

1 FOOD AND DRUG ADMINISTRATION  
2 CENTER FOR DRUG EVALUATION AND RESEARCH  
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5 JOINT MEETING OF THE  
6 ENDOCRINOLOGIC AND METABOLIC DRUGS AND  
7 DRUG SAFETY AND RISK MANAGEMENT  
8 ADVISORY COMMITTEES  
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12 Thursday, June 6, 2013

13 8:00 a.m. to 4:30 p.m.  
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19 FDA White Oak Campus  
20 Building 31, The Great Room (Room 1503)  
21 White Oak Conference Center  
22 Silver Spring, Maryland

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4     CDER, FDA

6     **Solomon Iyasu, MD, MPH**

7     Director

8     Office of Pharmacovigilance and Epidemiology

9     OSE, CDER, FDA

11    **Mary H. Parks, MD**

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13    Division of Metabolism and Endocrinology

14    Products (DMEP), ODE-II, OND

15    CDER FDA

17    **Karen M. Mahoney, MD, FACE**

18    Diabetes Team Leader

19    DMEP, ODE-II, OND, CDER, FDA

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Kenneth Burman, MD	17
5	Conflict of Interest Statement	
6	Minh Doan, PharmD	23
7	FDA Introductory Remarks	
8	Mary Parks, MD	28
9	<b>Guest Speaker Presentation</b>	
10	Feasibility of a Clinical Outcomes Trial with	
11	Rosiglitazone Today	
12	Hertzel Gerstein, MD, MSc, FRCPC	42
13	Clarifying Questions	64
14	<b>FDA Presentations</b>	
15	Rosiglitazone Risk Evaluation and	
16	Mitigation Strategy (REMS)	
17	Joyce Weaver, PharmD	78
18	Drug Utilization Patterns for Rosiglitazone	
19	and Pioglitazone-Containing Products	
20	July 2007-December 2012	
21	LT Justin Mathew, PharmD	85
22		

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14  
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C O N T E N T S (continued)

AGENDA ITEM	PAGE
Clarifying Questions	97
Open Public Hearing	127
Committee Discussion	167
Committee Discussion and Vote	229
Adjournment	383



P R O C E E D I N G S

(7:59 a.m.)

**Call to Order**

**Introduction of Committee**

DR. BURMAN: Good morning. I would first like to remind everyone to please silence your cell phones and any other devices.

If you have not already done so, I would also like to identify the FDA press contact, Morgan Liscinsky. If you are present, please stand. Thank you.

Let's now go around the table and have the panel reintroduce themselves. Please state your name and affiliation for the record. Let's start with Mads.

DR. RASMUSSEN: Mads Rasmussen from Novo Nordisk. I'm the industry representative.

DR. GELLER: Nancy Geller, statistician, National Heart, Lung, and Blood Institute.

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

DR. OAKES: David Oakes, Department of

1 Biostatistics and Computational Biology, University  
2 of Rochester.

3 DR. PROSCHAN: Michael Proschan. I'm a  
4 statistician at the National Institute of Allergy  
5 and Infectious Diseases.

6 DR. HAMMERSCHMIDT: Dale Hammerschmidt. I'm  
7 a hematologist and research ethicist at the  
8 University of Minnesota.

9 MS. KILLION: Rebecca Killion. I'm the  
10 patient representative. I'm the director of  
11 professional development at McKenna Long &  
12 Aldridge.

13 DR. FELNER: Eric Felner, pediatric  
14 endocrinologist, Emory University.

15 DR. COOKE: David Cooke, pediatric endocrine  
16 at Johns Hopkins.

17 DR. STANLEY: Charles Stanley, pediatric  
18 endocrinology, Children's Hospital of Philadelphia.

19 DR. WOODS: Mark Woods, clinical coordinator  
20 and residency program director in the pharmacy at  
21 St. Luke's Hospital in Kansas City, Missouri.

22 DR. SUAREZ-ALMAZOR: Good morning. I'm

1 Maria Suarez-Almazor of the University of Texas  
2 MD Anderson Cancer Center.

3 DR. PHILLIPS: Marjorie Shaw Phillips,  
4 Georgia Regent Health System, pharmacy department,  
5 and University of Georgia College of Pharmacy,  
6 clinical professor of pharmacy practice.

7 DR. SMITH: I'm Robert Smith. I'm professor  
8 of medicine and endocrinology in the medical school  
9 at Brown University.

10 DR. HIATT: William Hiatt, a professor of  
11 medicine, the Division of Cardiology, University of  
12 Colorado School of Medicine.

13 DR. SEELY: Good morning. I'm Ellen Seely.  
14 I'm an endocrinologist at Brigham & Women's  
15 Hospital in Boston, and professor of medicine at  
16 Harvard Medical School.

17 DR. BRITTAIN: Erica Brittain. I'm a  
18 statistician at National Institute of Allergy and  
19 Infectious Diseases, NIH.

20 DR. BURMAN: Good morning. Ken Burman,  
21 chief of endocrinology at the Washington Hospital  
22 Center and professor, Department of Medicine at

1 Georgetown.

2 DR. DOAN: Minh Doan, acting designated  
3 federal officer.

4 DR. SPRUILL: Good morning. Consumer  
5 representative Ida Spruill, Medical University  
6 College of Nursing, Charleston, South Carolina.

7 DR. KAUL: Good morning. Sanjay Kaul,  
8 cardiology, Cedars-Sinai Medical Center in Los  
9 Angeles.

10 DR. KONSTAM: Marv Konstam, cardiology,  
11 Tufts Medical Center.

12 DR. MOSS: Arthur Moss, cardiologist,  
13 University of Rochester Medical Center, Rochester,  
14 New York.

15 DR. FLEGAL: Katherine Flegal,  
16 epidemiologist, CDC's National Center for Health  
17 Statistics.

18 DR. HECKBERT: Susan Heckbert, Department of  
19 Epidemiology, University of Washington.

20 DR. BUDNITZ: Dan Budnitz, medical  
21 epidemiologist, CDC's Division of Health Care  
22 Quality Promotion.

1 DR. MORRATO: Good morning. Elaine Morrato,  
2 an epidemiologist and health services researcher at  
3 the Colorado School of Public Health.

4 DR. DAY: Ruth Day, director of the Medical  
5 Cognition Laboratory at Duke University.

6 DR. MAHONEY: Karen Mahoney, diabetes team  
7 leader, Division of Metabolism and Endocrinology  
8 Products, FDA.

9 DR. PARKS: Mary Parks, director, Division  
10 of Metabolism and Endocrinology Products.

11 DR. IYASU: Solomon Iyasu, director, Office  
12 of Pharmacovigilance and Epidemiology in OSE.

13 MR. DAL PAN: Gerald Dal Pan, director of  
14 the Office of Surveillance and Epidemiology in  
15 CDER.

16 DR. UNGER: Ellis Unger, director of the  
17 Office of Drug Evaluation I, Office of New Drugs,  
18 CDER, FDA.

19 DR. ROSEBRAUGH: Curt Rosebraugh, director,  
20 O-II.

21 DR. JENKINS: Good morning. John Jenkins.  
22 I'm the director of the Office of New Drugs in

1 CDER.

2 DR. BURMAN: For topics such as those being  
3 discussed at today's meeting, there are often a  
4 variety of opinions, some of which are quite  
5 strongly held. Our goal is that today's meeting  
6 will be a fair and open forum for discussion of  
7 these issues and that individuals can express their  
8 views without interruption. Thus, as a gentle  
9 reminder, individuals will be allowed to speak into  
10 the record only if recognized by the chairperson.  
11 We look forward to a productive meeting.

12 In the spirit of the Federal Advisory  
13 Committee Act and the Government in the Sunshine  
14 Act, we ask that the advisory committee members  
15 take care that their conversations about the topic  
16 at hand take place in the open forum of the  
17 meeting.

18 We are aware that members of the media are  
19 anxious to speak with the FDA about these  
20 proceedings. However, FDA will refrain from  
21 discussing the details of this meeting with the  
22 media until its conclusion. Also, the committee is

1 reminded to please refrain from discussing the  
2 meeting topics during breaks or during lunch.

3 Thank you.

4 Now I'll ask Minh Doan to read the conflict  
5 of interest statement.

6 **Conflict of Interest Statement**

7 DR. DOAN: The Food and Drug Administration  
8 is convening today's joint meeting of the  
9 Endocrinologic and Metabolic Drugs Advisory  
10 Committee and Drug Safety and Risk Management  
11 Advisory Committee under the authority of the  
12 Federal Advisory Committee Act of 1972.

13 With the exception of the industry  
14 representative, all members and temporary voting  
15 members of the committee are special government  
16 employees or regular federal employees from other  
17 agencies and are subject to federal conflict of  
18 interest laws and regulations.

19 The following information on the status of  
20 this committee's compliance with federal ethics and  
21 conflict of interest laws, covered by but not  
22 limited to those found at 18 USC Section 208, is

1       being provided to participants in today's meeting  
2       and to the public.

3               FDA has determined that members and  
4       temporary voting members of this committee are in  
5       compliance with federal ethics and conflict of  
6       interest laws. Under 18 USC Section 208, Congress  
7       has authorized FDA to grant waivers to special  
8       government employees and regular federal employees  
9       who have potential financial conflicts when it is  
10      determined that the agency's need for a particular  
11      individual's services outweighs his or her  
12      potential financial conflict of interest.

13              Related to the discussion of today's  
14      meeting, the members and temporary voting members  
15      of this committee have been screened for potential  
16      financial conflicts of their own as well as those  
17      imputed to them, including those of their spouses  
18      or minor children and, for purposes of 18 USC  
19      Section 208, their employers. These interests may  
20      include investments, consulting, expert witness  
21      testimony, contracts, grants, CRADAs, teaching,  
22      speaking, writing, patents and royalties, and



1 primary employment.

2 Today's agenda involves the discussion of  
3 the results of an independent readjudication of the  
4 Rosiglitazone Evaluated for Cardiovascular Outcomes  
5 and Regulation of Glycemia in Diabetes, RECORD  
6 trial, for new drug application 21071, Avandia.  
7 Rosiglitazone is a thiazolidinedione, indicated as  
8 an adjunct to diet and exercise to improve glycemic  
9 control in adults with type 2 diabetes. Avandia is  
10 manufactured by GlaxoSmithKline. This is a  
11 particular matters meeting, during which specific  
12 matters related to GlaxoSmithKline's product  
13 Avandia will be discussed.

14 Based on the agenda for today's meeting and  
15 all financial interests reported by the committee  
16 members and temporary voting members, no conflict  
17 of interest waivers have been issued in connection  
18 with this meeting.

19 To ensure transparency, we encourage all  
20 standing committee members and temporary voting  
21 members to disclose any public statements that they  
22 may have made concerning the product at issue.

1           With respect to FDA's invited industry  
2 representative, we would like to disclose that  
3 Dr. Mads Rasmussen is serving as a nonvoting  
4 industry representative, acting on behalf of  
5 regulated industry. His role at this meeting is to  
6 represent industry in general and not any  
7 particular company. Currently, Dr. Rasmussen is  
8 employed by Novo Nordisk.

9           With regard to FDA's invited guest speakers,  
10 the agency has determined that the information to  
11 be provided by the speaker is essential. The  
12 following interests are being made public to allow  
13 the audience to objectively evaluate any  
14 presentation and/or comments made by the speaker.

15           Dr. Hertzl Gerstein is currently employed  
16 by McMaster University Department of Medicine.  
17 Dr. Gerstein's employer currently has contracts  
18 with Eli Lilly and Sanofi; Dr. Gerstein is leading  
19 a trial of dulaglutide and a follow-up trial on  
20 insulin glargine, respectively. His employer also  
21 receives grants from Sanofi, Eli Lilly, Boehringer  
22 Ingelheim, Novo Nordisk, AstraZeneca, and Bristol

1       Myers Squibb for continuing medical education in  
2       diabetes.

3               Dr. Gerstein is the chair of a large  
4       outcomes trial sponsored by Roche regarding  
5       aleglitazar. Dr. Gerstein provides consulting  
6       services to Sanofi, Roche, Novo Nordisk,  
7       AstraZeneca, and Bristol Myers Squibb. He has also  
8       consulted for GlaxoSmithKline, which have been  
9       unrelated to rosiglitazone since 2010. As a guest  
10      speaker, Dr. Gerstein will not participate in  
11      committee deliberations nor will he vote.

12              We would like to remind members and  
13      temporary voting members that if the discussions  
14      involve any other issues not already on the agenda  
15      for which an FDA participant has a personal or  
16      imputed financial interest, the participants need  
17      to exclude themselves from such involvement, and  
18      their exclusion will be noted for the record.

19              FDA encourages all other participants to  
20      advise the committee of any financial relationships  
21      that they may have with firms that could be  
22      affected by the committee's recommendations. Thank

1       you.

2               DR. BURMAN:   Thank you.

3               We will now proceed with Dr. Parks'  
4       introductory remarks.   And if I might just mention  
5       a schedule issue, Dr. Parks indicated that she'll  
6       be speaking for a few moment and then we're going  
7       to ask the FDA to follow up on some of the issues  
8       that were brought up yesterday.   And then at 11:15,  
9       we're going to ask DCRI and GSK to follow up on the  
10      issues that they had mentioned that they wanted to  
11      follow up on as well.

12              Dr. Parks?

13                               **FDA Introductory Remarks**

14              DR. PARKS:   Thank you, Dr. Burman.   I  
15      actually don't have a whole lot to say in the  
16      introductory remarks that haven't already been  
17      covered by Minh and yourself.

18              Yesterday afternoon, several of the panel  
19      members had questions that you were seeking clarity  
20      on.   So over the course of the evening, FDA, GSK,  
21      and DCRI have worked on this.   I think at this  
22      point I'll just turn it back over to you, Dr.

1 Burman, to call on the individual parties to  
2 respond to these questions.

3 DR. BURMAN: Thank you. I'd be happy to.  
4 And I think it appropriate to ask the FDA first.  
5 Is Dr. Mahoney going to respond?

6 DR. MAHONEY: I can address two things from  
7 yesterday. First of all, the question about the  
8 analyses that were done to look at the estimates  
9 before and after the interim analysis. An  
10 observation was made that the numbers of patients  
11 in the analyses after the interim analysis, there  
12 was an observation that the denominator, the  
13 numbers of patients who were observed there, was a  
14 bit higher for rosiglitazone than it was for  
15 comparator. And they're asking why that was since  
16 there was an understanding that more patients on  
17 rosiglitazone withdrew from randomized treatment.

18 The reason was because that analysis was an  
19 intention-to-treat analysis and not an as-treated  
20 analysis. It used the intention-to-treat  
21 population.

22 You may recall that even though

1       rosiglitazone patients may have gone off randomized  
2       therapy, they continued to be followed for  
3       cardiovascular outcomes. At those points in  
4       the trial, there were still a few more  
5       rosiglitazone patients being observed. So that's  
6       the reason for that.

7               Then GSK is going to address some things  
8       that they've looked at regarding the issue of the  
9       interaction by baseline statins. But a committee  
10      member also asked what we know about PROactive. I  
11      did the review for PROactive, and I did go back to  
12      my review and take a look at the subgroup analyses.

13             Interestingly, qualitatively the same thing  
14      was observed in PROactive, with, when you look at  
15      patients who were not on statin at baseline, the  
16      point estimate for the hazard ratio was lower than  
17      it was for patients who were on statin at baseline.

18             That was true for the main primary composite  
19      endpoint, which you may recall was composed of a  
20      number of things -- all-cause mortality, nonfatal  
21      MI, excluding silent MI, stroke, acute coronary  
22      syndrome, major leg amputation, coronary bypass,

1 percutaneous coronary intervention, or leg  
2 revascularization.

3 It was also seen for a post hoc secondary  
4 composite of all-cause mortality, nonfatal MI  
5 excluding MI or stroke, a qualitatively similar  
6 observation.

7 So I think I'll go ahead and ask GSK if they  
8 can talk about some of the things that they've been  
9 able to do overnight regarding the baseline  
10 statins.

11 DR. KONSTAM: I'm sorry. Can --

12 DR. MAHONEY: Oh, I'm sorry. I should ask  
13 the chairman.

14 DR. KONSTAM: I think it would really worth  
15 us seeing the details of what you just said. You  
16 mentioned the findings qualitatively, but I would  
17 love to see the data about that, the numbers.

18 DR. BURMAN: Sure.

19 DR. BRITTAIN: It's a table, but it's on a  
20 slide. Right?

21 DR. BURMAN: Do you have that, Dr. Mahoney?

22 DR. MAHONEY: We have discussed this.

1       Unfortunately, we are not certain that we can  
2       present an actual slide with it because Takeda owns  
3       these data, and although we have taken an action  
4       and we do have a review on it -- because it was  
5       just brought up yesterday overnight, it hasn't had  
6       the opportunity to undergo the review by the  
7       Division of Information Disclosure policy. So we  
8       don't know that we can present the actual numbers.

9               DR. BURMAN: Understand. Thank you.

10              Any questions otherwise for Dr. Mahoney on  
11      the issues that she brought up? Dr. Geller?

12              DR. GELLER: Yes. I hate to obsess over  
13      denominators. But I'd like to know exactly who is  
14      in the denominators.

15              DR. BURMAN: Hold on one minute.

16              (Pause.)

17              DR. GELLER: Dr. Day?

18              DR. DAY: I'm sorry. I didn't request to  
19      speak.

20              DR. GELLER: I think the question is for  
21      the person next to you. I'm obsessing over the  
22      denominators in slides 43 through 46. So if a



1 person had the event in question, they're no longer  
2 in the denominator. And if they're dead, they're  
3 no longer in the denominator after 5 June 2007.

4 If you had any event, are you no longer in  
5 the denominator? Who is in the denominator after  
6 June 5th?

7 DR. MAHONEY: Because DCRI did the analyses,  
8 I think I'm going to defer to them to describe that  
9 in detail. I don't know if they've had the  
10 opportunity to address that in detail yet, but  
11 perhaps they can now or later.

12 DR. BURMAN: I think, given the  
13 time -- well, if GSK wants to make a comment now,  
14 that's fine, too. Do you want to make a comment?

15 DR. STEWART: This is Dr. Stewart from GSK.  
16 I don't know whether you want me to address some of  
17 the questions now or leave it till later, as you  
18 suggested.

19 DR. BURMAN: I think it depends on how long  
20 you think it will take, Dr. Stewart. How long will  
21 your presentation take?

22 DR. STEWART: If we show the first slide --

1 DR. BURMAN: Will it take less than  
2 10 minutes?

3 DR. STEWART: Yes.

4 DR. BURMAN: Thank you.

5 DR. STEWART: So if they're going to show  
6 the first slide that's here, we can address the  
7 statin question now because I know there's lots of  
8 concern about that, and I can go into the other  
9 questions later. If you particularly want me to do  
10 the statins, I'll try and do that in five minutes.

