, or just taking the HR out of  
7       parentheses. And it turns out that .73 and 1.38  
8       happen to be reciprocals of each other. The  
9       number in parentheses depends only on the number  
10      of events.

11              Now, look at RECORD. According to the  
12      sponsor's analysis, there are 125 MIs. Its  
13      hazard ratio is 1.14. Analogously, we can look  
14      at the confidence interval family for the RECORD  
15      trial, and note the similarity of the respective  
16      numbers for the meta-analysis in RECORD; that is,  
17      the 138 versus the 144 and the .73 and the .71.

18              Examination of the numbers in parentheses  
19      shows that the meta-analysis needed a hazard  
20      ratio greater than 1.38 to actually rule out a  
21      lower bound of 1.0. Analogously, RECORD needed  
22      greater than 1.44. That comes from simply

1 examining those numbers in parentheses.

2 Recognizing the similar information in each  
3 dataset and the observed hazard ratio of 1.14 in  
4 RECORD suggests that not ruling out 1.0 in RECORD  
5 was due to a weaker signal than that in the meta-  
6 analysis, not a deficient amount of information.

7 That concludes my remarks, and I will join  
8 Dr. Mahoney.

9 DR. BURMAN: Thank you very much. The floor  
10 is now open for questions from 1:40 to 2:00. Are  
11 you going to stay there, Dr. Mahoney?

12 DR. MAHONEY: I can. I can be wherever.

13 DR. BURMAN: Dr. Hoberman, you're going to  
14 join her there.

15 DR. HOBERMAN: Yes.

16 DR. BURMAN: Thank you. Questions from the  
17 committee? Dr. Fleming first.

18 DR. FLEMING: Since time is short, could I  
19 just flash through the slides? If you could  
20 follow the slides with me.

21 Number 23. So the issue here, as we're  
22 finding slide 23, was 40 percent of people had no

1 longer been taking rosiglitazone at the end, but,  
2 allegedly, 88 percent of the time, people were  
3 still on rosiglitazone.

4 The confusing thing here, 876 is 60 percent  
5 of 1,344; 60 percent of 8,176 is 5,350. So why  
6 weren't there 5,350 potential person years, in  
7 which case, now, it would be 80 percent, not 88,  
8 which is what I would expect if there was uniform  
9 withdrawal.

10 But let me keep going, because these are all  
11 very quick. Slide 25, we're putting forward here  
12 an issue that might explain why the unblinding  
13 may not have been problematic.

14 It's extraordinary difficult to go back and  
15 establish that unblinding didn't, in fact, induce  
16 bias. In fact, there is a 40 percent relative  
17 reduction in the events after IA, according to  
18 this calculation. Maybe there should have been a  
19 somewhat reduction, but should it have been 40  
20 percent.

21 Slide 27, is the rate lower than expected?  
22 According to this figure, it's about 30 percent

1 lower than expected, which is not inconsistent  
2 with Dr. Marciniak's types of analyses. That  
3 could be due to random variation, but I can't  
4 tell.

5 Then in slide number 3, for Dr. Hoberman,  
6 was RECORD powered? Yes, I think it was powered  
7 for the primary endpoint. Many of us would  
8 think, though, the primary endpoint,  
9 cardiovascular hospitalization, is insensitive to  
10 where the signal is. Is it properly powered for  
11 what we care about?

12 So you give slides 4 and 5. Slide 5, you're  
13 concluding it is properly powered, because, in  
14 fact, if you're saying a 1.43 or 1.44 is what the  
15 Nissen analysis showed and if you saw 1.44, you'd  
16 exclude 1. Well, then it's only 50 percent  
17 powered.

18 So in essence -- go back to the previous  
19 slide -- what you're saying here on RECORD, with  
20 120 events, and you're correct, is if you observe  
21 a 1.44 relative risk, you'll exclude zero or  
22 you'll exclude 1. That is correct.



1           If truth is 1.43 or 1.44, you only have 50  
2       percent chance of observing that, or better, to  
3       exclude 1, plus the concerns that have been  
4       raised of are you diluting with irregularities  
5       here toward seeing estimates that are less than  
6       truth.

7           So it's not clear how you're concluding that  
8       RECORD is properly powered to address the 1.43.

9           DR. HOBERMAN: You raise a lot of issues,  
10      but I think that they're kind of conflated with  
11      each other. I deliberately did not want to talk  
12      about the power to find an MI result, and the  
13      reason I didn't is precisely the kind of  
14      calculations that you've made about what the  
15      power might have been.

16          Then you said, how can I then say that  
17      RECORD was adequately powered. There are two  
18      totally different approaches that I used.

19          DR. FLEMING: So let's go to your last  
20      sentence, then, David. Go to your last sentence  
21      on slide 5.

22          DR. HOBERMAN: Yes. That had to do with the

1 primary endpoint and it had nothing to do with  
2 whether the primary endpoint was properly --

3 DR. FLEMING: Although the title says "MI  
4 continued."

5 DR. HOBERMAN: That was from the --

6 DR. FLEMING: So go back to the previous  
7 slide. So the previous slide relates to power  
8 for MI.

9 DR. HOBERMAN: No. It does not relate to  
10 power. That's exactly what I decided not to do.

11 DR. FLEMING: But if RECORD is 120 MIs, then  
12 you are correct that what would be ruling out  
13 with quality is 1.44 for MI.

14 DR. HOBERMAN: Yes. That the power to  
15 exclude, if, for instance, it was 1.2, for  
16 instance, I actually computed that. It's, I  
17 think, about 16 percent. But that's exactly why  
18 I didn't want to get into power, because I didn't  
19 want to go through all these scenarios that could  
20 have happened.

21 I simply wanted to say, look, Dr. Nissen's  
22 meta-analysis actually did show a significant

1 difference with the equivalent amount of  
2 information that he accrued. And what that does  
3 is avoid the whole issue of having to calculate  
4 powers and wondering whether a long shot horse  
5 should have come in when it, in fact, did.

6 My point about the primary endpoint is that  
7 it had nothing to do with whether it was a  
8 properly primary endpoint. It was simply a  
9 question of bean counting and pointing out that,  
10 for better or for worse, the 644 events had  
11 adequate power, I think, by anybody's reason. If  
12 the power is 60 percent, it's not too bad.

13 DR. FLEMING: Let me give two simple  
14 statements, two simple mathematical statements.  
15 If you have 120 MIs, your point estimate has to  
16 be 1.44 or higher to rule out equality, which is  
17 exactly what I think you're correctly showing  
18 here.

19 Next slide, next slide, bottom line,  
20 sentence says if you observe a 1.14 in RECORD,  
21 suggesting that you're not ruling out 1.0, in  
22 RECORD, was due to a weaker signal than that in

1 the meta-analysis, not to a deficient amount of  
2 information.

3 DR. HOBERMAN: Yes.

4 DR. FLEMING: If the meta-analysis -- I  
5 don't know if it's true. If it's correct, if  
6 it's 1.43, then it's entirely within random  
7 variability to observe a 1.14. And the fact that  
8 you didn't observe a 1.43 or better does, in  
9 fact, reflect a significant random chance.

10 You're only 50 percent powered when truth is  
11 1.43 to see 1.43 or better. So the bottom line  
12 conclusion from this is these calculations do not  
13 indicate that that 1.14 is, in fact, consistent  
14 with a weaker signal and inconsistent with a  
15 truth of 1.44.

16 DR. HOBERMAN: Well, I was hoping we  
17 wouldn't get into the business about the 1.14,  
18 because I only did this in order to try to  
19 illustrate that the RECORD trial had adequate  
20 information to show an MI difference if you  
21 compared it to the meta-analysis.

22 DR. FLEMING: For the reasons I have just

1       given, statistically, unless you consider 50  
2       percent power adequate power, furthermore, unless  
3       you consider that there's integrity and not  
4       attenuation to the null, what the quality of the  
5       study conduct, for those two reasons, I have  
6       serious concerns with your conclusion.

7           DR. HOBERMAN:   Okay.   I guess we'll just  
8       have to leave it, because I did not want to talk  
9       about power, and I think discussions of power can  
10      become subjective and I think we'll just have to  
11      leave it.

12          DR. FLEMING:   But your final conclusion is a  
13      power type of conclusion.   It is.   You raised the  
14      issue.

15          DR. BURMAN:    I think we'll move on.   This is  
16      a very sophisticated discussion that we will have  
17      more discussion tomorrow.

18          Dr. Konstam?

19          DR. KONSTAM:   This is to Dr. Mahoney.  
20      First, I just really enjoyed your presentation.  
21      I thought it was a terrific set of analyses and  
22      review of some very difficult issues.

1           I just wondered whether anything that you  
2       did or looked at can directly address or assuage  
3       the principal concern that Dr. Marciniak raised;  
4       that is, that a major degree of ascertainment  
5       bias may have had a major adverse effect on  
6       credibility of endpoints.

7           Is there anything that you showed us that  
8       sort of cold dissuade us from that?

9           DR. MAHONEY: Well, you're going to hear a  
10      little bit more about what the Division of  
11      Scientific Investigations did at their audit, but  
12      all of those cases that were cited as examples of  
13      referral bias were inspected.

14           When you look at those cases, when you  
15      actually look at all of the information and not  
16      just one or two pages of a case report form, you  
17      can understand why the investigator made the  
18      choice about whether to refer the event for  
19      adjudication nor not. And that's the bottom  
20      line.

21           DR. BURMAN: Thank you

22           Dr. Proschan?

1 DR. PROSCHAN: I wanted to try and settle  
2 the statin issue. The calculation that's been done to  
3 evaluate how much of an effect that might have had  
4 seems like it's oversimplified, because it seems to  
5 assume that the people who got statins are sort of  
6 like a random sample rather than the fact that they  
7 are the ones who are most likely to have had an event  
8 if they had not gotten statins.

9 So it seems like that .02 estimate is just  
10 not correct if you take into account the fact that the  
11 statin users are going to be the ones who are at  
12 higher risk of having the event.

13 The other issue I have is it was mentioned  
14 that, well, there was no benefit in terms of LDL in  
15 the rosiglitazone group, and so that should make us  
16 all feel better. But at the same time, the fact that  
17 they got statins might have prevented the signal from  
18 being a lot worse.

19 It could have been a lot worse if they  
20 hadn't gotten statins, and I'm not sure exactly how I  
21 should feel about that. One way of looking at it, you  
22 could say, well, part of any clinical trial is you

1 don't necessarily know that the concomitant medication  
2 used is going to be the same in the two arms.

3 But nonetheless, I don't feel particularly  
4 comforted by the fact that the rosiglitazone group  
5 didn't end up with lower LDL, given the fact that this  
6 drug increases LDL.

7 DR. MAHONEY: I understand. I just want to  
8 make one comment about the use of the population. In  
9 statin trials, for the ones that were used for the  
10 calculations that showed the 25 percent risk  
11 reduction, that assumption, those are also all  
12 patients who had an indication for a statin, just as  
13 these patients presumably were.

14 DR. PROSCHAN: Right. But that doesn't get  
15 to the point that I made, because that calculation of  
16 .02 does not take into account that those patients are  
17 higher.

18 I actually have some slides on this point,  
19 but I was told that I can't present them, because I  
20 was too late. I made them last night, unfortunately.  
21 So they can't be available to put on the Website in  
22 time, but they couldn't be.



1           That doesn't get around my point that it has  
2 a potential to have a lot more than just a .02 effect.

3           DR. HOBERMAN: I anticipated that objection  
4 and in my review, I have a calculation that tries to  
5 get at that. Are you familiar with it?

6           Could I have my one backup slide, please?  
7 Instead of comparing the treatment groups, what I  
8 attempted to do was to actually divide the group into  
9 two groups, those that had events and non-events.

10           So the idea was to compare over time the  
11 means of those who had events and those who did not  
12 have events. Obviously, it has plenty of caveats, but  
13 the striking thing about the slide is that those who  
14 did have events had virtually the same LDLs over time  
15 as those who did not have events, and, in some cases,  
16 even lower.

17           If you assume that achievement of a  
18 particular LDL level or mean LDL level is pretty  
19 insensitive to your baseline risk, then that seems to  
20 make some sense, because if the distributions are the  
21 same -- of LDL -- are the same over time, then that  
22 would suggest that getting an event is independent of

1 LDL.

2           So that in this study, there is little  
3 evidence of an association of LDL with events. And so  
4 it might not turn out to be a problem in the end.

5           DR. CAPUZZI: I have a comment about --

6           DR. BURMAN: Please, we'll get to you in one  
7 second. We have six minutes and I think we have Dr.  
8 Weide first, and then Dr. Capuzzi.

9           DR. WEIDE: This is just a follow-up with  
10 the statins. Looking at the LDLs that we have, I  
11 would say the means are all above goal. One of the  
12 things that struck me was the low percentage of  
13 statins, when, clinically, I would have expected a  
14 higher percentage. And some people would argue that it  
15 doesn't even matter what your LDL is, 100 percent of  
16 diabetics ought to be on a statin and we ought to put  
17 it in the water for them.

18           So I'm not sure -- some of the clinicians  
19 are going to have made decisions based on other than  
20 an LDL and if the percentages were about the same, I'm  
21 just not sure that the statins had a significant  
22 impact and the differences between the two groups.

1 DR. BURMAN: Thank you. Dr. Capuzzi,  
2 please.

3 DR. CAPUZZI: I just wanted to make a  
4 comment about the LDL cholesterol. It's pretty clear  
5 that just looking at the LDL cholesterol level is not  
6 sufficient to indicated risk.

7 The work of Ron Krauss and the people at  
8 LipoScience really show that the LDL particle  
9 concentration is likely to be a much more important  
10 indicator. There are issues that fish oil may raise  
11 LDL cholesterol, but it really doesn't raise the  
12 concentration of LDL particles. It's more buoyant.  
13 So you can't make a comment like that definitively.

14 Furthermore, the same applies to HDL. There  
15 are all forms of HDL called HDL particles that are  
16 problematic. Take the situation with torcetrapib,  
17 which raised HDL cholesterol and killed people. But  
18 that's across the board.

19 The HDL cholesterol is a very small part of  
20 the HDL molecule and it's the HDL subspecies. So you  
21 have to know more than just the HDL cholesterol and  
22 the LDL cholesterol, per se, to have any kind of

1 assurance about risk.

2 DR. BURMAN: Thank you. If I could ask, Dr.  
3 Mahoney, is anything known about the LDL particle size  
4 with any of these agents?

5 DR. MAHONEY: I don't have that information,  
6 although other kinds of lipid markers were measured.

7 DR. BURMAN: Does anyone on the panel know?  
8 Yes, please.

9 DR. STEWART: We did actually know what  
10 happens to the lipid particles. So we do know there's  
11 a change from small-dense to light-buoyant, and we do  
12 know the increase is less than predicted from the LDL.

13 DR. BURMAN: And for those who aren't  
14 endocrinologists or don't know, a low LDL is mean and  
15 lean. Small particles are mean and lean. So the  
16 higher they are, the less atherogenic they are, in  
17 theory.

18 DR. STEWART: So apoB is the protein that  
19 LDL circulates with. So we can actually look at  
20 particle number, as well. And we know the increase in  
21 LDL is driven more by the change in size of particles  
22 and the number of particles.

1           DR. BURMAN: Thank you. Any last questions?  
2   Then thank you very much. Let's move on then. We  
3   will now proceed with our presentation from the FDA  
4   presenter, Dr. Susan Leibenhaut.

5           DR. LEIBENHAUT: Good afternoon. My name is  
6   Susan Leibenhaut, and I am a medical officer in the  
7   Division of Scientific Investigations, Office of  
8   Compliance. I will review the FDA inspections for the  
9   RECORD trial.

10           First, I will review the background for  
11   inspections, including data flow in the trial; next,  
12   the inspections for the three clinical sites; then,  
13   the sponsor and CRO inspections, followed by summary  
14   of findings, conclusions, and, importantly, the  
15   limitations of the inspections.

16           The purpose of an inspection, sometimes  
17   referred to as an audit, is to detect violations  
18   concerning the 21 CFR sections listed on this slide  
19   that cover aspects of the clinical trial relating to  
20   data integrity and human research subject protection.

21           These regulations refer to how closely  
22   investigators abide by the protocol designed by the

1 sponsor and how closely the sponsor monitors the  
2 trial.

3           Inspections may also inform the review  
4 division concerning other aspects of clinical trial  
5 conduct that are not necessarily violations, but may  
6 be important to the review of an NDA.

7           For the RECORD trial, issues identified for  
8 inspection included errors or omissions in endpoint  
9 referral or adjudication; evidence that bias was  
10 introduced due to open label design; trial conduct  
11 issues concerning complex reporting requirements for  
12 endpoints and adverse events; changes in study conduct  
13 due to the unplanned analysis; and, of course,  
14 routinely, we investigate for fraud and violations.

15           This slide lists the procedures for event  
16 reporting by the clinical investigator for both  
17 serious adverse event and endpoint reporting for this  
18 trial. Documentation begins with the source document,  
19 which is the record of the subjects' office visit  
20 maintained by the clinical trial site.

21           In this trial, when a subject reported a  
22 hospitalization or emergency room visit, this was to

1 be recorded on three forms; the medical utilization  
2 case report form; a serious adverse event case report  
3 form; and, an event report fax cover sheet.

4 In addition, if a serious adverse event was  
5 considered as a potential cardiovascular  
6 hospitalization or was death, it was to be reported  
7 as a potential endpoint using a hospitalization  
8 endpoint form and the endpoint forms specific to the  
9 endpoints being reported.

10 This process was complex, as shown on this  
11 slide. This is the process, in diagrammatic form,  
12 taken from the clinical investigator's manual.

13 This slide states verbally the data flow  
14 depicted on this slide. This shows diagrammatically  
15 the flow of the fax event cover sheet, the SAE case  
16 report forms, the endpoint forms and supporting  
17 documents, and the other case report form pages from  
18 the clinical site.

19 The clinical investigator faxed these forms  
20 to the medical monitor, referred to in this trial as  
21 the clinical research associate, or CRA. The CRA  
22 forwarded the data to the appropriate data processing

1 center.

2 SAE case report forms were sent to GSK  
3 pharmacovigilance. Endpoint case report forms and  
4 documentation were sent to CEVA, the Clinical Event  
5 Validation and Adjudication Service that served as the  
6 administrative support for the clinical event  
7 committee. All other case report form data were sent  
8 to Quintiles Data Management.

9 All these entities were unblinded. It is  
10 obvious that site personnel and CRAs could readily  
11 know treatment assignment, because they were at the  
12 clinical sites in an unblinded study.

13 For GSK pharmacovigilance, the treatment  
14 assignment was written on the fax cover sheet used to  
15 send the SAE reports to GSK pharmacovigilance. The  
16 subject file folders at CEVA were not labeled as to  
17 treatment assignment, but it was the task of CEVA  
18 staff to redact any diabetes-lowering medication from  
19 the dossiers sent to the CEC. So the CEVA staff were  
20 aware of treatment assignment.

21 FDA conducted a total of five inspections  
22 for this NDA, including three clinical sites, the



1 sponsor, and the CRO. The three clinical sites were  
2 chosen on the basis of high enrollment relative to the  
3 other sites and represented the three types of sites  
4 participating in the trial, a tertiary referral  
5 center, a primary care site, and a dedicated clinical  
6 trial research site.

7           The number of subjects enrolled at each site  
8 is listed on this slide. The clinical sites were  
9 inspected in February and March, relatively early in  
10 the review cycle, and the sponsor/CRO inspections were  
11 conducted in May.

12           The three sites were less than 1 percent of  
13 the total number of sites participating in the trial  
14 and the 188 subjects enrolled at the sites represented  
15 about 4 percent of the total of subjects enrolled in  
16 RECORD. This is not unusual for inspections of large  
17 trials with multiple clinical sites.

18           Because the time allotted for a foreign  
19 inspection is brief and looking for adverse events is  
20 challenging and time-consuming, we prepared for the  
21 inspections by identifying subjects that had a higher  
22 chance of having unreported adverse events.

1           These subjects had at least one of three  
2 characteristics -- referral from the cardio-renal  
3 division, endpoint initially refereed and then  
4 withdrawn from consideration for adjudication, or  
5 subjects with an SAE or AE listing, such as angina or  
6 chest pain, that had not had any endpoints referred  
7 for adjudication.

8           FDA investigators from the Office of  
9 Regulatory Affairs targeted these subject records for  
10 their review. In other words, I provided the  
11 instructions to the investigator in the field that  
12 went out to do these inspections.

13           A total of 60 subjects' records were  
14 inspected at the three sites, including 15 of the 21  
15 subject records identified as potential problems by  
16 the cardio-renal division, the subjects chosen by DSI,  
17 and subjects also chosen randomly by the FDA/OR  
18 investigator.

19           We observed that the study was generally  
20 conducted according to the protocol and that no major  
21 issues were identified concerning data integrity. At  
22 one site, a potential endpoint of heart insufficiency

1 was referred for adjudication as a result of the SAE  
2 reconciliation process in which Quintiles reviewed  
3 serious adverse event reports to search for unreported  
4 events. This is one of the subjects referred to in  
5 Dr. Unger's slides as the CHF.

6 This endpoint was then withdrawn from  
7 consideration, and the reason for the withdrawal by  
8 the investigator is not clear and is not documented by  
9 the investigator.

10 But in reviewing the case report forms and  
11 the documents, I can presume to reconstruct what  
12 occurs. It appears that because the clinical  
13 investigator filled out a CHF endpoint form, but did  
14 not fill out the HAE endpoint form, the medical  
15 monitor, the CRA, thought that the subject had not  
16 been hospitalized.

17 The clinical investigator then themselves  
18 crossed out the signed endpoint form with the notation  
19 "print in error, no endpoint," to withdraw the  
20 endpoint from referral for adjudication. This is  
21 considered by FDA to be a protocol violation by the  
22 investigator and it's the only instance of a protocol

1 violation concerning endpoints that we found at the  
2 three clinical sites.

3 I give you this example as kind of n on-the-  
4 ground sort of feeling for how the trial was run this  
5 way. There was a lot of paper involved in this NDA,  
6 in this trial.

7 Inspections of GSK and Quintiles were  
8 conducted according to the sponsor inspection  
9 guidelines and covered the clinical trial master file.  
10 For this inspection, we considered the following to be  
11 the most important items -- contracts between GSK and  
12 Quintiles, monitoring reports, and data management and  
13 data flow, including the processes for adjudication.

14 FDA also inspected the clinical trial  
15 governance, including review of charters and meeting  
16 minutes of the steering committee, DSMB, and clinical  
17 endpoint committee.

18 In addition, we targeted subject records  
19 identified by cardio-renal with clinical issues or a  
20 longer time to adjudication.

21 Sponsor responsibilities overseen by GSK  
22 included data collection for pharmacovigilance,

1 choosing and contracting directly with the members of  
2 the steering committee, DSMB and clinical endpoint  
3 committee, and study site monitoring for Sweden.

4           Although the sponsor's original intent was  
5 to have Quintiles perform all statistical analysis for  
6 this trial, GSK statisticians performed the interim CV  
7 analysis in 2007 and the final analysis for the study.

8           Sponsor responsibilities overseen by  
9 Quintiles included processing of endpoints and  
10 providing administrative support to the clinical  
11 endpoint committee -- that's the CEVA that I referred  
12 to earlier -- monitoring of clinical trials, except  
13 Sweden, data management, except the pharmacovigilance,  
14 and the statistical analysis for reports to the DSMB  
15 and the interim analyses that were pre-specified in  
16 the protocol.

17           Thirty subjects' records chosen by the  
18 cardio-renal division were targeted for review based  
19 on issues concerning referral for adjudication or  
20 occurrence of late adjudication.

21           Forms FDA-483 were issued to both GSK and  
22 Quintiles based on preliminary findings concerning the

1 adequacy of the administration processes. Please note  
2 that the citations are preliminary findings issued to  
3 an inspected party.

4 For the inspections of GSK, we issued the  
5 form FDA-483 for a total of 13 instances, citing 21  
6 CFR 312-120 that refers to good clinical practice for  
7 studies conducted outside the U.S.

8 Six citations concerned timely processing  
9 and adjudication of events; four concerned lack of  
10 adequate documentation related to adjudication; one  
11 concerned lack of referral of a potential endpoint;  
12 and, the last citation concerned adequacy of  
13 adjudication of a events in could temporal  
14 relationship.

15 Of the 13 instances identified at GSK,  
16 review of additional documentation at Quintiles was  
17 able to resolve nine of the issues. An example is  
18 described on this slide is described on this slide in  
19 which a subject hospitalized for a GI bleed  
20 experienced chest pain and died.

21 FDA was concerned that the CDC did not have  
22 the appropriate documentation, because the

1 investigator deemed the event an MI, but it was  
2 adjudicated as a non-CV endpoint. Inspection at  
3 Quintiles provided documentation of ECG and a hospital  
4 discharge summary that did not support MI.

5 Quintiles was also cited for four of 13  
6 issues cited at GSK. There were two instances in  
7 which the CDC did not adjudicate events in a timely  
8 manner. Delayed adjudication, although not abiding by  
9 the protocol, did not impact data integrity, as the  
10 events were eventually adjudicated.

11 There is one instance in which Quintiles did  
12 not ensure the documentation critical for adjudication  
13 was submitted to the CEC. In this case, a discharge  
14 summary was not available to definitively adjudicate  
15 this CV event as a stroke.

16 There was one instance in which two events  
17 occurred in close temporal relationship in the same  
18 subject. One of the events was not always followed up  
19 and adjudicated properly.

20 This occurred when a subject was  
21 hospitalized for ventricular arrhythmia and died. The  
22 hospital discharge summary was not found. So the

1 death was adjudicated as unknown.

2           From our inspections of the RECORD trial,  
3 DFA observed the data reporting requirements and data  
4 flow were complex.

5           The threshold for positive adjudication of  
6 endpoints by the clinical endpoint committee was high,  
7 and clinical investigator requirements for referral of  
8 endpoints for adjudication were not clearly defined in  
9 the protocol. While the trial was ongoing, the  
10 sponsor and the CRO identified issues concerning low  
11 numbers of endpoints reported and delays in  
12 adjudication processes.

13           Efforts were undertaken to identify  
14 endpoints and improve adjudication processes by  
15 education and hiring of additional staff. An endpoint  
16 CRA and additional CEVA staff were also hired.

17           We found no evidence that performance and  
18 publication of the interim CV analysis in July 2007  
19 influenced the conduct of the trial. GSK asserts that  
20 statisticians were firewalled for the CV analysis.

21           The committees did not follow their charters  
22 in endorsing performance of the analysis, and that



1   only two members of the steering committee and the  
2   DSMB, the chairman and statisticians of each of the  
3   committees, verbally endorsed the performance of the  
4   interim CV analysis on May 14th, 2007, documented in  
5   an e-mail from GSK to these four individuals.

6           DSI closely evaluated cases identified by  
7   cardio-renal with respect to ascertainment of  
8   endpoints. No evidence of systemic problems with  
9   ascertainment were identified and no evidence of  
10   serious violations or significant data integrity  
11   concerns were noted.

12           Procedural issues concerning adjudication  
13   were noted during the inspection, but the findings  
14   were unlikely to impact the reliability of the data.

15           FDA inspections at three could sites, the  
16   sponsor and the CRA did not identify evidence of  
17   systematic or pervasive findings that would undermine  
18   the reliability of the data. However, there are  
19   limitations to the inspections.

20           Firstly, we were only able to review a small  
21   percentage of subjects' records. Secondly,  
22   inspections cannot address limitations imposed by

1 study design. In an open label trial, introduction of  
2 bias is difficult to detect. In general there is a  
3 challenge in detecting underreporting of events. To  
4 accomplish this, source documents are reviewed to  
5 determine if an adverse event has not been reported on  
6 a case report from.

7 In a trial of long duration, with 25 office  
8 visits, this can be time consuming. And because study  
9 sites may have been remote from actual points of care  
10 for subjects, the sites may not have had access to  
11 complete information concerning subject outcomes.

12 Complicated reporting requirements made it  
13 challenging to determine if the protocol was carried  
14 out correctly and the complexity of data flow made it  
15 difficult to demonstrate that blinding of selected  
16 study personnel was effectively maintained.

17 Another protocol issue is that this protocol  
18 had a high threshold with numerous requirements to  
19 ascertain a positive endpoint. The instructions to  
20 the investigators concerning referral for endpoint  
21 adjudication were ambiguous. So there was difficulty  
22 in assessing protocol adherence to these ambiguous

1 instructions.

2           We are unable to predict adjudication  
3 outcome from unREFERRED or withdrawn potential  
4 endpoints; and, lastly, source documents in a foreign  
5 language make it more difficult for FDA inspectors to  
6 assess whether there is a violation.

7           Therefore, DSI's conclusions regarding data  
8 reliability need to be considered in the context of  
9 these stated limitations.

10           Thank you for your attention.

11           DR. BURMAN: Thank you. The floor is now  
12 open for questions from the committee.

13           DR. VAN BELLE: You gave that there were 13  
14 citations. In your experience with this kind of a  
15 trial, is this an unusually higher number or low  
16 number? Can you give me a little bit of perspective o  
17 this particular issue?

18           DR. LEIBENHAUT: Yes. It's not only the  
19 numbers. It's actually the seriousness of the  
20 violations. And of those, we were left with -- when  
21 we went on the inspection, first, we went to GSK and  
22 there were a number of outstanding documents. And so

1    when we got to Quintiles, those documents were  
2    produced.

3                So with the review of the additional  
4    documents, we were left with the four violations.

5                But I have to tell you, also, it's not  
6    necessarily the numbers of violations.  It's also the  
7    quality.  So many times, if we're looking for items  
8    such as falsification of data, those could be much  
9    more serious.  So it's not necessarily the number.

10              DR. VAN BELLE:  So let me rephrase the  
11   question.  What about the seriousness of the  
12   violations, were they typical or were they unusual?

13              DR. LEIBENHAUT:       They were typical of  
14   what we may find.  So they were not considered serious  
15   violations.  I think the bigger issue here relates to  
16   the limitations, which is if the protocol is ambiguous  
17   about what needs to be referred, then we have  
18   difficulty citing an investigator for not referring  
19   something when the protocol is ambiguous.

20              Also, when we get to the sponsor, when it  
21   says that the clinical investigator withdrew that  
22   endpoint, then we have to take the sponsor's word for

1     that, unless we actually go to the clinical trial  
2     site.

3                 So we're looking at different things. I  
4     think Dr. Unger's slides kind of summed it up that  
5     there was a lot of ambiguity in terms of what needed  
6     to be referred.

7                 DR. VAN BELLE: Can I ask one more follow-up  
8     question?

9                 DR. BURMAN: Quickly, please.

10                DR. VAN BELLE: How was the investigation  
11     coordinated with the work of Dr. Marciniak?

12                DR. LEIBENHAUT: He referred cases to us,  
13     but it was also -- there was a timeline here. So that  
14     when we went to the clinical sites, those clinical  
15     sites were chosen on the basis of high enrollment, not  
16     necessarily where there may have been the most  
17     problems at a clinical site.

18                But, also, I think Dr. Marciniak alluded to  
19     that. Because of the distribution you see that there  
20     were over 4,000 subjects and there were about over 300  
21     sites. In order to cover those issues, we would have  
22     been -- we would have needed to go to very many sites

1 to look at those issues.

2 DR. BURMAN: Thank you. I see that we have  
3 six or seven questions for eight minutes. So I don't  
4 think we're going to get through them all. But,  
5 please, Dr. Rosen next.

6 DR. ROSEN: Thank you for your hard work. I  
7 heard you say about seven times that this is complex.

8 Can you put up slide 6, which is the most  
9 complex of a complex slide? There it is. And we saw  
10 that in a previous presentation.

11 So my question to you is, is this -- two  
12 very brief questions. One, is this more complex than  
13 what you see for reporting information? And, two, are  
14 there SAEs that were missed if they weren't reported  
15 initially as SAEs? Can we tell that in this system?

16 DR. LEIBENHAUT: That's the other point I  
17 want to make. In any trial, when you're inspecting  
18 for missed adverse events, you have to think about  
19 what you need to do. You need to go to the clinic  
20 record and you need to look at each visit to see if  
21 the subject said, "I was hospitalized." And then you  
22 have to match that up with what's on the case report

1 form.

2           So it's not like looking at hemoglobin A1C,  
3 hr you have the lab data and you match it up.

4           DR. ROSEN: You were not able to do that,  
5 then ? You were not able to go back and look at the  
6 records and then go back --

7           DR. LEIBENHAUT: We do, but we can only look  
8 at a limited number. And that was the point why I  
9 targeted. So I'd look at the line listings and I'd  
10 see angina pectoris as a diagnosis and I wouldn't see  
11 SAEs.

12           So my instruction to the inspector was to go  
13 and look at this subject's records, because I don't  
14 have in front of me, but I think there were 40  
15 subjects. We could do only 60 -- of those 188 in  
16 those total three sites, we only did 60 records. We  
17 only did half of those that were inspected.

18           The other thing about this trial, in  
19 particular, is you know that there's three places  
20 where data flowed. So data queries came from three  
21 different places. And there were a number of places  
22 where you could see where there was misunderstandings.

1           If you have my backup slide 9, I think Dr.  
2   Marciniak refers to this in his review, where the  
3   hospital -- where the medial adjudication -- it's one  
4   of the forms that says "Please send this."

5           Where the HHE form, this was a number of  
6   endpoints that were referred and then were later  
7   withdrawn. It's because some investigators filled out  
8   an HAE form, which is supposed to be an endpoint form  
9   only for cardiovascular, as you see here, they filled  
10   it out let's say, for prostate surgery, and it was  
11   hard to get through all this stuff.

12           DR. BURMAN: Thank you. Dr. Ball, you had a  
13   comment.

14           DR. BALL: I want to just comment, because  
15   there were a couple questions that I'm not sure were  
16   directly answered.

17           One was were the violations normal for an  
18   inspection of this type. And I would say that  
19   overall, there wasn't anything particularly concerning  
20   about either the number of the nature of the  
21   violations found at the inspection.

22           The second thing I wanted to address, the



1 other issue about the complexity. Overall, it was a  
2 fairly complex trial. The data flow was complex and,  
3 as a result, we mentioned that it's a limitation.

4           Given the fact that it was a long trial and  
5 there were a number of committees involved, I think  
6 that it is what it is. There were some limitations in  
7 terms of the data flow and the ability to assess  
8 whether or not blinding was maintained.

9           DR. BURMAN: Thank you. Dr. Platt?

10           DR. PLATT: Can you help me understand what  
11 your audit says about the cases that Dr. Marciniak  
12 referred to you.

13           So in broad strokes, were you able to  
14 satisfy yourselves that the concerns he raised could  
15 be effectively addressed or are you in the position of  
16 not having enough information to be able to  
17 definitively speak to his concerns?

18           DR. LEIBENHAUT: I think Dr. Unger did  
19 express it correctly in the ambiguities. Most of the  
20 ones, except the one with the CHF that I mentioned  
21 that we were able to catch, which clearly should have  
22 been sent to adjudication.

1           The other ones appear to be more complex.  
2    So you could understand potentially why they were not  
3    sent for adjudication. And some of them, we didn't  
4    have enough information because we were at the sponsor  
5    site for these others. We did not have the primary  
6    source data. So it was kind of a mixed bag there.

7           DR. BURMAN: Thank you. Dr. Felner, I think  
8    we have time for one or two quick --

9           DR. BALL: Can we just comment on that a  
10   little bit further ? I want to address the question  
11   about looking at the case that Dr. Marciniak had. We  
12   actually did look very closely at that and a number of  
13   those actually went away, either at the Quintiles  
14   inspection. But I do believe that it's a matter of  
15   looking at the protocol.

16          DR. PUROHIT-SHEFT: Susan, if you can go to  
17   your backup slide 27?

18          DR. TRAN: Can you announce yourself,  
19   please?

20          DR. PUROHIT-SHEFT: I'm sorry. This is  
21   Tejashri Purohit-Sheft. I'm a branch chief in Good  
22   Clinical Practice Branch II in the Division of

1 Scientific Investigations.

2 DR. TRAN: And what's your slide number  
3 again?

4 DR. PUROHIT-SHEFT: It is her backup slide  
5 number 27, if you could refer to this. The adverse  
6 events that Dr. Unger had highlighted in his  
7 presentation is eight, and what we had done is  
8 actually specifically looked at those and Dr. Ken Yu,  
9 who is a cardiologist from Division of Cardio-Renal,  
10 went on the inspection and he actually evaluated the  
11 documents that were available at the sites of GSK and  
12 Quintiles.

13 Of the eight, the majority -- what we found  
14 was that the protocol set a high bar for the positive  
15 adjudication and since it left the determination of  
16 potential endpoints to the investigator, it was very  
17 difficult. And we found that there were plausible  
18 reasons where the majority of these cases may not have  
19 been referred. There was a plausible reason why.

20 DR. LEIBENHAUT: Although I do have to add  
21 there was one there, also, and this is where you need  
22 to understand, it was that the investigator deleted

1 and we cannot -- at the sponsor inspection, we look  
2 for different items. So for that case, for example,  
3 we could not say plausibly. For the others, we had  
4 enough documentation for that.

5 DR. BURMAN: I think we're going to have to  
6 move on. There will be time later today and tomorrow.  
7 There's just, obviously, too many questions -- not too  
8 many, but an appropriate number of questions and it's  
9 important to go through them, but there just isn't  
10 time right now.

11 We will now proceed with our presentation  
12 from Dr. Kate Gelperin.

13 DR. GELPERIN: Good afternoon. During the  
14 next 20 minutes, I'll be presenting the results of the  
15 Cochran-type systematic review of observational  
16 epidemiologic studies that was conducted by a team of  
17 FDA reviewers from the Office of Surveillance and  
18 Epidemiology and the Office of Biostatistics.

19 I particularly wish to acknowledge the hard  
20 work of Dr. Esther Zhou, Dr. John Yap, and Dr. Laree  
21 Tracy on this project.

22 This systematic review of published

1 observational studies was undertaken primarily to  
2 address a knowledge gap and absence of direct  
3 comparisons of the two currently available  
4 thiazolidinediones, rosiglitazone and pioglitazone.

5           In the absence of data from cardiovascular  
6 outcomes trials comparing these two drugs, it may be  
7 reasonable to turn to other sources of relevant data,  
8 such as observational epidemiologic studies.

9           My primary focus today will be on studies of  
10 cardiovascular endpoints which directly compare  
11 rosiglitazone and pioglitazone, and I will also touch  
12 on results from studies which compare rosiglitazone or  
13 pioglitazone with other anti-diabetic agents.

14           Many of the studies identified in our  
15 systematic review utilize databases from commercial  
16 insured populations, which are often not  
17 representative of older patient populations.

18           However, a few studies were restricted to  
19 patients older than 64 years of age in the U.S. and  
20 Canada, and I will point out some possible differences  
21 in these two groups.

22           The FDA team developed a protocol for the

1 systematic review utilizing methods described in the  
2 Cochran handbook. Studies eligible for inclusion  
3 evaluated cardiovascular endpoints in populations of  
4 patients taking rosiglitazone or pioglitazone, could  
5 be case control or cohort design, and a full article  
6 was published in a peer-reviewed journal. The time  
7 span, I want to correct. Dr. Parks said it was after  
8 the last AC. Actually, we identified all published  
9 articles that were available to this review.

10 Comprehensive electronic database searches  
11 were conducted by the FDA biosciences librarian and  
12 independently by an epidemiology reviewer. Results  
13 were combined, duplicates removed, yielding 1,226  
14 abstracts.

15 These were reviewed independently by two  
16 epidemiology reviewers, and 57 full articles were  
17 identified for further review.

18 After pre-specified inclusion and exclusion  
19 criteria were applied, a final 21 studies were  
20 selected for inclusion. Quality was assessed using a  
21 standard instrument and was considered to be adequate  
22 for the 21 studies.

1           Data extraction and statistical review of  
2 individual studies were conducted, and they're  
3 described fully in the background package.

4           Study results were selected for display in  
5 forest plots based on pre-specified rules. If there  
6 were more than two studies with the same CV endpoint  
7 for a comparison of interest, results of risk  
8 estimates were displayed in a forest plot. No  
9 quantitative meta-analysis was planned or documented.

10          Of the 21 studies included in the review,  
11 seven were nested case control design and 14 were  
12 retrospective cohort studies. All of the nested case  
13 control studies were analyzed using conditional  
14 logistic regression models.

15          Twelve of the cohort studies used the COX  
16 proportional hazards model, one used Poisson  
17 generalized linear model, and one cohort study used  
18 logistic regression for the analysis.

19          As you will see in the forest plots each of  
20 these methods differ in the type of estimates they  
21 provide. In logistic regression, the adjusted odds  
22 ratio of one therapy group relative to another is

1 estimated for a dichotomous outcome. The odds ratio  
2 is the principal measure of risk in a case control  
3 study.

4 The COX proportional hazard model is used to model  
5 time to event and estimates the hazard ratio  
6 associated with one therapy group relative to another.

7           Because hazard ratios are computed by  
8 averaging instantaneous risks throughout the entire  
9 course of the study, the hazard ratio represents a  
10 summary relative risk of the endpoint for the entire  
11 study period.

12           The Poisson generalized model is used to  
13 model outcome counts per unit of time and to estimate  
14 rate ratios. As you can see, there were quite a few  
15 different outcomes identified in the 21 included  
16 studies, and each study had one or more than one.

17           I do want to point out that some of the  
18 studies had composite outpoints, such as serious  
19 atherosclerotic vascular disease, and these are not  
20 represented in the forest plots unless the individual  
21 components of the endpoint had the results reported in  
22 the publication.



1           The outcomes that did qualify for inclusion  
2   in forest plots were acute myocardial infarction,  
3   heart failure, total mortality and stroke.

4           The definition of outcome in the studies was  
5   typically defined using ICD-9 or ICD-10 codes, and  
6   read codes for the GPRD or thin databases. In many of  
7   the studies, patient deaths were not described. As  
8   you can see in this table, there was a geographic  
9   diversity and many different databases were  
10  represented in these studies.

11          Results of the systematic review will be  
12  presented in a series of forest plots. I'd like to  
13  thank Dr. Esther Zhou for preparing these forest  
14  plots.

15          The results of the studies are shown as  
16  squares or boxes centered on the point estimate for  
17  each study. The box size denotes the size of the  
18  study.

19          The width of the horizontal line running  
20  through each box denotes the 95 percent confidence  
21  interval for each point estimate. Point estimates are  
22  ratios, such as hazard ratios or odds ratios, and are

1 displayed on the X-axis using a log scale, which makes  
2 the confidence intervals appear symmetric around the  
3 line of no effect, which corresponds to a ratio of 1.

4 Study results are then viewed in relation to  
5 each other and to the line of no effect. The scale of  
6 the X-axis varies from slide to slide, depending on  
7 the range of the effect estimates on each forest plot.

8 Seven studies were identified which analyze  
9 the risk of acute myocardial infarction with  
10 rosiglitazone or pioglitazone compared to other anti-  
11 diabetic agents. The top section, in red, shows  
12 results for rosiglitazone and the bottom section, in  
13 blue, shows the results for pioglitazone. All of the  
14 risk estimates shown in this forest plot are the  
15 adjusted values.

16 If risks are similar for the comparison  
17 groups, there should be a roughly symmetric  
18 distribution of point estimates on either side of the  
19 line of no effect. In this slide, there are two of  
20 seven point estimates favoring rosiglitazone compared  
21 to other anti-diabetic agents, and five of seven point  
22 estimates favoring pioglitazone compared to other

1 anti-diabetic agents.

2           Four studies were identified which analyze  
3 the risk of congestive heart failure in patients  
4 receiving rosiglitazone or pioglitazone compared to  
5 other anti-diabetic agents. All of the point  
6 estimates were greater than 1 and were generally  
7 higher with rosiglitazone. None of the results for  
8 pioglitazone were statistically significant.

9           Three studies were identified which examined  
10 all cause mortality with rosiglitazone or pioglitazone  
11 versus other anti-diabetic agents. Results were  
12 inconsistent, but were statistically significant in  
13 three of the studies, one study showing increased risk  
14 of all cause mortality with rosiglitazone, the  
15 Lipscombe study, and two showing decreased risk with  
16 pioglitazone, the Tzoulaki and Habib studies.

17           As has been mentioned earlier today, there  
18 are challenges with comparisons of rosiglitazone or  
19 pioglitazone with other anti-diabetic agents, and this  
20 may be a reflection of the limitation of the methods  
21 in complex situations, such as the typical multi-drug  
22 treatment of Type II diabetes with frequent switching

1 and adding of drugs.

2           Of more importance are direct comparisons of  
3 rosiglitazone versus pioglitazone. The next series of  
4 forest plots describe studies with direct comparisons  
5 of rosiglitazone and pioglitazone. These were the  
6 most clinically relevant comparisons, because  
7 prescriber decisions about starting a  
8 thiazolidinedione involve making a choice between  
9 these two drugs.

10           As you can see on this forest plot, results  
11 of studies comparing rosiglitazone versus pioglitazone  
12 for acute myocardial infarction risk show a strikingly  
13 asymmetric distribution around the line of no effect,  
14 which is here.

15           The top part of the slide shows you the  
16 crude estimates and the bottom part of the slide are  
17 the adjusted risk estimates.

18           The top portion, the crude estimates, are  
19 from six studies and an additional crude odds ratios  
20 from an additional two studies for which calculations  
21 could be made from data included in the publication.

22           The bottom portion shows adjusted risk

1 estimates from eight studies directly comparing  
2 rosiglitazone and pioglitazone. Note that the crude  
3 estimates from six of these are also shown above, but  
4 were not reported in the publication for the other  
5 two.

6 Overall, results from a total of 10  
7 different studies are shown on this forest plot, all  
8 of which report point estimates favoring pioglitazone  
9 regarding risk of acute myocardial infarction.

10 For completeness, I want to mention three  
11 neutral studies which do not appear on this forest  
12 plot, two, because they didn't meet the inclusion  
13 criteria for the systematic review and one which did,  
14 but analyzed the unique composite endpoint, which  
15 included acute myocardial infarction, but the authors  
16 didn't report the results for the individual  
17 components.

18 The first one I'll mention is the  
19 preliminary results of a study that were presented  
20 during the public session of the Avandia advisory  
21 committee meeting in 2007 by Dr. Samuel Nussbaum from  
22 WellPoint, and reported a neutral effect. These study

1 results have not been published to date, to my  
2 knowledge.

3           One published study with neutral results for  
4 a composite endpoint, which the authors refer to as  
5 coronary artery disease, was not selected for  
6 inclusion in the systematic review because it was from  
7 a single institution and was not considered to be a  
8 population-based study.

9           One other neutral study was included in the  
10 systematic review, the Margolis study, but had a  
11 unique composite endpoint and did not report results  
12 for the individual components. However, the authors  
13 stated that the myocardial results were neutral,  
14 although they didn't provide their results.

15           Three studies were identified which analyzed  
16 acute myocardial infarction risk in patients receiving  
17 monotherapy rosiglitazone versus pioglitazone. In  
18 addition, a crude odds ratio for this comparison could  
19 be calculated from results presented in the Lipscombe  
20 paper, yielding a total of four studies. Point  
21 estimates were generally greater than 1, favoring  
22 pioglitazone.

1           Brownstein reported an adjusted relative  
2 risk of 2.2 favoring pioglitazone, which was  
3 statistically significant.

4           Four studies of acute myocardial infarction  
5 risk with rosiglitazone versus pioglitazone were from  
6 studies which were founded by the drug's  
7 manufacturers, three GSK and one Takeda which has been  
8 mentioned earlier, the Garrits study.

9           Two studies, Ziyadeh and Garrits, showed a  
10 statistically significant increased risk of acute  
11 myocardial infarction with rosiglitazone compared to  
12 pioglitazone. And I do want to point out that these  
13 studies were conducted by staff of GSK, in conjunction  
14 with other experts.

15           Three studies were identified which analyzed  
16 heart failure. Adjusted hazard ratios for the  
17 Jurrlink and Winkelmayr studies, excluded 1 and  
18 showed a 13 percent and a 30 percent increased risk of  
19 heart failure with rosiglitazone compared to  
20 pioglitazone.

21           Three studies analyzed all cause mortality  
22 with rosiglitazone compared to pioglitazone. Results

1 favored pioglitazone and were statistically  
2 significant, with adjusted hazard ratios of 1.16 and  
3 1.15, respectively, for the Jurrlink and Winkelmayr  
4 studies.

5           The next slide I just wish to point out  
6 something that I think we all feel like we know, which  
7 is that cardiovascular disease manifests itself  
8 differently at different times in life. These are the  
9 death rates for sudden cardiac death from the U.S.  
10 vital statistics for the year 1998, published by  
11 Zhang, et al, in 2001. And it's interesting to note  
12 that between this age group 55 to 64 and the 75 to 84-  
13 year-old age group, the incidence of sudden cardiac  
14 death is increases by nearly an order of magnitude.

15           So while this may be intuitively obvious, I  
16 think it's helpful to see the kind of numbers that  
17 we're talking about for the different manifestations  
18 at different times in life of cardiovascular disease.

19           This slide shows a subset of the results  
20 shown previously for analyses of acute myocardial  
21 infarction risks with rosiglitazone versus  
22 pioglitazone, and it excludes studies which were



1 restricted to patients older than 65 years.

2           Point estimates for each of the seven  
3 studies, as shown on this slide, are greater than 1  
4 favoring pioglitazone. Note that the magnitude of the  
5 X-axis in this slide differs from subsequent slides in  
6 order to accommodate the adjusted relative risk in the  
7 Brownstein publication.

8           This slide shows the results of studies  
9 which analyzed databases which were restricted to  
10 patients older than 65 years for acute myocardial  
11 infarction risk with rosiglitazone versus  
12 pioglitazone. Two such studies were included in the  
13 systematic review by Jurrlink and by Winkelmayr, and  
14 one additional study of Medicare patients was more  
15 recently published and will be discussed in the next  
16 talk by Dr. Graham, the first author.

17           It is interesting to note that the adjusted  
18 hazard ratios comparing acute myocardial infarction  
19 risk with rosiglitazone and pioglitazone are very  
20 similar in these three studies, each with broad  
21 confidence intervals and point estimates of similar  
22 magnitude and all favoring pioglitazone.

1 I do wish to point out that the years of the  
2 study population for the Winkelmayer study precede the  
3 advisory committee in 2007, and I think Dr. Graham  
4 will talk some more about that.

5 The same three studies analyzed heart  
6 failure risk in older patients and all three shows an  
7 increased risk of heart failure with adjusted hazard  
8 ratios of 1.13 to 1.30, which were statistically  
9 significant.

10 The same three studies analyzed all cause  
11 death with rosiglitazone versus pioglitazone. The  
12 adjusted hazard ratios were very similar across the  
13 studies and statistically significant. Results show a  
14 14 to 16 percent increased risk of all cause death  
15 with rosiglitazone compared to pioglitazone.

16 Very few studies were identified in this  
17 review which analyzed the risk of stroke with  
18 rosiglitazone and pioglitazone. The Winkelmayer  
19 study, shown here, did include a TIA in their  
20 definition of stroke, which possibly could increase  
21 the problem with misclassification bias.

22 This slide shows the results of the stroke

1 analysis from the Graham study in the context of the  
2 Winkelmayr results.

3           Of course, such a systematic review has  
4 strengths and limitations. I think the main strength  
5 is that it was a comprehensive and systematic data  
6 collection process. And perhaps the main limitation,  
7 other than these are not randomized, is that we cannot  
8 evaluate publication bias or we did not evaluate it,  
9 and we only include published articles.

10           So in summary, comparisons of rosiglitazone  
11 and pioglitazone in these data for outcomes, including  
12 acute myocardial infarction, congestive heart failure,  
13 and all cause mortality, favor pioglitazone. No  
14 studies were identified in this review with results  
15 suggesting a protective cardiovascular effect of  
16 rosiglitazone compared to pioglitazone.

17           The results are consistent with the results  
18 of FDA's recently completed meta-analysis of  
19 randomized clinical trials with rosiglitazone and  
20 pioglitazone. My view is that it's highly likely that  
21 rosiglitazone therapy is associated with increased  
22 risk of adverse cardiovascular outcomes.

1           In the absence of data from randomized  
2 cardiovascular outcomes trials directly comparing  
3 rosiglitazone and pioglitazone, it is reasonable to  
4 turn to the available body of evidence from well  
5 designed epidemiologic studies to inform clinical  
6 decision-making.