11 DR. BURMAN: Sure.

12 DR. STEWART: If we go to the next slide.

13 So it's important to recognize that the  
14 original RECORD study prespecified subgroup  
15 analysis. So there were eight, and you can see  
16 here sex, age, no difference.

17 On the next slide, we did look at statin  
18 use. And when we looked at the primary endpoint in  
19 the original RECORD of CV death and CV  
20 hospitalization, there was no interaction with  
21 statin. And I'll let DCRI comment on what they  
22 found when they looked at MACE and mortality.

1           So clearly, the question that the committee  
2   is grappling with is around, well, what's the  
3   impact on statin? What's the impact on LDL? So in  
4   the next slide, we were asked to -- I'll go to the  
5   next slide after this, actually -- well, how is  
6   statin actually defined at baseline?

7           So these were some of the medications people  
8   are on, and statin use at baseline was defined as  
9   patients who were on statin medication started  
10   prior to the first dose date of the study drug and  
11   continued it after randomization.

12           So what did that actually look like? On the  
13   next slide here, you can see that in the rosi  
14   group, there was 18 percent on statins at baseline;  
15   similar, 19 percent, in the comparator group. And  
16   here's an idea of some of the doses and the  
17   statins. So a lot of people were on atorvastatin,  
18   and you can see the other statins there.

19           So obviously, they were on statins. So the  
20   obvious question is what happened to their LDL?  
21   This is how much statin they were on. So they  
22   started on it, and you can see at the end of the

1 study, there was an 8 percent difference in statin  
2 use in the rosi group compared to the non-rosi.  
3 And at the bottom, you can see the change in statin  
4 doses.

5 So you can start to see that there was add-  
6 on therapies, and we do have a lot more backups.  
7 But the majority there on the bottom panel were on  
8 simvastatin, and atorvastatin accounted for  
9 80 percent of the statin use that was added in  
10 during the study.

11 This is looking at the rosi-metformin/rosi-  
12 sulfonylurea strategy. Although it's difficult to  
13 see, we've got the rosiglitazone in red. You can  
14 see that they came on statins -- sorry, it's very  
15 European, millimoles; I think you've got to  
16 multiply by 40 to get in mgs per deciliter -- but  
17 relatively normal LDLs at the time, given this was  
18 2000.

19 What you can see is that protocol allowed  
20 you to add in statin therapy based on natural  
21 guidelines. So it was not forced adding in statin.  
22 It was per guidelines.

1           What you can see is that we know that  
2       rosiglitazone includes LDL by about 10 to  
3       15 percent, so that flick-up represents the  
4       increase that rosiglitazone has on LDL. And then  
5       what you can see is that as per the previous graph,  
6       you start seeing increased statin use to lower it.

7           So the question is, what did this do in  
8       terms of incidence of events? In the next slide  
9       here -- and sorry it's small -- I'd like you to go  
10      to the incidence rate per 100,000 patient-years.  
11      And what you can see is we've got the rate for the  
12      primary endpoint here. And I've got MI as well,  
13      which is important.

14           Pre-statin period with rosiglitazone is 2.7  
15      per hundred patient years. And when they go on  
16      statins, it goes to 2.88. And in the met/SU,  
17      you've got pre-statin rate of incidence of endpoint  
18      2.74, going to 2.92. So there's not an imbalance  
19      in an increase in events of the primary endpoint.

20           If you look at the next slide on MI, what  
21      you can see is an increased incidence of MI by  
22      exposure to statin. So you've got pre-statin

1 period -- again, if you look at incidence rate per  
2 hundred patient-years -- you've got pre-statin  
3 period, 0.53 per hundred patient-years. When they  
4 go on statins, it's .52. If you look at the  
5 met/SU, there is a drop in incidence rate, 0.51 to  
6 0.37.

7 So it may just be worth looking at that and  
8 taking that in. So that's the impact. So what you  
9 can see if there was increased statin use. The  
10 LDLs did come down. And this is the incidence of  
11 MI.

12 Then moving on to the last slide, and this  
13 was just pasted together from the briefing document  
14 because everyone was saying, well, what was this on  
15 page 10? And this is not GSK's data. We just put  
16 this together, a slide for DCRI, and DCRI may want  
17 to comment on the statin effect when they looked at  
18 all-cause mortality and CV and unknown cause.

19 So Dr. Mahaffey, I don't know whether you  
20 want to comment on this slide.

21 DR. BURMAN: Dr. Mahaffey, do you want to  
22 make a quick comment?

1 DR. MAHAFFEY: Yes. I'd appreciate the  
2 opportunity, Mr. Chairman. Ken Mahaffey here.

3 When we did our subgroup analyses, we  
4 prespecified in our statistical analysis plan  
5 12 subgroups that we would look at. Those  
6 subgroups were based on the subgroups that were  
7 published in the original Holmes Lancet paper of  
8 2009.

9 You see here some of it. Why don't I go  
10 through three or four forest plots? Because I  
11 think it will be informative for you. So can I  
12 have the primary composite endpoint?

13 If you look in the middle of the slide at  
14 the baseline statin use, you can see that for the  
15 primary composite endpoint, using our primary and  
16 analytic method that Dr. Bigelow described for you  
17 yesterday, you can see that there is statistically  
18 significant interaction for the outcome by  
19 treatment by baseline statin use. Next slide.

20 I apologize for the quality of the slides  
21 here. We just were able to make them last night.  
22 But again, if you now look at CV death and you look

1 at baseline statin use, you see the similar  
2 statistically significant interaction that you've  
3 seen for the primary composite.

4 If you go to the next slide, you can see  
5 the MI endpoint. And here you do not see a  
6 statistically significant interaction. I think  
7 Dr. Kaul was particularly interested in these data  
8 yesterday.

9 Then finally, for the last endpoint, the  
10 all-cause mortality, you can see that by baseline  
11 statins, the FDA had asked us to show the number of  
12 patients who had died who were on statin at  
13 baseline. You can see those.

14 In the rosiglitazone, it was 34 patients; in  
15 the combined comparator arm, it was 29. And you  
16 see here that there's no statistically significant  
17 interaction by treatment by statin use at baseline  
18 for all-cause mortality.

19 DR. BURMAN: Thank you. We have time for  
20 one question.

21 DR. MAHAFFEY: Mr. Chairman, sorry. There's  
22 also this issue about the denominators on the



1       slide, and Dr. Bigelow here could address that and  
2       put it to rest if that would be the right time to  
3       do it.

4               DR. BURMAN: It depends. Does Dr. Bigelow  
5       think it will take a minute, or with you like to  
6       have more time at 11:00?

7               DR. MAHAFFEY: It'll take a minute or two,  
8       he says.

9               (Laughter.)

10              DR. BURMAN: Please proceed.

11              DR. MAHAFFEY: Do you want us to wait?  
12       Because we'll be back up here after the break going  
13       through the series of questions we were asked  
14       yesterday. Perhaps we'll just wait, then.

15              DR. BURMAN: What is your pleasure? Would  
16       you like to do it now or do it then?

17              DR. MAHAFFEY: Why don't we go ahead and  
18       wait, and we'll come back up later and address the  
19       series of questions that we were asked yesterday.  
20       Sorry for the confusion.

21              DR. BURMAN: No problem. Thank you. And I  
22       apologize to you as well, but we will have time at

1 11:15 to follow up on that.

2 I would now like to introduce the guest  
3 speaker, Dr. Hertzelt Gerstein. Please remember,  
4 when there are questions, to state your name.  
5 Dr. Gerstein, welcome.

6 **Guest Speaker Presentation - Hertzelt Gerstein**

7 DR. GERSTEIN: Thank you very much.  
8 Mr. Chairman, ladies and gentlemen, my name is  
9 Hertzelt Gerstein, and I appreciate the opportunity  
10 to speak to this committee.

11 I was asked by the agency to address the  
12 feasibility of a clinical outcomes trial using  
13 rosiglitazone that would start now or start after  
14 this committee. And I'm going to speak to this  
15 question, both as a clinical trialist who's engaged  
16 in the design and conduct of large, international  
17 cardiovascular outcomes trials in people with  
18 diabetes, and as a doctor who cares for people with  
19 diabetes.

20 Indeed, there are more and more of these  
21 people every day appearing, certainly in North  
22 America and around the world, because diabetes, we

1 know today, is a disease that affects 1 out of 10  
2 adults both in the United States as well as in many  
3 other developed countries and even developing  
4 countries throughout the world.

5 The prevalence of diabetes has been rapidly  
6 rising over the last 15 years and does not appear  
7 to be slowing down. And diabetes is a serious  
8 problem because it increases the incidence of a  
9 large variety of serious and often life-threatening  
10 and often quality of life-threatening outcomes,  
11 including things such as blindness, kidney failure,  
12 amputations, chronic neuropathic pain, heart  
13 attacks, strokes, dementia, cirrhosis, cancer,  
14 falls, erectile dysfunction, frailty, and other  
15 things.

16 Indeed, one can think of this disease as a  
17 disease of accelerated aging, and it behaves in  
18 that way in a lot of ways. And currently, because  
19 of all the consequences, last year in 2012, it  
20 cost, just in the United States alone, \$245 billion  
21 to care for people with diabetes.

22 Clearly, in this context, a therapy that can

1 both safely reduce the incidence of diabetes and  
2 reduce the consequences of diabetes could make a  
3 big difference to society and to individuals  
4 affected by this disease or individuals at risk for  
5 this disease.

6 So I'm going to address the question I've  
7 been asked according to the following outline.  
8 Given this context about diabetes, first, one slide  
9 I'm going to summarize what I think we know today  
10 about rosiglitazone, and then spend a few minutes  
11 discussing why this whole question that I've been  
12 asked to address is important. Why do we need  
13 clinical outcomes trials such as the one that we're  
14 talking about and other ones in the first place?

15 Then I'll spend a few minutes telling you  
16 what the global opinion leaders who were involved  
17 in the large clinical outcomes trial that was  
18 stopped I believe about the feasibility, and then  
19 finally I will conclude.

20 So just in one slide, what do we really  
21 know -- if we can know anything -- but what do we  
22 really know about rosiglitazone? Well, first, we

1 know that rosiglitazone improves glucose control,  
2 and it does so without causing hypoglycemia, for  
3 the most part, which is an important feature for  
4 people affected with diabetes.

5 We also know, from a very large, more than  
6 5,000-person diabetes prevention trial called the  
7 DREAM trial, that rosiglitazone prevents or at  
8 least delays the incidence of diabetes by more than  
9 60 percent compared to placebo. So it certainly  
10 has those two important features.

11 We saw yesterday and we've seen over the  
12 years many, many large observational studies or  
13 epidemiologic studies that have come to different  
14 conclusions. And these studies have suggested that  
15 rosiglitazone is either associated with a higher  
16 risk of cardiovascular outcomes, or a lower risk of  
17 cardiovascular outcomes, or no different risk of  
18 cardiovascular outcomes, depending on the  
19 epidemiologic study that's been looked at, and  
20 a systemic overview was shown yesterday.

21 We know from what we've heard all day  
22 yesterday, and I think this is the simplest message

1 to take from what we heard, that the RECORD trial  
2 showed that rosiglitazone is noninferior to both  
3 metformin and sulfonylureas regarding  
4 cardiovascular outcomes, and we heard yesterday  
5 that the results of that trial were confirmed  
6 following the independent review.

7 We also know that rosiglitazone, like all  
8 the thiazolidinediones, increases heart failure,  
9 which most of the studies suggest is nonfatal heart  
10 failure, and we know that it increases fractures in  
11 a small number of individuals prescribed this drug.

12 Finally, the most perhaps relevant thing  
13 that we know, which is relevant to the topic I'm  
14 asked to address, is that rosiglitazone is  
15 infamous. The drug has been withdrawn from the  
16 market in Europe completely. It's available in the  
17 United States and Canada under very, very  
18 restrictive conditions and circumstances. And the  
19 interest and attention in today's and yesterday's  
20 proceedings are a testament to the media interest  
21 in the drug.

22 Why do we need to have this discussion

1       related to clinical outcomes trials, and why is  
2       this a relevant discussion, especially in this day  
3       of big data, when there are huge databases that  
4       might provide answers to questions?

5               Well, we do large outcomes trials. And when  
6       we talk about outcomes, we're talking about things  
7       that are not important, necessarily, to physicians  
8       but things that are important to the public as well  
9       as physicians such as heart attacks, strokes,  
10      death. We do outcomes trials because both patients  
11      and society wants to prevent or avoid these  
12      outcomes from happening, clearly.

13             Outcomes trials are the only way -- and  
14      when I mean trials, I mean randomized, controlled  
15      trials -- are the only way to ensure that our  
16      conclusions regarding safety and efficacy are based  
17      on the best possible unbiased evidence because when  
18      you do big data analyses from databases, there are  
19      uncontrollable biases in such data.

20             So we do large outcomes trials to avoid  
21      unknown biases that are due to both measured and  
22      unmeasured -- which is probably the most

1       important -- confounding that characterizes all  
2       observational and all administrative data sets, and  
3       that cannot be eliminated no matter how many clever  
4       adjustments and innovative approaches are used.

5               We do outcomes trials, randomized,  
6       controlled outcomes trials, to minimize the chance  
7       of making our decisions or policies or being swayed  
8       by strongly-held opinions that are based on  
9       observational data, which I've already said are  
10      biased, or small trials for which random chance and  
11      a number of other things can clearly get involved  
12      that affect the results.

13             We also do large outcomes trials because,  
14      really, controlled clinical trials represent the  
15      best evidence that we can generate. It can resolve  
16      uncertainty based on weaker evidence. They can  
17      reliably determine whether new therapies that we're  
18      testing can prevent the serious health consequences  
19      of diabetes, do more good than harm, on  
20      average -- and that's important -- and whether our  
21      new therapies are better than older therapies.

22             We could outcomes trials to democratize



1 decision-making so that the patient can be  
2 presented the results of these large comparisons of  
3 drugs versus alternatives or placebo, and they can  
4 be actively involved in decision-making processes  
5 regarding the medications that they're taking. And  
6 clearly, they are to allow healthcare providers to  
7 treat their patients better tomorrow than we can  
8 treat them today.

9           The lessons that have been taught by large  
10 outcomes trials are well known to clinical  
11 trialists and to people, and I think probably many  
12 of the people sitting around the table. And there  
13 are many examples, many examples, of therapies that  
14 have been deemed or that were deemed harmful or  
15 helpful based on observational studies and based on  
16 collections of small trials that, when the large  
17 outcomes trial were done, were shown to be  
18 beneficial or harmful.

19           For example, I have a number of examples on  
20 this slide. So erythropoietin and treating anemia  
21 was felt to be a very important way for managing  
22 people. And indeed, there were many people who

1       said that it was unethical to not give  
2       erythropoietin to people with chronic anemia based  
3       on observational studies and small trials. The  
4       large, international outcomes trial showed clearly  
5       that it is not beneficial and in fact may be  
6       harmful.

7               Insulin therapy for treating diabetes has  
8       been saddled with claims of harm and has been  
9       alleged to cause a number of bad outcomes,  
10      including cardiovascular disease and cancer, for  
11      years based on epidemiologic studies, physiologic  
12      reasoning, and small trials. The large, 12 and a  
13      half thousand person, seven-yearlong outcome trial  
14      showed that it has a totally neutral effect on  
15      serious health outcomes.

16             For many years, estrogen replacement therapy  
17      was touted as the therapy go give all  
18      postmenopausal women until the large Women's Health  
19      Initiative showed that that was indeed not the  
20      case.

21             Metformin was felt to be a drug to be used  
22      with extreme care in people with diabetes in the

1 '70s and '80s, was not even available in the United  
2 States until 1995, until the United Kingdom  
3 Prospective Diabetes Study suggested it may reduce  
4 events and changed the whole approach in thinking  
5 to metformin.

6 Perioperative beta blockade was felt to  
7 prevent mortality in people undergoing noncardiac  
8 surgery based on small trials, and meta-analyses  
9 that showed clear benefits in meta-analyses of  
10 small trials, until the large outcomes trial called  
11 POISE showed that they were indeed not effective  
12 and may be harmful. And we all know about  
13 ventricular arrhythmia suppression, which was felt  
14 to be important until the CAST trial showed that it  
15 was indeed not helpful and may be harmful.

16 So I think it's clear that we need to do  
17 these large outcomes trials because they can often  
18 provide us with answers that we did not expect and  
19 that we need to know as clinicians and as society.

20 So in order to help answer the question  
21 that I was asked to address here, I thought it  
22 would be appropriate to get the opinion of those

1 international experts who were involved in the only  
2 large outcomes trial that was designed to clearly  
3 assess the cardiovascular effects of rosiglitazone  
4 compared to placebo.

5           You heard this discussed briefly yesterday.  
6 This was the TIDE trial, which was put on full  
7 clinical hold by FDA after the 2010 advisory  
8 committee. And just very briefly, this was a  
9 16,000-person trial of people with diabetes that  
10 was being conducted in 39 countries, including the  
11 United States.

12           It was sponsored by GSK, but it was  
13 independently designed -- with input, but  
14 independently designed by an international group of  
15 leaders. And it was designed and led by myself and  
16 my colleague Dr. Salim Yusuf at the Population  
17 Health Research Institute in Hamilton, where this  
18 was coordinated, and by international experts in  
19 cardiovascular disease or diabetes around the  
20 world.

21           The question that this trial was asking were  
22 two co-primary questions. Two. The design was

1 people were being randomized to either  
2 rosiglitazone or pioglitazone or placebo in a 3 to  
3 3 to 4 ratio.

4 It was designed to answer two co-primary  
5 questions. The first question was whether the  
6 thiazolidinediones as a class, which would be  
7 either rosi or pio, were superior to placebo with  
8 respect to cardiovascular outcomes; and the second  
9 co-primary question was whether rosiglitazone was  
10 noninferior to pioglitazone with respect to  
11 cardiovascular outcomes. And the trial, with  
12 16,000 individuals, had sufficient power to answer  
13 those questions.

14 It was stopped after 1120 people were  
15 randomized. But I thought, for this session, it  
16 would be useful to survey the people who were  
17 leading this trial around the world regarding their  
18 opinions pertaining to the feasibility of another  
19 cardiovascular outcomes trial with rosiglitazone,  
20 and so that's what we did.

21 So a survey was sent to the 53 TIDE national  
22 leaders -- these were experts around the world who

1        were leading their various countries -- and the  
2        people on the executive or operations committee, as  
3        well as the five-member Data Safety Monitoring  
4        Board.

5                All of them were enthusiastic at the time  
6        regarding the importance of TIDE. All are highly  
7        respected and experienced diabetes and  
8        cardiovascular outcomes trialists from 39 different  
9        countries.