7           Comparisons of rosiglitazone with  
8 pioglitazone consistently show a clinically meaningful  
9 increased risk of adverse cardiovascular outcomes,  
10 notably, acute myocardial infarction.

11           The increased risk of all cause mortality  
12 with rosiglitazone in older patients demonstrated in  
13 three well designed observational studies may be a  
14 reflection of the increased cardiovascular risk with  
15 rosiglitazone.

16           I wish to acknowledge that this Cochran type  
17 systematic review was the result of a lot of work from  
18 quite a few people from cross-divisional and cross-  
19 office collaboration, and thank them.

20           DR. BURMAN: Thank you very much. We have  
21 10 minutes for discussion. Dr. Morrato?

22           DR. MORRATO: Thank you very much. Thank

1 you for the very detailed review. I had a question  
2 with regard to the period of time in which the  
3 observational studies were actually -- that they were  
4 observing the events.

5 So in other words, we heard discussion from  
6 Dr. Mahoney that the prescription treatment patterns  
7 changed dramatically after the 2007 advisory  
8 committee. And so I wanted to see if you could give  
9 us an update on -- and I notice that the study  
10 publication dates on all of these were after that  
11 fact.

12 But I do recall from the briefing materials  
13 that the observation periods of the studies were  
14 really -- the majority at least occurred before. So I  
15 wanted to confirm that.

16 But assuming that is correct, did you look  
17 at any of the treatment practices during the time  
18 period that these studies were observing events and  
19 whether or not there were any possible or theoretical  
20 differences in the patterns of use between  
21 rosiglitazone and pioglitazone and what that might  
22 have, in your estimation, as an effect on either

1 channeling bias or a measure of confounding that  
2 couldn't be addressed in the studies?

3 DR. GELPERIN: Thank you. Yes. You are  
4 correct that for, I would say, the majority of these  
5 studies, the time period included in the patient  
6 populations precedes the advisory committee meeting,  
7 even though they may have published their study the  
8 following year, which is correct.

9 I did not do that ay that you're referring  
10 to. However, I think Dr. Graham did and maybe he  
11 would like to address your question.

12 DR. GRAHAM: Dave Graham from the Office of  
13 Surveillance and Epidemiology, and I'll be speaking in  
14 a couple minutes.

15 I wasn't planning to present this at this  
16 advisory meeting, but we looked at physician  
17 prescribing behavior before and after this meta-  
18 analysis in national Medicare data and what we  
19 observed was actually quite surprising.

20 We thought that there would be a change in  
21 rosiglitazone prescribing and no real change in  
22 pioglitazone prescribing.

1           What we observed is that three phenomena  
2 occurred. One, a sizeable proportion of physicians  
3 stopped prescribing TZDs all together, just stopped,  
4 period. Second, a sizeable proportion of physicians  
5 who were previously rosiglitazone only prescribers --  
6 sort of like 70 percent of the time or more, they  
7 prescribed rosiglitazone -- a substantial proportion  
8 of those switched to being pio only prescribers.

9           Third, physicians who prescribed  
10 rosiglitazone or pioglitazone applied the same, in a  
11 sense, selection criteria to the patients, regardless  
12 of the drug.

13           So what you see is that if you compare  
14 baseline characteristics of patients in our study, for  
15 example, for patients who started the drug at six-  
16 month intervals after the Nissen meta-analysis, what  
17 you see is the baseline characteristics in the  
18 rosiglitazone cohort and in the pio cohort are  
19 identical.

20           So in other words, physicians were hanging  
21 their prescribing behavior. So they were prescribing  
22 TZDs to less seriously ill, from a cardiovascular

1 perspective, less high risk patients, but they were  
2 doing it equally to both rosiglitazone and  
3 pioglitazone, so that there was no channeling bias.

4 DR. GELPERIN: Actually, that information is  
5 in the background package, in the summary  
6 characteristics of the studies. And so sort of  
7 overnight, I could do a quick look and see if I can  
8 give you more information tomorrow.

9 DR. BURMAN: That would be great. Dr.  
10 Konstam?

11 DR. KONSTAM: First, a very quick comment  
12 about the last presentation, which I wanted to get in.  
13 There was this debate about whether there were a lot  
14 or not a lot of, quote, "violations" in the RECORD  
15 trial.

16 My take-home from Dr. Marciniak was not in  
17 reference to how many violations there were, but that  
18 the number of problems he saw occurred far more often  
19 in the rosiglitazone group than they did in the  
20 control group, or, rather, they tended to favor  
21 rosiglitazone far more than control. And I think that  
22 was really the key point of his presentation, not



1 counting how many violations there were. So I just  
2 wanted to sort of comment on that.

3 With regard to your presentation, could you  
4 just put up slide 8? So two questions about this  
5 slide. First, do you think that the top panel  
6 substantiates the results of the RECORD trial?

7 And the second question is I think you make  
8 a pretty convincing case that the direct head-to-head  
9 comparisons with pio look to favor pio. But if that's  
10 the case, why does pioglitazone and rosiglitazone look  
11 so similar in this analysis?

12 DR. GELPERIN: Well, as actually the sponsor  
13 mentioned earlier today, I think there are a lot of  
14 problems comparing the two thiazolidinediones with  
15 other anti-diabetic agents, because even with  
16 adjusting for risk factors, I think that patients are  
17 often embarking on the therapies at very different  
18 points in their course of disease.

19 So I do think it's problematic and I would  
20 not -- I think that one of the big problems will be  
21 misclassification bias, which, if it's random, will  
22 bias towards a null effect.

1           So I don't take reassurance about the lack  
2 of definitive asymmetry in this slide. And I also  
3 sort of noticed that there is some amount of  
4 asymmetry. If we did summary estimates, which our  
5 statisticians advised us they weren't comfortable  
6 doing, you would see that there are some differences.

7           But to me, when I look at this slide, what I  
8 see is my usual skepticism about the ability of  
9 observational studies to deal with issues where  
10 there's a relatively small effect size, even though  
11 it's got strong, strong public health significance.  
12 Or observational studies, this is a small effect size  
13 that we're trying to tease out, and misclassification  
14 can just completely obfuscate it.

15           DR. KONSTAM: Well, I certainly wouldn't  
16 take home anything definitive from this slide, and I  
17 wasn't suggesting that. And I have a lot of respect  
18 for what you've done and presented, but I'd be really  
19 careful about you picking and choosing that you really  
20 like those other slides, but you don't like this one.  
21 And I'm a little concerned about sort of going there.

22           DR. GELPERIN: I think it's a fair criticism

1   that observational studies are not randomized. But I  
2   do think that you will shortly be hearing some data  
3   about similarities of the baseline characteristics of  
4   the rosiglitazone and pioglitazone groups in the  
5   Medicare study that I think was pretty typical with  
6   what I saw in the studies included in this review,  
7   which is really not -- when you compare a group of  
8   patients starting on thiazolidinedione versus  
9   metformin or insulin, they are just not very similar  
10  groups.

11           DR. BURMAN: Thank you. Ms. Killion?

12           MS. KILLION: I apologize if I missed this in  
13  the briefing materials, which is entirely possible.  
14  But since what we're talking about here are two  
15  glucose lowering drugs, do we have any head-to-head  
16  comparisons on the efficacy of these two drugs with  
17  respect to glucose control?

18           DR. GELPERIN: I think that's such a  
19  wonderful question. The only head-to-head comparison  
20  I'm aware of is the GLAI study, which was actually an  
21  investigation of the lipid effects.

22           But perhaps Dr. Mahoney would like to

1 comment on this, or Dr. Parks, or if there are any  
2 other studies other than the GLAI.

3 DR. PARKS: No. That's the only head-to-  
4 head study between the two and it was designed to look  
5 at lipid altering effects , but it was also to  
6 evaluate for glycemic control, and they're comparable  
7 in that trial.

8 DR. BURMAN: Thank you. We have three  
9 minutes. Dr. Kaul?

10 DR. KAUL: Thank you. I have one brief  
11 comment and then two quick questions. There are,  
12 obviously, major caveats, but I wanted to draw your  
13 attention to the conclusion and recommendations  
14 section of the statistical review by John Yap, on page  
15 472 of the briefing document.

16 They were, obviously, hesitant to draw any  
17 inferences from all the trials that you just  
18 presented, but they felt compelled to emphasize 11  
19 caveats that challenge the interpretability of the  
20 findings. Therein lies the challenge for this  
21 advisory panel.

22 Two quick questions. How many of these

1 analyses had a pre-specified hypothesis and how many  
2 cases was that hypothesis justified, and how were  
3 multiplicity issues handled in your analyses?

4 DR. GELPERIN: I'm going to ask Dr. Yap or  
5 Dr. Tracy to answer that. I think that you're  
6 absolutely right. The statisticians who have even  
7 more skepticism than I bring to evaluating  
8 observational data, and they were concerned about --  
9 there were very few studies, I think maybe three, that  
10 adjusted for multiplicity.

11 Here is Dr. Tracy.

12 DR. TRACY: I'll certainly answer that,  
13 although Dr. Yap,. Who is in the back there, can come  
14 up and add to anything that I have to say, because he  
15 was a primary reviewer.

16 I'm the statistical team leader in Division  
17 of Biometrics VII within the Office of Biostatistics.

18 Among all 21 observational studies, if I  
19 recall, there was one that had pre-specified an  
20 objective. We hydromorphone a pre-specified  
21 hypothesis. No, there were -- well, there was also, I  
22 think, maybe one or two studies that also adjudicated

1 for multiplicity across all 21 studies.

2 And what was the third question you had?

3 DR. KAUL: What was that pre-specified  
4 hypothesis and was it justified from that one study? I  
5 mean, if it was mortality, what is the evidence for  
6 the differential effect of these two agents on  
7 mortality.

8 DR. TRACY: I do not recall the exact  
9 hypothesis, but we can look that up and get back to  
10 you tomorrow.

11 DR. BURMAN: That would be graft. Thank you  
12 very much. We'll move on now. Thank you, Dr.  
13 Gelperin.

14 We will now proceed with the presentation  
15 from the FDA presenter, Dr. David Graham. Dr. Graham  
16 will present review of a study in elderly patients, as  
17 part of his official government duties, with a 10-  
18 minute question-and-answer session. Dr. Graham will  
19 then share his personal views regarding the TIDE  
20 trial, with a 5-minute question-and-answer session.  
21 Dr. Graham's personal views do not necessarily reflect  
22 those of the FDA.

1           I would like to remind public observers at  
2   his meeting that while the meeting is open for public  
3   observation, public attendees may not participate,  
4   except at the specific request of the panel.

5           DR. GRAHAM: Thank you. This afternoon, I'd  
6   like to describe an observational epidemiologic study  
7   which we conducted using Medicare data for the entire  
8   country. This is a list of our co-investigators from  
9   the Food and Drug Administration and the Centers for  
10   Medicare and Medicaid Services; Acumen, LLC, who are  
11   the contractors to CMS, who are the actual holders of  
12   the Medicare data and who performed all the analyses  
13   per our specifications.

14          Funding for this study was from the  
15   assistant secretary for planning and valuation, HHS,  
16   from CMS and FDA, and none of the co-investigators had  
17   any conflicts of interest to disclose.

18          This study was made possible through an  
19   interagency agreement with the Centers for Medicare  
20   and Medicaid Services, named SafeRx.

21          Medicare provides health insurance for all  
22   U.S. citizens over the age of 65 and for selected

1 groups below age 65 if they have permanent disability,  
2 end stage renal disease, or ALS.

3           There are four components to Medicare data.  
4 There's Part A, which is hospitalization data covering  
5 in-patient skilled nursing facilities. About 45  
6 million Americans are enrolled in Part A.

7           Part B covers physician outpatient visits.  
8 About 42 million patients, so there's 3 million who  
9 have Part A who don't also have Part B.

10           Part C represents a managed care environment  
11 of care. That's about 10 million patients, and they  
12 are carved out of the 45 and 42 million. And then,  
13 finally, the prescription Part D data covers about 26  
14 million. But if you limit it the population with  
15 Parts A and B data, so they have outpatient and  
16 inpatient coverage, and they're over the age of 65,  
17 that's about  
18 15 million and that's the population within which our  
19 study was conducted.

20           In designing this study, we thought that the  
21 most appropriate comparison would be rosiglitazone  
22 versus pioglitazone, for a number of reasons. One,



1 we've heard that diabetes is a progressive disease and  
2 so we thought that in treatment algorithms, that when  
3 a physician decided that a patient needed some  
4 additional medication, that they would think in terms  
5 of a class of medications as opposed to a specific  
6 drug and that once they had made that decision about  
7 going, say, to TZD, then they would choose between  
8 rosiglitazone and pioglitazone.

9           We thought that it would strengthen this  
10 comparison, because the likelihood of these patient  
11 populations being intrinsically more comparable at the  
12 start would be greater than a comparison, say, between  
13 research and metformin or relationship and  
14 sulfonylurea.

15           We also thought that it was the clinically  
16 most relevant comparison, because this is where  
17 physician and patients live. If it turns out that one  
18 of these drugs has a decided advantage or disadvantage  
19 compared to the other, in the light of no meaningful  
20 difference in health benefit with respect to glycemic  
21 control, then it should be a pretty simple decision,  
22 which drug is best for patients.

1           So the purpose of the Medicare study was  
2   does rosiglitazone increase the risk of these  
3   endpoints compared to patients taking pioglitazone in  
4   patients aged 65 years or older?

5           These endpoints were chosen from a review of  
6   the literature and the fact that when we looked at the  
7   studies, all of them suggested that rosiglitazone  
8   increased risk compared to pioglitazone.

9           So this study was designed to test that  
10   hypothesis head-to-head. It was pre-specified and it  
11   was in the protocol that was submitted to the risk in  
12   human subjects committee at FDA at the time that we  
13   began the study.

14           This is a brief overview of showing the  
15   study design. It was an inception cohort, time to  
16   event study. So if we focus on the naught, that's the  
17   time when a patient first received their first TZD  
18   prescription in Medicare.

19           Having =received that prescription, we then  
20   looked backwards to see if they had at least 183 days  
21   of enrollment in part D, which would allow us to see  
22   whether or not they had prior TZD use, what their

1 other diabetes therapy was, and what other drug  
2 covariates might be for the treatment of co-morbid  
3 conditions.

4 We also required that patients have at least  
5 one year of prior history in Medicare Part A and Part  
6 B. This would allow us to establish health care  
7 utilization and medical co-morbidities.

8 Patients who satisfied these requirements  
9 and who, at the time of receiving this drug, were 65  
10 or older, and were not hospitalized or in some other  
11 long-term care facility, were entered into the cohort.  
12 So every patient in Medicare between the years of 2006  
13 and 2009 who met these criteria were in the study.

14 We follow these patients for up to three  
15 years for the occurrence of these endpoint events.  
16 This is in the background package, but MI, stroke,  
17 heart failure were defined by ICD-9 coding, using  
18 coding from hospitalization claims that had been  
19 previously well validated in Medicare data itself.

20 Death was ascertained using the Social  
21 Security master debt file, so that -- at least  
22 Medicare doesn't like paying benefits on patients who

1 are deceased.

2           Then we also had a series of composite  
3 endpoints, and the reason why we had these composites  
4 was that different people within FDA have different  
5 preferences for the combinations of outcomes they like  
6 to hear.

7           In this discussion we've heard people talk  
8 about all cause mortality. We've heard other people  
9 talk about MACE. We've heard people talk about MI and  
10 death. So we decided we would do them all.

11           As a cohort study, we could have done four  
12 separate studies, one for MI, one for stroke, one for  
13 heart failure, or one for death, because we had four  
14 separate hypotheses. But we thought it would be most  
15 efficient to do them all at once in one study.

16           Patients were followed until they switched  
17 to TZD. So they went from rosi to pio, pio to rosi.  
18 There was a gap in therapy that exceeded seven days in  
19 coverage, and we chose this tight coverage clostridium  
20 difficile we wanted to be sure that patients were on  
21 therapy.

22           We were concerned about misclassification

1   that might be introduced by unexposed time being in  
2   the cohorts. And since this was a study for safety,  
3   we wanted to make pretty sure the patients were on the  
4   drug.

5               The endpoint, that would be a censoring  
6   point. And if they were hospitalized for a non-  
7   endpoint reason, this was also a censoring event. And  
8   the reason for that was that we discovered that over  
9   75 percent of patients who are hospitalized for a non-  
10   endpoint reason, they went on a TZD and they left no  
11   longer on the TZD.

12              In other words, the TZD was stopped while  
13   they were hospitalized. So to deal with that, we  
14   decided on a 14-day extended follow-up period from the  
15   moment that someone would be ha, that we would follow  
16   them, to get around this problem. We were concerned,  
17   also, about informative censoring, especially for  
18   death. Someone might e hospitalized, say, with  
19   congestive heart failure or with ischemic chest pain,  
20   get admitted on day one, die on day three, and if we  
21   censored them, we might not capture the actual event.

22              So the next several slides review the

1 baseline covariates of the tow cohorts, the  
2 rosiglitazone and pio cohorts.

3           We had nearly 68,000 rosiglitazone patients  
4 to nearly 160,000 pioglitazone patient. We compared  
5 them using a measure called the standardized mean  
6 difference, which shows the difference between groups  
7 in terms of standard deviations, assuming that both of  
8 them came from the same distribution.

9           If you have a difference that's greater than  
10 one-tenth of one standard deviation, that's considered  
11 to be a non-negligible or a meaningful difference.

12           So you can see, for demographic  
13 characteristics and background cardiovascular  
14 diseases, that these cohorts were remarkably similar.

15           Likewise, for medications used to treat  
16 various cardiovascular conditions, these cohorts were  
17 also, once again, very, very similar, also with  
18 respect to insulin use, metformin use and sulfonylurea  
19 use.

20           I thought it would be interesting to show  
21 how comparable our cohorts were in the Medicare study  
22 compared to cohorts in randomized controlled clinical

1 trials.

2           In this slide, what I've done is taken  
3 characteristics that were present in the RECORD study,  
4 that had the most characteristics of any of the  
5 studies we looked at, and then compared the exposed  
6 cohort, the TZD cohort, to the control cohort, and  
7 then present the difference in those cohorts for those  
8 measures in terms of a standard mean difference.

9           Basically, what you can see is -- for  
10 example, here, we'll go with RECORD. There are 15  
11 characteristics here that there is information from  
12 both cohorts on. In 11 of those characteristics, the  
13 variation between cohorts in our Medicare study was  
14 smaller than in RECORD. In one study, RECORD'S  
15 difference was different and the remaining four, they  
16 were comparable. And you can do the same for  
17 PROactive, where it was fairly even; for DREAM and  
18 ADOPT, where our cohort was actually much more similar  
19 with respect to these matrix covariates than in the  
20 randomized trials.

21           This table summarizes the major information  
22 from the study. There were nearly 8,700 events in

1 this study that we performed, and you can see the  
2 numbers listed here in these two columns.

3 The incidence rates per 100 person years are  
4 summarized here, and then in this last column we have  
5 the attributable risk or that's the rate difference  
6 per 100 person years, with 95 percent confidence  
7 intervals.

8 The important thing to note is that the  
9 attributable risk, the rate difference was increased  
10 for all endpoints favoring pioglitazone. That is the  
11 rates were higher in the rosiglitazone cohort.

12 These differences were statistically  
13 significant for all of the endpoints, except for  
14 myocardial infarction, where the attributable rate  
15 across the -- zero.

16 We'll now move to several Kaplan-Meier  
17 curves showing time to event, and I'll go through them  
18 very quickly. They're in the background package and  
19 I'm sure the committee has looked at them.

20 This shows the Kaplan-Meier curve for acute  
21 myocardial infarction, rosiglitazone in red,  
22 pioglitazone I blue.



1           The axis, the Y-axis changes in terms of the  
2   measurements from graph to graph. So the same  
3   measure, .02 or 2 percent is shown in blue in each of  
4   the successive slides.

5           Along the X-axis we have the time of follow-  
6   up since treatment. So this is time on drug. And  
7   then below that, the number of patients who are still  
8   on the drug over time.

9           I think it's important to note that even  
10   though we've been talking today about the long-term  
11   use of the TZDs and the importance of long-term  
12   clinical trials, that the way medicine is practiced in  
13   the United States, most patients do not stay on these  
14   drugs very long in the Medicare population.

15           So in the United States, if you're over 65  
16   and you have diabetes, you stayed on a TZD and you  
17   were prescribed a TZD. You were only on it, on  
18   average, for about 3.5 or 4 months, and that's just  
19   the reality of the way these drugs are used.

20           In younger populations, this information  
21   wasn't included in the background package, but we  
22   sampled -- we have a contracts program and we sampled

1 three very large health care systems, and there, where  
2 the average age is in the 50s, the median duration of  
3 use for the TZDs was only about a year and it was the  
4 same in all three of the databases.

5           So patients do not, as a rule, stay on these  
6 drugs for three years or five years or even for a  
7 lifetime. If you're older than 65, you really only  
8 stay on it for a few months and then the drug is  
9 stopped and you're moved on to other therapies. So I  
10 think that's important to keep in mind, as well, when  
11 you're looking at these risks and thinking about what  
12 the long-term benefits might be of a drug that you  
13 only stay on for a short period of time.

14           This shows the Kaplan-Meier curves for  
15 stroke, and we can see that there is an increase early  
16 in use with relationship that continues for the  
17 duration of use. We see the same for heart failure,  
18 where you can see separation within probably about a  
19 month of use of the drug. For all cause mortality, we  
20 see the same thing. And then for each of the  
21 composites, also.

22           COX proportional hazards modeling was done

1 in which all the covariates in the background package  
2 were included in the model, and you can see here  
3 summarized the unadjusted hazard ratios and the fully  
4 adjusted hazard ratios.

5           The first thing I'd like to point out is  
6 adjustment made very little difference in this study  
7 and you'd expect adjustment to have almost effect if  
8 the cohorts are very, very similar, and these cohorts  
9 were similar.

10           So when you look, you go from 1.07 to 1.06,  
11 1.31 to .27, you see the pattern. Adjustment didn't  
12 make much of a difference, because the cohorts were  
13 similar.

14           The point estimates for the hazard ratio for  
15 increased for all endpoints, statistically  
16 significantly so in all except acute myocardial  
17 infarction, and you can see the confidence intervals  
18 there. Even though for acute myocardial infarction,  
19 the difference was not statistically significant, the  
20 confidence interval was compatible with a clinically  
21 meaningful and important risk.

22           Now, we describe it at some length in the

1 background package. This little double-hatch sign  
2 here is to indicate that these regression analyses,  
3 when we did the test for proportional hazards  
4 assumption to see if that test was met, that the test  
5 was not met for these analyses.

6           And so as a result of that, we did  
7 additional analyses that were not planned at the start  
8 of the study, but were done to explore the robustness  
9 of the findings and to see if we could identify the  
10 cause for this non-proportionality.

11           One of those analyses is this, where we  
12 looked at zero days of extended follow-up or 28 days  
13 of extended follow-up. In zero days of extended  
14 follow-up, this would be where someone is admitted to  
15 the hospital and we censor them right there. We don't  
16 follow them to see families they die in the hospital.

17           In that type of analysis, what we'd expect  
18 is informative censoring. That is, patients who are  
19 admitted with a mortal condition who die in the  
20 hospital after admission, that they would be censored,  
21 and so we wouldn't be counting their deaths.

22           So in this analysis, we expected to see that

1 he all cause death would become possibly not  
2 statistically significant, and that happened.  
3 However, for the stroke and heart failure endpoints,  
4 those were not really changed by this.

5           What I will point out is that with the zero  
6 day adjustment, death and AMI or death no longer had  
7 violated the proportional hazard assumption, but,  
8 also, they were no longer statistically significant.

9           If we extended the follow-up for 28 days,  
10 now our main analysis was a 14-day extended follow-up,  
11 here we've gone to 28 days, we see that there's no  
12 real change if you compare these findings to the  
13 findings on the previous slide.

14           We also examined what happened before and  
15 after the publication of the Nissen meta-analysis in  
16 May of 2007. So here you've got the pre-Nissen  
17 period, if you will, that's like for the common error,  
18 and then you have the post-Nissen period.

19           You can see here the number of patients  
20 enrolled in the study. In this pre period, it's about  
21 50/50 rosi/pio. In this period, it's a ratio of  
22 almost 7 to 1 rosi to pio, because treatment patterns

1 changed. After the missing meta-analysis, the  
2 prescribing of rosiglitazone to the elderly in the  
3 United States went from prescribing 1-to-1 to  
4 prescribing 7-to-1 in favor of pioglitazone.

5           What you can see in the pre period is that  
6 the findings that we had in our main analysis are  
7 basically replicated, and that, in addition, for death  
8 and MI or death, we now meet the proportional hazards  
9 assumption, which we didn't in the main analysis. So  
10 some of that could have been introduced by changes in  
11 the way medicine was practiced with the publication of  
12 the Nissen paper.

13           In the post-Nissen period, we find that we  
14 still have increases in stroke, in heart failure.  
15 Death is increased, but it's no longer statistically  
16 significant. But when we get down to the composite of  
17 MI, stroke, heart failure, or death, that is. And of  
18 note, it now meets the proportional hazards  
19 assumption.

20           So we thought that it would be useful to  
21 place this in a population context, since these drugs  
22 are being given -- they've been given to millions of

1 elderly in the United States and it would be important  
2 to put this in a population context. What exactly  
3 does it mean when you have an attributable risk that's  
4 elevated? For example, an elevated attributable risk  
5 for MI, stroke, heart failure, or death, and what that  
6 translates to is a number needed to harm of 60.

7           So this would be 60 people treated for a  
8 year would generate one extra event, an event that  
9 wouldn't occur had these patients been on pioglitazone  
10 instead of rosiglitazone. And what that translates to  
11 over the time that rosiglitazone and pioglitazone had  
12 been on the market is roughly 48,000 excess events in  
13 the elderly because of this.

14           Now, some people at FDA in the past have  
15 said that heart failure, for example, isn't important,  
16 because it's just a little bit of extra fluid, it's  
17 pedal edema, give them a diuretic and they're okay.

18           Well, tell that to the people who are  
19 hospitalized with congestive heart failure. And in  
20 our study, heart failure carried a 2.5 percent case  
21 fatality rate and engendered medical care costs of  
22 about \$30,000. So I would challenge the notion that

1 heart failure itself isn't an important outcome.