10               In the letter to them, they were told of  
11        this meeting that was coming up and reminded that  
12        when the FDA suspended the trial, Europe withdrew  
13        rosiglitazone from the market and there was  
14        restrictions on its use in the United States. I  
15        was able to get responses from 38 of these  
16        individuals, and I'm going to show you what those  
17        responses were.

18               They were asked two sets of questions. The  
19        first was their opinions about the efficacy -- or  
20        the effect, excuse me -- of this drug on serious  
21        outcomes. And the second set of questions was  
22        related to feasibility. So the first set of

1        questions, if you like, is assessing their  
2        equipoise, and the second their belief about  
3        whether such a trial would be possible.

4                So it's a series of slides that I'm going to  
5        show now, and they all are showing the results to  
6        this survey. And so if the answer is to the right,  
7        it means that they think that -- in response to  
8        this question, for instance, "What do you believe  
9        is the effect of rosiglitazone on the following  
10       important health outcomes?" to the right they would  
11       think it's beneficial; to the left of the  
12       neutrality line or the unsure answer, they would  
13       think it's harmful.

14               In response to the question, "What do you  
15       believe is the effect of rosiglitazone on  
16       myocardial infarction?" this was the response of  
17       these experts who were initially engaged in this  
18       trial. I think it's a pretty good example of that  
19       they're not sure. Neutrality or equipoise on the  
20       question.

21               What about stroke? The same thing. What  
22       about cardiovascular death, what do you believe is

1 the effect on that? This is their belief based on  
2 what they've read and their media and everything  
3 else that they've seen. What about major adverse  
4 cardiovascular events? Neutrality, perhaps a  
5 slight shift towards they think possibly  
6 beneficial. And those are those sets of answers.

7 What about death from all causes? Again,  
8 either neutrality or perhaps slightly to the right  
9 of neutrality. What about hospitalization for  
10 heart failure? Well, they know this and it's what  
11 you would have expected, so yes, less.

12 What about death from heart failure?  
13 Despite the fact that the trials have not shown a  
14 clear signal of heart failure death, the belief of  
15 the committee was that it may increase heart  
16 failure death, but there's a lot of uncertainty  
17 there as well. And those are those answers.

18 What about fractures in men? Well, despite  
19 the fact that the most of the fracture signals had  
20 been in women, there is some uncertainty or perhaps  
21 concern about that amongst the group. Fractures in  
22 women, reflecting the data. Yes, they think that



1       it's harmful with respect to that.

2               Lethal fractures, there's mostly neutrality  
3       on that question.  Cancers, because of the concerns  
4       raised by pioglitazone, they feel that there's  
5       neutrality with rosiglitazone related to this.  And  
6       even with bladder cancer, either neutrality, or  
7       perhaps slightly to the left because of a potential  
8       signal with pioglitazone.

9               So that's the opinion, if you like, the  
10       sense of equipoise, that at least people who were  
11       at one time very dedicated to answering this  
12       question believed.

13               Now, what about the outcome trial's  
14       feasibility?  The way that this question was asked  
15       was the following.  Assume that a new 10,000-person  
16       trial of add-on treatment with rosiglitazone versus  
17       placebo on cardiovascular outcomes was approved by  
18       the FDA today.

19               Is it feasible to do this trial in today's  
20       environment?  We asked, do you support and promote  
21       such a trial?  Do you think your national  
22       regulatory agency will approve this trial?  Because

1 the thinking was that it would be conducted  
2 internationally.

3 Do you think your ethics committee will  
4 approve this trial? Do you think at least half of  
5 the sites who were once upon a time involved in  
6 this trial a few years ago -- would these sites now  
7 participate in this trial? And do you think that  
8 if they were to participate, they'd be able to  
9 recruit, at any site would be able to recruit at  
10 least 20 or more individuals for this trial?

11 So here are there answers to this questions.  
12 Do they think such a trial is feasible today? And  
13 this is what the opinion is of these leaders  
14 before. So people just don't know. And it's right  
15 across the spectrum, but there's a lot of concern  
16 that it may not be clearly based on this answer.

17 What about the next question, would they  
18 support such a trial? Despite their concerns about  
19 feasibility, clearly there's a shift that many  
20 would support such a trial, but some would not.

21 Would their regulator in their country  
22 support such a trial? And I think there's a

1       somewhat more neutral or pessimistic opinion  
2       regarding that. Would their local ethics committee  
3       support such a trial? And I think probably,  
4       possibly, maybe unsure, seems to be the trend in  
5       there.

6                Would more than half the sites who used to  
7       participate in TIDE participate in such a trial?  
8       And they really don't know. I think that a lot  
9       were -- a few said possibly, but clearly there  
10      was uncertainty.

11              Would a site that was participating recruit?  
12      And I think that there's a sense that if they were  
13      participating, they would be able to recruit. But  
14      even then, there was concern over whether that  
15      would be possible.

16              So this is clearly not a publishable survey.  
17      This is an opinion-based thing based on the opinion  
18      of people. But I think it's relevant because if  
19      these individuals, who were leading the  
20      international trials and leading their sites in  
21      their countries, have these opinions, then I think  
22      that would give a reflection for what a broader

1 community of scientists and physicians and  
2 clinicians may feel.

3           So where does this leave us? Well, in  
4 conclusion, I think the TIDE researchers certainly  
5 remain uncertain regarding the cardiovascular  
6 effects of rosiglitazone, and they just don't  
7 know. And I think the RECORD study showing that  
8 rosiglitazone may be noninferior to metformin,  
9 which many believe to have cardioprotective  
10 properties, is part of the driving of that  
11 uncertainty.

12           Equal proportions of researchers are  
13 negative and positive regarding the feasibility of  
14 an outcomes trial. There is much uncertainty  
15 regarding whether it would be approved by  
16 regulatory agencies or ethics committees, and the  
17 ease of recruitment in the current climate, and it  
18 goes to say that I think sponsorship would  
19 certainly be a challenge and an interesting  
20 discussion.

21           It's in some ways really unfortunate -- had  
22 TIDE been allowed to proceed -- and at the time it

1        was stopped, 1120 people had already been  
2        randomized and there was every indication that  
3        recruitment could continue. Had it been allowed to  
4        proceed, by now all 16,000 people would have been  
5        enrolled. They would have now had a median  
6        follow-up of 1 and a half years, representing  
7        24,000 person-years of follow-up, which is way more  
8        than any other study had had.

9                There would be ongoing independent safety  
10       auditing by the very experienced and knowledgeable  
11       independent Data Monitoring Committee. However,  
12       even so, the relevance of the answer by 2016 may  
13       have been uncertain if, while it was proceeding,  
14       the same sort of hype was ongoing.

15                So that is a question which is somewhat  
16       unanswerable. But we would clearly have a lot more  
17       data and information and confidence had the study  
18       been allowed to proceed rather than being put on  
19       hold.

20                So I think the message here that is most  
21       important to hear, I think, is that there is no  
22       question that large cardiovascular outcomes

1 trials -- and in fact, other outcomes as well, not  
2 just cardiovascular; and in the TIDE trial and  
3 other trials, many other outcomes are being  
4 measured. So large outcomes trials, outcomes being  
5 things that are important to the public as well as  
6 physicians, should be done. And they should be  
7 done before strong opinions based on unreliable  
8 data become entrenched in people's psyche and  
9 subconscious. And they should be done when the  
10 results of these outcomes trials are relevant to  
11 patients and when they are relevant to providers.

12 The FDA's current policy -- as a result  
13 perhaps of the rosiglitazone story several years  
14 ago, the FDA's current policy regarding outcomes  
15 trials for diabetes drugs I think goes a very long  
16 way to minimizing the likelihood of us as a society  
17 being placed in the conundrum that we're in today,  
18 where a potentially cardioprotective drug has not  
19 been assessed and is not being properly assessed,  
20 and probably will never be assessed.

21 But I think the good news is that as a  
22 result of FDA's current policy, there are

1 approximately 125- to 150,000 people with diabetes  
2 who are currently involved in large, international  
3 outcomes trials of a number of new classes: DPB4  
4 inhibitors, GLP1 analogues, SGLT2 inhibitors, a  
5 PPARalpha/gamma analogue, alpha-glucosidase  
6 inhibitor, one thiazolidinedione, a pioglitazone  
7 trial still ongoing, and a novel agent.

8           So if you add up the numbers on the right,  
9 you see that these are all outcomes trials. They  
10 all have data monitoring boards. Safety signals  
11 will be detected. And in the end, they will  
12 provide very important answers that will help guide  
13 the use of these drugs once these trials are  
14 finished.

15           However, when one thinks to the question  
16 that I've been asked to address, these trials are  
17 ongoing, and the relevance today of a large  
18 cardiovascular outcomes trial with rosiglitazone,  
19 given the baggage that it carries with it -- and it  
20 is a considerable amount of baggage related to  
21 perceptions and all the discussion that we've  
22 had -- would certainly make doing an outcomes trial

1       challenging. It would not be impossible, but it  
2       would certainly be very challenging and something  
3       that would be very interesting to discuss.

4               Thank you very much for your attention.

5                       **Clarifying Questions**

6               DR. BURMAN: Thank you, Dr. Gerstein.

7               We'll open the floor up for clarifying  
8       questions, and remember to state your name. And  
9       I'd like to ask the first question, if I might.

10              That was a very nice presentation, but to  
11      get to the bottom line, what's your  
12      recommendation --

13              (Laughter.)

14              DR. BURMAN: -- with regard to the study and  
15      to the feasibility?

16              DR. GERSTEIN: Well, I don't think we know  
17      the feasibility. And I think the uncertainty that  
18      I showed around the world really reflects that. I  
19      think to make such an outcomes trial feasible, we  
20      would need to have a clear and unequivocal  
21      statement by the FDA, very publicly, saying that  
22      there is a lot of importance and public health



1 importance of doing such a trial; that the FDA  
2 strongly endorses the importance of answering this  
3 question in such a way.

4 It would have to be designed fairly  
5 autonomously by an academic group, such as ours or  
6 another academic group. It would have to be  
7 appropriately sponsored, and the sponsor would have  
8 to make the right business decisions to sponsor  
9 such a trial and to allow arm's length conduct of  
10 such a trial.

11 It would require the societal attitude  
12 towards this drug to acknowledge the importance of  
13 the trial and a fairly clear message from important  
14 opinion leaders and certainly within the United  
15 States, that this was an important trial to  
16 conduct.

17 Absent that, I think we would be dealing  
18 with artillery from all over the place. And so it  
19 would be extremely challenging and questionable  
20 whether it could be done.

21 DR. BURMAN: But with that assurance, would  
22 you recommend it be done?

1 DR. GERSTEIN: If all those things were in  
2 place, yes, we could do it. And I think it's  
3 certainly possible and feasible, if all those  
4 things were in place.

5 DR. BURMAN: Thank you.

6 Dr. Temple, welcome. For the record, would  
7 you please introduce yourself again?

8 DR. TEMPLE: Bob Temple. I'm a deputy  
9 center director for clinical science.

10 DR. BURMAN: Thank you.

11 A few questions for Dr. Gerstein.

12 Dr. Konstam?

13 DR. KONSTAM: Two questions. First, just a  
14 detail about the TIDE design. So you have a  
15 placebo group. You had a placebo group in there.  
16 And can you comment on what would likely happen or  
17 what were you planning in terms of post-  
18 randomization, differences between the management  
19 in those groups, and how would you handle that  
20 post-randomization imbalance that might arise?

21 DR. GERSTEIN: Great. The TIDE trial was a  
22 double-blind, randomized controlled trial. And so

1       this was not meant to test the glycemic effect of  
2       the drug. It was meant to test its cardiovascular  
3       efficacy.

4               So clinicians were allowed to use any  
5       therapy they wanted to manage diabetes in this  
6       trial, which would be added onto their blinded  
7       therapy. So the issue of glycemic control rescue  
8       was not an issue whatsoever. They could use what  
9       they wanted, except a TZD, to treat diabetes.

10              DR. KONSTAM: Okay. The second question I  
11       had, really, for GSK about this, which is that if  
12       the FDA at this point in time said to you, you  
13       need to do this trial on condition of keeping  
14       rosiglitazone on the market, would you do it as  
15       opposed to withdrawing the drug? And if you did,  
16       what degree of enthusiasm would you place behind  
17       the actual performance of the trial?

18              DR. STEWART: GSK would be willing to  
19       clearly work with the FDA on the matter. But I'd  
20       like to maybe pose two questions another way. If  
21       people believe in the RECORD readjudication and  
22       there is no difference, then you could argue

1       there's no need to do a trial.  If you believe  
2       there is an imbalance, then it's ethical to do a  
3       trial.

4               DR. BURMAN:  Please state your name for the  
5       record.

6               DR. STEWART:  Sorry.  It's Dr. Stewart.

7               DR. BURMAN:  Thank you very much.

8               DR. STEWART:  But certainly coming back to  
9       the question specifically, would we work with the  
10      FDA and people to do that?  I think if we were  
11      requested to do so, we would work with the FDA.

12              DR. KONSTAM:  And would you put your full  
13      support -- if a company isn't really enthusiastic  
14      about getting a trial done -- assume you would be  
15      the financial support for the trial -- it doesn't  
16      usually get done very well.  So what degree of  
17      enthusiasm do you think you'd bring to the table  
18      with that?

19              DR. STEWART:  I'd think I'd wait to see what  
20      the outcome of today's meeting is.

21              DR. GERSTEIN:  May I just interject?  I  
22      think if such an outcomes trial were to be done, it

1 would need to be testing a superiority question.  
2 There is enough width of the confidence intervals  
3 regarding the effect, the noninferiority effect, of  
4 this drug to suggest that there may indeed be a  
5 benefit related to this.

6 DR. BURMAN: Thank you.

7 Dr. Smith?

8 DR. SMITH: Yes. Dr. Gerstein, I just  
9 wanted you to comment briefly on meta-analysis. In  
10 your summary of what is known, your slide 5, you  
11 didn't really make much comment on meta-analysis.  
12 And I think in the real world, even though there  
13 may be a shift to a more aggressive focus on  
14 randomized controlled studies, as you described, we  
15 also live in a world where I think we're going to  
16 continue to see meta-analysis data popping into the  
17 picture.

18 So as just for clarity, where you are with  
19 your summary of what we know about rosiglitazone  
20 and how to manage through the meta-analysis data on  
21 that.

22 DR. GERSTEIN: Well, I think meta-analyses

1       are very good. When you have large trials that  
2       you're meta-analyzing, which were designed to  
3       answer a question related to outcomes, meta-  
4       analyses can give you a better estimate of the  
5       effect size. But when one is meta-analyzing a  
6       large number of small trials, often designed for  
7       other reasons, one has to just look at those  
8       analyses as hypothesis-generating analyses at best.  
9       And there are very few examples of situations where  
10      meta-analyses of small trials yielded a potentially  
11      harmful signal because no one has gone ahead and  
12      done the large outcomes trial after that.

13               However, based on the literature, if there's  
14      lot of examples where meta-analyses of small trials  
15      suggest benefit, which have substantively shown to  
16      be harmful or neutral in the large outcomes trial,  
17      there are probably just as many examples of drugs  
18      where a meta-analysis of small trials would show  
19      harm that, if the large trial had been done, would  
20      go ahead and show benefit. And perhaps digoxin  
21      might be an example. That might be an example of  
22      the latter.

1 DR. BURMAN: Thank you.

2 We have five minutes. Dr. Hiatt?

3 DR. HIATT: Just to follow-up on the  
4 implications of what's transpired. So if this  
5 committee were to decide later today that a signal  
6 of cardiovascular harm is still present, I can  
7 understand the implications of that. But if the  
8 committee were to decide that there is no signal,  
9 that essentially the original RECORD result holds.  
10 And that was information that was available to the  
11 people you surveyed, and I did notice that  
12 equipoise was maintained generally in interest in  
13 answering the question, but it was not by ethics  
14 committees and by regulators.

15 What I'm asking is, if the committee says  
16 that we don't see a MACE signal, then do you think  
17 that that information would change the viewpoint of  
18 the ethics committees and the regulators?

19 DR. GERSTEIN: I think that it's very  
20 difficult to predict what the regulators around the  
21 world and the ethics committees will say. People  
22 will interpret the data in different ways.

1           So I'm not sure I can answer the question,  
2       really, better than that. It's hard to predict,  
3       and I know that there would be ethics committees  
4       that would say yes, absolutely, this is important,  
5       and other ones that would say that given the  
6       environment, it's not appropriate to do this.

7           DR. HIATT: But you see where I'm going with  
8       this.

9           DR. GERSTEIN: I'm sorry. Yes.

10          DR. HIATT: We're basically reanalyzing the  
11       same data.

12          DR. GERSTEIN: Yes.

13          DR. HIATT: And I'm not going to predict  
14       what's going to happen. But if -- I'm just asking  
15       if -- the decision is that the reanalysis supports  
16       an original conclusion that everyone has had for  
17       many years, that it would seem to me that the  
18       process led to an outcome that essentially led to a  
19       rather negative result on further investigation,  
20       which you seem to think is a good idea. Right?

21                So my question is, if we reanalyze the same  
22       data and come up with the same result, is that



1       going to matter?

2               DR. GERSTEIN: Well, I think it doesn't  
3 really matter. I think many people believe the  
4 RECORD results --

5               DR. HIATT: It does or doesn't?

6               DR. GERSTEIN: I think people believed the  
7 RECORD results originally. But what's happened in  
8 the last three years is the trial was stopped.  
9 There's been a lot more attention. There's been a  
10 lot more articles, a lot more media. A lot more  
11 biases have become entrenched. So that's what  
12 would change the discussion for the ethics  
13 committee. The science, I think, is the same.

14              DR. HIATT: Then that's the thing I'm just  
15 trying to put out on the table, that what actually  
16 transpired led to a series of opinions and biases  
17 and conclusions. But now we're looking at the same  
18 data.

19              DR. GERSTEIN: Exactly. And we spent  
20 yesterday excruciatingly looking at this data. And  
21 I think this has probably been the most  
22 interrogated database that I recall in the history

1 of clinical trials.

2 DR. HIATT: So you think that there's  
3 equipoise, from what you've heard?

4 DR. GERSTEIN: I think there's equipoise of  
5 both the scientific question, absolutely, today.  
6 And if you look at the confidence intervals  
7 surrounding outcomes such as death and other  
8 things, it's compatible with a 20 to 30 percent  
9 benefit and a 10 to 20 percent risk/harm. So there  
10 is, I think, clear equipoise around the important  
11 questions.

12 DR. HIATT: Did you think there was  
13 equipoise a couple years ago?

14 DR. GERSTEIN: Yes. That's why we were  
15 doing the trial.

16 DR. HIATT: Thank you.

17 DR. BURMAN: We only have a minute or two.  
18 Dr. Hammerschmidt, did you have a comment as well?

19 DR. HAMMERSCHMIDT: Well, as someone who's  
20 chaired ethics committees for a quarter century, I  
21 might have some guesses about how the ethics  
22 committees might look at this sort of thing.