2           Now, there's also some question why would  
3 studies in younger patients show an increase in acute  
4 myocardial infarction in observational studies, and  
5 ours would not find a statistically significant  
6 increase in acute myocardial infarction.

7           One possibility is that there's a change in  
8 demography in the expression of cardiovascular disease  
9 with advancing age. Dr. Nissen spoke early in the  
10 meeting about this. Dr. Gelperin presented some  
11 statistics.

12           What I've presented here is the ratio by age  
13 group for myocardial infarction that survives the  
14 hospital, because in our study, to be counted as a  
15 myocardial infarction, you had to live long enough to  
16 get admitted to hospital. If you died before that  
17 happened, you might be counted as a death, but you  
18 wouldn't be counted as an MI.

19           In the 45 to 64 age group, which is like  
20 most of the non-elderly studies that Dr. Gelperin  
21 showed, it's about 60 MIs for every sudden cardiac  
22 death. This comes from national health care data from



1 the Centers for Disease Control and a national  
2 inpatient sample from AHRQ.

3 By the time you get to 85 or so, the ratio s  
4 now 13 to 1. In our study, nearly 20 percent of our  
5 patients fell into this latter category. Just  
6 remember, the mean age in our study was 74 and we had  
7 a substantial number of patients who were 80 or 85 or  
8 older.

9 So one possibility for why we have an  
10 increase in all cause mortality, it's not that people  
11 are dying of COPD or dementia because they took  
12 rosiglitazone. We think it's because it's a  
13 cardiovascular manifestation of the drug and that  
14 would most likely be expressed as sudden cardiac  
15 death.

16 One other possibility that could be also  
17 contributing to this is that there is a change with  
18 increasing age in the ratio of MI to stroke. Older  
19 people have a -- they're more likely to have a stroke  
20 than younger people. The same with MI. But the ratios  
21 of that difference are different with age.

22 In younger patients, the ratio of MI to

1 stroke is 1.7 to 1. And by the time you get to the 85  
2 plus, you're more likely to have -- it's like .9 to 1.  
3 So you're more likely to have a stroke than you are to  
4 have a heart attack.

5           So what we might be seeing in our study, as  
6 well, is what would be called competing risks and  
7 differential manifestation of vascular disease. If  
8 the underlying mechanism were, for example, rupture of  
9 plaque caused by turning on a gene for metalla-  
10 proteinase, well, we have plaque in our carotid  
11 arteries, we have plaque in our middle cerebral  
12 arteries, we have plaque in our upper vertebral  
13 arteries. So the mechanism of plaque rupture in those  
14 arteries is probably no different than the rupture of  
15 plaque in coronary arteries.

16           Now, what I'd like to do is focus on --  
17 there are only three observational studies that have  
18 been done in patients who are 65 or older exclusively.  
19 So those data are summarized here.

20           The Winkelmayer paper, which has been  
21 discussed a little bit before, was discussed in New  
22 Jersey and Pennsylvania, patients who were eligible

1 for both Medicaid and Medicare during the years 2000  
2 to 2005.

3 The Jurrlink study was conducted in Ontario,  
4 Canada for the years 2002 to 2008, and it's basically  
5 the Canadian version of Medicare for the elderly for  
6 this one province.

7 Then the study that I and my colleagues  
8 completed in Medicare is for the entire country for  
9 2006 to 2009. What I'd like to show you is that for  
10 acute myocardial infarction, the definitions used in  
11 all three studies for AMI was the same definition, and  
12 we got the same results.

13 For stroke, the definition used by  
14 Winkelmayr, it included transient ischemic attack,  
15 which, A, isn't a stroke; B, is highly misdiagnosed.  
16 I'm a neurologist and I can attest to that. But it  
17 also included this term, "other ill-defined  
18 cerebrovascular disease, which has been shown to have  
19 a notoriously low positive predictive value for  
20 stroke. So what I would submit is that although  
21 Winkelmayr and colleagues looked for stroke, the  
22 definition that they used, TIA and this other code

1 would, if national statistics apply, have affected 40  
2 percent of their case material That's more than  
3 enough to bias towards the null. A 27 percent of risk  
4 can now make it statistically significant.

5 All three studies found increased risks and  
6 for all cause mortality, all three found increased  
7 risks.

8 So this now summarizes, as a meta-analysis,  
9 the data for AMI in observational studies comparing  
10 rosiglitazone to pioglitazone in older patients. As  
11 you can see here, there is very little heterogeneity  
12 between these groups. The point estimate was 1.06,,  
13 and it's on the cusp of statistical significance.

14 But the important thing isn't so much the  
15 statistical significance as to say what's more likely.  
16 It's more likely that this drug is increasing the  
17 risk, even in the elderly, than that it's not, and  
18 that, I think, is the important thing. The search for  
19 definitive proof of harm is not protective of public  
20 health.

21 DR. BURMAN: Dr. Graham, it's 3:23. If you  
22 would, please, sum up.

1 DR. GRAHAM: Two more slides, I will. Thank  
2 you.

3 We, here, look at heart failure and , once  
4 again, see that there is an increased risk and very  
5 tight confidence intervals. And then for all cause  
6 mortality, 14 percent increase, very tight confidence  
7 intervals.

8 So any observational study has limitations.  
9 Ours has limitations, as well. We discuss those I our  
10 background package and I'd e happy to discuss those  
11 more during the question-and-answer session.

12 Our conclusions are that in older adults,  
13 compared to pioglitazone, rosiglitazone increased the  
14 risk of hospitalized heart failure; it increased the  
15 risk of stroke; it increased the risk of death.; and,  
16 it increased the risk of composites for MI, MI stroke  
17 or death, and MI, stroke, heart failure or death.

18 This increase in all cause mortality, we  
19 believe is most likely due to an increase in out of  
20 hospital sudden cardiac death. We've heard previously  
21 that about 70 percent of deaths in diabetic patients  
22 are of an ischemic cardiac nature.

1           It seems unlikely to us that the increase in  
2   mortality that we're seeing with this drug is due to a  
3   non-specific increase in all the other multiple causes  
4   of death that could affect the elderly, it's more  
5   likely due to a specific -- increase in a specific  
6   cause of death and we believe that would be sudden  
7   cardiac death, which could then reduce survivorship  
8   plausibly to be counted as AMI in our study.

9           Then, finally, although MI is not  
10   statistically significantly increased, the upper bound  
11   of the confidence interval does not exclude a could  
12   clinically important excess risk.

13           Thank you.

14           DR. BURMAN: Dr. Graham, thank you. Thank  
15   you for the discussion. We'll open the floor for  
16   questions.

17           DR. KNOWLER: Did I understand you to say  
18   that the average duration of use of TZDs was about six  
19   months, at least in the elderly.

20           DR. GRAHAM: It was actually a little less  
21   than that, yes. The mean use, right, was about six  
22   months. The median use is about 3.5 months.

1 DR. KNOWLER: Is that for both pio and rosi?

2 DR. GRAHAM: Yes. They were the same for  
3 both groups.

4 DR. KNOWLER: Now, is this just a matter of  
5 administrative censoring, the study wasn't long  
6 enough? So why do they go off? Do they need to go on  
7 insulin or are they going off because of side effects?

8 DR. GRAHAM: We haven't explored what the  
9 reasons are. One, we're not able to go back to  
10 medical records to look at that. It would be an  
11 incredible number. But I can tell you that most of  
12 the patients who go off the drug went off the drug  
13 because they entered hospital.

14 Most of those patients entered hospital for  
15 -- actually, for management of their diabetes and when  
16 they left the hospital, they were no longer taking the  
17 TZD.

18 So things happened in the hospital, their  
19 management was changed, and they were taken off the  
20 TZD. We have not looked in this study -- that's  
21 something -- a very interesting question to look at,  
22 but I can't tell you what drugs these patients left

1 the hospital on that they weren't on when they went  
2 into the hospital.

3 DR. KNOWLER: So I'd just like to end with a  
4 comment. If this is really generalizable that the  
5 drugs are only used for several months, on average, it  
6 seems like despite the safety concerns, that they  
7 can't be having a huge beneficial impact on the  
8 lifelong course of a chronic disease if they're only  
9 used for a few months.

10 DR. GRAHAM: I've argued that back since  
11 rezulin. So go back to 2000 and read the transcript  
12 for that advisory meeting, and that's exactly the  
13 point. If you don't stay on a drug long enough to get  
14 a benefit, then all you're buying is the risk. And in  
15 this case, what we tried to do is focus on rosi and  
16 pio, two drugs where you just heard Dr. Parks say  
17 there is no difference in their glycemic control; so  
18 theoretically, there's no difference in their  
19 benefits.

20 So what we're looking at then is a  
21 difference in their harms or relative harms.

22 DR. BURMAN: Thank you. Dr. Platt?



1 DR. PLATT: So first, a comment. For those  
2 who don't swim in this sea, this kind of use of  
3 Medicare data is really first of its type and quite  
4 extraordinary. So you've really accomplished quite a  
5 lot in showing the way to use large datasets,  
6 especially from CMS.

7 Since I think we're going to focus quite a  
8 lot on all cause mortality, I'm interested in your  
9 view of why there is a difference in direction between  
10 your all cause mortality observation and the several  
11 studies we've already seen discussed that showed a  
12 rosiglitazone benefit, not compared to pioglitazone,  
13 but to other agents.

14 DR. GRAHAM: Well, a couple things. One,  
15 it's important to note that our study doesn't have  
16 sort of an external reference to say is the risk of,  
17 say, rosiglitazone absolutely increased in some cosmic  
18 sense compared to some great unknown out there. But  
19 relative to pioglitazone, it is increased.

20 For congestive heart failure, we do have the  
21 benchmarking compared to other treatments and placebo,  
22 where we know that both drugs increase heart failure.

1 So if there's a difference in one increases it more  
2 than the other, then I think you can point at that and  
3 say it's a true harm.

4 Now, to get to your question, looking at the  
5 other data, I personally believe, and I'm on record as  
6 having said this about RECORD back in 2007, I think  
7 that we have underestimated the impact of an open  
8 label design on the capacity for bias to be introduced  
9 into the study and that that bias could affect all  
10 outcomes, all cause morality included.

11 If all it takes is an investigator going to  
12 a person who is an extremist and saying, "I don't  
13 think it's a good idea for you to be in the trial  
14 anymore, do you want to be off it," and the patient,  
15 "Yes," and they check the box and they're removed from  
16 the study and their death doesn't counted or if the  
17 investigator just decides on their own, "This patient  
18 is going down the tubes. I'm just going to check the  
19 box 'withdrew from the study.'"

20 The fact that it's open label -- see, me, I  
21 would be reversing the roles. I'll talk about this in  
22 the next talk, but I'll introduce it now. There is a

1 great asymmetry in the way the agency handles safety  
2 and efficacy.

3 If the RECORD trial was a study to get  
4 registration of the drug, to get approval of  
5 rosiglitazone for some indication, it wouldn't even be  
6 presented. You wouldn't even hear about it, because  
7 it's garbage.

8 So why would we consider using RECORD that  
9 would be garbage for approval as being something  
10 that's so perfect, so holy, that it could exonerate a  
11 drug or that it actually can be used to establish that  
12 its safe.

13 That asymmetry does not protect public  
14 health. And so I personally believe that everything  
15 we've seen up to now, talking about RECORD, as Dr.  
16 Marciniak said, you can't trust it; and if we do trust  
17 it, we're engaging in the willing suspension of  
18 disbelief.

19 DR. BURMAN: One last question. Ms.  
20 Killian?

21 MS. KILLIAN: I don't have a question as  
22 much as I have two short observations. One is that

1 when I'm thinking back as to what we were going for in  
2 our original 2007 meeting in terms of labeling  
3 requirements, et criteria, it seems to me that the  
4 Medicare population is precisely the population to  
5 whom we were targeting that label, because they seem  
6 to be more at risk for cardiovascular risk.

7           So it doesn't surprise me that we would see  
8 these kind of events or risks in a population that was  
9 prone to it anyway. I personally told my mother not  
10 to take Avandia after that meeting, because she was a  
11 cardiac patient and had been for 20 years. I think  
12 that we're sort of preaching to the choir there.

13           The second observation that occurred to me  
14 was that when we're talking about pio and rosi being  
15 comparable in terms of glucose control, which is what  
16 they're designed to do, and they're saying so there's  
17 no difference in benefit, my thought, as a patient,  
18 acknowledging the progressive nature of the disease  
19 and how drugs tend to lose efficacy over use, is that  
20 the benefit of having a drug like this, if you can  
21 control, limit it or suggest it for populations who  
22 have less of a risk, the benefit might be having

1 another drug in the arsenal that you can turn to when  
2 the one you're on starts to fail you.

3 So that's just my observation as a patient.

4 DR. GRAHAM: Could I just make one response  
5 to that, which is that if it were true that patients  
6 who fail pioglitazone do well on rosiglitazone, that  
7 might be at least something to actually seriously  
8 consider. I'm not aware that any such study has been  
9 done and I've never heard anyone within OND --  
10 actually, I've heard them say the opposite. They  
11 don't believe that if you fail one you're going to  
12 respond to the other.

13 MS. KILLIAN: Right. That might be worth  
14 looking at.

15 DR. BURMAN: Thank you all. I think we have  
16 to move on. Dr. Graham will now proceed with a  
17 presentation of his personal views of the TIDE trial.

18 DR. GRAHAM: Right. I'd just like to make  
19 one clarification on that, which is that as part of my  
20 job that I was paid to do, in 2008, I and Dr. Gelperin  
21 wrote a benefit-risk assessment of rosiglitazone to  
22 pioglitazone that we submitted in proper channels,

1 .had a discussion with the Office of New Drugs, and  
2 which was signed off on by our office director. And  
3 what I'm presenting here is basically a summary of  
4 what was there.

5           So it may be a personal opinion, deeply  
6 held, but it was also part of my official job, and it  
7 was actually signed off by my office.

8           So I would like to talk a little bit about  
9 TIDE and benefit-risk considerations. And the reason  
10 I want to talk about TIDE is because I want to talk  
11 about medical ethics and harm. And the reason I want  
12 to talk about this is because -- and it's a touchy  
13 issue and the things I'm going to say, people might  
14 take offense at them. If you do, I'm not  
15 intentionally or intending to criticize any  
16 individuals or their motivations. What I'm talking  
17 about is this is a paradigm that I think it's the  
18 wrong paradigm for what we face now.

19           Clinical trials and the whole realm of  
20 medical ethics really, for the large part, emerged from  
21 trying to show that drugs do good, trying to show  
22 beneficial effects.

1           They weren't designed to show that drugs  
2   harm people, that they hurt people. So the whole  
3   notion of medical ethics was in the context of we're  
4   doing a study to show if a drug has a benefit, and how  
5   do we protect patients from being used the way you  
6   might use al laboratory rat, from exploiting them, and  
7   that was the context.

8           We're now talking about trials that are  
9   being done to definitively prove harm, and that's a  
10   very, very different situation. And so if you have  
11   that backdrop, you'll understand maybe a little bit  
12   better what I'm trying to say, maybe not quite  
13   eloquently enough or intelligibly enough about TIDE  
14   AND MY CONCERNS AND Dr. Gelperin's concerns, and,  
15   actually, other people's concerns, as well.

16           First, I just want to point out TIDE,  
17   thiazolidine intervention with vitamin D evaluation.  
18   Can anybody in this room tell from that title that  
19   this is a cardiovascular risk study? I didn't think  
20   so. I can't either.

21           Now, I've described this slide before and  
22   I've explained to you why we thought rosiglitazone and

1 pioglitazone would be the best comparison.

2 Well, when CDER ordered GSK to do the TIDE  
3 study, it was to establish definitive proof of harm.  
4 That was it. It was we're here now because we don't  
5 have a p-value that everybody will agree is below .05  
6 that rosiglitazone increases risks. This is very  
7 different than saying, oh, does rosi increase the risk  
8 or decrease the risk.

9 This is one-sided. This is not a two-sided  
10 p-value. This is all one-sided. Does it increase  
11 harm?

12 The purpose of the study was to establish  
13 with definitive certainty that the risks are increased  
14 with this drug.

15 Now, you saw in Dr. Parks' initial  
16 presentation that the purpose of the study was to  
17 compare rosiglitazone to pioglitazone. But  
18 rosiglitazone versus pioglitazone is not the primary  
19 analysis of TIDE.

20 The primary analysis of TIDE is basically a  
21 repeat of the RECORD study. And you have to wonder,  
22 well, why is this a secondary analysis. Because FDA



1 doesn't traditionally use the secondary analysis of  
2 anything to regulate on. They use it as hypothesis  
3 generation.

4  
5 So the primary analysis compares  
6 rosiglitazone versus non-TZD, not rosi versus pio.  
7 We, in our office, vigorously oppose this and we're  
8 ignored. The most clinically relevant comparator , we  
9 thought, was pioglitazone, and FDA has an historical  
10 disregard for secondary analyses.

11 The study involved enrollment of patients or  
12 inclusion of patients who got switched onto insulin or  
13 nitrates, and it had a non-inferiority margin of 30  
14 percent.

15 Now, I want to say a little something here  
16 about the FDA guidance. It allows drugs to come on  
17 the market initially that have an upper bound of the  
18 confidence interval below 80 percent increased risk  
19 in, say, myocardial infarction.

20 Then they have to go and do another study to  
21 show that the risk is actually then below 30 percent.  
22 But during those five years, they can sell zillions of

1     dollars of drug.

2                 In the FDA guidance, there is no written  
3     justification citing the evidence base that says that  
4     these are, in quotes, "acceptable margins." What are  
5     we buying for a 1 percent reduction in hemoglobin A1C  
6     or .5 percent reduction in hemoglobin A1C in terms of  
7     meaningful health benefits?

8                 The whole reason -- one of the big reasons  
9     we treat people with diabetes in the first place is to  
10    prevent this 80 percent or this 30 percent increase in  
11    myocardial infarction.

12                So I would ask FDA to give us justification  
13    for that, because I disagree with these numbers and I  
14    think that this committee is in a position to ask FDA  
15    to consider population impacts of drugs before it  
16    issues guidances.

17                The other thing about the TIDE trial is it's  
18    a non-inferiority study. The null hypothesis there is  
19    basically rosiglitazone increases cardiovascular risk.  
20    That's the null hypothesis. That's the state of  
21    nature.

22                The drug increases risk. Now, do the study

1 and prove to me, reject that hypothesis. Well, why  
2 would anybody roll on a study like that?

3           This is just to show you that we did,  
4 indeed, do a benefit-risk assessment of this drug in  
5 2008. In that benefit-risk assessment, we looked to  
6 see what are the documented health benefits of  
7 rosiglitazone, of pioglitazone, and of other  
8 treatments for diabetes. And we found that with  
9 respect to macrovascular disease and microvascular  
10 disease, that there's no evidence that rosiglitazone  
11 confers a health benefit to patients who take it.

12           It doesn't mean that maybe it doesn't do  
13 that. It just means there's no evidence. But if  
14 we're evidence-based, aren't we supposed to follow the  
15 evidence?

16           This is just another slide that emphasizes  
17 the same thing. There were published meta-analyses  
18 before the 2007 advisory meeting that showed  
19 pioglitazone seeming to have increased risks, but less  
20 of an increased risk than rosiglitazone with respect  
21 to congestive heart failure.

22           So now I want to get to ethical

1 considerations of TIDE. Is the TIDE trial ethical?  
2 First, it's a study to establish harm. Is it ethical  
3 to subject human subjects to a clinical trial where  
4 the purpose is to establish harm? The answer to that  
5 is no, and that was established at the time of World  
6 War II, when unethical human experiments were  
7 conducted to see what's the human tolerance for  
8 things.

9           So if the purpose of a study is to do harm,  
10 it's unethical right off the bat. You can do that to  
11 laboratory animals. You don't do it to human beings.

12           The next question is, well, are we at  
13 equipoise, and equipoise requires the equivalent  
14 evidence or equally distributed uncertainty, and, from  
15 the observational data, a pio versus rosi. We don't  
16 have that. You saw from Dr. Gelperin's analysis 10  
17 different studies. Not one of them were on the other  
18 side that favors rosi.

19           You saw the analyses that we've done looking  
20 in the elderly. None of them are favoring rosi. Why  
21 would you think then there is equivalent evidence?  
22 Unless you're prepared to say that observational data

1 is not evidence at all. And if that's the case, we'll  
2 do away with post-marketing and FDA and save it a  
3 bundle of money.

4 Now, the Belmont report talked about  
5 positive expected value. What that means is if you go  
6 into a clinical trial, you, as a human subject, expect  
7 to get something good out of being in the trial. What  
8 good do you get out of entering a trial, the purpose  
9 of which is to establish harm; when the treatments  
10 you're going to be given are no different with respect  
11 to any health benefit that might possibly accrue?

12 So there is no positive expected value. It  
13 fails. It's a bad deal trial. What does a bad deal  
14 trial mean? It means the people going into the trial,  
15 the best that they can hope for us not to get the drug  
16 that causes a problem. They're not going to get  
17 anything good out of the trial.

18 Now, in order to do a bad deal trial,  
19 there's only a couple of ways you can do it.  
20 Basically, they all involve what's called human  
21 subject exploitation. Not my words. Bioethicist's  
22 words.

1           Now, if you can enroll 15 or 20,000 people  
2   who are completely altruistic, perfectly altruistic,  
3   willing to sacrifice their lives for science. Maybe  
4   you could do it, but that's humanly impossible.

5           Are the distribution of benefits and harms  
6   of participation equally distributed? Well, the  
7   benefits go to the company. Right? They're doing the  
8   trial. The patent life of the drug is extended. It  
9   goes to FDA. They can say we're waiting for the  
10  results, so we don't have to make a decision now.

11          Who gets hurt? It's the patients. The  
12  patients who participate in the study get hurt. So  
13  there is not equal distribution of benefits or harm of  
14  participation. So it fails.

15          The duty of nonexploitation, well, it fails  
16  on the face of that. Investigators have a primary  
17  responsibility not to exploit human subjects. This  
18  study is intrinsically exploitative.

19          Nash equilibrium, I could talk about it, but  
20  I don't understand it. Fair subject selection and  
21  favorable benefit-risk balance are different ways of  
22  describing the same thing as this, benefits of

1 participation.

2           So finally, we get down to informed consent.

3 A couple things I'd like to say about informed  
4 consent.

5 First, the presence of informed consent does not  
6 render ethical a study that is intrinsically not  
7 ethical. So an unethical study is not made ethical by  
8 the presence of informed consent.

9           Two, patients cannot consent to be  
10 exploited. They can sign the paper, but that's not  
11 consent. And finally, informed consent does not make  
12 exploitation ethical.

13           So here is the informed consent form that we  
14 got from actually Senator Grassley's Website. We had  
15 a copy from the company, but I wasn't sure if I could  
16 present that. So I had to present one that was in the  
17 public domain.

18           We did ask the company for updated versions  
19 of the informed consent form, and we got this big  
20 submission, but all the informed consent forms looked  
21 like this one. So if there's a difference, it's one  
22 that escapes my immediate observation, and I and four

1 other people looked and compared them to see.

2           In any event, what I want you to focus on  
3 is, first, the title, then reading the purpose, and  
4 just sort of getting a sense here of the language.  
5 People with Type II diabetes can have all these  
6 different things, even death. They can also have  
7 broken bones and cancers. And some studies suggest  
8 that a class of drugs, TZDs and/or vitamin D, may  
9 change some of these things.

10           When you read through all this, do you get  
11 any sense that we're talking about problems with  
12 rosiglitazone? I don't.

13           The study title is misleading.  
14 Cardiovascular endpoint trials typically have some  
15 reference to the fact that they're talking about the  
16 heart, the vascular system, or some endpoints. This  
17 doesn't mention any of that.

18           It doesn't mention that rosiglitazone is  
19 actually the sole source of cardiovascular concern.  
20 You can't get that from that purpose statement. I  
21 defy you to diagram that purpose statement and come up  
22 with the conclusion that they're talking about



1   rosiglitazone and which risks rosiglitazone is -- the  
2   concern exists about. There's no clear statement of  
3   purpose.

4               Rosiglitazone and pioglitazone are lumped  
5   together as if they share the same risks. Well, they  
6   don't. There's no mention that the purpose is to  
7   definitively establish harm. There's no mention that  
8   GSK was ordered by FDA to do the study.

9               Vitamin D and cancer. Why on earth is a  
10   cardiovascular risk study have vitamin D in it? WE  
11   fought this tooth and nail in our Office of  
12   Surveillance and Epidemiology and, once again, the  
13   miracles of equal voice, we got stepped on. And so  
14   vitamin D and cancer are part of that study. I don't  
15   know what it has to do with the cardiovascular  
16   endpoint.

17              The association of vitamin D and cancer, A,  
18   is weak; B, it's irrelevant to cardiovascular disease;  
19   it introduces confusion; and, my own belief and Dr.  
20   Gelperin's belief and the belief of many people I have  
21   talked to about this is that it was probably intended  
22   to mask the bad deal nature of the study.

1           Now, the emphasis in TIDE is really shifted  
2   from its true cardiovascular purpose. MI is mentioned  
3   five times in the informed consent, cancer four times,  
4   and vitamin D 18 times. What is this study about?  
5   It's not about MI.

6           There's no mention of the 2007 advisory  
7   committee vote. I think if I was enrolling in this  
8   study or a loved one was going to enroll in this  
9   study, I'd want to know that an FDA advisory committee  
10   voted 20-3 that rosiglitazone increases ischemic  
11   cardiac risk. I would want to know that, but it's  
12   nowhere to be found in the consent form.

13          There's no mention of a labeling difference  
14   for rosiglitazone or pioglitazone. I think that if I  
15   was to enroll in the study or if a loved one were to  
16   enroll in the study, they or I would want to know that  
17   fact.

18          There's no mention that FDA has no  
19   cardiovascular concerns with pioglitazone. We were  
20   having concern about heart failure, but this study  
21   isn't about heart failure. I would want to know that.

22          DR. BURMAN: Dr. Graham, I apologize.

1 Please, it's 3:45.

2 DR. GRAHAM: I'll bring this quickly to a  
3 close.

4 DR. BURMAN: Thank you.

5 DR. GRAHAM: The primary analysis is a  
6 repeat of RECORD. There's no mention that, okay, it's  
7 not the ADA, it's the ADA treatment guidelines  
8 committee. But you know what? If the world's leading  
9 experts in diabetes said rosiglitazone isn't  
10 recommended to be used in the treatment of diabetes, I  
11 think that's something that should be in an informed  
12 consent form. Maybe I'm wrong, but I think that most  
13 consumers would want to know that fact. And I think  
14 if they knew that fact, they wouldn't enroll in the  
15 study.

16 The most important analysis, rosi versus  
17 pio, is relegated to secondary status. We went over  
18 that.

19 Now, FDA handles benefit and risk  
20 asymmetrically. I don't have enough time to talk  
21 about that, but the panel has seen the slides.

22 The most important thing to note here is

1   that FDA focuses on definitive proof of harm.  So  
2   we're not even going to talk about the fact that  
3   there's no difference in benefits of these drugs.

4               So if you're going to do a benefit to risk  
5   or risk to benefit, you've got a big zero on the  
6   difference between these two drugs for benefits.  So  
7   all we're talking about is risk.  You would think that  
8   that would be an easier discussion.  But the way FDA  
9   works, you have to establish definitive proof of harm  
10  first.  Then once you've done that, then we can talk  
11  about whether there's definitive proof that the drug  
12  actually helps, and I think that that asymmetry is  
13  something that needs to be addressed, as well.

14              I'll close there.  Thank you.

15              DR. BURMAN:  Thank you very much.  I don't  
16  think we have time for questions at the moment.  We  
17  will take a 15-minute break.  Panel members, please  
18  remember there should be no discussion of the meeting  
19  topic during the break among yourselves or other  
20  members of the audience.  We will reconvene at 4:00.

21              [Whereupon, a recess was taken.]

22              DR. BURMAN:  Please, let's get started.  We

1 will now proceed with our presentation from the FDA  
2 presenter, Dr. Fiona Callahan.

3 Dr. Callahan?

4 DR. CALLAHAN: Thank you. Good afternoon.  
5 I will be presenting the update of the 2007 FDA meta-  
6 analysis of rosiglitazone, with 10 additional trials.

7 In the first half of the talk, I will be  
8 discussing the goals and the statistical analysis plan  
9 for both the pioglitazone meta-analysis and the  
10 rosiglitazone meta-analysis. In the second half of  
11 the talk, I will discuss the results of the  
12 rosiglitazone meta-analysis alone.

13 Following this talk, Dr. McEvoy will present  
14 a parallel analysis of pioglitazone and a comparison  
15 of the meta-analyses of rosiglitazone and  
16 pioglitazone. Firstly, I will cover some background  
17 and then the two goals of the meta-analyses, and the  
18 statistical analysis plan for both pioglitazone and  
19 rosiglitazone.

20 Then for rosiglitazone alone, I will  
21 summarize the patient information and trial  
22 information, before moving on to the results of the

1 meta-analysis for rosiglitazone. I will finish by  
2 summarizing these findings.

3           The previous FDA meta-analysis of  
4 rosiglitazone was presented at an FDA advisory  
5 committee meeting in 2007. It was comprised of 42  
6 trials from the GSK database, and some of the results  
7 are summarized here. An observation of greater than 1  
8 indicates an increased risk of a cardiovascular event  
9 on rosiglitazone compared to control.

10           In 2007, total myocardial ischemia was shown  
11 to have an odds ratio of 1.4 and was statistically  
12 significant. Serious myocardial ischemia also had an  
13 estimate of 1.4, but was not statistically  
14 significant. MACE, the composite endpoint comprised of  
15 myocardial infarction, stroke, and cardiovascular  
16 death, had an estimate for the odds ratio of 1.2, and  
17 myocardial infarction had an estimate of 1.5. Neither  
18 of these results were significant.

19           Since 2007, 10 additional trials have become  
20 available and in the second half of this talk, I will  
21 focus on the results from the total of the 52 trials.  
22 For pioglitazone, there have been no previous FDA

1 meta-analyses.

2           The goals for the rosiglitazone and  
3 pioglitazone meta-analysis are presented here. There  
4 are two main goals. The first is to update the  
5 previous FDA meta-analysis with the 10 new trials for  
6 rosiglitazone. This first goal is the one that I will  
7 be addressing here, and the second is to conduct a  
8 meta-analysis of pioglitazone in order to potentially  
9 compare the cardiovascular risks. Dr. McEvoy will be  
10 covering the second point.

11           Before outlining the statistical analysis  
12 plan that was used for both pioglitazone and  
13 rosiglitazone, I will discuss some of the general  
14 issues that arose when planning the meta-analyses.  
15 The total clinical trial database for rosiglitazone  
16 and pioglitazone consisted of many short-term trials  
17 and a few long-term trials, and, in general, a  
18 complete picture of the safety of the two drugs can  
19 only be made by considering information from both of  
20 these types of trials.

21           In the FDA analysis of rosiglitazone in  
22 2007, three large trials, DREAM, ADOPT and RECORD,

1 were not included in the meta-analysis, but were  
2 instead analyzed separately where the data was  
3 available.

4           These large clinical trials were viewed as  
5 independent sources of information. The results from  
6 the large trials could instead be used to confirm  
7 potentially the results seen in a meta-analysis.

8           Furthermore, these large trials would  
9 dominate the meta-analysis in the sense that the meta-  
10 analysis with these trials would basically give the  
11 same results as those obtained individually from the  
12 larger trials.

13           Information from the smaller trials can only  
14 be evaluated when they are not combined with the  
15 larger trials. The 2010 FDA meta-analysis does not  
16 include these large trials.

17           It is also important to note that the large  
18 trials of rosiglitazone and pioglitazone tended to  
19 have different characteristics. Including them would  
20 further limit the comparability of the rosiglitazone  
21 and pioglitazone meta-analysis, and Dr. McEvoy will  
22 talk more about this issue.



1           The trials for the pioglitazone meta-  
2 analysis were selected using the same criteria for the  
3 studies as selected for rosiglitazone. This was done  
4 to limit the qualitative differences between the two  
5 meta-analyses, which might preclude comparisons of  
6 risk.

7           I will now consider the plan for the  
8 statistical analysis. A nearly identical plan for the  
9 meta-analyses of both rosiglitazone and pioglitazone  
10 was planned in order to maximize the similarity  
11 between the two analyses, in order to aid  
12 comparability between the two drugs.

13           Nonetheless, it was also recognized that the  
14 trial designs and the patient populations differed  
15 between the two drugs. Groups of similar trials, for  
16 example, trials that had the same randomized control,  
17 were analyzed individually. Not only are these trial  
18 level groups of interest in and of themselves, the  
19 trials of the two drugs within the trial level groups  
20 were expected to be more similar to each other than in  
21 the overall trial set.

22           Unless otherwise stated, all the methods are

1 stratified by trial as opposed to pooling the  
2 information from all of the trials. This is an  
3 important feature of the analysis, as it preserves the  
4 randomized comparisons within each of the trials.  
5 Without stratification, differences in the trial  
6 characteristics can confound the summary results, in a  
7 phenomenon known as Simpson's paradox.

8           This slide gives the outline of the  
9 statistical analysis plan. In subsequent slides, I  
10 will describe the trial inclusion criteria, the  
11 endpoints, the trial level groups, the subgroups that  
12 were considered, and the statistical methodology that  
13 was used.

14           This statistical analysis plan was used for  
15 both the rosiglitazone and pioglitazone meta-analysis.

16           The trial inclusion criteria for the meta-  
17 analyses are given here. All of the trial data was  
18 taken from either the GSK database for rosiglitazone  
19 or the Takeda database for pioglitazone. The  
20 inclusion criteria were as follows. Trials had a  
21 randomized comparator. Trials had between two months'  
22 and two years' duration. Patients in the trials had

1 to have Type II diabetes at baseline. The trials had  
2 to be double-blinded.

3 The total daily dose was either 4 or 8  
4 milligrams for rosiglitazone or 30 or 45 milligrams  
5 for pioglitazone. In addition, the data was typically  
6 centrally monitored, and patient level data had to be  
7 available. Finally, the investigative drugs in the  
8 trials were FDA approved.

9 The primary and secondary cardiovascular  
10 endpoints for the meta-analyses of pioglitazone and  
11 rosiglitazone are given here. The primary endpoint  
12 was MACE, or Major Adverse Cardiovascular Event, and  
13 is a composite endpoint comprised of cardiovascular  
14 death, stroke, and myocardial infarction.

15 Each of the components of MACE was also  
16 considered separately as secondary endpoints. The  
17 other secondary endpoints were all cause death, serous  
18 myocardial ischemia, total myocardial ischemia, and  
19 congestive heart failure.

20 Myocardial ischemia is a broadly defined  
21 cardiovascular endpoint, including such events as  
22 angina and myocardial infarction. Serious myocardial

1 ischemia is comprised of only those ischemic events  
2 associated with serious adverse events. And total  
3 myocardial ischemia is comprised of all the events of  
4 myocardial ischemia, adverse events of myocardial  
5 ischemia.

6           It should also be noted that only the FDA-  
7 defined endpoints were used in the analysis, except  
8 where there were prospectively adjudicated endpoints  
9 for a trial. The FDA-defined endpoints differ from  
10 the GlaxoSmithKline-defined endpoints, and the FDA  
11 endpoints used in the 2007 analysis differ from those  
12 used in the 2010 analysis.

13           Before I move on to describing the trial  
14 level groups, I will take a moment to explain how  
15 trials were assigned to the trial level groups. An  
16 important feature of the analyses of rosiglitazone and  
17 pioglitazone was to group similar trials together  
18 based on various trial level characteristics. This  
19 enabled comparisons of the results from similar trials  
20 between the pioglitazone and rosiglitazone meta-  
21 analysis.

22           An example of assigning the trials to these

1 trial level groups is given here. For example, a  
2 trial with a rosiglitazone plus metformin arm and a  
3 placebo plus metformin arm would be considered both a  
4 placebo-controlled trial and a metformin add-on  
5 therapy trial.

6 Furthermore, it should be noted that the  
7 trials with three or more arms may contribute to more  
8 than one trial level group.

9 The first type of trial level group was  
10 based on randomized comparator. These trial level  
11 groups included placebo-controlled trials and active-  
12 controlled trials, and, in addition, the actively-  
13 controlled trials were broken up into sulfonylurea-  
14 controlled and metformin-controlled trials.

15 A second type of trial level group was based  
16 on add-on therapy. Typically, an add-on therapy is  
17 one where all of the patients are given a particular  
18 therapy in addition to their randomized therapy. For  
19 example, all the patients included in, say, the  
20 metformin add-on group were receiving metformin in  
21 addition to their randomized therapy; and, similarly  
22 for sulfonylurea, metformin and insulin and the

1     sulfonylurea plus metformin add-on.

2             A monotherapy trial is one with no add-on  
3     therapy. Patients are given only one therapy, for  
4     example, in a trial with two arms, a rosiglitazone arm  
5     and a metformin arm.

6             Add-on or background medication trials are  
7     any trials that are not monotherapy trials. And  
8     finally, a third type of trial level group was based  
9     on trial duration, six months or less, greater than  
10    six months, and less than or equal to 12 months, and  
11    greater than a year to less than or equal to two  
12    years.

13            Various subgroup analyses were performed  
14    based on demographic groups, baseline medication  
15    groups, prior cardiovascular conditions, and dosage  
16    groups.

17            I will now discuss the statistical methods  
18    used in the meta-analysis. The primary analysis  
19    method was a stratified exact estimate of the odds  
20    ratio. This was consistent with the previous FDA  
21    meta-analysis in 2007.

22            This method is a fixed effects method in

1   that it assumes an underlying constant odds ratio  
2   across the trials. As previously noted, the estimate  
3   was stratified to preserve randomized comparisons. It  
4   should also be noted that trials with zero events in  
5   both arms do not contribute to the estimate of the  
6   odds ratio.

7               Several other methods for analyzing the data  
8   were considered in order to examine the robustness of  
9   the primary analysis method. The data was analyzed  
10   using the stratified estimate of the risk difference.  
11   This is an important estimate, as it does incorporate  
12   the information from the trials with zero events.

13              Proportional hazards regression, again,  
14   stratified by trial, was used to estimate the hazard  
15   ratio. This method was used to account for  
16   differences in follow-up times and hazard functions  
17   over time.

18              A generalized linear mixed model or random  
19   effects model was used to estimate the odds ratio.  
20   This method helps to account for between-trial  
21   heterogeneity.

22              There are, of course, limitations to any

1 meta-analysis and a few of the limitations are  
2 mentioned here. Firstly, the vast majority of trials  
3 were not designed to evaluate the cardiovascular  
4 endpoints. The results of the trials were known  
5 before the statistical analysis plan was developed.

6           There was no adjustment for multiple testing  
7 or multiple comparisons. And finally, it is difficult  
8 to compare the results of the meta-analyses of  
9 pioglitazone and rosiglitazone, because the trials  
10 differed in their trial level characteristics. Dr.  
11 McEvoy will speak more on this point in his  
12 presentation.

13           I will now consider some of the trial level  
14 and patient summaries of the rosiglitazone data, and,  
15 from this point on, I will focus only on the  
16 rosiglitazone meta-analysis.

17           This slide summarizes the trials and  
18 patients by randomized comparator. I would note that  
19 the numbers of trials do not add up to 52, because the  
20 trials were allowed to contribute to more than one  
21 category; similarly, for the patient counts and  
22 percentages.



1           We can see that most of the trials in the  
2   rosiglitazone meta-analysis were placebo-controlled,  
3   with 46 out of 52 trials, or 81 percent, of the  
4   patients falling into that category. In contrast, 24  
5   percent of the patients were in the active-controlled  
6   trials, 18 percent in the sulfonylurea-controlled and  
7   4 percent in the metformin-controlled trials.

8           Note that, also, overall, there are many  
9   more patients, 10,039, in the rosiglitazone arms than  
10   in the comparator arms, with 6,956.

11           This slide summarizes the trials and the  
12   patients by trial duration. Most of the rosiglitazone  
13   trials, 40 out of the 52, or 69 percent of the  
14   patients were in trials of six months or less. Only 5  
15   percent of the patients were in trials of greater than  
16   one year.

17           I now consider some of the patient  
18   characteristics. Most of the patients, or 71 percent,  
19   were less than 65 years old, and 59 percent were male;  
20   44 percent of the patients participated in sites in  
21   the U.S.; and, the average body mass index was 30.

22           This slide summarizes the exposure or actual

1 treatment duration for the rosiglitazone patients.

2 The average duration for patients taking rosiglitazone  
3 was 186 days compared to 191 days for control.

4 I now move on to the counts and the  
5 percentages for the eight outcomes. There were a  
6 total of 109 MACE events in the 52 trials, with .7  
7 percent occurring in the rosiglitazone arm and .6  
8 percent occurring in control arms.

9 Sixteen trials were zero event trials, with  
10 zero MACE events in both arms. There were 17  
11 cardiovascular deaths among rosiglitazone patients and  
12 nine among control patients. Recall that there were  
13 more rosiglitazone patients than control, which makes  
14 it difficult to compare the raw counts.

15 There were 45 patients with MIs among the  
16 rosiglitazone patients and 20 among the control  
17 patients. There were 18 patients with stroke events  
18 among the rosiglitazone patients, and 16 among the  
19 control patients.

20 This slide summarizes the events in the 10  
21 new trials that were not included in the 2007 FDA  
22 meta-analysis. The 10 trials contributed 2,758

1 patients in total, with 1,435 rosiglitazone patients  
2 and 1,323 control patients.

3           The 10 trials contributed 21 MACE events in  
4 total, with 13 among the rosiglitazone patients and  
5 eight among the control patients.

6           The 10 trials also contributed four  
7 cardiovascular deaths, with one among the  
8 rosiglitazone patients and three among the control  
9 patients.

10           I will now review the results of the  
11 rosiglitazone meta-analysis. This graph depicts the  
12 overall results for rosiglitazone for all 52 trials  
13 for both primary and secondary outcomes in the form of  
14 a forest plot.

15           The outcomes are listed in the column along  
16 the left, and along with the estimate of the  
17 stratified odds ratio and the corresponding 95 percent  
18 confidence interval. On the right of the graph, the  
19 estimates for the odds ratio is, for each outcome,  
20 depicted with a small square, and the confidence  
21 limits are represented with a horizontal line.

22           The horizontal axis is given in terms of the

odds ratio and is plotted on a log scale. The vertical line is given at an odds ratio value of 1 for reference. An odds ratio of greater than 1 corresponds to an increased risk of cardiovascular event for rosiglitazone compared to control.

Caution should be shown when attempting to look for trends across these endpoints, as the outcomes are not independent. For example, myocardial infarction is included in the definition of the myocardial ischemia outcomes.

We see that most of the point estimates are greater than 1, except for the stroke outcome. MACE has an estimated odds ratio of 1.44, which means that patients taking rosiglitazone have an estimated 44 percent increased risk of a major adverse cardiovascular event compared to comparator.

The lower confidence limit is near 1, indicating that this finding comes near to statistical significance.

The estimated risk of myocardial infarction has an odds ratio of 1.8, indicating an 80 percent greater risk for patients taking rosiglitazone than

1 patients taking a comparator medication. This is a  
2 statistically significant finding, as the confidence  
3 interval does not include 1.

4 In addition, serious myocardial ischemia,  
5 total myocardial ischemia, and congestive heart  
6 failure all have odds ratios significantly greater  
7 than 1.

8 This is a graph of the survival curve of the  
9 MACE outcome, with the data pooled across the trials.  
10 The risk states of the number of patients remaining  
11 every 90 days is given along the X-axis. That may be  
12 a little difficult to see. And the probability of not  
13 having a MACE event is given along the vertical axis.

14 The rosiglitazone group is indicated by a  
15 solid red line and the control group is indicated by  
16 the dashed black line. Note that the number at risk  
17 falls dramatically after 180 days, or six months, from  
18 approximately 12,000 in both arms to approximately  
19 2,000 by 270 days.

20 Approximately, only 150 patients are left in  
21 the trials by the end of two years. Caution should be  
22 used in interpreting the right-hand side of the graph.

1           In general, the rosiglitazone curve is below  
2   the control curve, indicating a possible higher risk  
3   for rosiglitazone compared to control over this time  
4   span.

5           This slide summarizes the results for the  
6   MACE outcome only for the trials grouped by randomized  
7   comparator. The results are given for the placebo-  
8   controlled trials, the active-controlled trials, and  
9   the active-controlled trials are broken down into  
10   sulfonylurea-controlled and metformin-controlled.  
11   For comparison, the overall odds ratio for MACE is  
12   given at the bottom of the graph.

13           Also, note that when a confidence limit goes  
14   outside the bounds of the horizontal axis, it is  
15   indicated with an arrow, as we can see on the lower  
16   limit of the metformin control group. Again, an odds  
17   ratio of greater than 1 indicates an increased risk of  
18   the events for rosiglitazone.

19           The estimated odds ratio for MACE for each  
20   randomized comparator group are generally greater than  
21   1, except for the metformin control group. The  
22   metformin control groups had a wide confidence

1 interval, owing to the small number of patients in  
2 this group.

3           The result for the placebo-controlled trials  
4 was borderline significant. However, the results for  
5 the placebo control group tend to agree with the  
6 overall results for MACE, because the placebo-  
7 controlled trials make up most of the trials in the  
8 meta-analysis. None of these outcomes are  
9 significant.

10           We now move on to some of the sensitivity  
11 analysis and the results for the risk difference.  
12 Recall that the risk difference analysis incorporates  
13 the results from the trials with zero MACE events.

14           The results are given here for all 52 trials  
15 and the primary and secondary outcomes are given along  
16 the left-hand side. A risk difference of greater than  
17 zero indicates an increased risk of an event for the  
18 rosiglitazone compared to control.

19           Overall, we see a very similar pattern to  
20 the one seen for the odds ratio. Most of the point  
21 estimates are greater than zero and the outcomes that  
22 were significant for the stratified odds ratio are

1 also significant for the stratified risk difference.

2 MACE has a point estimate for the risk  
3 difference of 2.3, indicating 2.3 in excess of the  
4 rosiglitazone per 1,000 patients. Recall that the  
5 average treatment exposure for all the patients was  
6 188 days, or about half a year.

7 Other sensitivity analyses described in the  
8 statistical analysis plan gave consistent results for  
9 the MACE endpoint.

10 I will now summarize the results of the talk  
11 in the context of the previous meta-analyses of  
12 rosiglitazone. This slide summarizes the results of  
13 the 2007 FDA meta-analysis and the 2010 FDA meta-  
14 analysis. For each outcome, the estimate of the odds  
15 ratio and the corresponding confidence interval from  
16 2007 are given, and the corresponding estimates from  
17 the 2010 FDA meta-analysis are given on the right-hand  
18 side.

19 It should be noted that there are some  
20 differences between these two meta-analyses methods,  
21 including the definitions of the outcomes and the  
22 stratification methods. The meta-analysis in 2007



1 consisted of 42 trials, and the current meta-analysis  
2 consists of 52 trials. The 2007 analysis was based on  
3 approximately 14,000 patients compared with the 17,000  
4 patients for the current analysis.

5           None of the results have changed  
6 dramatically, as one might expect, given that the  
7 meta-analyses share most of the data in common. Most  
8 of the estimates are greater than 1, indicating a  
9 greater risk of an event for rosiglitazone, with the  
10 exception of stroke.

11           The overall estimate for MACE has increased  
12 from 1.2 in 2007 to 1.4 in 2010. The point estimates  
13 for some outcomes have increased, while others have  
14 decreased. Of note, the estimate for myocardial  
15 infarction was borderline significant in 2007 and is  
16 now significant in 2010, with an estimate of 1.8.

17           We now compare the FDA's meta-analysis of  
18 the 52 trials to GlaxoSmithKline's analysis of the 52  
19 trials. Some of the main differences between GSK's  
20 analysis and FDA's meta-analysis are given on this  
21 slide. Firstly, in the GSK analysis, all of the data  
22 from the trials are pooled, which means that the

1 randomized comparisons from the individual trials are  
2 lost.

3 As previously noted, this form of analysis  
4 is vulnerable to the phenomenon known as Simpson's  
5 paradox, where the overall results may be confounded  
6 by differences in the trial characteristics.

7 The hazard ratio was the primary measure of  
8 risk in the GSK analysis as opposed to odds ratio in  
9 our analysis, and this was calculated using an  
10 unstratified proportional hazard model.

11 Finally, GSK's analysis focused on two  
12 outcomes, MACE and total myocardial ischemia, and the  
13 definitions of these outcomes were different from the  
14 FDA's definitions.

15 This table summarizes the results for the  
16 FDA and GSK analysis for MACE and total myocardial  
17 ischemia outcomes. The FDA estimates for the odds  
18 ratios are given in the first column, here. The  
19 estimates for the hazard ratios from the FDA analysis  
20 are given here, followed by the GSK estimates of the  
21 hazard ratios, which are given in the third column.  
22 The analyses are all based on the same 52 trials. All

1 of these estimates are greater than 1.

2 GSK obtained a hazard ratio estimate of 1.1  
3 for both MACE and total myocardial ischemia, whereas  
4 the FDA analysis had a hazard ratio of 1.4 for MACE  
5 and 1.3 for total myocardial ischemia.

6 The FDA's result for MACE was borderline  
7 significant, and the result for total myocardial  
8 ischemia was significant. Neither of these results  
9 from the GSK analysis were significant.

10 So to summarize, based on the 2010 FDA meta-  
11 analysis, there is no statistically significant  
12 increased risk of MACE for rosiglitazone, although the  
13 lower limit of the confidence interval is near 1. The  
14 estimate for the odds ratio was 1.44, which means that  
15 rosiglitazone patients have an estimated 44 percent  
16 increase in risk of a major cardiovascular event  
17 compared to control.

18 Results from the 2007 meta-analysis have  
19 been reinforced. The odds ratio for myocardial  
20 infarction in this analysis was 1.8, which means that  
21 the rosiglitazone patients have an estimated 80  
22 percent increase in the risk of myocardial infarction.

1 This result is statistically significant in the  
2 updated analysis.

3 Total myocardial ischemia and congestive  
4 heart failure continue to be statistically  
5 significant, and serious myocardial ischemia was  
6 statistically significant in the updated meta-  
7 analysis.

8 Thank you. The statistical team leader for  
9 the meta-analysis, Mark Levinson, and I are prepared  
10 to answer your questions.

11 DR. BURMAN: Thank you very much. We have  
12 five minutes for questions.

13 DR. FLEMING: Fleming. Slide 33, just to  
14 make sure I understand. So you're explaining the  
15 differences between the MACE and MI, 1.4 and 1.3  
16 against GSK's 1.1.

17 When you're pooling together many different  
18 studies, the real critical issue, and I think you're  
19 saying this, is if the randomization fractions are  
20 different, you can't just pool the data. So if, in  
21 low risk patients, it's 2-to-1 randomization for  
22 rosiglitazone and, in high risk patients, you have a

1 1-to-1 randomization, you pool those data together,  
2 you're systematically creating an imbalance favoring  
3 rosiglitazone.

4 So you, obviously, have to stratify these  
5 analyses by trial. You're saying you did that, and  
6 you're saying GSK didn't do that.

7 DR. CALLAHAN: Yes, that's exactly right.  
8 So we stratified by trial for the estimate of the odds  
9 ratio. We stratified by trial for the estimate of the  
10 hazard ratio. The estimate here is just pooled, all  
11 the data from all the trials grouped together in one  
12 dataset.

13 DR. BURMAN: Thank you. Dr. Konstam?

14 DR. KONSTAM: First, were all of these  
15 trials blinded?

16 DR. CALLAHAN: Yes. They're all double  
17 blind.

18 DR. KONSTAM: They're all double blind. Can  
19 you explain, again, why you didn't include ADOPT and  
20 DREAM in this?

21 DR. CALLAHAN: Sure. I can go back to --

22 DR. TRAN: Just let me know the slide

1 number.

2 DR. CALLAHAN: I think it's early on.

3 DR. FLEMING: It's 5, number 5.

4 DR. CALLAHAN: Slide 5. Perhaps Mark  
5 Levinson might want to say more on this. But the  
6 trials were large. There are several reasons. The  
7 trials were large. So if we include them in the  
8 analysis, we get the results from those trials back  
9 again, we lose the -- we don't get any signal from  
10 these small trials.

11 In addition, they were quite different, more  
12 importantly perhaps, they were quite different in  
13 their patient characteristics. DREAM and ADOPT both  
14 had treatment-naive patients. DREAM did not actually  
15 have Type II diabetes patients in the trial. It had  
16 pre-diabetic patients.