1           I think one of the major problems that you  
2       would encounter in the ethical evaluation of such a  
3       study is that when you're testing whether a signal  
4       of harm that somebody's found credible is real or  
5       not, that creates an obligation in the consent  
6       process that creates a real tension that's hard to  
7       resolve.

8           So you might decide that there's equipoise.  
9       You might be quite satisfied that there's  
10      equipoise. But it may be very hard to both do  
11      honest disclosure of why you're doing the study and  
12      get your subjects to believe that there's  
13      equipoise. I think that is a major pragmatic  
14      problem in carrying out such a study.

15           DR. GERSTEIN: That's true. Correct.

16           DR. BURMAN: Good point.

17           One last question. I apologize. Dr.  
18      Suarez-Almazor?

19           DR. SUAREZ-ALMAZOR: Yes. Thank you,  
20      Dr. Gerstein, for your presentation. I think we  
21      all understand the importance of outcome trials and  
22      examples like the WHI and some of the ones you gave

1 are always given to show how observational studies  
2 may have biases.

3 I think that in general, for beneficial  
4 outcomes, that's the case. But the FDA may want to  
5 comment on this. If we look, for instance, at drug  
6 withdrawals and safety signals that lead to black  
7 box warnings, in general those come from  
8 observational studies. And in trials, we don't  
9 find these safety signals.

10 So I wouldn't necessarily dismiss the  
11 importance of observational studies for this. So I  
12 would just to get your response on that.

13 DR. GERSTEIN: Sure. I think it's important  
14 that one needs to look at the effect size that is  
15 being suggested by observational studies. So if an  
16 epidemiologic observational study shows that a drug  
17 increases the risk of a bad outcome three times,  
18 like a hazard ratio of 3, 5, 7, 8, 10, there is no  
19 question, and in fact the signal-to-noise ratio is  
20 such that -- well, 2 to 3 is sort of on the line.  
21 But certainly when you get effect sizes of 3, 4,  
22 5, 6 -- in other words, hazard ratios of 3 and

1       above -- it becomes much more compelling  
2       information.

3               But we're talking about observational  
4       studies where meta-analyzed effect sizes are 1.8,  
5       1.3, 0.7, 0.9, and that's where there's tremendous  
6       uncertainty. One doesn't even have to do a trial  
7       if you have effect sizes of 10, like smoking and  
8       cancer, for instance.

9               DR. SUAREZ-ALMAZOR: Well, yes. But here we  
10       are talking about death, so a 25 percent increase  
11       in the risk of death I think would be significant.

12              DR. GERSTEIN: Well, but I think --

13              DR. SUAREZ-ALMAZOR: I agree that 10 times  
14       increases the risk of death and would be even more  
15       convincing.

16              DR. GERSTEIN: It has to do with effect  
17       sizes. Death --

18              DR. SUAREZ-ALMAZOR: But even 25 percent --

19              DR. GERSTEIN: But even death, if you have  
20       effect sizes of 1.7, 1.8, it's not that the result  
21       of the outcomes trials are wrong. It's that  
22       they're biased. And you cannot measure or ever

1 account for the biases that lead to that result.  
2 And that's the problem with it.

3 DR. SUAREZ-ALMAZOR: So why would all of the  
4 observational studies that compare pio with rosi  
5 show a consistent difference?

6 DR. GERSTEIN: Well, one has to look at the  
7 best evidence they have. And if all you have are  
8 observational studies, we have an obligation as  
9 scientists to look at that evidence. But it  
10 doesn't, I think, relieve of us the obligation to  
11 collect better evidence and to actually answer a  
12 question clearly.

13 DR. BURMAN: Thank you. I'm sorry, we have  
14 to move on. But hopefully we're going to have at  
15 least an hour later for questions as well.

16 We'll now proceed with the FDA  
17 presentations, from first Dr. Joyce Weaver and then  
18 Dr. Justin Mathew.

19 **FDA Presentation - Joyce Weaver**

20 DR. WEAVER: Good morning. I'm Joyce Weaver  
21 from the Division of Risk Management, and I'm going  
22 to present the REMS that is in place for the

1       rosiglitazone-containing products and the results  
2       of assessment of the REMS.

3               In 2010, the agency made a decision that a  
4       REMS with restricted distribution was needed for  
5       the rosiglitazone-containing products to remain on  
6       the market. In May 2011, the REMS was approved.

7               The REMS had a six-month phase-in period to  
8       allow patients and prescribers to transition to the  
9       REMS with the new restricted distribution scheme,  
10      and the REMS was fully in place as of November 18,  
11      2011. The REMS was modified in January of this  
12      year to include generic products.

13              The first goal of the REMS is to restrict  
14      access to rosiglitazone so that only prescribers  
15      who acknowledge the potential increased risk of  
16      myocardial infarction associated with the use of  
17      rosiglitazone are prescribing the drug.

18              The second goal was to restrict access to  
19      patients who have been advised by a healthcare  
20      provider about the potential increased risk of  
21      myocardial infarction associated with the use of  
22      rosiglitazone and/or one of the following: either

1 already taking rosiglitazone or, if not already  
2 taking it, they are unable to achieve glycemic  
3 control on other medications and, in consultation  
4 with their healthcare provider, have decided not to  
5 take pioglitazone for medical reasons.

6 The REMS has a medication guide to provide  
7 risk information to patients. The REMS also has  
8 Elements to Assure Safe Use. Healthcare providers  
9 who prescribe rosiglitazone for outpatient or long  
10 term care use are specially certified.

11 Rosiglitazone is dispensed only by specially  
12 certified pharmacies, and it is only dispensed to  
13 patients with evidence or other documentation of  
14 safe use conditions.

15 The safe use condition for patients is the  
16 myocardial risk discussion that occurs between  
17 patients and prescribers for all patients, both  
18 patients who were receiving the drug before the  
19 REMS was put into place and new patients who began  
20 receiving the drug after the REMS was put into  
21 place. For new patients, the prescriber must also  
22 determine that the patient is unable to achieve



1       glycemic control on other medications.

2               The sponsor submitted an assessment report  
3       in May 2012 that provided data from the start of  
4       the REMS, May 19, 2011, through the data cutoff in  
5       March 2012. After November 18, 2011, according to  
6       the requirement of the REMS, patients should obtain  
7       rosiglitazone-containing products only from  
8       specially certified pharmacies and no longer could  
9       get these products from their local pharmacies.

10              This slide presents basic data about  
11       patients, prescribers, and pharmacies in the REMS.  
12       This information was supplied by GSK in their REMS  
13       assessment report. They reported that about 2200  
14       prescribers were enrolled in the REMS at that time.

15              Of the 2800 patients enrolled in the REMS,  
16       96 percent of them were already taking  
17       rosiglitazone before the REMS was put into place.  
18       There are a total of four certified pharmacies in  
19       the REMS, and these four pharmacies dispense via  
20       the mail. Most prescriptions, 63 percent, were  
21       written for Avandia, followed by 31 percent written  
22       for Avandamet.

1           This slide compares prescription data from  
2           the initial four months of the REMS. The columns  
3           highlighted in yellow show the data for the first  
4           two months immediately preceding required  
5           restricted distribution and then data for the first  
6           four months of restricted distribution. Finally,  
7           in the last column, we have included preliminary  
8           data from the most recent REMS assessment report,  
9           currently under review.

10           So we have information from the first  
11           assessment report and then two columns showing the  
12           second assessment report, divided between when  
13           restricted distribution was not required and then  
14           when it was required, and then preliminary data  
15           from the most recent REMS assessment report. Keep  
16           in mind, though, that the columns present data  
17           covering differing numbers of months.

18           The total number of prescriptions written  
19           has decreased from an initial 257,000 in the first  
20           reporting period to 3600 from November 18, 2011 to  
21           March 19, 2012, and then about 13,000 for the last  
22           reporting year.

1           So we see a decrease in prescriptions  
2       written, with a big drop occurring when the  
3       restricted distribution began to be required. On  
4       a per-month basis, there was a decrease in the  
5       number of prescriptions written per month from  
6       64,306 to 1,066 in the past reporting year.

7           Initially, after the REMS was approved,  
8       the majority of prescriptions written were by non-  
9       enrolled prescribers for non-enrolled patients.  
10      This was during the period that enrollment was not  
11      required.

12           The post-November 18, 2011 data shows what  
13      happened when the restricted distribution  
14      components of the REMS became required. The number  
15      of prescriptions was lower. The certified  
16      pharmacies received some prescriptions for non-  
17      enrolled patients and some written by non-enrolled  
18      prescribers.

19           But except for a couple of instances that  
20      GSK described yesterday, the certified pharmacies  
21      did not dispense drug for non-enrolled entities  
22      after November 18, 2011, the date that the

1       restricted distribution began to be required.

2               There was some dispensing from non-certified  
3       pharmacies after November 18, 2011 representing  
4       dispensing of product that had not been removed  
5       from retail pharmacies. This dispensing from non-  
6       certified pharmacies has been decreasing over time.  
7       As of the last month of data that we have for  
8       February 2013, there were 19 instances of  
9       rosiglitazone being dispensed by non-certified  
10      retail pharmacies.

11             Knowledge surveys of prescribers and  
12      patients were part of the REMS assessment.  
13      Prescribers and patients had good knowledge  
14      regarding the potential risk of myocardial  
15      infarction with rosiglitazone, and patients had a  
16      good understanding of what to do if they  
17      experienced symptoms of an MI. GSK is going to  
18      share more survey information with you, as was  
19      discussed yesterday.

20             The conclusions reached by the FDA regarding  
21      the assessment report are that the report was  
22      complete in addressing all issues outlined in the

1       REMS assessment plan, and overall, the REMS was  
2       determined to be meeting its goals.

3               DR. BURMAN:   Dr. Mathew?

4                       **FDA Presentation - Justin Mathew**

5               DR. MATHEW:   Good morning, everyone.   My  
6       name is Justin Mathew, and I'm a drug utilization  
7       analyst in the Division of Epidemiology, Office of  
8       Surveillance and Epidemiology.   Today I will be  
9       presenting the drug utilization patterns for  
10      rosiglitazone- and pioglitazone-containing products  
11      from July 2007 through December 2012.

12              Here is an outline of my presentation.   I  
13      will first present the sales distribution analysis,  
14      followed by the dispensed prescriptions and  
15      patient-level analysis.   Then I will presented the  
16      prescriber specialty and diagnosis data, and  
17      finally, the limitations of my analysis and  
18      conclude with a summary of my presentation.

19              My analysis contained the following products  
20      on the market.   Rosiglitazone-containing products  
21      included both single-ingredient and combination  
22      products.   No generic products were ever marketed

1       for rosiglitazone-containing products.  
2       Pioglitazone-containing products included single  
3       ingredient and combination products. Currently,  
4       only the generics for Actos and Actoplus Met are  
5       being marketed.

6               Let's begin with the sales data from years  
7       2008 through 2012. To illustrate the sales  
8       distribution patterns through different settings of  
9       care, the IMS Health IMS National Sales Perspective  
10       database was used to obtain the sales of  
11       rosiglitazone- and pioglitazone-containing  
12       products. This database measures the volume of  
13       products in units and dollars moving from the  
14       manufacturers to retail, non-retail, and mail order  
15       specialty pharmacy channels of distribution.

16               During year 2011 and years prior, at least  
17       59 percent of rosiglitazone-containing products  
18       were distributed from the manufacturer to the  
19       outpatient retail pharmacy settings. However, by  
20       year 2012, after the establishment of REMS,  
21       97 percent of rosiglitazone-containing products  
22       were distributed from the manufacturer to the mail

1       order setting. Therefore, the drug utilization  
2       analysis in my presentation focused on the U.S.  
3       outpatient retail pharmacy settings as well as mail  
4       order specialty pharmacy settings.

5               Next, I will be presenting prescription-  
6       and patient-level data from Symphony Healthcare  
7       Analytics and IMS Health database. Because of the  
8       shift in dispensing patterns over the years,  
9       especially for rosiglitazone, we had to use  
10      multiple data sources in order to capture exposure,  
11      which you will see in the following slides.

12             Before I begin, the outpatient analysis  
13      focused on the following time periods. The first  
14      advisory committee meeting was held in July 2007,  
15      the second advisory committee meeting was held in  
16      August 2010, and the REMS was approved in 2011.  
17      The intervening time periods were grouped into the  
18      post-AC1 period, post-AC2 period, and post-REMS  
19      period.

20             Based on the previous sales distribution  
21      analysis, we used two different sources to measure  
22      prescription volume. The first, the IMS Vector

1 One: National, was used to analyze U.S. outpatient  
2 retail pharmacy utilization patterns.

3 Data were obtained from a sample of  
4 59,000 pharmacies throughout the U.S. and projected  
5 to the national level. The pharmacies in this  
6 endpoint include chain, independent, food stores,  
7 and mass merchandisers. This database does not  
8 include mail order pharmacies.

9 The Symphony Healthcare Analytics PHAST  
10 database was used to obtain the nationally  
11 projected number of prescriptions dispensed through  
12 retail and mail order specialty pharmacies. This  
13 database covers over 42,000 retail pharmacies in  
14 the sample, including mail order and specialty  
15 pharmacies.

16 Dispensed prescriptions in the sample  
17 represent approximately 82 percent of all U.S.  
18 retail prescriptions, as well as 60 percent of all  
19 U.S. mail order prescriptions. The retail and mail  
20 order prescriptions are sourced from pharmacy  
21 benefit managements and health plans as well as  
22 chain pharmacies, independent pharmacies, and mail



1 order specialty pharmacies. Both data captures  
2 cash, Medicaid, and third party prescriptions.

3 For patient count data, the IMS Vector One  
4 Total Patient Tracker was used to analyze U.S.  
5 outpatient retail pharmacy utilization patterns.  
6 Similar to VONA, this database only captures  
7 patients who've received prescriptions from the  
8 outpatient retail pharmacy setting.

9 In order to capture patients receiving  
10 prescriptions through mail order and specialty  
11 pharmacies, we used Symphony Healthcare Analytics  
12 ProMetis database to determine the number of unique  
13 patients with a pharmacy prescription claim for  
14 rosiglitazone-containing products.

15 To provide some perspective, this graph  
16 shows the nationally estimated number of  
17 prescriptions dispensed for rosiglitazone- and  
18 pioglitazone-containing products through U.S.  
19 retail pharmacies from market launch in 1999  
20 through year 2012. This does not include the mail  
21 order pharmacy prescriptions.

22 The pioglitazone-containing products is

1 represented by the red dashed lines, while the  
2 rosiglitazone-containing products are represented  
3 by the blue solid lines. Dispensed prescriptions  
4 for rosiglitazone-containing products reached a  
5 peak of 12.7 million prescriptions during year  
6 2006, while pioglitazone-containing products  
7 reached a peak of 14.2 million prescriptions during  
8 2008.

9 Even prior to the establishment of REMS, a  
10 decline of dispensed prescriptions can be seen. My  
11 presentation will primarily focus on years 2008  
12 through 2012.

13 This chart shows the nationally estimated  
14 number of prescriptions dispensed for  
15 rosiglitazone- and pioglitazone-containing products  
16 through U.S. retail and mail order specialty  
17 pharmacies for years 2008 through 2012. Dispensed  
18 prescriptions for pioglitazone-containing products  
19 accounted for 76 percent of the TZD market in year  
20 2008, increasing to over 99 percent of the market  
21 in year 2012.

22 During year 2012, approximately 8.1 million

1 pioglitazone-containing prescriptions were  
2 dispensed, while 12,600 rosiglitazone-containing  
3 prescriptions were dispensed. The single-  
4 ingredient products accounted for the majority of  
5 the TZD markets.

6           Similar trends were observed in unique  
7 patient data. This table shows the nationally  
8 estimated number of patients who received dispensed  
9 prescriptions for rosiglitazone- and pioglitazone-  
10 containing products from U.S. outpatient retail  
11 pharmacies, excluding mail order and specialty  
12 pharmacy channels.

13           The total number of patients receiving  
14 dispensed prescriptions for pioglitazone-containing  
15 products decreased by nearly 50 percent, from  
16 2.5 million patients during 2008 to approximately  
17 1.3 million patients during year 2012, while the  
18 total number of patients receiving dispensed  
19 prescriptions for rosiglitazone-containing products  
20 decreased by approximately 99 percent, from 821,000  
21 patients during 2008 to less than 1,000 patients  
22 during year 2012.

1           This slide will show the breakdown of  
2   patients by sex for rosiglitazone-containing  
3   products during the following three time periods.  
4   During the post-AC1 period, approximately  
5   1.6 million patients received a dispensed  
6   prescription for rosiglitazone-containing products,  
7   during the post-AC2 period, approximately 249,000  
8   patients, and during the post-REMS period,  
9   approximately 45,000 patients had a prescription  
10   claim for rosiglitazone-containing products.

11           The post-AC1 and AC2 time periods only  
12   include patients from a retail pharmacy setting,  
13   while the post-REMS period includes patients from  
14   the retail and mail order specialty setting. There  
15   was a slight male predominance of patients  
16   receiving dispensed prescriptions for  
17   rosiglitazone-containing products during the three  
18   time periods examined.

19           Because there was six-month lead-in period  
20   for the establishment of REMS, we also looked at  
21   just year 2012, when the full REMS program was in  
22   place. The number of patients dropped down further

1 to approximately 4,600 patients after the  
2 implementation of REMS, and again, there was a  
3 slight predominance of males.

4 This slide shows the estimated number of  
5 patients who received dispensed prescriptions for  
6 rosiglitazone-containing products stratified by  
7 patient age. During all three time periods  
8 examined, patients age 60 to 69 years accounted  
9 for approximately 30 percent of the patients who  
10 received prescriptions for rosiglitazone-containing  
11 products, followed by patients age 50 to 59 years  
12 old and patients 70 to 79 years old.

13 Again, this chart shows just year 2012,  
14 after the establishment of the full REMS program.  
15 Again, the age distribution was similar to the  
16 previous time period, with 33 percent in the 60 to  
17 69 age group, 27 percent in the 50 to 59 age group,  
18 and 20 percent in the 70 to 79-year-old age group.

19 Next, I will be discussing the prescriber  
20 specialty data from outpatient retail and mail  
21 order pharmacies.

22 This table shows the nationally estimated

1     number of prescriptions dispensed for  
2     rosiglitazone-containing products from U.S.  
3     outpatient retail and mail order specialty  
4     pharmacies by top ten prescribing specialties from  
5     the three distinct time periods from July 2007  
6     through December 2012.

7             During each time period examined, family  
8     practice/general practice specialists were the top  
9     prescribing specialty, accounting for approximately  
10    51 to 53 percent of total rosiglitazone-containing  
11    prescriptions dispensed.