17 RECORD, as you've heard, there's a lot of  
18 different opinions on RECORD, so it's --

19 DR. FLEMING: I guess we're going to see a  
20 pioglitazone meta-analysis that does include  
21 PROactive, however.

22 DR. CALLAHAN: Yes. There's a sensitivity

1 analysis where the larger trials are included just to  
2 see if the results change radically.

3 DR. FLEMING: Just one last thing. Could  
4 you put up slide 28?

5 DR. CALLAHAN: Twenty-eight, I think.

6 DR. FLEMING: Do you have a slide like this  
7 for MI that separates out the different kinds of  
8 trials?

9 DR. CALLAHAN: That was certainly done in  
10 the review, but I don't have the information here.

11 DR. FLEMING: I just wanted to know whether  
12 it continues to support -- that the signal is really  
13 being driven by placebo-controlled trials. I would  
14 guess it would.

15 DR. CALLAHAN: I'd have to refer to my  
16 review, but I can certainly do that and get that  
17 answer to you by the end of the day.

18 DR. BURMAN: Thank you. I think we only  
19 have time for one question. Mike?

20 DR. PROSCHAN: I like the fact that you did  
21 this exact method, but one of the consequences of that  
22 is that the trials with no events get zero weight;

1   therefore, they're essentially excluded. And some  
2   would argue that if you have no events in either arm,  
3   that's sort of supportive of no increased harm.

4           I'm wondering how sensitive these results  
5   are to trying to do some sort of correction to the  
6   events in those trials, like adding .5 to all the  
7   cells. And admittedly, you can't do an exact  
8   analysis, but what do those kinds of sensitivity  
9   analyses show?

10           DR. CALLAHAN: We did not do the continuity  
11   correction where you add .5 to the cells. Instead, we  
12   did the risk difference analysis, which does include  
13   those zero event trials. We use that for that  
14   particular type of sensitivity analysis.

15           DR. PROSCHAN: Thank you.

16           DR. BURMAN: You have no other comments?  
17   Thank you. Thank you, Dr. Callahan. We will now  
18   proceed with our presentation from the FDA presenter,  
19   Dr. Bradley McEvoy.

20           DR. MCEVOY: Today I will present a meta-  
21   analysis evaluating the cardiovascular safety of  
22   pioglitazone, as well as compare and contrast that



1 meta-analysis with the rosiglitazone meta-analysis Dr.  
2 Callahan just presented.

3 In general cross-meta-analysis comparisons  
4 are not advised since differences in the trial and  
5 patient characteristics may lead to unfair  
6 comparisons.

7 DR. BURMAN: Excuse me for just a second.  
8 Please, step a little closer to the microphone. Thank  
9 you.

10 DR. MCEVOY: Should I repeat the -- start  
11 over?

12 DR. BURMAN: No. Just go ahead.

13 DR. MCEVOY: Because of these limitations,  
14 an emphasis of our comparison is to contrast trial  
15 characteristics to gain insight into the comparability  
16 of the meta-analyses.

17 Here is an outline of the presentation. I  
18 will start by providing a brief background, followed  
19 by summarizing the primary findings from the  
20 pioglitazone meta-analysis. After that overview, I  
21 will summarize the pioglitazone mega-analysis in  
22 greater detail and simultaneously present the

1 corresponding summaries from the rosiglitazone meta-  
2 analysis.

3 This will include summaries of trials,  
4 patients, and the meta-analysis results. I will  
5 compare and contrast the corresponding information  
6 from the two meta-analyses.

7 As my colleague, Dr. Callahan, stated, there  
8 are two goals of the pioglitazone and rosiglitazone  
9 meta-analyses. The first goal was to update the 2007  
10 rosiglitazone meta-analysis. The second goal was to  
11 perform a parallel pioglitazone meta-analysis in order  
12 to compare indirectly the cardiovascular safety of the  
13 two drugs in short-term trials.

14 As Dr. Callahan discussed, the parallel  
15 meta-analyses was achieved by having both reviews use  
16 the same statistical analysis plan, including the same  
17 trial inclusion criteria, statistical methodology, and  
18 patient and trial groups. I will not go over the  
19 analysis plan, since it was outlined in the previous  
20 talk.

21 Prior to the pioglitazone meta-analysis I am  
22 presenting today, FDA has not performed a mega-

1 analysis evaluating the cardiovascular safety of this  
2 drug, although other meta-analyses have looked into  
3 this issue. In 2006, Takeda did two meta-analyses of  
4 this drug, which included 19 trials. In 2008, they  
5 updated their initial meta-analysis with an additional  
6 four trials.

7 In 2007, Linkoff published a meta-analysis  
8 in the Journal of the American Medical Association.  
9 This meta-analysis used the same trials that are  
10 included in the 2006 Takeda meta-analysis and used a  
11 similar statistical methodology.

12 The FDA pioglitazone meta-analysis was based  
13 on the clinical trial database of Takeda. AS  
14 mentioned by Dr. Callahan, the 2010 meta-analyses did  
15 not include large trials. These trials were viewed as  
16 independent sources of information. Additionally, the  
17 large rosiglitazone and pioglitazone clinical trials  
18 tend to have different characteristics. Including  
19 them would further limit the comparability of the  
20 rosiglitazone and pioglitazone meta-analyses.

21 In total, 29 pioglitazone trials satisfied  
22 the primary trial inclusion criteria and had enrolled

1 a total of 11,774 patients. These 29 trials comprise  
2 the primary pioglitazone analysis set.

3 The Takeda pioglitazone database also  
4 included two large trials, PROactive and OPI-506,  
5 which were not included in the primary analysis set.  
6 These two trials enrolled a total of 7,335 patients.

7 PROactive was a 2.5 to 3-year placebo-  
8 controlled trial that enrolled approximately 5,200  
9 patients with an established history of macrovascular  
10 disease. OPI-506 was a three-year sulfonylurea-  
11 controlled liver safety trial that enrolled  
12 approximately 2,100 patients. These two trials were  
13 included in with the primary analysis set in the  
14 sensitivity analysis.

15 I will now present the primary findings from  
16 the pioglitazone meta-analysis. This slide shows the  
17 breakdown of trials and patients in the primary  
18 pioglitazone analysis set by the type of randomized  
19 comparator.

20 I would like to point out that across the  
21 different trial groups, in this case, randomized  
22 comparator, groups may not be exclusive since trials

1 with two or more arms can contribute to multiple  
2 groups.

3 Of the 11,774 patients included in this  
4 meta-analysis, 6,132 patients, representing 52 percent  
5 of the sample, were randomized to pioglitazone and  
6 5,462 patients, representing 48 percent of these  
7 sample, were randomized to control.

8 Most patients were in active control trials  
9 compared to placebo-controlled, 62 percent compared to  
10 39 percent; 37 percent of the total number of patients  
11 were in sulfonylurea-controlled trials and 19 in  
12 metformin-controlled trials.

13 This slide shows the treatment exposure  
14 overall and in the different treatment arms. Patients  
15 had, on average, 265 days of treatment exposure. By  
16 treatment arm, the average exposure was longer for  
17 patients in the control arm than in the pioglitazone  
18 arm. However, based on stratified estimates, as seen  
19 in the least-squares mean, this difference was not as  
20 great.

21 This slide displays a number of  
22 cardiovascular events for the different endpoints

overall and by treatment arm for the pioglitazone primary analysis set. In total, there were 117 MACE events, representing 1 percent of the total sample. There were 54 MACE events, representing .9 percent in the pioglitazone arm, and 63 events, representing 1.1 percent, in the control arm.

Seven of the 29 trials were zero event trials, with zero MACE events in both arms. There were 22 cardiovascular deaths among pioglitazone patients and 18 among control patients. There were 31 myocardial infarctions among pioglitazone patients and 33 among control patients. And for stroke, there were 10 events among pioglitazone patients and 16 among control patients.

This slide displays the forest plot for all endpoints of the primary analysis set. The vertical line at 1 signifies no difference in the estimated rates between pioglitazone and comparator. Each endpoint is displayed on the left axis, and the corresponding box corresponds to the point estimate, and the horizontal line denotes the 95 percent confidence interval for that endpoint.

On the right axis, the numeric estimates and confidence intervals are given. Odds ratios less than 1 imply that pioglitazone had a lower risk than control. An odds ratio of greater than 1 imply that pioglitazone had a higher risk than control.

For MACE, the estimated odds ratio was 0.83, corresponding to a 17 percent risk reduction for pioglitazone compared to control. This odds ratio was not statistically significant since the confidence interval included 1.

Among the components that comprise MACE, pioglitazone had a greater estimated risk for cardiovascular death, but an estimated odds ratio less than 1 for myocardial infarction and stroke.

For congestive heart failure, pioglitazone had a greater estimate of risk that was statistically significant.

Different statistical methods were used to evaluate the robustness of the primary statistical method. I will not present results from these sensitivity analyses, but I will discuss the results.

1 Risk differences were used to examine the  
2 contribution of zero event trials and gave results  
3 that are consistent with the results on this slide.

4 The other sensitivity analyses also gave  
5 results that were aligned with the results in this  
6 slide.

7 This slide shows a Kaplan-Meier survival  
8 curve for MACE for the primary pioglitazone analysis  
9 set. The orange solid line corresponds to  
10 pioglitazone and the dashed green line to comparator.  
11 At day 360, 34 percent of the total sample remained in  
12 the risk set, and at day 710, the risk set contained 9  
13 percent of the total sample.

14 The two survival curves were similar for  
15 much of the time period, but the curves separated well  
16 after initiating treatment, with the pioglitazone  
17 curve tending to be above the comparator.

18 This slide displays a forest plot of the  
19 endpoints of the two large trials that were not part  
20 of the primary analysis set. In just these two  
21 trials, there were considerably more events than the  
22 29 trials that make up the primary analysis set, with



1 most of the events coming from PROactive.

2 For instance, PROactive had a total of 500  
3 MACE events. OPI-506 had 34, while the 29 trials  
4 combined had a total of 117.

5 Across the safety endpoints, the odds ratio  
6 estimates were below 1, except for congestive heart  
7 failure. As Dr. Callahan mentioned, when interpreting  
8 trends from these forest plots, use caution, since  
9 some of the endpoints are not independent. For  
10 example, all cause death encompasses cardiovascular  
11 death.

12 The estimated odds ratio for MACE based on  
13 just these two trials is .8, similar in magnitude to  
14 the estimate from the primary analysis set. However,  
15 the confidence interval based on just these two trials  
16 did not include the value 1.

17 Likewise, the confidence interval for  
18 myocardial infarction and total and serious myocardial  
19 ischemia based on just these two trials did not  
20 contain a value of 1, either.

21 This slide, on the left, has the forest plot  
22 for the 29 trials in the primary analysis set, and, on

1 the right, the forest plot for the sensitivity  
2 analysis set, consisting of the 29 trials, plus the  
3 two large trials.

4 Comparing the two forest plots, risk trends  
5 from the sensitivity analysis were broadly consistent  
6 with the primary analysis. However, the estimates in  
7 the sensitivity analysis set were considerably more  
8 precise.

9 Also, results from the two large trials were  
10 similar to the results from the sensitivity analysis  
11 set. Therefore, having included these two trials into  
12 the meta-analysis, mainly PROactive, the meta-analysis  
13 would have been dominated by PROactive.

14 From this brief overview of the pioglitazone  
15 meta-analysis, pioglitazone tended to have a lower or  
16 similar estimated risk as control, except for  
17 congestive heart failure. Second, pioglitazone had an  
18 increased risk for congestive heart failure that was  
19 statistically significant.

20 Findings from these two large trials were  
21 broadly aligned with the primary analysis set, but the  
22 estimates were considerably more precise.

1           For the next part of this talk, I will  
2 summarize the pioglitazone meta-analysis in greater  
3 detail. As the trials, patients and results are  
4 summarized, I will compare and contrast the  
5 corresponding information from the rosiglitazone meta-  
6 analysis.

7           Before displaying the meta-analysis results  
8 overall and for the trial level groups, I will  
9 summarize the trial characteristics between mega-  
10 analyses to provide insight into the comparability of  
11 the results.

12           I will start by summarizing the overall  
13 trial set. This slide summarizes the patients and the  
14 trials by the type of randomized comparator. The  
15 primary pioglitazone analysis had consisted of 29  
16 trials with approximately 11,800 patients. The  
17 primary rosiglitazone analysis set had 52 trials with  
18 approximately 17,000 patients.

19           There were differences between meta-analyses  
20 for this trial level group. The pioglitazone meta-  
21 analysis had more patients in the active-controlled  
22 trials, 62 percent, while 81 percent of rosiglitazone

1 patients were in placebo-controlled trials.

2           This slide summarizes the meta-analyses by  
3 the type of treatment add-on medication. For example,  
4 in an insulin add-on trial, all patients received  
5 insulin. As with the type of randomized comparator,  
6 there were differences between the drugs for this  
7 trial characteristic. About half of the pioglitazone  
8 patients were monotherapy trials, compared to about a  
9 third for the rosiglitazone meta-analysis.

10           The pioglitazone had proportionally more  
11 patients in the background therapies, but fewer in the  
12 sulfonylurea add-on trials compared to rosiglitazone.

13           For the other treatment add-on groups, so  
14 metformin, insulin add-on, and the combination  
15 sulfonylurea and metformin add-on, the differences  
16 between meta-analyses were not too large.

17           This slide summarizes the two meta-analyses  
18 by the nominal trial duration. The two meta-analyses,  
19 again, differed overall for this trial characteristic.  
20 Most patients in the rosiglitazone meta-analysis were  
21 in trials less than a year, while patients in the  
22 pioglitazone meta-analysis were more equally

1 distributed across these categories.

2 In the pioglitazone meta-analysis, 24  
3 percent of the patients were in trials greater than  
4 one year in duration, compared to 5 percent in the  
5 rosiglitazone meta-analysis.

6 In summary, patients in the rosiglitazone  
7 meta-analysis were primarily in shorter and placebo-  
8 controlled trials. Patients in the pioglitazone meta-  
9 analysis tended to be in longer trials and active-  
10 controlled.

11 DR. BURMAN: Dr. McEvoy, could I interrupt  
12 for one second? Excuse me. You have five minutes,  
13 but I just want to give you a warning. You have  
14 something like 16 slides left. So please use your  
15 time as you deem appropriate.

16 DR. LEVINSON: I believe Dr. McEvoy is down  
17 for two talks in a row, if you look at the schedule.  
18 Is that the case?

19 DR. TRAN: That is correct, but the total  
20 time of -- his presentation time is 30 minutes.

21 DR. MCEVOY: So I guess the way this talk  
22 was organized was these two talks were integrated into

1 one.

2 DR. BURMAN: I apologize. You can go on to  
3 5:00.

4 DR. MCEVOY: You messed up my flow with that  
5 one, so I have to get back on it.

6 [Laughter.]

7 DR. MCEVOY: I am now going to compare  
8 overall patient characteristics between the two meta-  
9 analyses. This slide shows baseline summary  
10 statistics for age, gender, location, and body mass  
11 index by meta-analysis.

12 Patients had a similar average age, 57 in  
13 the pioglitazone meta-analysis and 58 in the  
14 rosiglitazone meta-analysis. The pioglitazone meta-  
15 analysis had slightly more males, 55 percent compared  
16 to 59 percent, and had less patients in the U.S., 30  
17 percent compared to 44 percent.

18 Note that 13 percent of the patients in the  
19 pioglitazone meta-analysis had region missing. For  
20 body mass index, patients in the two meta-analyses had  
21 similar body mass index, 31 for pioglitazone and 30  
22 for rosiglitazone.

1           This slide shows percentage of  
2   cardiovascular medications used at baseline. There  
3   were not too large a differences between meta-analyses  
4   for this patient characteristic. There were slightly  
5   more patients in the pioglitazone meta-analysis that  
6   used nitrates, loop diuretics, and beta blockers, but  
7   had fewer that used ace inhibitors.

8           This slide shows additional baseline patient  
9   cardiovascular risk factors by meta-analysis.  
10   Patients in both meta-analyses had similar average  
11   duration of diabetes, six years for pioglitazone and  
12   seven years for rosiglitazone. The pioglitazone meta-  
13   analysis had more patients that were not previously  
14   treated for diabetes, 35 percent compared to 22  
15   percent. However, note that 7 percent of the patients  
16   in the pioglitazone meta-analysis had this information  
17   missing.

18           Both meta-analyses had a similar percentage  
19   of patients with a history of coronary heart disease,  
20   and the pioglitazone meta-analysis had slightly more  
21   patients with a history of congestive heart failure.

22           This slide shows the average treatment

1 exposure by meta-analysis. Patients in the  
2 pioglitazone meta-analysis had, on average, 77 more  
3 days of treatment exposure than patients in the  
4 rosiglitazone meta-analysis. This difference is not  
5 surprising, since the pioglitazone meta-analysis had  
6 more patients enrolled in trials between one and two  
7 years.

8           Now, I'll present the results from the  
9 primary analysis set from both meta-analyses. Before  
10 I do, though, I'd like to say that there were  
11 differences in the trial characteristics between meta-  
12 analyses that limit the comparability of results.

13           Therefore, as risk trends are compared and  
14 contrasted for each drug, please consider how the  
15 trials comprising each meta-analysis differ and how,  
16 in turn, these differences affect the comparisons.

17           This slide shows a number of events across  
18 the safety endpoints per treatment arm by meta-  
19 analysis. It also exemplifies the problem of a cross-  
20 meta-analysis comparison.

21           Notice, if we compare the percentages in the  
22 pioglitazone meta-analysis with the corresponding



1 percentages in then rosiglitazone meta-analysis across  
2 the different endpoints, the percentages were  
3 consistently greater in the pioglitazone meta-  
4 analysis.

5           For instance, the control arm in the  
6 pioglitazone meta-analysis had a greater percentage of  
7 events than the control for the rosiglitazone. There  
8 are myriad of possible explanations for this  
9 difference, which underscore the difficulties of  
10 making direct comparisons between meta-analyses. For  
11 example, this difference could be attributed to longer  
12 exposure for patients in the pioglitazone meta-  
13 analysis.

14           This slide displays a forest plot from both  
15 meta-analyses. The forest plots on the left  
16 correspond to pioglitazone, and the right to  
17 rosiglitazone. In the pioglitazone meta-analysis, the  
18 odds ratio estimates tended to be near or below 1,  
19 except for congestive heart failure. In the  
20 rosiglitazone meta-analysis, the odds ratio estimates  
21 tended to be larger than 1.

22           For the primary endpoint MACE, rosiglitazone

1 had a greater estimated risk than the control, which  
2 was approaching statistical significance.

3 In the pioglitazone meta-analysis, the  
4 estimate -- sorry. In the pioglitazone meta-analysis,  
5 for MACE, pioglitazone had a lower risk that was not  
6 statistically significant.

7 For myocardial infarction and total and  
8 serious myocardial ischemia, the odds ratio estimates  
9 in the rosiglitazone meta-analysis were greater than 1  
10 and the confidence interval excluded 1.

11 In the pioglitazone meta-analysis, these  
12 estimates were either below or near 1. Both drugs had  
13 a greater risk of congestive heart failure that was  
14 statistically significant.

15 Now, I will compare the drugs within  
16 different trial level groups. I will start with the  
17 type of randomized comparator, presenting only the  
18 results for the active and placebo-controlled trials.

19 Ideally, by examining the drugs within these  
20 groups, they become more comparable than they were  
21 overall and the comparisons become more reasonable.  
22 For each randomized comparator, I will compare the

1 trial characteristics between drugs before displaying  
2 the meta-analysis results.

3           This slide shows the breakdown of the  
4 placebo-controlled trials by the treatment add-on  
5 group. There are a total of 18 pioglitazone placebo-  
6 controlled trials, with approximately 4,600 patients.  
7 Rosiglitazone had 46 placebo-controlled trials, with  
8 approximately 13,800 patients.

9           Between drugs, there are a similar  
10 percentage of patients in the monotherapy in  
11 combination sulfonylurea and metformin add-on trials.  
12 For the other treatment add-on groups, there were  
13 differences between the meta-analyses.

14           None of the pioglitazone placebo-controlled  
15 trials were background add-on trials, while  
16 rosiglitazone had five such trials. The pioglitazone  
17 trials had proportionally fewer patients that were in  
18 the sulfonylurea add-on trials, but proportionally  
19 more patients that were in the metformin or insulin  
20 add-on trials.

21           This slide shows the breakdown of the  
22 placebo-controlled trials by trial duration. This

1 trial characteristic was reasonably similar between  
2 the two drugs. The main difference between the  
3 pioglitazone and rosiglitazone placebo-controlled  
4 trials was that rosiglitazone had one long two-year  
5 trial, but it only represented 2 percent of this  
6 group. The percentage of patients in the other  
7 categories were relatively similar for the two drugs.

8           Between the drugs, the placebo-controlled  
9 trials were somewhat similar in terms of trial  
10 duration, but differed in the type of treatment add-on  
11 medication.

12           This slide shows a forest plot from the  
13 meta-analyses of placebo-controlled trials. Again,  
14 the left panel corresponds to pioglitazone and the  
15 right to rosiglitazone.

16           For the rosiglitazone meta-analysis, the  
17 results and trends were similar to those in the  
18 primary analysis set. Odds ratio estimates were  
19 greater than 1. This observation is not surprising,  
20 since most of the trials overall were placebo-  
21 controlled.

22           In the pioglitazone meta-analysis, there is

1 greater uncertainty around the risk estimates. For  
2 the primary endpoint, MACE, rosiglitazone had a  
3 greater risk compared to placebo. In the pioglitazone  
4 meta-analysis, pioglitazone had a lower estimated  
5 risk. In both meta-analyses, odds ratio estimate  
6 for congestive heart failure was greater than 1.

7 Now, we're going to compare the active  
8 control trials between drugs. The majority of active  
9 controls were either metformin or sulfonylurea. This  
10 slide shows the distribution of the treatment add-on  
11 groups for the active control trials.

12 There were differences between the drugs for  
13 this trial characteristic. The rosiglitazone active  
14 control trials were exclusively monotherapy or  
15 metformin add-on trials.

16 Seventy-two percent of the rosiglitazone  
17 patients were in the monotherapy trials. The  
18 pioglitazone active control trials also had trials  
19 that were background add-on, sulfonylurea add-on, and  
20 insulin add-on. Most of the patients in the  
21 pioglitazone meta-analysis were in monotherapy trials.

22 This slide shows the duration of the active

1 control trials by drug. Notice that the active  
2 control trials tended to be longer than the placebo-  
3 controlled trials for both drugs. Nonetheless, the  
4 active control trials still differed between drugs.

5 Patients in the pioglitazone active control  
6 trials were roughly uniformly enrolled across the  
7 trial duration categories, while most patients in the  
8 rosiglitazone trials were enrolled in trials between  
9 six months and a year. On average, patients in the  
10 pioglitazone trials had an additional 79 days of  
11 treatment exposure.

12 Between drugs, rosiglitazone and  
13 pioglitazone active control trials were different in  
14 terms of type of treatment add-on medication and the  
15 duration of exposure.

16 This slide presents the forest plot for the  
17 meta-analyses of the active control trials; on the  
18 left, from pioglitazone, and on the right,  
19 rosiglitazone. In both estimates, the odds ratios  
20 tended to be near 1. The estimates in the  
21 rosiglitazone meta-analysis tended to have less  
22 precision than in the placebo-controlled trials.

1           For MACE, the odds ratio estimate for  
2   rosiglitazone was near 1, and in the pioglitazone  
3   meta-analysis, the estimate was slightly below 1. For  
4   congestive heart failure, the odds ratio estimate was  
5   greater than 1 for both drugs.

6           In the interest of time, I will not present  
7   trial characteristics and results for either the  
8   sulfonylurea-controlled trials or metformin-controlled  
9   trials. If you have questions regarding these trials,  
10   these types of trials, I can address them during the  
11   question session.

12           Now, I will present results for the insulin  
13   add-on trials. This trial group was presented since  
14   it represents a unique risk set. This slide shows a  
15   breakdown of the insulin add-on trials and patients by  
16   the type of randomized comparator. All patients in  
17   these trials received insulin in addition to the  
18   randomized drug.

19           There were seven rosiglitazone insulin add-  
20   on trials that enrolled approximately 1,800 patients.  
21   All these trials were placebo-controlled.

22           There were five pioglitazone insulin add-on

1 trials that enrolled approximately 1,200 patients; 86  
2 percent of these patients were in placebo-controlled  
3 trials. The remaining patients were in a  
4 sulfonylurea-controlled trial.

5 This slide shows the insulin add-on trials  
6 by duration. In the pioglitazone insulin add-on  
7 trials, 76 percent of the patients were in trials less  
8 than six months. All rosiglitazone patients were in  
9 trials six months or less.

10 For the insulin add-on trials, between the  
11 drugs, they were not too different in terms of  
12 randomized comparator and trial duration, although  
13 there were some differences. I would like to  
14 emphasize that there were not a lot of patients for  
15 this trial level group compared to the other ones.

16 This slide shows a forest plot of the meta-  
17 analysis of insulin add-on trials by drug. I would  
18 like to point out the width of the confidence  
19 intervals for these estimates and that there were no  
20 strokes observed in the pioglitazone insulin add-on  
21 trials, as denoted by this.

22 In the pioglitazone meta-analysis, the odds



1 ratio estimates tended to be less than 1, except for  
2 congestive heart failure.

3 In the rosiglitazone meta-analysis, the risk  
4 estimates tended to be greater than 1.

5 In the interest of time, I'm not going to  
6 present results for different patient subgroups. If  
7 you have questions regarding these results, I can  
8 address them during the question section.

9 I will now provide the summary of my  
10 presentation. There are several important limitations  
11 that need to be considered when interpreting results  
12 from a meta-analysis, in addition to making  
13 comparisons between meta-analyses.

14 Although Dr. Callahan had the same slide in  
15 her presentation, it is important to reiterate these  
16 points. First, most of the trials included in the  
17 meta-analysis were not prospectively designed to  
18 evaluate the cardiovascular endpoints.

19 Second, results of these trials were known  
20 before the statistical analysis plan was developed.  
21 Third, no adjustment was made for multiple  
22 comparisons. And lastly, comparisons between meta-

1 analyses are subject to the deficiencies across meta-  
2 analysis or across trial comparisons.

3 In terms of trials in patients, there were  
4 differences between meta-analyses that limit the  
5 comparability of the cardiovascular safety profile  
6 between rosiglitazone and pioglitazone.

7 Trial characteristics that were contrasted  
8 between the meta-analyses, randomized comparator,  
9 trial duration, and treatment add-on group differed  
10 overall and within the different trial level groups.

11 Lastly, while the patient characteristics  
12 overall did not differ too much between meta-analyses,  
13 there were some differences.

14 AT the bottom of this slide is a forest plot  
15 for the primary endpoint, MACE, overall and for the  
16 different randomized comparators. For pioglitazone,  
17 the estimated risk for MACE tended to be less compared  
18 to control, both overall and across different  
19 randomized controls.

20 For rosiglitazone, the estimated risk tended  
21 to be greater compared to control, both overall and  
22 across the different randomized controls.

1           At the bottom of this slide is a forest plot  
2   for congestive heart failure overall and for the  
3   different types of randomized comparators. For both  
4   drugs, the estimated risks for congestive heart  
5   failure tended to be greater than controls, both  
6   overall and across the different randomized  
7   comparators.

8           Thank you. Mark Levinson, statistical team  
9   leader for the meta-analyses, and I are prepared to  
10   answer your questions.

11           DR. BURMAN: Thank you, Dr. McEvoy. The  
12   floor is now open for questions for Dr. McEvoy.

13           DR. GELLER: A simple question. How many of  
14   the pioglitazone trials had no events?

15           DR. MCEVOY: Seven.

16           DR. GELLER: And this is probably for your  
17   colleague. How many of the rosiglitazone had no  
18   events, 16?

19           DR. CALLAHAN: That is correct, 16.

20           DR. GELLER: I suggest that an analysis  
21   putting those trials in would make these results much  
22   less dramatic.

1 DR. MCEVOY: I guess to respond to that, I'm  
2 not sure if we have the extra slides for this, but we  
3 included in the backups the risk differences for  
4 pioglitazone, as well as the 29 trials.

5 DR. GELLER: Maybe you could show some of  
6 that.

7 DR. MCEVOY: Slide 51. So this is risk  
8 differences per 1,000 patients for the 29 trials.

9 DR. GELLER: So this is not exactly what I  
10 was thinking of nor equivalent to it. I was thinking  
11 of a method of meta-analysis that does, as Mike  
12 Proschan said earlier, adds one-half to the cells to  
13 include all those zero trials.

14 DR. MCEVOY: IO think that's a --

15 DR. GELLER: I actually think that's what  
16 was done three years ago.

17 DR. LEVINSON: Mark Levinson, statistical  
18 team leader, Office of Biostatistics in CDER. What  
19 was done, in 2007, this continuity correction I think  
20 you're referring to was not done in the primary  
21 analysis. It was done for display purposes in the  
22 forest plots.

1           Overall, methodologically, we were against  
2   the use of continuity corrections, because by adding  
3   these quantities to both treatment groups, like, say,  
4   one-half, you move the result to the null. So we  
5   don't favor the use of continuity corrections for  
6   these no event trials.

7           DR. GELLER: The fact that there were no  
8   events in those trials should indeed move it toward  
9   the null.

10          DR. BURMAN: Maybe you could explain why you  
11   didn't use it, why you didn't favor it.

12          DR. LEVINSON: We made use of the risk  
13   difference to examine the sensitivity to these zero  
14   event trials and that's how we handled that. In terms  
15   of how much it moves it to the null, I'm not sure one-  
16   half to both is the proper quantity, considering an  
17   odds ratio is a relatively quantity. The zero event  
18   trials do not naturally make sense in this ratio.

19          But I think by looking at the risk  
20   differences in both meta-analyses, you see that the  
21   overall results are very consistent between the odds  
22   ratio outcome and the risk difference.

1 DR. BURMAN: Thank you. We have a couple of  
2 questions and about five minutes. Dr. Konstam?

3 DR. KONSTAM: Two things. One, did you do  
4 a sensitivity analysis, I guess, with rosiglitazone as  
5 you did with pioglitazone, looking at adding PROactive  
6 and the other large trial? Did you do the same thing,  
7 adding DREAM and ADOPT with rosiglitazone?

8 DR. MCEVOY: In these analyses or for the  
9 risk differences?

10 DR. LEVINSON: No. We did not do a  
11 sensitivity --

12 DR. KONSTAM: Well, that is the  
13 rosiglitazone.

14 DR. LEVINSON: For rosiglitazone, no, we did  
15 not include the large trials in a sensitivity  
16 analysis.

17 DR. KONSTAM: Would it be worth doing that?  
18 Yes? Nancy thinks yes. And Dr. Nissen showed data  
19 that included them and I'm just wondering why you did  
20 it for pio and you didn't do it for rosi.

21 DR. LEVINSON: Well, in 2007, the FDA meta-  
22 analyses of rosiglitazone did a more careful analysis

1 of the long-term trials that we're doing presently.

2 One of the main objectives of our current work was to  
3 compare the meta-analyses and, as was stated, these  
4 large trials differed quite a lot.

5 DR. KONSTAM: I'm just wondering why you did  
6 it -- okay. It seems like it would be worth --

7 DR. MCEVOY: I'm not sure if they requested  
8 the data from GSK for those two trials.

9 DR. KONSTAM: Just one other thing. Put up  
10 slide 30. So this is the most helpful slide to me in  
11 your whole presentation, because it's at least apples  
12 to apples vis-à-vis the placebo control and with the  
13 same endpoints.

14 But there are other things that are  
15 imbalanced, like the duration of treatment was  
16 imbalanced, with longer duration of treatment with  
17 pioglitazone.

18 The other thing that's nagging at me and  
19 maybe some others, as it's come up once or twice, is  
20 what the relative glycemic effects of these two agents  
21 are. We're mixing different doses. What doses were  
22 used? I just want to throw out that if I wanted to

1 postulate that part of what's going on here is short-  
2 term aggressive reduction in blood sugars, it might  
3 have some adverse effects, and there's a lot of reason  
4 to believe that might happen.

5 I wonder whether some work could not be done  
6 on this analysis to at least look at these results  
7 relative to those two factors. One is how long the  
8 patients were on the drugs and two is what the  
9 relative hypoglycemic effects of the two different  
10 drugs were. I think that might be worth doing.

11 DR. MCEVOY: Thank you.

12 DR. BURMAN: I agree, but we don't have that  
13 at the moment. For just a couple of minutes, Dr. van  
14 Belle.

15 DR. VAN BELLE: I think I had the same  
16 question relative to the dose. Was there any  
17 adjustment made for length of time on dose in any of  
18 these analyses?

19 DR. MCEVOY: No. We just included the  
20 predicted for the treatment.

21 DR. VAN BELLE: Thank you.

22 DR. BURMAN: Dr. Moss?



1           DR. MOSS: Just a couple of questions. In  
2 none of the analyses have I seen any comment about the  
3 subgroups with regard to ECG characteristics, since  
4 these are all patients who have diabetes and have -- a  
5 good portion have clinical or subclinical  
6 cardiovascular or cardiac disease.

7           There is nothing with regard to left  
8 ventricular hypertrophy, Q wave infarctions, left  
9 branch block, intraventricular conduction disturbance,  
10 and QT effects, which are a very important part of  
11 many drugs.

12           So maybe there is information, but it  
13 certainly didn't surface. So that's one point. These  
14 second thing is we've seen an enormous number of  
15 forest plots, but the event rates are just very low  
16 and the interpretation of these leave a little bit to  
17 be desired.

18           The third thing is that I gather you're not  
19 able to do any statistical comparisons between these  
20 two groups, the rosiglitazone and the pio, with regard  
21 to any of the meta-analyses. So that leaves one sort  
22 of a bit empty in just seeing the patterns which are

1 very low event rates.

2 So I just wondered if there are any  
3 comments.

4 DR. LEVINSON: While we agree, we did not  
5 perform any tests of the meta-analyses. We felt the  
6 differences were too large to justify use of a test  
7 like that.

8 In terms of the event rates, they're  
9 presented early on. I think it's a clinical judgment  
10 of how important they are, but they're not extremely  
11 low.

12 DR. BURMAN: Thank you. Dr. Weide, do you  
13 have a question?

14 DR. WEIDE: Yes. I would be very  
15 interested, and I don't know if you can do it and  
16 bring it to us tomorrow or not, I doubt you have it  
17 available, I would like to separate the people with  
18 congestive heart failure from the people without  
19 congestive heart failure and look at the data and see  
20 what happens to the comparisons between pioglitazone  
21 and rosiglitazone.

22 It might be very instructive for us and for

1 the patients to do that.

2 The other question I would have is, looking  
3 at this stuff, we've had some information that  
4 suggests that rosiglitazone -- and don't hold me to  
5 the exact, I'm using generalities -- rosiglitazone is  
6 about as bad as other diabetic agents and pioglitazone  
7 is better than rosiglitazone.

8 So the question I have, and it has, I think,  
9 been asked in various forms, is, are we suggesting  
10 that pioglitazone is what everybody should use and you  
11 have to throw out glyburide and glipizide and  
12 metformin and stuff, because they're as bad as  
13 rosiglitazone? I'm just trying to put a handle on  
14 what's being asked and what you're telling us.

15 DR. MCEVOY: The purpose of this  
16 presentation is mostly to present the results from the  
17 pioglitazone meta-analysis and the -- I mean, that's  
18 the title of it, pioglitazone and rosiglitazone.

19 We're not saying directly pioglitazone is  
20 safer than rosiglitazone. We're not making these  
21 direct comparisons. We're just making the -- what are  
22 the general trends.

1           In terms of how they compare to the other  
2   diabetic medications, that was not part of our  
3   intention for the review.

4           DR. WEIDE: But that's been earlier today.  
5   But what about the congestive heart failure? Are we  
6   able to separate the data into two different  
7   components?

8           DR. MCEVOY: We have --

9           DR. WEIDE: Not who has it, but in each one,  
10   separating the group with congestive heart failure  
11   comparing to the group without, and the same for  
12   rosiglitazone. So you'd actually have four  
13   comparisons. Am I not making myself clear?

14          DR. MCEVOY: Could you go to slide 41? I'm  
15   not sure if this will answer your question. But on  
16   the bottom, we have the kind of baseline subgroups.  
17   So this was the meta-analysis for congestive heart  
18   failure in the patients with a history of congestive  
19   heart failure; for pioglitazone, without a history of  
20   congestive heart failure; and, the same way, likewise,  
21   for the rosiglitazone.

22          But beyond that, we don't have anything --

1 DR. WEIDE: That's the history, and then  
2 later on you give us who develops it, right?

3 DR. MCEVOY: No. I have -- yes, for these.

4 DR. WEIDE: What I would like to see is the  
5 people who develop it being separated from the people  
6 who don't develop it to see if those populations are  
7 different, not who has it to start with, but who  
8 develops it with each of the drugs. Does that make  
9 sense?

10 DR. MCEVOY: Makes sense, but I don't think  
11 I can get it done tonight. My wife will be mad if I'm  
12 working late tonight.

13 DR. BURMAN: Thank you. Let's move on. Dr.  
14 Thomas has a quick point of clarification.

15 DR. THOMAS: I just wanted to make a comment  
16 to this issue about falling in glycemia as a risk  
17 factor.

18 In the ACCORD study, where there was the  
19 signal for increased cardiovascular events in the  
20 intent to treat group, it also had the fastest falling  
21 A1C of any of the other major studies. There is a  
22 published paper that's out that looked at this. Of

1 course, it's a post-study analysis, but did not show  
2 that the rate of fall in A1C was related to the  
3 outcome.

4           So that might be an important consideration  
5 in terms of these issues. And because the fall was  
6 actually in a timeframe that it would actually fit in  
7 with many of these studies for several months, the  
8 timeframe is actually comparable.

9           DR. BURMAN: Thank you. We will now proceed  
10 with our presentation from the first guest speaker,  
11 Dr. Maria Brooks.

12           DR. BROOKS: So I will present the data  
13 about rosiglitazone use and cardiovascular outcomes  
14 and the bypass angioplasty revascularization  
15 investigation-2 diabetes trial.

16           BARI-2D was sponsored by the National Heart,  
17 Lung and Blood Institute and received major support  
18 from the National Institute of Diabetes, Digestive and  
19 Kidney Diseases. In addition, we got major funding  
20 from GlaxoSmithKline, as well as some other  
21 pharmaceutical companies, and we received  
22 rosiglitazone free of charge, along with other drugs

1 for use in patient care.

2           BARI-2D had 49 clinical sites in six  
3 countries, and it was coordinated at the University of  
4 Pittsburgh. The purpose of this study is to look at  
5 patients with Type II diabetes and coronary artery  
6 disease who are at high risk for complications of  
7 inadequate glycemic control and for adverse  
8 cardiovascular events.

9           These analyses were designed to examine  
10 long-term cardiovascular outcomes among patients with  
11 Type II diabetes and established coronary artery  
12 disease who were treated with rosiglitazone in the  
13 BARI-2D trial.

14           I'm going to start by reviewing the BARI-2D  
15 trial as a whole. The BARI-2D clinical trial compares  
16 existing treatment strategies for patients with Type  
17 II diabetes and heart disease; in particular, all  
18 patients in the study have documented coronary artery  
19 disease, which means at least one lesion with 50  
20 percent stenosis or more, and documented ischemia.

21           The trial goals were to look at in the  
22 setting of intensive medical therapy for all patients;

1 that is, we controlled glycemia, lipids, hypertension,  
2 angina, and lifestyle factors for all patients. And  
3 then within this setting of good control, the trial  
4 objective was to compare prompt revascularization with  
5 intensive medical therapy versus medical therapy with  
6 delayed or no revascularization.

7 Simultaneously, the trial was designed to  
8 compare a diabetes treatment strategy of insulin  
9 sensitization versus insulin provision. Both of these  
10 strategies were supposed to use a target of HbA<sub>1c</sub> less  
11 than 7 percent.

12 BARI-2D used a 2-by-2 factorial design.  
13 That means that every patient was randomized to a  
14 cardiovascular treatment strategy of the prompt  
15 revascularization or intensive medical therapy, and a  
16 glucose control strategy; and, in particular, 1,185  
17 patients were randomized to an insulin provision  
18 treatment strategy and 1,183 patients were randomized  
19 to an insulin sensitization treatment strategy.

20 The BARI-2D outcomes are listed here. The  
21 primary outcome is all cause mortality and the  
22 principal secondary outcome we called major



1 cardiovascular events, which was the composite of  
2 death, MI and stroke.

3 In addition, for this presentation, I'll be  
4 presenting the individual outcomes of myocardial  
5 infarction, stroke, the composite of cardiac death,  
6 MI, and congestive heart failure.

7 There was an average follow-up of 5.3 years  
8 for the mortality endpoint and 4.5 years are available  
9 for the other endpoints and drug use. It should be  
10 noted that myocardial infarction was classified by a  
11 core laboratory and stroke and cause of all deaths  
12 were adjudicated by an independent committee in this  
13 study.

14 So we randomized insulin sensitization  
15 versus insulin provision. The insulin sensitizing  
16 drugs were biguanide or metformin, and the TZDs are  
17 the glitazones. The insulin-providing drugs or what  
18 we call the IP drugs were primarily insulin and  
19 sulfonylureas.

20 Patients assigned to the IS treatment group  
21 could receive IP drugs and patients assigned to the  
22 IPO group could receive IS drugs, if the HbA<sub>1c</sub> level

1 was not otherwise maintained below 8 percent.

2           This chart shows the drug distribution for  
3 the two treatment groups and at the three-year time  
4 point. What you see is that at three years in the IS  
5 group, 75 percent of the patients were receiving  
6 metformin, 62 percent were receiving a TZD; however,  
7 28 percent in this IS group were also receiving  
8 insulin and 18 percent were receiving a sulfonylurea.  
9 In the IP group, only 4 percent were receiving a TZD  
10 at the three-year time point.

11           One of the main focuses in this trial, as I  
12 said, was the background emphasis on risk factor  
13 control. Clinic visits were monthly for the first six  
14 months and quarterly thereafter. You can see a  
15 comparison here of the baseline and the three-year  
16 comparison and risk factor control, and this shows the  
17 proportion of patients that were above the targets, as  
18 outlined by the protocol.

19           So there was a significant decline in terms  
20 of the patients above target for glycemic control, for  
21 LDL, and for blood pressure within the trial.

22           The primary results of the BARI-2D study

1 were presented a year ago at the ADA and published in  
2 the New England Journal of Medicine.

3           For the diabetes treatment comparison, what  
4 we saw is shown here on the slide. Basically, there  
5 was no difference between an insulin sensitization  
6 strategy and an insulin provision strategy in terms of  
7 the primary outcome of all cause mortality.

8           In terms of the principal secondary endpoint  
9 of death, myocardial infarction or stroke, there was  
10 not a statistically significant difference between an  
11 insulin sensitization strategy and an insulin  
12 provision strategy.

13           What I show here are not only the principal  
14 and the secondary endpoints, but, also, the other  
15 endpoints. The trial was designed to look at the  
16 five-year Kaplan-Meier rates and to use long-range  
17 statistics to compare them. But in order to be  
18 consistent with some of the other analyses, we also  
19 provide here the relative risks from the COX  
20 proportional hazards regression models and those p-  
21 values.

22           So what you see is that at five years, 12

1 percent of the patients in the IS group had a  
2 myocardial infarction, an estimated 13.6 percent in  
3 the IP group had a myocardial infarction. This was a  
4 relative risk of insulin sensitization versus insulin  
5 provision of .86. This p-value was not statistically  
6 significant, meaning that this risk reduction was no  
7 different than no treatment effect.

8           So for this analysis, we're going to focus  
9 on the post hoc analysis of rosiglitazone use within  
10 the BARI-2D trial. We're going to compare the  
11 endpoint frequencies expressed as a number per 100  
12 patient years for patients while on drug treatment  
13 with rosiglitazone versus patients not on a TZD  
14 treatment, which is effectively active diabetes  
15 treatment that does not include pioglitazone.

16           We'll present unadjusted and adjusted  
17 relative risks from the COX proportional hazards  
18 regression model, analyzing drug use or the diabetes  
19 drug use as a time varying covariate.

20           Multivariable adjustment includes baseline  
21 characteristics, both demographic and clinical, and  
22 the use of other diabetes drugs during the trial.

1           In addition, we did some analyses where we  
2   examined a potential legacy effect of rosiglitazone by  
3   including events that occur in the three months  
4   following discontinuation of the drug and attributing  
5   them to rosiglitazone, as was discussed in some of the  
6   other presentations.

7           So let's look at rosiglitazone use in BARI-  
8   2D. Prescription of rosiglitazone, as I said, is at  
9   the discretion of the treatment investigator. This  
10   was not something that was randomized. In terms of  
11   patient years, we have 3,025 patient years of  
12   rosiglitazone exposure.

13           Within the IS group, 54 percent of the  
14   patient years involve rosiglitazone. And within the  
15   IP group, 2 percent involved rosiglitazone use.

16           When we look at patients who received  
17   rosiglitazone at some point during the trial, there  
18   were 992 versus those who did not receive a TZD at any  
19   time during the trial, 1,199, we see that there are  
20   some differences. In particular, patients who  
21   received rosiglitazone entered the trial with a  
22   slightly higher HbA<sub>1c</sub>, slightly longer duration of

1 diabetes, 10.8 years versus 10.0 years, and slightly  
2 worse renal function, as I've shown here as micro or  
3 macroalbuminuria.

4           There were no differences in terms of age,  
5 which, in this study, the average age is 62, or  
6 history of myocardial infarction; and, again, 32  
7 percent of the patients in this study had a history of  
8 myocardial infarction or the other variables, like  
9 history of CHF or history of stroke or TIA and prior  
10 revascularization.

11           This is a busy slide that shows all the  
12 numbers and then we'll go more into the pictorial  
13 representations of the slides. Basically, this is the  
14 unadjusted comparison using the 4.5 years of follow-up  
15 for each of the endpoints that we'll be discussing  
16 throughout this talk for rosiglitazone use versus no  
17 TZD use.

18           For example, under death MI, stroke, you can  
19 see that there were 105 patients who had a death MI or  
20 stroke out of 2,769 patient years of exposure, which  
21 gives 3.79 rate per 100 patient years compared to a  
22 5.81 rate per 100 patient years.

1           When you use the COX regression analysis,  
2   our estimate was a relative risk of .71, with a p-  
3   value of .002. This is an unadjusted comparison. And  
4   so when we look this way at comparing rosiglitazone  
5   versus no TZDs, what we see is that we have a  
6   significant reduction in terms of stroke, death,  
7   myocardial infarction and stroke, and cardiac death  
8   and MI, and basically we see a consistent pattern  
9   where the relative risks are below 1, except for CHF,  
10   which is above 1.

11           This is the same data, but shown in a  
12   pictorial form; so that the height of the bars is the  
13   number of events per 100 patient years, and then above  
14   we show the relative risks and the p-value for each of  
15   the endpoints that we're examining.

16           The blue bars are those using rosiglitazone  
17   at that time versus the gold with no TZDs. Once we  
18   adjust for the baseline characteristics of the  
19   patients, as well as the other diabetes drug use  
20   during the trial, we get these as our adjusted  
21   estimates of on-therapy relative risks.

22           DR. BURMAN: Dr. Moritz?

1 DR. MORITZ: Sorry for the delay here. I'm  
2 here to discuss the use of rosiglitazone and the VA  
3 diabetes trial and how we dealt with worrying about  
4 the possible harm of rosiglitazone once the Nissen  
5 meta-analysis came out.

6 Disclaimer, GlaxoSmithKline donated all the  
7 drug, all the rosiglitazone for the study and also  
8 gave funding support, but they had no active part in  
9 the study in terms of planning or statistical analyses  
10 or anything of that sort. And I have no conflicts of  
11 interest or nothing to disclose.

12 The VADT trial was a prospective randomized  
13 trial to compare intensive glycemic control versus  
14 standard in patients that were not responding to their  
15 current oral agents or insulin. And other than that,  
16 as was described in the BARI trial, every effort was  
17 made to keep the rest of patient management similar in  
18 the two treatment groups. So lipid control and diet  
19 and exercise and smoking, lifestyle things, were all  
20 tried to be maintained the same in the two treatment  
21 groups. And we actually did a very excellent job as  
22 in the BARI trial of controlling all the other risk



1 factors. And so treatment differences are probably  
2 attributed to the actual treatment strategy.

3 Here's the eligibility criteria. You had to  
4 have a A1c level of above 7.5. Again, they were  
5 unable to be controlled on their standard oral agents  
6 or insulin. Patients were over 40 years or older. We  
7 wanted fairly normal creatinine and liver function.  
8 And men and women were both eligible, but being the  
9 VA, it's predominantly males.

10 So the idea since this was a strategy  
11 trial -- it wasn't a Drug A versus Drug B trial. The  
12 idea was we would see the kind of treatment effect we  
13 wanted if we could get a A1c difference in the two  
14 strategies of at least 1.5 percent. And the way we  
15 were going to try to achieve that was we -- in the  
16 intensive patients, we wanted to bring their A1c  
17 levels down to 6 or below, if possible. And in the  
18 standard group, we wanted to keep the A1c's somewhere  
19 between 8 and 9 percent.

20 So this was the medication strategy. We  
21 were starting patients on either metformin or  
22 glimepiride plus rosiglitazone. If goals were not met

1 in either treatment group, we would add insulin. If  
2 there was still trouble reaching goals, then we would  
3 include any combinations of those drugs or any other  
4 approved diabetic medication.

5           So this is some of the baseline  
6 characteristics of our population. Its duration of  
7 diabetes were over 10 years. Their mean age was 60  
8 years old. Our patients were rather overweight, BMI  
9 of 31. I think the average weight was 214. Very high  
10 HbA1c levels, over 9.

11           We had a pretty good race, ethnicity  
12 distribution with about two-thirds of the patients  
13 were white and 16, 17 percent were African American  
14 and Hispanic. And as you see there, it was  
15 predominantly males, 97 percent.

16           This shows that our patients were rather  
17 ill. We had a high rate of history of hypertension, 72  
18 percent. Forty percent of our patients had prior  
19 cardiovascular event, including revascularization, MI,  
20 stroke, CHF. And then we also had a pretty high rate  
21 of microvascular issues, nephropathy, neuropathy,  
22 retinopathy. So we were dealing with a sick

1 population.

2           Here's just again some initial data on the  
3 rosiglitazone use. Approximately 25 percent of the  
4 visits, it was not prescribed. Another 25 percent of  
5 the visits, it was low dose. And roughly 50 percent  
6 of the visits was high dose. So we have a lot of use  
7 of rosiglitazone in the study.

8           I did mention this was a seven-and-a-half-  
9 year study. It was two and a half years of patient  
10 accrual that began basically in 2001 and five more  
11 years of follow-up. So the study ended in May of  
12 2008, so large use of rosiglitazone.

13           Then I don't know if the next information  
14 makes sense, but I'm trying to get an idea of again  
15 dosing. This is on a per patient basis. There was  
16 5 percent of the patients never got rosiglitazone.  
17 Sixteen percent of the patients got at most a low  
18 dose, and then the rest, about 79 percent, got high  
19 dose at least once during the study.

20           This is showing the dose by visit broken  
21 down by treatment. So again, in the standard group,  
22 40 percent of the visits was on low dose. That was

1    their highest rate. But in the intensive group, there  
2    was about 65 percent of the patients had maximum dose.  
3    So it just shows that there really is a difference in  
4    terms of how the patients were treated by treatment  
5    group.

6                So this is showing over six-month intervals  
7    the percentage of time that rosiglitazone was  
8    prescribed. And you can see that over time, there is  
9    a gradual decline in the use. But it's a steeper  
10   decline after the Nissen article came out in May of  
11   2007. So the last year, rosiglitazone use did  
12   decline. And that was an option given to both the  
13   patients and the physicians after the Nissen article  
14   that they were fully allowed to use some other drugs  
15   if they felt it was in the patients' best interest.

16               So after the Nissen article came out, we  
17   obviously felt obligated to see if we were doing any  
18   harm to our patients looking at rosiglitazone. And so  
19   we convened our data safety monitoring committee, and  
20   they gave some suggestions on how they wanted to see  
21   the data analyzed to see if we were showing any harm.  
22   And we were hypothesizing. We were hoping that we

1 were not seeing any effect either positive or  
2 negative, and we were going to see if we could refute  
3 that.