12            Internal medicine specialists followed,  
13    accounting for approximately 32 to 34 percent of  
14    total prescriptions dispensed. And endocrinology,  
15    diabetes, and metabolic specialists accounted for  
16    approximately 4 to 5 percent of the total  
17    rosiglitazone-containing prescriptions dispensed.

18            Next we analyzed the diagnosis data.  
19    Encuity Research Treatment Answers is a monthly  
20    survey that monitors disease states and physician  
21    intended prescribing habits on a national level.  
22    The database contains data from 3,200 prescribers

1 in a panel that report on all patient activity  
2 during one typical workday per month, which is then  
3 projected nationally. It includes diagnosis,  
4 patient characteristics, and treatment patterns.

5 This table shows the diagnosis most commonly  
6 associated with use of rosiglitazone-containing  
7 products, as reported by office-based physician  
8 surveys in the U.S. ICD-9 diagnosis codes were  
9 linked to each drug product mentioned during  
10 patient encounter.

11 Diabetes mellitus accounted for the highest  
12 proportion of rosiglitazone-containing product uses  
13 among the three time periods, with 96 percent of  
14 the total drug use mentioned during the post-AC1  
15 period, 81 percent during the post-AC2 period, and  
16 100 percent during the post-REMS period.

17 Here are the strengths and limitations of my  
18 presentation. Numerous data sources were used to  
19 provide the national-level prescription and patient  
20 counts. However, patients counts that include mail  
21 order and specialty pharmacy data are not  
22 nationally projected, and no statistical tests were

1 performed to determine statistically significant  
2 changes over time.

3 In conclusion, prior to the establishment  
4 of REMS, the majority of prescriptions for  
5 rosiglitazone-containing products were dispensed  
6 through U.S. outpatient retail pharmacies during  
7 years 2008 through 2011. By year 2012, almost all  
8 rosiglitazone prescriptions were dispensed through  
9 mail order specialty pharmacies due to  
10 implementation of REMS.

11 The number of patients who received a  
12 dispensed prescription for rosiglitazone-containing  
13 products decreased by 99 percent over the study  
14 periods, from the post-AC1 period, with 1.6 million  
15 patients, to post-AC2 period, 249,000 patients, to  
16 the post-REMS approval period, when approximately  
17 45,000 patients were exposed, and even further,  
18 looking at just year 2012 after the full  
19 establishment of the REMS program, 4,600 patients.

20 Family practice/general practice specialists  
21 were the top prescribing specialty for  
22 rosiglitazone-containing products, and diabetes



1 mellitus, uncomplicated, was the top diagnosis  
2 associated with the use of rosiglitazone-containing  
3 products.

#### 4 **Clarifying Questions**

5 DR. BURMAN: Thank you. Thank you both to  
6 Dr. Weaver and Dr. Mathew. It's 9:30, and thank  
7 you for being on time; in fact, ahead of time. So  
8 we can open the floor up for clarifying questions  
9 for perhaps five minutes, and then maybe we could  
10 then go back to the GSK update.

11 Dr. Day?

12 DR. DAY: Thank you. I know that the  
13 sponsor will give the details. But I would like to  
14 ask Dr. Weaver that when the sponsor submitted the  
15 REMS assessment report, was the following  
16 information included: Three things. One,  
17 selection criteria for the subjects, both the  
18 prescribers and the patients; the actual survey  
19 questions for both the prescribers and the  
20 patients, and percent correct answers for all of  
21 the questions in both waves 1 and 2.

22 Was all of that information provided,

1       please?

2               DR. WEAVER:   Yes.   That was all provided.

3               DR. DAY:   Thank you.   I guess it just didn't  
4       make it into the summary report of the sponsor for  
5       that section -- I think it's section 5.3.55 or  
6       something -- in the sponsor briefing materials.  
7       It's very, very brief, and we'll look forward to  
8       actually seeing all of this information later  
9       today.

10              DR. BURMAN:   Dr. Phillips?

11              DR. PHILLIPS:   Yes.   For Dr. Mathew, I just  
12       wanted to clarify the number of patients post-REMS,  
13       4600, approximately, based not on projections but  
14       on actual mail order numbers.   If I remember  
15       correctly, that's almost 50 percent more than the  
16       total number of patients enrolled in the REMS.   So  
17       how do you explain that discrepancy in patient  
18       numbers?

19              DR. WEAVER:   This is Joyce Weaver.   What  
20       we know is that when the restricted distribution  
21       was first required, there actually was as much  
22       rosiglitazone being dispensed outside the REMS as

1       there was in the REMS. So for a period there, the  
2       non-REMS prescribing was actually up there with the  
3       REMS prescribing.

4               DR. PHILLIPS: Even in 2012, when the REMS  
5       was fully in effect? About 4600?

6               DR. WEAVER: There still was significant  
7       non-REMS prescribing, which does represent the  
8       product that had not been pulled back from the  
9       retail pharmacies.

10              DR. BURMAN: Thank you.

11              Dr. Heckbert?

12              DR. HECKBERT: Yes. A quick follow-up on  
13       that question for Dr. Mathew. On your slide 9, you  
14       say that the Symphony Healthcare Analytics data  
15       source is a sample of approximately 42,000 retail  
16       and mail order pharmacies. And then in your  
17       strengths and limitations slide, number 23, you say  
18       patient counts that include mail order specialty  
19       pharmacy data are not nationally projected.

20              I'm trying to understand. Did the data  
21       sources you have available -- you say that's a  
22       sample. Is it a small sample? Is it most of the

1 mail order? I'm trying to get an idea if, when you  
2 give the mail order numbers, is that most of the  
3 mail order in the U.S., or a small amount, or what?

4 DR. MATHEW: So the mail order, there isn't  
5 a definitive scope they have within their database.  
6 That's why when mail order prescriptions are  
7 included, that's why it's an estimate. It can't be  
8 nationally projected.

9 DR. GOVERNALE: Also -- this is Laura  
10 Governale, Division of Epidemiology -- in the  
11 Source Healthcare Analytics database, 80 percent of  
12 retail prescriptions are captured in their source,  
13 and that's projected to the national level. And  
14 then 60 percent of mail order prescriptions are  
15 captured.

16 DR. BURMAN: Thank you.

17 Dr. Brittain?

18 DR. BRITTAIN: Yes. I wanted to go back to  
19 the question I asked yesterday about the voting  
20 question about possible modifications to the REMS,  
21 and hoping that, since I have no idea what possible  
22 modifications there could be, if there are any

1 proposals.

2 DR. WEAVER: Thank you. This is Joyce  
3 Weaver. I think that what we start with is the  
4 data that we've been evaluating over the past day  
5 or so. So that's sort of the underpinning of the  
6 whole thing.

7 Now, in terms of what could be recommended,  
8 if you think that the myocardial infarction risk is  
9 not real, then it could be removal of the REMS.  
10 And yesterday we heard some talk, possibly, about  
11 questioning the patients -- what was the situation  
12 of the patients who were in -- there was medical  
13 necessity for the product. So that's a  
14 possibility, that we could better define that.

15 In terms of restriction, this REMS is pretty  
16 restrictive. So except for possibly defining what  
17 medical need would be, I'm not sure how we get  
18 really more restrictive. Another possibility, we  
19 heard yesterday from Dr. Day about possibly using  
20 the difference between cognition and metacognition  
21 to possibly work on understanding better. So those  
22 are all possibilities.

1 DR. BURMAN: Thank you.

2 DR. KONSTAM: Just a follow-up on that?

3 DR. BURMAN: Sure.

4 DR. KONSTAM: Could you expand? You said  
5 one option is to remove the REMS. So what options  
6 could you visualize of reducing the REMS without  
7 eliminating it?

8 DR. WEAVER: It would depend on what it is  
9 that you're trying to achieve. What is it in the  
10 REMS that you are trying to change? What's the  
11 outcome that you're trying to change?

12 DR. KONSTAM: Let's say, for example, that  
13 we came to the conclusion that we're less certain.  
14 We're still concerned, but less certain. So you  
15 posed the hypothetical, let's say we decide there's  
16 no concern. Let's pose a different hypothetical,  
17 that we're still concerned but less concerned.  
18 Could you give us some ideas about what could be  
19 done?

20 DR. WEAVER: I think it still comes down  
21 to considering, really, the existence of the REMS  
22 because for the REMS with ETASU to be in place, we

1       have to decide that for the continued marketing,  
2       that ETASU needs to there.

3               So if you're thinking that we don't need to  
4       have prescribers declare that they understand the  
5       risk, we don't need to have patients declare that  
6       they've been advised of the risk, and that labeling  
7       alone would handle it, then that actually does away  
8       with the REMS.

9               DR. BURMAN: Thank you.

10              Dr. Day?

11              DR. DAY: Yes. I hate to disagree with  
12       Dr. Weaver, but I don't think it does away with the  
13       REMS. But we can discuss that this afternoon.

14              The point I wanted to make now is, I wish we  
15       could know something about the effects of the REMS  
16       on patients. Are patients who are on rosiglitazone  
17       any safer now than before the REMS went into  
18       effect? There hasn't been enough time. What would  
19       be the nature of the data that we could get that  
20       would tell that, and so on?

21              But it goes to the point of REMS perhaps  
22       increasing safer prescribing and safer actions by

1 patients if they get adverse events. And so I  
2 would like to ask the FDA, have there been cases  
3 with a restrictive REMS, then, providing data about  
4 patient safety?

5 DR. BURMAN: Anybody from the FDA want to  
6 address that?

7 MR. DAL PAN: Yes. This Gerald Del Pan, and  
8 maybe Dr. Karwoski could follow up. It depends on  
9 what the goal of the REMS is. A lot of the goals  
10 here were to ensure proper patient selection, and  
11 that physicians had the proper knowledge of the  
12 risks and the patients had that.

13 There was nothing specific to mitigate a  
14 risk. This is distinguished from other type of  
15 risk management plans we have -- for example, for a  
16 teratogen, where we don't want a pregnant woman to  
17 be prescribed a teratogen, or a woman to become  
18 pregnant while she's on a teratogenic medicine.

19 It would be a very different kind of REMS  
20 where there's monthly pregnancy testing, and some  
21 of those have been brought before the Drug Safety  
22 Committee before. In those cases, we would have



1       some outcomes about pregnancies.

2               DR. DAY:   Just a brief comment.   So the REMS  
3       has, really, two big parts to it for rosiglitazone.  
4       One is about restriction, and all the data that  
5       we've seen, yes, there's been restriction.   Fine.  
6       The other part is about understanding.   And it's  
7       not saying just the metacognition, I understand,  
8       but that people really do, so real cognitive  
9       testing.

10              But if indeed the prescribers are now not  
11       prescribing insulin at the same time, would there  
12       then be better outcomes?   So although the REMS was  
13       not designed in order to look at safety, can we  
14       envision a time, if this were in place long enough,  
15       of being able to look and see if there are better  
16       patient outcomes?

17              MR. DAL PAN:   As you know, this REMS isn't  
18       measuring specific patient outcomes.   Other REMS  
19       do -- the ones we have for certain medicines that  
20       may result in progressive multifocal  
21       leukoencephalopathy, things where we tend to  
22       measure the outcomes in those cases where we really

1 know that a given event would be the result of the  
2 drug exposure, so something like the progressive  
3 multifocal leukoencephalopathy or a certain adverse  
4 outcome because of non-adherence to the REMS  
5 restrictions, like a pregnancy when a teratogen is  
6 administered.

7 Here, I think, as we've been discussing,  
8 things like myocardial infarction do have a  
9 substantial background risk amongst persons with  
10 diabetes. So any individual case is going to be  
11 really impossible to adjudicate. And in a case  
12 series of 3,000, you're not going to be able to  
13 tell what's the drug, what's not, et cetera.

14 DR. BURMAN: Thank you.

15 Ms. Killion?

16 MS. KILLION: I'd like to take Dr. Day's --

17 DR. BURMAN: Ms. Killion, excuse me for one  
18 second. Did Dr. Temple have -- Dr. Jenkins, I'm  
19 sorry -- have a comment on that?

20 DR. JENKINS: Well, I was going to go back  
21 to the question about potential modifications of  
22 the REMS, just to help explain it a little further.

1 Can we go back to slide 5 of Dr. Weaver's slide  
2 set?

3 So as Dr. Weaver said, in order for us to  
4 impose a REMS, we have to conclude that the REMS is  
5 necessary to ensure that the benefits of the drug  
6 outweigh the risk. So there are basically three  
7 major buckets of components of elements that can be  
8 in a REMS.

9 One is a medication guide. One is called a  
10 communication plan -- it's not listed on this  
11 slide, but that's usually communication/ education  
12 materials for doctors or patients, Dear Healthcare  
13 Provider letters, those types of things that can be  
14 sent out. And then there are Elements to Assure  
15 Safe Use, which are sometimes referred as  
16 restricted distribution. Those are the most  
17 significant restrictions.

18 Here you can see, for the rosiglitazone  
19 REMS, we determined that in order to ensure that  
20 the benefits outweighed the risks, there needed to  
21 be a medication guide to inform the patients about  
22 the concern, and then there needed to be elements

1 to assure safe use, which include only doctors who  
2 have been specially certified can prescribe the  
3 drug.

4 It can only be dispensed by certain  
5 pharmacies, who have been specially certified that  
6 they will follow the rules, that they will only  
7 dispense when they receive a prescription from a  
8 certified prescriber. And then it will only be  
9 dispensed to patients who meet the Safe Use  
10 conditions, meaning that they meet the criteria for  
11 medical need.

12 So if you were thinking about any changes to  
13 those, then you could obviously remove one or all  
14 of those restrictions. As you're thinking about  
15 what's the current assessment of the risk, going  
16 back to what I said at the beginning, we have to  
17 conclude that the elements of the REMS are required  
18 to ensure that the benefits outweigh the risks.

19 So if you think that these go beyond what's  
20 required, given current assessment, you could  
21 recommend that we remove some of them. You could  
22 recommend that there be a communication plan in

1 place of some of these elements. But that's kind  
2 of the range of possibilities.

3 You could leave it the way it is. You could  
4 take it away completely. You could recommend that  
5 it be modified in any way that you might think  
6 would be appropriate. And of course one of the  
7 other options we have on the question you'll be  
8 addressing later today is you could conclude that  
9 the drug should no longer be marketed.

10 DR. BURMAN: Thank you. That was very  
11 helpful.

12 Ms. Killion? Sorry for the interruption.

13 MS. KILLION: I think I remember what I was  
14 going to say. So Dr. Day asked about the effect of  
15 the REMS. I want to flip it a little bit but ask  
16 sort of the same question.

17 If the purpose of the REMS was to assure, as  
18 the last bullet point on this slide indicates, that  
19 it was basically that there would be more  
20 knowledge, more informed prescribers, better-  
21 informed patients, and that it would only be  
22 dispensed to patients with evidence of Safe Use

1 conditions. What I was surprised to see in the  
2 second presentation was that even under the REMS,  
3 when usage dropped off dramatically, that the  
4 majority of the patients that were taking the drug,  
5 remained on the drug, were elderly.

6 I would assume, in my lay person's fashion,  
7 that elderly patients with longstanding exposure to  
8 the disease would be at more risk of heart disease  
9 and have more pronounced conditions. And yet the  
10 usage in that group remained the majority of the  
11 usage, even under the REMS.

12 So to me, that questions what is the effect  
13 of the REMS? But more importantly, what was the  
14 harm? In 2007, we were assailed in the media with,  
15 you know, this drug is killing people. We're not  
16 hearing that under the REMS now.

17 I have to ask, then, the purpose of the REMS  
18 was to restrict it. But what is the outcome of  
19 that? I don't know that we're seeing any harm from  
20 patients who probably should not have been using  
21 the drug, and yet we're not hearing that they've  
22 been harmed by that use.

1 DR. WEAVER: Well, a couple things with  
2 that. One is that if you think that the risk is  
3 true, on a population basis there are fewer  
4 patients being exposed, including in the elderly  
5 groups. If there are data to show specific harm to  
6 specific groups, that's something that would need  
7 to be reviewed by the reviewing division, put into  
8 the labeling, and then could be considered for the  
9 REMS.

10 DR. BURMAN: Thank you.

11 Dr. Stanley?

12 DR. STANLEY: I had a question, maybe for  
13 Dr. Weaver, which is with the current prescribing  
14 pattern with the very few patients that are on it,  
15 I assume that most of these are patients that have  
16 been long-time users and don't want to switch off.

17 Are there any new prescriptions, new starts  
18 for rosiglitazone? Or are we seeing the dwindling  
19 tail of patients that have been successful on it  
20 and gradually that will drop off to zero?

21 DR. WEAVER: I think that yesterday GSK  
22 presented some data on new patients, and it was

1 low.

2 I don't know, Justin, if you have other  
3 information you want to add to that.

4 DR. MATHEW: The databases we have can't  
5 capture that currently within mail order setting.

6 DR. BURMAN: Does GSK know those numbers off  
7 the top of their head or with a slide?

8 DR. STEWART: Yes. There was 96 percent  
9 were repeat prescriptions. It was 4 percent that  
10 were new.

11 DR. BURMAN: Dr. Stewart, thank you.

12 It's a quarter to 10:00. This is an  
13 important topic, I got the sense from the panel,  
14 and it is one of the questions that we're going to  
15 discuss later and related to the voting.

16 So if the panel agrees, we'll continue with  
17 a couple more questions until 10:00 when we take  
18 our break, if that seems to be the consensus. And  
19 then -- I apologize to GSK and Duke -- we're going  
20 to move you back to 11:15, if that's okay.

21 So to continue on, Dr. Morrato?

22 DR. MORRATO: Thank you. This is for



1 Dr. Weaver. As we consider, did the REMS meet the  
2 educational informational goals, you concluded that  
3 there was good knowledge regarding potential risk  
4 of MI. And I was just seeking to understand how  
5 you define what is "good knowledge."

6 Are you using a certain threshold? How are  
7 you defining that, and what data would you have to  
8 support that in light of we're hoping to see more  
9 specifics around the questionnaire, as Dr. Day has  
10 talked about.

11 DR. WEAVER: That question was asked in  
12 several different ways in the survey, and the  
13 knowledge on patients hovered around 75 percent  
14 however the question was asked. And we don't have  
15 a threshold. We did consider that acceptable.

16 In that same survey, I think there were  
17 over 20 percent of patients who did not know that  
18 diabetes itself conferred extra risk of  
19 cardiovascular events. So looking at that, it  
20 seemed like 75 percent perhaps is a good number.

21 DR. MORRATO: So from public health  
22 standpoint, that's good. You're not trying to get

1 higher knowledge.

2 DR. WEAVER: We would like higher, and we  
3 would like higher knowledge on the other questions  
4 that perhaps don't speak directly to the risk that  
5 the REMS is intended to mitigate. But we would  
6 like to see better knowledge on everything, both  
7 with the patients and with the prescribers.

8 But the decision that we make is, is it  
9 acceptable or do we ask for further regulatory  
10 action.

11 DR. MORRATO: Thank you.

12 DR. BURMAN: Thank you.

13 Dr. Woods?

14 DR. WOODS: I have two quick questions. I  
15 would doubt if you've got an answer to the first  
16 one. But increasingly, patients are turning to new  
17 mail order alternatives, international  
18 alternatives, to obtain their medicines. And a  
19 quick Google search a minute ago, I was able to  
20 find a couple of sources that would be able to see  
21 me Avandia or Avandamet direct as long as I provide  
22 them a prescription.

1           Do we have any sense of the number of  
2       patients that may be obtaining these drugs via  
3       those mechanisms?

4           DR. MATHEW: Currently, the databases that  
5       we have don't capture that because it's outside of  
6       U.S. If they're going to Canada, we don't have  
7       that.

8           DR. WOODS: So the exposure may be greater  
9       than indicated from the data that you guys have  
10      presented us.

11          My second question is, and maybe this was in  
12      the packet or has been addressed earlier, but in  
13      the patients currently in the program, do we have  
14      any spontaneous ADE reports?

15          DR. WEAVER: I don't know the answer to  
16      that. As Dr. Dal Pan described, though, it would  
17      be of questionable usefulness to us because we're  
18      talking about an event with a fairly high  
19      background rate. And so if we're getting a report  
20      of an MI for a patient who's taking Avandia, we  
21      really wouldn't know what to do with that in terms  
22      of attributing it to the Avandia.

1 DR. BURMAN: Thank you. And a very good  
2 point with regard to the international mail orders.

3 We have 10 minutes and it looks like five or  
4 six people. I'm not sure we're going to get to  
5 them all. Dr. Kaul, I believe you're next.

6 DR. KAUL: Thank you. I think my specific  
7 question has already been asked by Dr. Day and  
8 Ms. Killion. But I'm tempted to ask a broad  
9 question.

10 We were asked to weigh in on a specific REMS  
11 related to rosiglitazone. But my question to the  
12 FDA is that now FDA has had four years since the  
13 REMS was first instituted in 2008, and over 200  
14 REMS have been applied.

15 Do we have a better sense that the REMS is  
16 effective in improving drug safety? And how do you  
17 respond to the Office of the Inspector General  
18 report that came out early this year that did not  
19 exactly paint a rosy picture about the  
20 effectiveness of REMS?

21 MR. DAL PAN: This is Gerald Del Pan.  
22 Understanding the effectiveness of REMS is

1 something that's actually one of our highest  
2 priorities. We are required under the Amendments  
3 Act to have an annual meeting to discuss one or  
4 more REMS and its effectiveness. We've had a few  
5 of those.

6 The large number of REMS you mention, the  
7 bulk of those are REMS that only have a medication  
8 guide as an element and nothing further. So the  
9 number of REMS with the further restrictions, the  
10 Elements to Assure Safe Use, are much lower in  
11 number.

12 A lot of our attention has been placed on  
13 understanding the effectiveness of them. They're  
14 quite diverse in their nature. They get at a lot  
15 of different things. So they have to get at them  
16 in different ways. We are working on a lot of  
17 these issues.

18 With regard to the patient comprehension, we  
19 had a public meeting I think about a year ago, June  
20 of last year, to discuss the best ways to  
21 understand how to assess the knowledge measures,  
22 the patient communication measures. So these are

1 really all evolving as we go along.

2           The Elements to Assure Safe Use also are a  
3 subject of a lot of our attention. We've brought a  
4 number of these, or a few of these, at least, to  
5 advisory committees, understanding the balance  
6 between the patient protection on the one hand and  
7 the burden of a plan on the other hand, how perhaps  
8 people who might benefit from the medicine might  
9 not be getting it because there's burden involved  
10 for both the patient and the prescriber and the  
11 system at large.

12           So this is still a work in progress. Quite  
13 a lot is going on in this area.

14           DR. BURMAN: Thank you. Dr. Temple?

15           DR. TEMPLE: Gerald, in Janet's memo on all  
16 this that invoked the REMS, the clear intent was to  
17 say that this drug should be reserved for a narrow  
18 subset of the population, not for everybody. And  
19 the decline in use certainly reflects the success  
20 of the REMS in doing that.

21           Do we know whether everybody understood why  
22 and all that? Of course we don't. And you're

1 right, we do want to. But on its face, it had the  
2 described effect, which was to trim use down  
3 substantially.

4 DR. KAUL: If I may respond to that, the  
5 data that was shown to us suggested otherwise, that  
6 most of the dropoff, the precipitous dropoff,  
7 occurred prior to the implementation of the REMS.  
8 So the question is, do we really have a sufficient  
9 data set to assess the efficacy of this REMS  
10 program?

11 You can show slide number --

12 DR. TEMPLE: It's a fair question to ask  
13 whether the wide publicity and all the discussion  
14 would have de facto had the same effect.

15 DR. KAUL: Slide 11.

16 DR. TEMPLE: But the REMS is intended to put  
17 this into a more permanent place after the press  
18 goes away and all that stuff. It's hard to say,  
19 given the use, that that didn't occur.

20 DR. BURMAN: Thank you. We have five  
21 minutes, and unfortunately don't have time for all  
22 the questions.

1 Dr. Seely, you had a point or a question?

2 DR. SEELY: I want to get your opinion about  
3 the difference between REMS versus a black box  
4 warning. A black box warning, as an  
5 endocrinologist, we have a number of drugs that  
6 have black box warnings. That's something patients  
7 are very aware of. When I prescribe a drug that  
8 has a black box warning, I document in my record  
9 why I'm prescribing it.

10 So what does REMS accomplish beyond a black  
11 box warning, is my first question.

12 DR. WEAVER: We see the black box warning as  
13 something that's the highest degree of labeling to  
14 warn stakeholders of a risk. Generally, a REMS  
15 would be used to amplify what's in a boxed warning.

16 DR. SEELY: But you don't have any data at  
17 this point that the REMS does anything more than  
18 the black box warning, or comparative data, black  
19 box warning alone versus black box warnings with  
20 REMS?

21 DR. WEAVER: I guess I'd have to think about  
22 that a little bit. For example, with this one, if



1       you had the myocardial infarction in a boxed  
2       warning, would that have resulted in prescribers  
3       making that decision that the patient's glycemic  
4       control was not possible with other products? I  
5       don't know.

6               DR. SEELY: The other related question that  
7       I had is, what is the availability of the certified  
8       pharmacies nationwide? I have not done the  
9       certification, specialty certification. But I'm  
10      incredibly burdened as a prescriber by all the  
11      certifications I have to do to get a prescription  
12      in to the patient's home. So I want to get a sense  
13      of how burdensome is the specialty certification.

14             DR. WEAVER: We do attempt to reduce  
15      stakeholder burden to the extent that we can. And  
16      so we try to offer several modalities to actually  
17      accomplish it. We try to make it a simple process.  
18      Perhaps GSK could comment on whether they've  
19      received feedback that it's burdensome.

20             DR. SEELY: Or just how much time does it  
21      take to fill it out would be very helpful.

22             DR. WEAVER: To me it looks very simple.

1 DR. OSEI: Yes. We do address the question  
2 of burden in our surveys of the prescribers. And  
3 we ask the question, is it very burdensome, is this  
4 sometimes burdensome, or is it not burdensome? And  
5 what we found in our first survey was that  
6 25 percent said it was very burdensome, 50 percent  
7 said it was somewhat, and 25 said it was not.

8 In the subsequent survey, the percent that  
9 said it was very burdensome decreased, which  
10 suggests it decreased and there were more people  
11 who found it less burdensome. So this suggests at  
12 the time that it was working efficiently.

13 The only caveat is that this is really a  
14 survey of people who are enrolled. And so by  
15 default, they are people who already have made that  
16 extra step.

17 DR. SEELY: And about the availability of  
18 the pharmacies? Are they very available and easy  
19 for patients to be able to get the --

20 DR. WEAVER: I do believe that they are.  
21 Again, for GSK, have you had feedback?

22 DR. OSEI: Yes. It's distributed by a mail

1       order system, but that works pretty much  
2       efficiently by standard pharmacy processes. Once  
3       you get into the system, it's a one-time  
4       enrollment, and so subsequently you get  
5       automatically processed. The pharmacies do contact  
6       the doctor for refills and so forth.

7               DR. SEELY: And you work with the insurance  
8       companies to get the coverage?

9               DR. OSEI: That's correct. The pharmacies  
10      do.

11              DR. BURMAN: Thank you very much. Please  
12      state your name for the record.

13              DR. OSEI: Suzette Osei.

14              DR. BURMAN: Thank you.

15              Before we take a break, I'd like to make a  
16      quick comment as well. In my mind, and I don't  
17      know if the panel agrees, there's a big difference  
18      between a black box warning and REMS. A REMS has  
19      all the restrictions that we're talking about here,  
20      and a black box warning, as you mentioned, there  
21      are many examples of drugs, and endocrine drugs we  
22      use in particular, to have black box warnings. But

1       those medications are on the market, commercially  
2       available. The physician prescriber doesn't have  
3       to have any special certification, and the pharmacy  
4       doesn't, either.

5               Does anybody have any other -- everyone  
6       agrees with that? Yes?

7               DR. MORRATO: This is Elaine Morrato. There  
8       have been numerous studies that have shown that  
9       black box warnings alone are not effective in  
10      changing behavior. So I think part of your  
11      question of what was an incremental value, maybe,  
12      of these Elements to Assure Safe Use, not in all  
13      cases but there have been several well-publicized  
14      studies that have shown warnings alone aren't  
15      effective.

16              DR. WEAVER: This is Joyce Weaver. Just to  
17      comment on an endocrinologist asking that question,  
18      on all of our surveys for the endocrinology drugs,  
19      the endocrinologists do the best. So from your  
20      point of view, I would think that perhaps where  
21      you're sitting maybe it doesn't look so necessary.

22              DR. BURMAN: Thank you for the comment, but

1 we assumed that at the beginning.

2 (Laughter.)

3 DR. BURMAN: Dr. Jenkins?

4 DR. JENKINS: On the question about the  
5 boxed warning, first of all, Avandia was given a  
6 boxed warning for this cardiovascular risk in 2007  
7 after the first advisory committee meeting. So you  
8 can assess from the prescribing trends and use  
9 trends whether that was an effective tool at  
10 communicating and limiting use or not.

11 I think historically we've found that  
12 labeling changes can have some impact on use  
13 patterns and behavior. But they definitely don't  
14 have the same impact on use patterns and behavior  
15 that a REMS with ETASU has, such as the REMS here  
16 where you can only prescribe if you're a certified  
17 prescriber. You can only dispense if you're a  
18 certified pharmacy.

19 So there's no doubt that labeling changes  
20 can have an impact on changing practice behavior.  
21 But I don't think we have any examples where we can  
22 say that labeling changes alone completely led to

1 the change in behavior that might have been  
2 desired.

3 I think we've learned that it's very hard to  
4 change medical practice behavior once it's started.  
5 I always tell people that if you want to change  
6 behavior, you need to put it in the label when the  
7 drug's approved because then you help establish the  
8 behavior from the beginning, versus trying to put  
9 the horse back in the barn after the behavior has  
10 been established.

11 So we don't want to discount the value of  
12 labeling warnings and boxed warnings. I think they  
13 are effective. They do lead to changes in how  
14 formularies manage drugs, for example. But they're  
15 not totally effective in communicating the risk and  
16 changing the behavior.

17 Too often at these meetings we hear from  
18 even committee members who say, I don't read the  
19 label. So that's one of the challenges of how you  
20 can use the label to be an effective risk  
21 management tool because they're often not read by  
22 the prescribers who are making decisions about

1       whether to prescribe the drug.

2               DR. BURMAN: Thank you.

3               I apologize to the other people who had  
4       questions, but it's 10:00 and we will now take a  
5       15-minute break. Panel members, please remember  
6       there should be no discussion of meeting topics  
7       among yourselves or with the audience. We'll  
8       resume at 10:15 with the open public hearing.

9               (Whereupon, a brief recess was taken.)

10                               **Open Public Hearing**

11               DR. BURMAN: Let's get started for the open  
12       public hearing.

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

20               For this reason, the FDA encourages you, the  
21       open public hearing speaker, at the beginning of  
22       your written or oral statement to advise the

1       committee of any financial relationship that you  
2       may have with the sponsor, its product, and if  
3       known, its direct competitors. For example, this  
4       financial information may include the sponsor's  
5       payment of your travel, lodging, or other expenses  
6       in connection with your attendance at the meeting.

7               Likewise, FDA encourages you at the  
8       beginning of your statement to advise the committee  
9       if you do not have any such financial  
10      relationships. If you choose not to address this  
11      issue of financial relationships at the beginning  
12      of your statement, it will not preclude you from  
13      speaking.

14             The FDA and this committee place great  
15      importance on the open public hearing process. The  
16      insights and comments provided can help the agency  
17      and this committee in their consideration of the  
18      issues before them.

19             That said, in many instances and for many  
20      topics there will be a variety of opinions. One of  
21      our goals today is for this open public hearing to  
22      be conducted in a fair and open way, where every



1 participant is listened to carefully and treated  
2 with dignity, courtesy, and respect.

3 Therefore, please speak only when recognized  
4 by the chairperson. Thank you for your  
5 cooperation.

6 Will speaker number 1 step up to the podium  
7 and introduce yourself? Please state your name and  
8 any organization you may be representing.

9 DR. BRINDIS: Hello. My name is Ralph  
10 Brindis. I'm here representing the American  
11 College of Cardiology, and offering both an oral  
12 and written statement for the FDA advisory panel.  
13 I'm employed as the senior medical officer for  
14 external affairs for the ACC NCDR, and have served  
15 as past president of the ACC. Could I have my  
16 first slide, please?

17 Here are my disclosures. The ACC has paid  
18 for my travel expenses.

19 The ACC has 43,000 members representing  
20 greater than 90 percent of U.S. cardiologists. We  
21 have over 20 million patients records in our seven  
22 national cardiovascular data registries. Slide 4.

1           The mission of the ACC is to advocate for  
2           quality cardiovascular care through education,  
3           research, promotion, development and application of  
4           standards and guidelines. Slide 5.

5           The ACC and the AHA co-published a  
6           scientific advisory in 2010 on thiazolidinedione  
7           drugs and cardiovascular risks in the Journal of  
8           the American College of Cardiology. I acknowledge  
9           the expertise of Sanjay Kaul, serving on the FDA  
10          advisory panel today, as a first author of the  
11          scientific advisory.

12          In addition to analyzing the scientific  
13          evidence of the cardiovascular safety of  
14          rosiglitazone, the advisory called on academic  
15          researchers, industry, and governmental agencies to  
16          collaborate on definitive randomized trials with  
17          focused attention on cardiovascular outcomes to  
18          more definitively answer this vital question.

19          Slide 6.

20          The problem: Rosiglitazone is not the only  
21          treatment that may infer an unintended risk for  
22          cardiovascular events. Here's a small sample, and

1       there are others.

2               The key message is from the ACC for the  
3       future in optimizing and assessing new drugs and  
4       their cardiovascular safety. We need to continue  
5       to develop new methodologies for assessing  
6       cardiovascular safety that are cost-effective and  
7       efficient.

8               We need to harmonize safety assessment  
9       endpoints worldwide. We need to harmonize  
10      adjudication strategies worldwide. We need to  
11      better understand best practices for adjudication  
12      of observational and postmarket data endpoints.

13              Although they are the gold standard,  
14      randomized clinical trials have issues. They  
15      require thousands of patients. They take many  
16      years to conduct. They cost millions of dollars.  
17      There are subjective judgments that are used in  
18      adjudicable events. There are regional differences  
19      in these. There's inconsistencies in data, and  
20      individual biases.

21              In terms of new premarket methodologies,  
22      randomized clinical trials can be augmented by

1 consistent and unbiased adjudication. New methods  
2 need to be developed that are cost-effective and  
3 efficient, that save money, that reduce cost of  
4 drug development, and bring new therapies to market  
5 more quickly.

6 In terms of the adjudication process,  
7 clinicians want consistent definitions across  
8 trials so we can translate the findings of pivotal  
9 trials into everyday clinical care. We need  
10 consistency and quality in the data presented for  
11 adjudication. What is the quality and quantity of  
12 data needed to support an adjudicated decision?

13 In terms of adjudicating observational and  
14 postmarket data endpoints, how is this different,  
15 in registries and observational studies versus  
16 prospective studies? We need to understand better  
17 considerations in terms of prospective versus  
18 retrospective and observational versus  
19 interventional approaches. And we certainly need  
20 better understanding for reasonable case  
21 ascertainment strategies.

22 New postmarket methodologies: Postmarket

1 surveillance may be the area in which the ACC can  
2 help immediately, collaboration between regulators,  
3 sponsors, clinicians, and patients with a common  
4 goal of protecting patients.

5 Utilization of the FDA's Sentinel  
6 Initiatives in PCORI: The ACC national registry  
7 and its outpatient registries, input registries,  
8 and the strategy of longitudinal linkage with CMS  
9 and pair administrative data and clinical records  
10 can be important.

11 Our ambulatory clinical registry collects  
12 data on patients, medication lists, intermediate  
13 outcomes, adverse events, and can be used to target  
14 recruitment of patients for clinical trials and  
15 observational studies. The PINNACLE Registry is  
16 linked to other NCDR registries, collecting data,  
17 understanding treatment patterns, clinical  
18 outcomes, drug safety, and overall quality of care  
19 provided to high risk myocardial infarction  
20 patients.

21 In terms of standardizing endpoints, we have  
22 worked with the FDA in terms of standardization of

1 cardiovascular data for clinical research, and also  
2 are now working on a paper on data transparency.

3 The FDA should require adaptation and adoption of  
4 standard definitions and data elements by industry  
5 for cardiovascular safety assessments, allowing  
6 patients, clinicians, and others to compare risk  
7 profiles.

8 In summary, improved realtime surveillance  
9 is critical. Rehashing clinical trial data only  
10 goes so far. Registries can be an important part  
11 of that surveillance system. Surveillance systems  
12 will improve greatly if we all speak the same  
13 language regarding safety in terms of common  
14 definitions and common rigor of documentation.

15 The story of rosiglitazone is a cautionary  
16 tale. We are 14 years since the FDA approval,  
17 still lacking conclusive evidence related to its  
18 safety. We look forward to working with the FDA,  
19 researchers, and industry in harnessing the power  
20 of national registries and improved methodologies  
21 to better assess cardiovascular safety of promising  
22 drugs. Thank you.

1 DR. BURMAN: Thank you.

2 Will speaker number 2 please step up to the  
3 podium and introduce yourself? Please state your  
4 name and organization that you're representing.

5 DR. WOLFE: I'm Sid Wolfe of Public Citizen  
6 health research group. I do not have any financial  
7 conflicts of interest.