4 Now, the outcomes here are the outcomes that  
5 I'm going to talk about here. It's everything, what  
6 we've been talking about all day with the MACE  
7 outcomes. But in terms of our study, we had a large  
8 composite endpoint which included MIs, stroke,  
9 revascularization of any kind, amputation, CV death  
10 and congestive heart failure. That was our study main  
11 outcome. But for the data safety monitoring  
12 committee, we were just interested in MI and CV death  
13 because that's what Dr. Nissen focused on. And I'm  
14 including stroke today because that's of interest.

15 Obviously, this is not the best data to look  
16 at this, but we were obligated to see if we were doing  
17 any harm to our patients. But the study was not  
18 designed, never intended to be designed to look at any  
19 particular diabetes medication. It was a strategy  
20 treatment of intensive glycemic control versus  
21 standard glycemic control. So we apologize. We know  
22 all of the flaws in what we were trying to do, but we

1 did have an obligation to see if we could find  
2 anything bad.

3 So the first two things that the data safety  
4 monitoring committee wanted to see was the case  
5 control analysis. I know I'm, after the last speaker,  
6 very reluctant to say that we did a time-dependent  
7 covariate analysis. But I'm old, and I can take it.

8 [Laughter.]

9 DR. MORITZ: And the third analysis that I'm  
10 going to present is a propensity-score analysis which  
11 was actually suggested to us by a group of  
12 statisticians that reviewed our rosiglitazone  
13 manuscript that we submitted a few months ago. And  
14 they came back saying -- they said it was okay to put  
15 in the time-dependent covariate analysis. But they  
16 also suggested doing a propensity analysis, so I'll  
17 show that data to you.

18 So with the case control methods, what the  
19 data monitoring committee wanted to see was to take an  
20 outcome like MI, find all of the patients that had an  
21 MI and then try matching them with patients in our  
22 study that did not have an MI. And so listed on this

1 slide are the different criteria that we used for  
2 matching. And one of the key ones -- and I don't  
3 think it's stated correctly there. I think it says  
4 under the categorical, the third one, is --

5 DR. TRAN: Did you mean bullet number 3?

6 DR. MORITZ: Time to event, that's obviously  
7 not a categorical measure. But the point was if you  
8 found the first person had an MI at 14 months, you  
9 wanted to match a non-MI patient that had at least 14  
10 months of follow-up and actually truncate the  
11 information at 14 months. So each pair has exactly  
12 the same amount of time because what we're going to do  
13 is look at measures of rosiglitazone use.

14 So the two measures of rosiglitazone use  
15 that we were interested in is the number of visits it  
16 was prescribed and the mean dose over the course of  
17 the follow-up that we're considering.

18 The advantage of doing this is by doing this  
19 matching, both the cases, the group that had an MI and  
20 the controls, the group that didn't, should have  
21 similar characteristics. They should be -- it's a  
22 pseudo-randomization. You've got balance in the two

1 groups. Disadvantages, obviously, you're losing a lot  
2 of information by only having twice -- your sample is  
3 twice the number of whatever your number of cases are,  
4 so it's a small sample size. You're losing a lot of  
5 patients.

6           So this is a slide of all of our outcomes  
7 for the number of visits that rosiglitazone was  
8 prescribed. And in every case here, numerically,  
9 rosiglitazone was prescribed more often in the group  
10 that did not have the event than the group that did  
11 have the event. And the differences are significant  
12 for CV death and MACE. They're not significant for MI  
13 or stroke.

14           Same thing for mean dose, and in this case,  
15 the only comparison that is statistically significant  
16 is again the MACE. But again, in each situation,  
17 there's a higher mean dose numerically in the group  
18 that did not have the event than did have the event.  
19 Borderline significant for -- I think MI is .06 and CV  
20 death is .07.

21           So based on this analysis, it satisfied our  
22 data monitoring committee that they did not see harm



1 in giving our patients rosiglitazone.

2 Time-dependent covariate analysis, what we  
3 feel is -- there's a strength. And from what was  
4 mentioned before, it might actually not be a strength,  
5 and it is you're actually using all the information in  
6 the study. You're using every single visit. You're  
7 using whether rosiglitazone was prescribed or not, and  
8 you can do the same thing with all your other  
9 measures. You can use the actual values of blood  
10 pressure and weight, BMI, things like that. So you're  
11 continually adjusting your survival analysis for the  
12 most current information. We've already heard the  
13 negatives for it, so we'll go on to the next slide.

14 So these are the forest plots, and I  
15 actually looked at dose. So in each pair here, the  
16 first line is low dose. The second line is high dose.  
17 And the reference group is no rosiglitazone, so we're  
18 comparing low dose versus no dose, no rosiglitazone  
19 and high dose versus zero dose. And again, the  
20 confident intervals tend to be on the protective side.  
21 For low dose, it crosses 1, and they did two different  
22 kinds of adjusted analysis. I did an unadjusted

1 analysis first, then I adjusted for baseline  
2 covariance and then the third set is adjusting for  
3 baseline covariate and other time-dependent  
4 covariates.

5           So this is stroke, and we have the same  
6 relationships going on there. CV events, again,  
7 everything tends to be on the protective side and  
8 MACE, same thing.

9           So quickly moving on, that was the analyses  
10 I did for our data monitoring committee and our human  
11 rights committee. And after seeing those data, they  
12 felt there was no sign of additional risk to our  
13 patients using rosiglitazone, and so they voted to  
14 keep the trial going the last year without any  
15 protocol modifications or without any need to change  
16 treatment, though we did offer patients a letter  
17 indicating the results from the Nissen analysis. And  
18 patients or physicians were welcome to stop rosi if  
19 they wanted to.

20           So now, the propensity analysis, this is a  
21 way of looking at two groups that are not comparable.  
22 And we had various patterns of rosiglitazone use in

1 the study, but I thought the cleanest one and the  
2 simplest one to understand would be to look at the  
3 group of patients that never took rosiglitazone  
4 through the course of the study versus patients that  
5 were on rosiglitazone the entire course.

6 This is a table showing those patients.  
7 There was 100 patients that never took rosi, and there  
8 were 425 patients that took rosi at every visit. And  
9 you can see these two groups are very different in  
10 their characteristics. The never taken rosiglitazone  
11 is a sicker group.

12 So the way this propensity matching goes is  
13 you take these two groups, the never used versus the  
14 always used, and you do a model seeing if you can find  
15 what variables predict the likelihood of someone using  
16 rosiglitazone. And we found a set of variables that  
17 predicted the use of rosiglitazone, and the C index  
18 for it was pretty good. It was about .76 so that's a  
19 measure of good classification.

20 So then what you do is you use the equation  
21 that you got from this logistic regression, and you  
22 actually calculate the probability of using

1   rosiglitazone. And we had a range of probabilities  
2   between .36 and .96. So then what you do is you take  
3   all of the never used rosiglitazone, that group of  
4   100, and you take the first patient and you find out  
5   what his probability of using rosiglitazone was. Say  
6   it's .36. So then you look at the group of always  
7   used rosiglitazone, and you find somebody that has the  
8   same probabilities. So unlike the case control where  
9   you're matching on factors, now you're matching on  
10   this likelihood of using rosiglitazone. And you do  
11   that for the whole set of never used, and you come up  
12   with two groups that are comparable in terms of the  
13   likelihood of using rosiglitazone.

14           So this is a table of those same baseline  
15   characteristics that we just saw but now this is after  
16   matching. And you can see the groups are now  
17   comparable in terms of these different baseline risk  
18   factors. And so we've sort of jerry-rigged a pseudo-  
19   randomization here for a group of never used versus  
20   always used.

21           So here's the forest plot for these  
22   outcomes, and I got pairs again. I have unadjusted

1 and adjusted analysis. And again, everything is on  
2 the left side.

3 So in summary, based on these flawed  
4 analyses, we do not see any harm in the use of  
5 rosiglitazone.

6 I just want to thank our veterans. They are  
7 the most amazing patients in clinical trials. Thank  
8 you.

9 DR. BURMAN: Thank you, Dr. Moritz. If you  
10 wouldn't mind staying up there for some questions?

11 DR. MORITZ: Sure.

12 DR. BURMAN: Let me ask the FDA if this  
13 approach is okay. It's 6:12. We were going to end at  
14 6:10, but with your permission, we'd like to go to  
15 6:30. And if anybody on the committee has to leave,  
16 please do so, if the FDA approves. And also open the  
17 floor for question for Dr. Moritz. But also to ask  
18 some of the other questions that we didn't have time  
19 for this morning. Does that meet with your approval?

20 DR. WOODCOCK: Yes, certainly.

21 DR. BURMAN: Dr. Moritz, if you don't mind,  
22 just stay up there, and we'll see how many questions

1 are for you.

2 So let me open the floor up for questions  
3 for anybody or to Dr. Moritz.

4 Dr. Proschan.

5 DR. PROSCHAN: I was just wondering if in  
6 your analyses, you didn't show anything on congestive  
7 heart failure. And I'm wondering if you did those  
8 analyses.

9 DR. MORITZ: Yes, we did those. I think  
10 those were presented. Another individual presented  
11 our data at European meetings a year and a half ago,  
12 and I believe that was one of the measures we  
13 included. And we basically saw the same relationships  
14 as I showed today.

15 DR. BURMAN: Thank you.

16 Dr. Teerlink.

17 DR. TEERLINK: I would like to second your  
18 shout-out for our veterans in studies and things. And  
19 also, I guess the issue was just addressed in terms of  
20 the -- one part I am also interested in terms of  
21 myocardial infarctions, I assume were also looked at  
22 in the same manner and had the same direction as the

1 first question?

2 DR. MORITZ: Yes.

3 DR. TEERLINK: And the second question is:

4 Did baseline insulin use, did that come up as a  
5 baseline predictor independently in your propensity  
6 analysis, so then you adjusted for it secondarily?

7 DR. MORITZ: Well, yes. Yes, it was one of  
8 the four factors, and so it was in the equation when  
9 we created the propensity scores. And it originally,  
10 we just were going to do an unadjusted analysis just  
11 as rosi yes or no, predict outcome. And it was  
12 suggested that it'd be a good idea to also adjust for  
13 those characteristics again. So I don't know if  
14 that's over fitting.

15 DR. TEERLINK: Okay. Thank you.

16 DR. BURMAN: Any other questions for  
17 Dr. Moritz or for anybody else that spoke today? I  
18 know there's some questions left over.

19 Yes, Dr. Kaul.

20 DR. KAUL: I would like to ask the question  
21 of Dr. Nissen about his meta-analysis. Slide number  
22 25 where you show the results of all 56 trials,

1 including those with zero event trials.

2 DR. TRAN: What's the slide number again?

3 DR. KAUL: I think it's 25, I believe.

4 Your corrected estimates that allowed for  
5 zero total event trials, which were 15 for MI and 29  
6 for cardiovascular death, are virtually identical.

7 Can you explain the approach you used in  
8 those zero event trials? I mean, is it conventional  
9 and did you do sensitivity analysis to evaluate all  
10 different approaches to including zero event trials,  
11 including the one that was brought up, the continuity  
12 correction or use different measures of relative risk  
13 or risk difference adjusted for treatment exposure or  
14 approximation three models such as the Bayesian  
15 approaches?

16 DR. NISSEN: Yes, I know you're a big  
17 proponent of the Bayesian approach, Sanjay, but we  
18 chose the method simply because we wanted to do the  
19 sensitivity analysis. The method we used, if you read  
20 the paper, is that we pooled trials of different  
21 randomization ratios, and so that couldn't allow us to  
22 include all those zero events trials in each of the



1 bins. And when you do that, you end up with these  
2 results.

3 I think the data is all in there. Anyone  
4 can calculate this any way they want. Our task was  
5 not to choose every imaginable meta-analysis  
6 technique. We wanted to show the primary analysis  
7 which was prespecified and then show this sensitivity  
8 analysis. I fully recognize that there are more ways  
9 that you can analyze the data.

10 I also would say that we fully recognize  
11 that using study level data as we did was not the most  
12 powerful approach. I was hoping that we would see the  
13 patient-level analysis from the FDA. And  
14 unfortunately, it's not in your briefing packet  
15 because there is no analysis of patient-level data  
16 from the FDA that includes all the trials. It just  
17 isn't in here.

18 DR. KAUL: If I can follow up? If I read  
19 your paper correctly, what you did is you basically  
20 pooled trials according to randomization ratios. So  
21 this treated as one trial approach is prone to bias  
22 because it ignores the between study differences as

1 well as the relative importance of studies. And that  
2 is precisely the point I was making.

3           If your estimates are sensitive to your  
4 choice of a particular methodological approach,  
5 achieving statistical significant with one but not  
6 with the other, it exposes the fragility of the  
7 underlying data. And such fragile data are deserving  
8 of conservative or what I call frugal interpretation,  
9 not liberal interpretation. And the regulatory and  
10 clinical implications of these interpretations could  
11 be profound. Caution is warranted before drawing any  
12 definitive conclusions.

13           DR. NISSEN: Let me answer that question for  
14 you, Sanjay, because you're absolutely right. The  
15 data are fragile, and the question is: Whose fault is  
16 that? We have a drug that's been on the market for 11  
17 years. The company has had every opportunity to do  
18 large outcomes trials adequately powered and properly  
19 run to answer this question. They didn't do it.  
20 They, in fact, if you read the "New York Times" today,  
21 know that they did look at the other drug,  
22 pioglitazone, decided that they didn't want to compare

1 to it and chose not to.

2           So the problem of having fragile data 11  
3 years after a drug has been marketed to hundreds of  
4 thousands of patients, that's not my problem. Now,  
5 you can say that there's no problem with this drug,  
6 but I would argue that the absence of evidence is  
7 certainly not evidence of absence.

8           So I would put this right on the sponsor.  
9 They've given us very little data to work with. We  
10 have suggested that there is an increase in the risk  
11 of these events per FDA analysis and per our analysis.  
12 And the fact that we don't have better, it's not our  
13 problem. It's theirs.

14           DR. BURMAN: Thank you.

15           DR. PROSCHAN: So GSK has suggested that  
16 there's a benefit, perhaps, on stroke. And we saw  
17 some comparisons in the observational data between  
18 pioglitazone and rosiglitazone with respect to stroke.  
19 But I didn't see in the comparison of the -- there  
20 were some other analyses where rosi and pio were  
21 combined and compared to other diabetes medications.  
22 And I didn't see for those kind of analyses the

1 comparison for stroke. It seemed to me there were  
2 comparisons for all the other kinds of outcomes, and I  
3 didn't see it for stroke. And I'm wondering do you  
4 have that. This was -- I guess, Dr. Gelperin  
5 presented those other analyses.

6 DR. GELPERIN: Yes, there are two backup  
7 slides that present those two forest plots, and I  
8 didn't show them because I wasn't sure I could finish  
9 in 20 minutes. But we can show them now. They are  
10 two backup slides. I don't know.

11 DR. TRAN: Which slides?

12 DR. GELPERIN: Slides 30 and 31.

13 So this slide shows that for the comparison  
14 of rosiglitazone versus pioglitazone, there were two  
15 studies. One, the Azoulay study, where we were able  
16 to calculate accrued odds ratio, and then the  
17 Winkelmayr study actually do two comparisons, one in  
18 any exposed and one in patients with no prior  
19 cerebrovascular disease. And as mentioned previously,  
20 the Winkelmayr definition of a stroke outcome  
21 included some problematic ICD codes that may have  
22 introduced misclassification.

1           Then the other slide, there were three  
2 studies. The top section shows in red rosiglitazone  
3 versus other anti-diabetic agents, and the bottom  
4 portion in blue is pioglitazone versus other anti-  
5 diabetic agents. And there were three studies that  
6 actually did those comparisons for the outcome of  
7 stroke, Azoulay, Hsiao and Habib. And you can see  
8 those results there for yourself.

9           DR. BURMAN: Thank you. We have about seven  
10 minutes.

11           Dr. Thomas.

12           DR. THOMAS: I have a question that's going  
13 back to the statin issue for Karen Mahoney, and slide  
14 13 would be representative. But essentially, just  
15 from my memory, it was stated, I think, that after  
16 three years the statin use was unchanged. So there  
17 were no effects over time once they reached a certain  
18 time period; the statin usage was the same.

19           But if you look at the slide, it also  
20 mentioned that the cholesterol had gone up early and  
21 then went down. It was a stable pattern over the last  
22 part of the study. Since usual care or local care was

1 the decision in terms of initiation for a statin, I  
2 kind of want to get a sense because there was a  
3 difference in statin usage, how much of that statin  
4 usage was affected by this initial rise in LDL where  
5 suddenly someone who wasn't motivated to use a statin  
6 in a subject suddenly decided, oh, this is too high  
7 and started using a statin? Because statin impact  
8 probably does take some time to have an impact on a  
9 cardiovascular event. If that statin disparity was  
10 early in the study, you might see the effect later on,  
11 which would diminish the effects of rosiglitazone  
12 being potentially harmful.

13 DR. MAHONEY: Can you tell me a little bit  
14 more about what your question is for me?

15 DR. THOMAS: Well, if you look at it, they  
16 both had similar cholesterols, and I don't know  
17 exactly offhand what the statin usage was at the  
18 start. In 1,000 pages of material, it's hard to  
19 remember. But the cholesterol rises up fairly early  
20 and then it comes down. So if we have an idea of the  
21 statin usage early in the trial in the rosiglitazone  
22 arm, it's going to take some time for a statin to have

1 an impact on a cardiovascular outcome. It's not going  
2 to be instantaneous. As the trial goes on longer, if  
3 there's a disparity between the two arms of statin  
4 usage, that may have an impact on the actual outcome  
5 that you see.

6 DR. HOME: I wonder if I can help Dr.  
7 Mahoney here. Perhaps we could have the slide up  
8 here. We don't know, of course, what motivated  
9 individual investigators to actually start a statin,  
10 but you're right in your assumption. And you can see  
11 from the bars here on the number of subjects  
12 initiating statin at three-monthly intervals that it  
13 occurred relatively early. And it would be my  
14 presumption, too, since we know the statin difference,  
15 the percentages that occurred fairly early on, that it  
16 was a reaction to change in LDL cholesterol. But, of  
17 course, there's no way we can know that.

18 DR. BURMAN: Thank you.

19 Dr. Mahoney, do you have any further  
20 comments?

21 [Dr. Mahoney shakes head no.]

22 DR. BURMAN: Okay. Then let's move on for

1 just a couple minutes.

2 Dr. Furberg.

3 DR. FURBERG: I have a question for  
4 Dr. Nissen.

5 Could you comment on the potential mechanism  
6 of action behind all rosiglitazone that's behind the  
7 observed increase in MIs? Is it the increase in LDL  
8 cholesterol? And if so, I don't understand how you  
9 can see harm in short-term trials.

10 DR. NISSEN: That's a great question.

11 DR. FURBERG: In other words, there is no  
12 lag time to harm.

13 DR. NISSEN: Yes, that's a great question.  
14 I also want to just finish my response to Sanjay.

15 If you look at the two datasets, you have  
16 very fragile data for rosiglitazone. But look at our  
17 meta-analysis in my slides of pioglitazone data where  
18 you've got a large outcome trial done in a high-risk  
19 population, where the point estimates and the  
20 confidence intervals are such that they're really  
21 insensitive to any kind of sensitivity analysis. And  
22 so the problem is absence of data in the rosiglitazone



1 slide and lots of data on the pio slide. Go back and  
2 look at my slides and see if you agree or disagree  
3 with that.

4 Now, Curt, no one can tell you -- and you  
5 probably know this better than I because you've been  
6 around a long time -- why a particular drug has the  
7 effects that it does. What I had hoped to be able to  
8 do, but we ran out of time, is to show you those gene  
9 profile plots. And what you see is every TZD is  
10 affecting different genes. Now, we know what some of  
11 them are. MMP3 is up-regulated by rosiglitazone, and  
12 if you look at the literature on MMP3, it appears to  
13 be highly associated with a plaque rupture kind of an  
14 event. Well, if you're turning on the gene for MMP3,  
15 that would be a very early effect. You'd have  
16 vulnerable plaques, and those vulnerable plaques would  
17 then rupture, and that might actually explain an early  
18 event.

19 The LDL hypothesis may be one mechanism. I  
20 only included that because I wanted everybody at this  
21 table to understand that we have one drug in the class  
22 that really pushed up LDL. It increases

1 triglycerides. It increases non-LDL by amounts that,  
2 by regulatory policy, if they actually were  
3 reductions, would allow a drug to get approved. And  
4 so how much that plays into all of this, I don't know.

5 But I do know that it's very important this  
6 committee understand that TZDs are not a class of  
7 drugs. They're an individual drugs within individual  
8 risk profiles.

9 I will also disagree with Mary Parks. If  
10 you look at the slides from Jeri El-Hage, the FDA  
11 toxicologist, there are a lot of these drugs that have  
12 failed due to cardiovascular toxicity. The reason you  
13 don't know about them is they didn't publish any of  
14 the results. And so of the 50 drugs that failed  
15 during development, a significant number of them  
16 failed because they had cardiovascular toxicity. That  
17 means, to use a term that Bob Temple likes to use,  
18 there is a prior history for this class causing  
19 cardiovascular problems, and it makes it much more  
20 plausible that rosiglitazone would cause it.

21 DR. BURMAN: Thank you.

22 Dr. Kaul, you had a quick follow-up, and

1 then we ask Ms. Killion.

2 DR. KAUL: I was going to use Dr. Nissen's  
3 quote against himself, which is the road to hell is  
4 paved with biological plausibility.

5 [Laughter.]

6 DR. NISSEN: Thank you.

7 DR. BURMAN: And Ms. Killion.

8 MS. KILLION: Dr. Nissen, don't sit down  
9 yet. I'm going to assume -- I'm sure I'm correct here  
10 -- that as a cardiologist, a significant, significant  
11 number of patients you see in cardiac intensive care  
12 are diabetics?

13 DR. NISSEN: Fifty percent.

14 MS. KILLION: Okay. Fifty percent. So I  
15 know that basically every morning I down the  
16 immortality cocktail. It consists of a statin, a  
17 blood pressure medicine, baby aspirin with a floater  
18 of fish oil. Now, I take this every morning not  
19 because I -- I actually have great cholesterol. I  
20 have great HDLs. But my doctor, who I credit with my  
21 good state of health to this day, put me on that quite  
22 some time ago, and I've been taking that.

1           So I guess my question to you is: Of the 50  
2 percent of your patients who are diabetics who come to  
3 you because they are now having cardiac distress, what  
4 percentage of them have been on this immortality  
5 cocktail, and if they had been, what would you surmise  
6 to be the mitigating effect on that of something like  
7 rosiglitazone?

8           DR. NISSEN: Well, first of all, there is  
9 under-treatment of diabetics. And one of the  
10 frustrations I have as I review -- I'm not getting a  
11 lot of these diabetes trials that have cardiovascular  
12 endpoints to review by the major journals. And  
13 frankly, I am not happy to see how low the percentage  
14 is of the patients in these trials, in some of them.  
15 If you look at the Advance trial, for example, very  
16 low use of statins, very low use of concomitant  
17 therapies. And so, the issue here, of course, is  
18 that's an entirely separate problem. It's one that  
19 certainly needs to be addressed.

20           The point estimates, which as Sanjay points  
21 out, are fragile, but when you see point estimate  
22 after point estimate in the range of 1.4, the FDA's

1 analysis for MACE is 1.44. Ours for MI is 1.39. The  
2 FDA's for MI is 1.8. Let's assume that the true  
3 treatment effect is half of that. Let's suppose it's  
4 only a 20 percent increase in myocardial infarction.  
5 The best drugs we have, statins, reduce risk by  
6 perhaps 20 or 25 percent, maybe a little bit more. If  
7 that's the case with rosiglitazone, we are talking  
8 about something that has as large an effect in the  
9 opposite direction as the best therapies we have.

10 Now, you want to wait to find out definitive  
11 proof until 2020, that's fine. But what happens to  
12 people over the next 10 years?

13 DR. BURMAN: Thank you. Thank you to all.  
14 Thank you, Dr. Nissen.

15 Now, I think we have to quit. We'll bring  
16 these up tomorrow. I apologize. But it's 6:30.

17 Please?

18 DR. KONSTAM: I just am struggling that how  
19 little we understand about this meta-analysis relative  
20 to the dose that the patients were on, the duration of  
21 therapy and the glycemic control. And I think we'd be  
22 helped from the sponsor and maybe the folks from

1 Takeda if we could understand the relative short-term  
2 glycemic effects. You can answer now if you want to,  
3 but I was thinking for tomorrow, between the two  
4 drugs, if that could help us at all.

5 DR. BURMAN: Very quickly.

6 DR. STEWART: Can I just quickly answer  
7 that?

8 DR. BURMAN: Sure.

9 DR. STEWART: I think it's -- when I look at  
10 the placebo and the active, you've got to realize that  
11 placebo-controlled studies, they come in and the  
12 difference is in glycemic control. So those patients  
13 lose glycemic control when they're on placebo.  
14 They're more likely to drop out of the short-term  
15 studies. You have a differential in follow-up, of  
16 lost follow-up of 15 percent in the placebo compared  
17 to those who remain on a drug that's lowering their  
18 glucose. So I think the difference between placebo  
19 and active-control studies is driven by the design and  
20 the drop of follow-up in the placebo patients.

21 DR. KONSTAM: Right, but I'm interested in  
22 the relative short-term potency of the doses that are

1 typically used for pio and for rosiglitazone.

2 DR. STEWART: Yes, that's probably also  
3 relevant to the design. So in the rosiglitazone  
4 studies, the doses used were 4 and 8 started together,  
5 which in retrospect in clinical practice, I would have  
6 rather titrated. So in the active arm studies, you  
7 see titration. Coming back to the only head-to-head  
8 study, in the lipid study, the gly study, there were  
9 different doses. So the PI dose was pushed up to 45  
10 milligrams against 4 milligrams BID of rosiglitazone  
11 to produce the similar glycemia in the short term.

12 DR. BURMAN: Thank you.

13 Any last words from the FDA?

14 DR. WOODCOCK: Thank you all for your  
15 attention and comments during this time. Thank you.

16 DR. BURMAN: Thank you. We will adjourn and  
17 reconvene tomorrow at 7:45 a.m.

18 (Whereupon, the meeting was adjourned at  
19 6:36 p.m.)

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