8 I'm just going to briefly go through the  
9 history of our involvement with this drug. As you  
10 all know, the first drug in the so-called glitazone  
11 class came off the market in 2000 after just three  
12 years because of hepatic toxicity.

13 In 1999, rosiglitazone was approved, as you  
14 know, and in March 2000 we petitioned the FDA to  
15 revise the labeling because of toxicity such as  
16 heart failure. There was animal and some human  
17 evidence then. A lot of our work in that period of  
18 time and since then is by former pharmacologist and  
19 toxicologist Dr. Elizabeth Barbehenn, who was in  
20 the Metabolic Endocrine Division of the FDA until  
21 about 12 years ago, when she joined our group.

22 In 2005, a GSK meta-analysis showing

1 increased risk of MI. Nissen analysis 2007. And  
2 at the first of these three meetings that I've  
3 attended, the one in July, we testified that the  
4 risks clearly outweighed the benefits, in our view,  
5 and asked for the drug to be taken off the market.

6 We petitioned in October of 2008, and in  
7 December of 2008 -- I'll go through the American  
8 Diabetes Association thing in a minute -- in  
9 December of 2008 an FDA guidance came out, an  
10 important one, beginning to look forward as to  
11 what sort of lack of risk or reduced amount of  
12 cardiovascular risk there needed to be prior to a  
13 drug coming on the market for diabetes.

14 This is just a summary from our petition  
15 in October 2008 to take the drug off the market.  
16 Clear, unequivocal evidence that rosiglitazone  
17 causes a variety of toxicities. Many of these are  
18 life-threatening -- heart attacks, heart failure,  
19 liver failure; also, toxicities which harm the  
20 health of patients, even though not life-  
21 threatening, including increased bone fractures,  
22 impairment of vision, anemia, and edema.



1           Unlike older treatments, which actually  
2   lessen the risk of heart attacks and all-cause  
3   mortality, such as metformin, rosiglitazone  
4   increases cardiovascular outcomes such as heart  
5   attacks and heart failure.

6           Finally, pointing out that FDA certainly had  
7   the legal authority then to start the process of  
8   taking this off the market. The upper paragraph,  
9   there's already a significant decrease, as has been  
10   pointed out by other people before, in terms of  
11   responding prior to the REMS program.

12           The American Diabetes Association committee  
13   along with the European one said, given that other  
14   treatment options are now recommended, the  
15   consensus group members unanimously advised against  
16   using rosiglitazone. This was not official ADA  
17   policy, but it was their committee. David Nathan  
18   of Harvard Medical School was involved in that.

19           I mention this because this was to me one of  
20   the more cogent things, of many relatively cogent  
21   things, that happened at the advisory committee  
22   meeting in July of 2010. The Institute of Medicine

1       had been asked to weigh in on the TIDE study, and  
2       had looked more broadly at the whole issue of how  
3       do you evaluate the risks and benefits of a drug,  
4       in this case the risks.

5               They pointed out you've got to look at pre-  
6       clinical pharmacology data; receptor information,  
7       in the PPAR gamma receptor in this case; clinical  
8       trials; high quality epidemiological studies;  
9       postmarketing surveillance -- all of these  
10      combined. A large picture, not just one thing, a  
11      RECORD study, for instance.

12             Early reports of edema, weight gain, heart  
13      failure -- again, that was the basis of our  
14      petition in 2000. Mechanism: Stimulation of renal  
15      is the mechanism for the fluid accumulation;  
16      stimulation of renal, PPAR gamma, increased sodium,  
17      and water retention.

18             Pioglitazone: Again, some receptor  
19      differences. Less potent than rosi at the PPAR  
20      gamma, particularly the cardiac sites, but more  
21      favorable effects on blood lipids.

22             Part of my presentation in 2010 was with

1 Dave Juurlink. I read his testimony. He was a  
2 principal investigator of the study, looking at the  
3 essentially single pair database in Canada of  
4 people 66 and older.

5 Everyone who was taking either pioglitazone  
6 or rosiglitazone, the numbers are there, and the  
7 outcomes, the primary outcome, was a composite of  
8 CHF, AMI, all-cause mortality, and secondary was  
9 the individual outcomes of each of these.

10 The composite adjusted hazard ratio favoring  
11 pioglitazone was .83. Said differently, we project  
12 one additional composite outcome for every 93  
13 patients treated with rosiglitazone rather than pio  
14 for one year. And these were the numbers. You've  
15 seen these before, just for CHF, AMI, and death,  
16 some of them crossing over 1, the first and third  
17 not.

18 However, the common kinds of comments about,  
19 it's not an RCT, maybe it's just bias and  
20 confounding. But as Dave Juurlink pointed out,  
21 they were similar to the results of Winkelmayer and  
22 Dave Graham from the FDA. And there was a

1       remarkable -- as you'd expect with it, the entire  
2       population of Ontario in this case -- comparability  
3       of the rosi and pio groups at the baseline.

4               Burden of harm: His estimates, their  
5       estimates. If one million patients received  
6       rosiglitazone for one year -- instead they could  
7       have received pioglitazone -- 8300 excess  
8       hospitalizations for heart failure, 3700 excess  
9       deaths.

10              The conclusions here were among older  
11       patients to diabetes. Rosiglitazone is associated  
12       with a significantly higher risk of heart failure  
13       and death compared to pio. Given the lack of the  
14       therapeutic advantage, difficult to argue for  
15       continued use of pio.

16              These things that I've mentioned before.  
17       I'll skip over this slide.

18              So differences between rosi and pio, all  
19       unfavorable to rosi; differential PPAR gamma  
20       agonist strengths, differential effects on lipids.  
21       We now go to the pharmacology review, which, as the  
22       Institute of Medicine said, looking at even pre-

1 approval, pre-clinical pharmacology is worth doing.

2 At the high doses, rosiglitazone produced  
3 various toxicities, such as left atrial thrombosis  
4 and so forth. And what is in red, not visible  
5 here, is that the pharmacologists who reviewed this  
6 drug thought it should not be approved for human  
7 use because of the signals. The same  
8 pharmacologists did approve pio because it did not  
9 have anywhere near the cardiac signals in the  
10 animal toxicology pharmacology.

11 I show this slide because just look at the  
12 top panel. The exposure ratio of the animal to the  
13 human was just 1.2. And yet in male and female  
14 dogs, there was cardiac hypertrophy believed to be  
15 as a result of the fluid, sodium, and water  
16 accumulation.

17 So we've talked about differential strength,  
18 affects on lipids, pre-clinical, observational  
19 studies such as the Dave Juurlink one. What about  
20 meta-analysis?

21 This was a slide presented at the 2010  
22 meeting just looking at meta-analysis of heart

1 failure. I won't spend any more time on that. And  
2 this was another one. This is the meta-analysis of  
3 all the RCTs, showing generally a move towards more  
4 risk, not in every single case.

5 These are from the current. FDA did some  
6 very nice analyses, regrouping some of these RCTs  
7 by what the comparator group was, a placebo or  
8 another drug and so forth. And this is just the  
9 first slide, showing that the MACE endpoint,  
10 although it wasn't statistically significant, the  
11 stratified odds ratio was 1.44, with a moderate  
12 number. This is 6900 comparator and 10,000  
13 rosiglitazone patients.

14 These are more of these analyses, which were  
15 presented to you, I'm sure, yesterday, some of the  
16 different ways of grouping the RCTs, all showing  
17 worse evidence of increased cardiovascular risk.

18 I want to go through this because there were  
19 12 people voted to take this drug off the market in  
20 2010. And the comments, I think, are interesting  
21 in view of what has subsequently happened.

22 "Serious adverse effects" -- he was the

1 author, as you know, of one of the meta-  
2 analyses -- "overwhelmingly outweigh any benefit.  
3 Benefit is modest at best. There are other  
4 treatments. That's why I voted E," which was to  
5 ban. Heckbert. "No unique benefits that I could  
6 discern. It has a safety problem in terms of  
7 myocardial ischemia, and there benefits don't  
8 outweigh the risks."

9 One of the more interesting comments was  
10 Dr. Thomas, who I think may have been chair of the  
11 panel. He had said that when he had lunch before  
12 this meeting, someone was discussing the  
13 intersection between public policy and science.

14 "Look at this that way. We can't always  
15 have the absolute truth to make a decision. We  
16 have a lot of alternatives as a result. We can  
17 still take care of diabetes. There may be a few  
18 patients who do very well on rosiglitazone, but I  
19 can treat them other ways, and all other  
20 endocrinologists can as well." And obviously,  
21 you're seeing that as this precipitous fall in  
22 people getting the drug.

1           Dr. Woods, who's here today, said, "I'm not  
2       sure REMS works. When the rubber hits the road, I  
3       voted for E." So REMS works, we'll talk about that  
4       later, because it clearly works to significantly  
5       decrease, by 99-plus percent, the number of people  
6       that get it. But there's a down side to all of  
7       that.

8           Dr. Winterstein: "I think that the  
9       quality" -- she's a pharmacist and an  
10      epidemiologist -- "quality of pharmaceutical care  
11      that is delivered to patients is not as good as it  
12      could be, and I think we have a great opportunity  
13      here to protect patients from additional harm."

14          Dr. Tom Fleming, an epidemiologist  
15      statistician: "There's very concerning data about  
16      safety."

17          Platt, epidemiologist: "From a public  
18      health perspective, it seems to me that it's a  
19      benefit that can be obtained from another drug. So  
20      from a public health perspective, I think it's  
21      pretty clear the public would be best served by not  
22      having the drug available." I'll skip that last



1       one.

2               This is a slide looking at the  
3       difficulty -- that's a generous way of describing  
4       it -- in resolving the conflicts that frequently  
5       happen here at the FDA between the Office of  
6       Surveillance and Epidemiology, the Office of New  
7       Drugs, and the resolution by Dr. Woodcock or  
8       others.

9               Here is an example having to do with this  
10       drug. In July of 2007, David Graham thought the  
11       drug should be withdrawn. Mr. Dal Pan said, "The  
12       balance of benefits and risks do not favor the  
13       drug." They didn't withdraw it, and Dr. Woodcock  
14       confirmed that.

15              Later on, following our petition, Mr. Dal  
16       Pan said, "The benefits of rosiglitazone do not  
17       outweigh the risks," and announced that he thought  
18       that the agency should grant our petition to take  
19       it off the market. OND disagreed, and the  
20       resolution was not to take it off the market. And  
21       then the following year, the same kind of thing  
22       happened.

1           I want to switch gears to what would be  
2       called almost a tale of two regulatory agencies,  
3       not two cities. This was the announcement in the  
4       fall of 2010 by the EMA: "Availability of recent  
5       studies has added to the knowledge, and overall,  
6       the accumulated data support an increased  
7       cardiovascular risk." Accumulated data, all the  
8       sources.

9           "In view of these restrictions already in  
10      place on the use of rosi, the Committee could not  
11      identify additional measures that would reduce the  
12      cardiovascular risk." Not reduce the number of  
13      prescriptions, but reduce the risk. "The Committee  
14      therefore concluded that the benefits no longer  
15      outweigh the risks, and recommended suspension.  
16      They will no longer be available in a few months."

17          The reason stated -- I don't need to read  
18      all of this -- they pointed towards Dr. Graham's  
19      study and the subsequent study by Dr. Nissen as the  
20      new reasons for re-looking at this issue when they  
21      started re-looking at it in summer of 2010.

22          The conclusions, pretty much summarized in

1       their decision: "Evidence this increased risk is  
2       coming from a variety of sources -- observational  
3       studies, published literature -- had accumulated to  
4       the extent that the benefits could no longer  
5       outweigh the risks."

6               The last part of this, which I stuck in  
7       italics, says, "The Committee therefore recommends  
8       marketing authorization be suspended until the  
9       company can supply convincing data to identify a  
10      patient population in which the clinical benefits  
11      of rosiglitazone outweigh the risks." And that  
12      obviously has not happened in the last three years.

13              Recommendations for patients: Talk with  
14      your doctors. Discuss suitable alternatives.  
15      Don't stop without talking to your doctors. And  
16      then for prescribers, the recommendation was, stop  
17      prescribing rosiglitazone. Patients who are  
18      currently receiving it should be reviewed in a  
19      timely manner. They did not recommend any specific  
20      alternative, but given that there are ten other  
21      classes, there was easily a possibility of finding  
22      another alternative.

1           This is verbatim from the Criminal  
2 Information, which was filed in July of 2012. And  
3 I'm not putting it in here to reiterate the fact  
4 that Glaxo, as you know, got in trouble, amongst  
5 other things, for withholding information from the  
6 FDA for the progress of RECORD.

7           The main reason I'm showing it is it's the  
8 first piece of information which I was not aware  
9 of. GSK initiated the RECORD study at the request  
10 of European regulatory agencies to evaluate cardiac  
11 safety of Avandia. And then, according to the FDA  
12 and HHS, they did not timely file reports on that  
13 study or even the acknowledge the existence of it  
14 at the FDA initially.

15           So here is a question which I think cuts  
16 across why this meeting is occurring and broader  
17 issues. Why did the RECORD study, requested by the  
18 EMA, not require readjudication by the agency, the  
19 EMA, as part of its decision to ban Avandia?

20           As part of the decision not to ban Avandia,  
21 as you know, in addition to the REMS, FDA  
22 temporized by requiring readjudication of

1 support -- that was an explicit requirement of  
2 GSK -- while restricting use with a REMS designed  
3 to make the drug available to those who might  
4 benefit from it, and to educate physicians and  
5 pharmacists.

6 The EMA, reviewing the same data as the FDA,  
7 exactly the same data, without support being  
8 readjudicated, even though they had mandated the  
9 study, concluded, "The marketing authorization be  
10 suspended until the company can supply convincing  
11 data to identify a patient population," which I'd  
12 already read previously.

13 The slide I skipped was what Dr. Mathew's  
14 presentation was.

15 How many American diabetics were exposed  
16 to Avandia between the time of the EMA market  
17 withdrawal and now? And this is according to the  
18 data that you saw.

19 According to the FDA data, the IMS and other  
20 data, from the end of 2010, after the EMA market  
21 withdrawal, and the present, an estimated 132,000  
22 patients received the drug, with GSK sales -- that

1 was not the FDA data; that was IMS data -- of  
2 approximately \$75 million since the EMA withdrawal.

3 How much harm has occurred? Either using  
4 the Juurlink comparison with pioglitazone or a  
5 number of the meta-analyses that you have seen  
6 presented now or earlier, there's a reasonable  
7 likelihood that hundreds of American diabetics,  
8 because they were prescribed a drug not available  
9 in Europe instead of other, safer drugs, suffered  
10 harm due to the FDA's failure to ban Avandia,  
11 including not only cardiovascular risk but the  
12 well-established increased risk of fracture, heart  
13 failure, and so forth, hospitalization for heart  
14 failure.

15 To finish the sentence, a drug not available  
16 in Europe instead of other, safer drugs, suffered  
17 harm due to FDA's failure to ban Avandia, as  
18 recommended by 12 advisory committee members in  
19 2010 and as effected by the EMA.

20 I think that's the last slide. I will just  
21 comment briefly on both the issue of REMS, broadly,  
22 and the issue of postmarketing studies. I'm very

1 concerned -- there have been a number of examples,  
2 and there's no time to go into them now -- that for  
3 certain drugs, where the evidence of the risk so  
4 outweighs the benefits that the proper decision  
5 would be either not to approve it, if it's pre-  
6 approval, or to take it off the market, that FDA is  
7 increasingly using REMS and/or postmarket studies.

8 We aren't sure about the risks of these two  
9 diet drugs, so do a postmarket study; the FDA  
10 properly has authority to do these, but the  
11 question is, are they doing them in circumstances  
12 where the drugs shouldn't come on the market, or in  
13 this case, are they doing a REMS as a substitute  
14 for taking it off the market?

15 There's no doubt the REMS was successful in  
16 terms of greatly reducing the number of people  
17 getting the drug. Do we have any evidence that  
18 those several thousand, or whatever the number is,  
19 people who are getting it now actually have some  
20 unique problem that could not be benefitted by  
21 something else? As Dr. Thomas has said, he can  
22 switch all these people to other things, ranging

1 from insulin to other drugs.

2 So I think that what's happened in this  
3 country, in contrast to the tale of two regulatory  
4 agencies, is that using the precautionary  
5 principle, the EMA decided to protect Europeans.  
6 There was enough concern from all the multiple  
7 sources, not just the RECORD study, that there was  
8 a problem with the drug, and they said, let's just  
9 take it off the market.

10 It would be interesting to find out why the  
11 EMA chose not to readjudicate the study that they  
12 had required GSK to do, the RECORD study. I'm sure  
13 that they will look at the adjudication that was  
14 done by DCRI, but why did they not need to do this  
15 in order to get the drug off the market?

16 I think the answer has a lot to do with an  
17 increasingly different philosophy between the EMA  
18 and the FDA about drug safety. Thank you.

19 DR. BURMAN: Thank you.

20 Will speaker number 3 step up to the  
21 microphone and introduce yourself? Please state  
22 your name and the organization you are



1       representing.

2               DR. RATNER:   Mr. Chairman, before I begin,  
3       could I just get some clarification for the time  
4       allocation for the public hearing speakers?

5               DR. BURMAN:   Five minutes.

6               DR. RATNER:   Thank you.

7               DR. BURMAN:   Thank you.

8               DR. RATNER:   Good morning.   My name is  
9       Dr. Robert Ratner.   I'm an endocrinologist and  
10      chief scientific and medical officer at the  
11      American Diabetes Association, representing over  
12      15,000 professional members and 26 million  
13      Americans with diabetes.   I have no conflicts.

14              Although the American Diabetes Association  
15      does not testify in support of individual products,  
16      we strongly support the need for further research  
17      and improved therapies for the treatment of  
18      diabetes.

19              First, I want to congratulate and thank the  
20      agency for this review and consideration of the  
21      science.   Continued evaluation of data is the  
22      appropriate process for advancing science, and the

1       only way we can arrive at the truth and avoid  
2       hyperbole or public confusion and anxiety.

3               We are now at the 30th anniversary of the  
4       initiation of the landmark NIH-sponsored Diabetes  
5       Control and Complications Trial, which definitively  
6       demonstrated the impact of glycemic control on the  
7       development and progression of microvascular  
8       complications.

9               There is no further debate about the  
10      relationship of glucose control, as measured by  
11      hemoglobin A1c, and the development of retinopathy,  
12      renal disease, or neuropathic complications, while  
13      its relationship to macrovascular complications  
14      remains controversial.

15              From a public health perspective, we have  
16      seen a progressive 24 percent reduction in the  
17      incidence of vision loss, a 35 percent reduction in  
18      end-stage renal disease, and a 50 percent reduction  
19      in amputations over the last 10 years.

20              Since 2000, we have also seen a 24 percent  
21      relative risk reduction in cardiovascular risk,  
22      with a 40 percent decline in cardiovascular

1 mortality, according to a recent report from the  
2 CDC. The overall incidence of cardiovascular  
3 events in patients with diabetes has dropped to  
4 approximately 2 percent per year. This falling  
5 hazard ratio makes current and future CVD outcome  
6 trials problematic.

7 The temporal reduction in complications has  
8 been accompanied by increased public and medical  
9 perception of the importance of glucose, blood  
10 pressure, and lipid control. But it has also been  
11 associated with a quadrupling in the available  
12 classes of agents to treat diabetes in the last  
13 10 years.

14 With these additional therapeutic options,  
15 we have seen the percent of individuals achieving  
16 good glycemic control, defined by a hemoglobin A1c  
17 of less than 7 percent, now exceeding 50 percent.  
18 However, we still have a long way to go, as over  
19 20 percent of Americans with diabetes continue to  
20 have a hemoglobin A1c exceeding 8 percent.

21 The American Diabetes Association, together  
22 with the European Association for the Study of

1     Diabetes, has modified their approach to the  
2     treatment of individuals with type 2 diabetes  
3     to emphasize the importance of glycemic control  
4     within the context of other patient-centered  
5     characteristics.

6             Diabetes is a chronic disease in which  
7     individuals must manage their disease on a daily  
8     basis for 30 to 60 years. Outcomes of importance  
9     to people with diabetes go well beyond the hard  
10    events we have just reviewed to encompass the  
11    impact on daily activities. The American Diabetes  
12    Association strongly believes that we need a wide  
13    variety of classes of therapeutic agents to treat  
14    this very heterogeneous disorder over a lifespan.

15            Comparative effectiveness research has, as  
16    its core, the determination of what works best for  
17    whom under what circumstances. As a very astute  
18    member of this committee previously stated,  
19    "Although a drug may not be appropriate for  
20    everyone, that doesn't mean it is inappropriate  
21    for everyone."

22            We request that the agency provide guidance

1       for drug review and approvals in the future that  
2       incorporate the diverse needs of the diabetes  
3       community and address the whole spectrum of  
4       outcomes of importance to people living with  
5       diabetes. Thank you very much.

6               DR. BURMAN: Thank you.

7               Will speaker number 4 step up to the  
8       microphone, introduce yourself, state your name and  
9       organization you are representing for the record.

10              MR. KEYSERLING: Good morning. My name is  
11       Charles Keyserling. I'm representing myself. I am  
12       a 71-year-old diabetic, 17 years a type 2 diabetic,  
13       diabetes caused by insulin resistance.

14              I am one of the fortunate 3405 type 2  
15       diabetics using Avandia. I only hope that  
16       GlaxoSmithKline will continue to manufacture  
17       Avandia. TZDs have given me 15 quality diabetic  
18       years, and I owe 13 to Avandia. By the FDA keeping  
19       Avandia available in the U.S., you have given me  
20       three more great years. Thank you.

21              I would also urge that you would perform a  
22       test like TIDE. I think it's desperately needed.

1           While it may be acceptable to some of you to  
2     take away my choice to take a drug that doesn't  
3     accelerate the development of bladder cancer,  
4     having seen friends and relatives die from bladder  
5     cancer, no one can convince me that Actos is safer  
6     than Avandia.

7           The amount of blood flow increase that  
8     causes the AMIs is dosage-dependent, and so taking  
9     a lower dose of Avandia can make it as safe or  
10    safer than Actos without the risk of bladder  
11    cancer. My doctor told me that he does not  
12    prescribe Actos any more because of the threat of a  
13    lawsuit from a patient that develops bladder  
14    cancer, and he would deserve such a suit if he does  
15    not check for bladder cancer before prescribing  
16    Actos.

17          CDC's Edward W. Gregg, PhD, published the  
18    following statement: "The death rate from  
19    cardiovascular disease in the U.S. adults with  
20    diabetes fell 40 percent from 1997 to 2004." He  
21    also said, "This analysis of national  
22    representative samples of adults with and without

1       diabetes reveals an impressive reduction in  
2       cardiovascular disease and all-cause mortality  
3       between 1997 and 2006."

4               The dates selected are over the period when  
5       TZD use started in 1997, and rose until 2007. I  
6       could not find any statistics later than 2006. But  
7       it is my belief that cardiovascular deaths in  
8       diabetics have risen as use of TZDs falls, and  
9       without Avandia there is no safe TZD.

10              After reviewing Dr. Nissen's 2007 report, I  
11       chose Avandia over Actos because the low AMI rate  
12       was higher for Avandia than Actos, and that meant  
13       that Avandia is a stronger medication because it  
14       increased blood flow the most.

15              It is the lack of blood flow that causes  
16       diabetic complications, and increasing blood flow  
17       plus strengthening the heart is the way to prevent  
18       and delay diabetic complications. Just like  
19       type 1s need insulin to meet their underlying  
20       problems, type 2s need a way to lower insulin  
21       resistance, and TZDs or exercise are the options.

22              Just like the RECORD study, long-term

1 studies like the Veterans III study show use of  
2 Avandia reduces cardiovascular events. The BARI-2D  
3 study showed Avandia was associated with a  
4 28 percent relative drop in death, MIs, and stroke,  
5 and a 64 percent decrease in the risk of stroke. I  
6 believe that the use of Avandia can be made safer  
7 with a program that minimizes the chances of AMI.

8 As insulin resistance goes untreated, the  
9 buildup of plaque occurs. We know this because  
10 two-thirds of type 2 diabetics die from  
11 cardiovascular disease, and any treatment to  
12 increase blood flow increases the risk of AMIs.  
13 Reducing insulin resistance when plaque buildup is  
14 low is essential to lower the risk of AMIs.

15 The present REMS program is very bad for new  
16 diabetics because it makes Avandia the drug of last  
17 choice, when the most plaque buildup has occurred  
18 and when the pancreas produces little insulin. A  
19 small amount of insulin is required for TZDs to  
20 work.

21 Dr. David J. Graham clearly proved this in  
22 his Medicare study, in which an older, high-plaque-



1       buildup population had a high level of cardiac  
2       events. Use of TZDs in pre-diabetics is the safest  
3       because of the low plaque buildup and the  
4       pancreas's ability to produce lots of insulin.

5               A look at the DREAM study will give insight  
6       into how this program should work. This study of  
7       pre-diabetics had 15 AMIs and 13 died from  
8       cardiovascular causes, an event rate of about 1 in  
9       every --

10              (Microphone turned off, time expired.)

11              DR. BURMAN: Excuse me. The microphone was  
12       cut off, but I would like you to finish, if you  
13       could turn on the microphone for another minute or  
14       so, because I think it's very important.

15              MR. KEYSERLING: Thank you for the extended  
16       time.

17              DR. BURMAN: Of course.

18              MR. KEYSERLING: A similar size, ADOPT, for  
19       new diabetics on Avandia only had two deaths. The  
20       question is, why the difference? The answer is in  
21       how Avandia works. By lowering insulin resistance,  
22       one feels great, has lots of energy, strength, and

1        stamina because muscles can suddenly, within two  
2        months, get the glucose they need to function.

3                Pre-diabetics are given less restrictions on  
4        exercise, and they tend to exercise at a more  
5        intense level. In a person with plaque buildup,  
6        increased blood flow can break loose a piece of  
7        plaque, causing an AMI. By detecting those with  
8        high plaque buildup and either not prescribing  
9        Avandia or ramping up the dosage of Avandia slowly,  
10       most of the deaths and AMIs in DREAM would never  
11       have happened.

12               Some of you have said Avandia increases the  
13       risk of an AMI. But because Avandia increases  
14       blood flow, it cannot increase the buildup of  
15       plaque. The plaque must have been there before  
16       starting Avandia. The causes of plaque are  
17       untreated insulin resistance, inactivity, smoking,  
18       and obesity.

19               The steps to make Avandia safer are to use  
20       it in as early a stage of diabetes development as  
21       possible, checking for plaque buildup and adjusting  
22       Avandia use to plaque buildup. Increasing blood

1 flow is what results from either aerobic exercise  
2 or a drop in insulin resistance. Ramping up  
3 Avandia use like one ramps up exercise will also  
4 make Avandia even safer. The use of Avandia should  
5 be terminated in those that retain too much water  
6 or have rapid weight increase.

7 The bottom line is that Avandia is the most  
8 effective drug to treat insulin resistance, and the  
9 one that doesn't accelerate bladder cancer. Use of  
10 Avandia as suggested above will make it among the  
11 safest drugs ever approved by the FDA.

12 I think the broad use of Avandia could  
13 greatly reduce the cardiovascular death rate in  
14 type 2 diabetics, as shown in the RECORD study.  
15 Thank you very much.

16 DR. BURMAN: Thank you.

17 Will speaker number 5 step up to the  
18 microphone and introduce yourself? State your name  
19 and organization you are representing.

20 DR. YTTRI: Thank you, Mr. Chairman, for  
21 allowing me the opportunity to speak today. I am  
22 Dr. Jennifer Yttri, and I am speaking today on

1       behalf of the National Research Center for Women  
2       and Families. Our organization does not accept  
3       funding from pharmaceutical companies, and  
4       therefore I have no conflict of interest.

5               Our nonprofit research center includes  
6       scientists, medical, and public health experts who  
7       analyze and review research on important health  
8       issues. We conduct research, publish our findings  
9       in medical journals, and provide unbiased and  
10      understandable information to patients, health  
11      professionals, and policy makers through CMEs,  
12      briefings, testimonies, and other reports.

13             We have a major focus on FDA policies, and  
14      our president, Dr. Diana Zuckerman, is on the board  
15      of directors of two nonprofit organizations  
16      dedicated to helping the FDA obtain the resources  
17      it needs, the Reagan-Udall Foundation and the  
18      Alliance for a Stronger FDA.

19             The adjudication of the RECORD trial by DCRI  
20      has the same findings as the original FDA review of  
21      the RECORD trial. The same safety signals arise.  
22      Concerns about the quality of the original trial

1 design and the data are really beyond the scope of  
2 adjudication.

3 We can debate all day long, or all  
4 yesterday, about the biases and questionable  
5 reporting, but that will bring us no closer to  
6 conclusions about the validity of the RECORD trial.  
7 The study was poorly designed and conducted, so the  
8 data are flawed and that undermines all analysis,  
9 whether it's the first round by the FDA, the second  
10 round by a second FDA reviewer, or a third round by  
11 an independent outside entity funded by  
12 GlaxoSmithKline.

13 The bottom line is still that taking Avandia  
14 increases the risk of heart failure. This safety  
15 signal is consistent. This finding supports the  
16 REMS and Elements to Assure Safe Use restrictions  
17 that are currently in place.

18 I think many of us would agree that other  
19 diabetes drugs have their own risks. The FDA  
20 should do more to evaluate those risks so that  
21 patients, physicians, and advisory committees can  
22 understand the safety of comparator drugs like

1 pioglitazone. In the meantime, we need the  
2 safeguards that are currently in place for Avandia  
3 in order to provide patients and physicians with  
4 the information they need regarding this drug.

5 With the halt of the TIDE trial in 2010, no  
6 new data have been provided. The committee must  
7 therefore consider other sources of information  
8 such as adverse reports or published scientific  
9 literature since rosiglitazone was originally  
10 approved in 2007.

11 When we consider independently performed  
12 studies, so those that are not sponsored by any  
13 drug company, most of the studies have found that  
14 patients taking rosi have an increased risk in  
15 myocardial infarction compared to patients taking  
16 other drugs, including pioglitazone. Most  
17 importantly, any study that measured heart failure  
18 found increased risk with rosiglitazone over any  
19 other treatment.

20 Is Avandia needed in the battle against  
21 type 2 diabetes? Sales have steadily decreased.  
22 There is no clear profile for patients who are

1 currently using Avandia. And, as we have seen, the  
2 majority of these patients are patients who were on  
3 it before 2010's restrictions were put in place and  
4 have continued, with their doctor's consent.

5 We believe that the documented safety risks  
6 would justify FDA removing this failed drug from  
7 the market entirely. That would eliminate concerns  
8 that some patients and physicians do not fully  
9 understand the risks of using this hazardous drug.

10 We are disappointed that the FDA continues  
11 to waste their limited resources reopening what  
12 should really be a closed case. If you're not  
13 ready to make the recommendation for withdrawal,  
14 then please keep the current safeguards in place.  
15 Thank you.

16 **Committee Discussion**

17 DR. BURMAN: Thank you.

18 The open public hearing portion of the  
19 meeting has now concluded, and we will no longer  
20 take comments from the audience. The committee  
21 will now turn its attention to address the task at  
22 hand, that is, the careful consideration of the

1 data before the committee as well as the public  
2 comments.

3 Now, as a general comment, we have about an  
4 hour until noon before lunch, and then in the  
5 afternoon we have the votes to do as well. I've  
6 gotten discordant comments from panel members; on  
7 the one hand, some feel that they haven't had  
8 enough time to ask all of their questions, and on  
9 the other hand, people who have to leave early  
10 because of flights and transportation.

11 So I'm going to try to mediate those two and  
12 satisfy both aspects, if that's possible. And I  
13 was thinking that from -- it's 11:00. From 11:00  
14 till 12:00, we will have two aspects.

15 The first aspect will be an update of the  
16 loose ends that we have had before from the FDA,  
17 GSK, and Duke, and Hopefully, that will take  
18 30 minutes or so total. And then for the last  
19 30 minutes, we will raise questions from the panel  
20 for anybody. And then hopefully we'll be able to  
21 go right into the questions for voting and  
22 discussion in the afternoon.



1           So I hope that's okay with everyone. I  
2       would like to start with Dr. Jenkins, who had a  
3       comment from the FDA.

4           DR. JENKINS: Yes. Thank you. I wanted to  
5       follow up on some of the discussion from  
6       yesterday -- sorry, I'm trying to get to the  
7       document I want to refer to -- about why FDA  
8       ordered Glaxo to have a third party do the  
9       readjudication versus having our own staff do the  
10      readjudication of RECORD.

11           That decision is consistent with our policy.  
12      We have a map -- it's MAPP 6010.6. MAPPs for us  
13      are standard operating procedures. And it's about  
14      how we manage the use of clinical source data.

15           I think it's important to understand, when  
16      you're doing a clinical trial, the amount of  
17      information from that trial that comes to FDA for  
18      our review is only a subset of all the information  
19      that's collected in conducting that trial.

20           For example, companies report to us the  
21      results of lab tests. They don't report to us the  
22      actual lab data, the slips themselves, for example.

1       They report the results of X-rays. They don't send  
2       us the X-rays to look at. They report the results  
3       of MIs and EKGs. They don't necessarily send those  
4       to us to look at.

5               So our policy on adjudication is stated in  
6       this MAPP as -- let me get to it -- "The  
7       adjudication of clinical endpoints is the  
8       responsibility of the applicant and not the  
9       clinical review staff at FDA."

10              It goes on to say that applicants should  
11       have developed, as part of their protocol, a plan  
12       for how they're going to do the adjudication of  
13       endpoints. FDA often comments and opines on the  
14       adequacy of those plans for adjudication. We often  
15       work with the sponsor on monitoring plans for how  
16       the adjudication is done.

17              Then once the data are submitted, we get the  
18       results of the adjudication. So we get whether  
19       someone was considered to have an MI or not. We  
20       don't get all the clinical background information  
21       about their EKGs, et cetera, that were actually  
22       obtained at the site where the patient was cared

1       for.

2               We do encourage our staff, as they're going  
3       through the review of applications, to consider  
4       doing an audit of whether they can look at how the  
5       adjudications were done and see if it makes sense  
6       how the adjudication rules were applied to generate  
7       the data that are in the application.

8               We do say that if there are questions raised  
9       about how the adjudication was conducted and we  
10       believe that readjudication is needed, that,  
11       "Clinical review staff should establish acceptable  
12       readjudication procedures with the applicant, and  
13       the applicant is in most instances expected to  
14       conduct the readjudication and the appropriate  
15       reanalysis. Instances in which clinical review  
16       staff conduct the readjudication itself, excluding  
17       the applicant, should be rare and well-justified."

18              The policy goes on to explain that when  
19       those situations arise where we consider doing the  
20       readjudication ourselves, there has to be a clearly  
21       defined protocol with all the usual blinding  
22       procedures, setting up an adjudication committee

1       like we would expect the applicant to have done.

2               So it's rare that we take on the task of  
3       doing a readjudication. I can't think of any  
4       example where we've taken on a readjudication that  
5       would be as extensive as was required for the  
6       RECORD trial.

7               We heard there were over 4,000 patients  
8       enrolled, so DCRI got literally a mountain of  
9       information about those patients, far beyond the  
10      information that we normally receive from the  
11      applicant, such as the source data behind all those  
12      issues.

13              We also heard that in addition to DCRI,  
14      there were two CROs that were employed in addition  
15      to the work that was done by Glaxo to prepare the  
16      database for the readjudication. And we heard that  
17      that readjudication employed a large number of  
18      staff resources at those organizations and a lot of  
19      time and money.

20              So there are reasons that we don't take on  
21      the task of doing readjudication, and that's  
22      spelled out in our policy. So I just wanted to try

1 to clarify that.

2           There were also some questions yesterday  
3 about how can we be certain that Glaxo gave DCRI  
4 all the information about the RECORD trial. I  
5 would point out, the sponsor is always the source  
6 of the information about the clinical trials that  
7 they provide us as part of the marketing  
8 applications.

9           There are legal requirements about what  
10 they're expected to provide us, and there are legal  
11 consequences of failure to provide accurate  
12 information about the clinical trials that they're  
13 submitting to FDA for supporting a marketing  
14 application.

15           In this case, the readjudication of RECORD  
16 was a postmarketing requirement under the FDAAA  
17 legislation that was passed in 2007. So it has the  
18 enforceability of law that Glaxo is required to do  
19 this readjudication, and I think the same law  
20 applies as far as consequences if they failed to do  
21 the readjudication in a proper manner.

22           I'm not aware of any evidence that's been

1 brought to our level of awareness that there's any  
2 evidence that they did not provide DCRI with all  
3 the data that they had for the RECORD trial. We  
4 did audit Glaxo, DCRI, and as you heard, some of  
5 the other sites as part of the clinical  
6 investigations, and that's part of our MAPP, also,  
7 that says that we can do investigations, clinical  
8 site audits.

9 So I just wanted to clarify why we ordered  
10 Glaxo to do the readjudication versus taking it on  
11 ourselves.

12 DR. BURMAN: Thank you.

13 We'd like to continue on for the next  
14 15 minutes or so with refinements and discussion  
15 from the issues that are left. First, from the FDA  
16 standpoint, are there any other issues that were  
17 brought up yesterday or this morning that you  
18 wanted to clarify?

19 DR. MAHONEY: We have received clearance  
20 from the Division of Information Disclosure Policy  
21 regarding the PROactive baseline statin  
22 information. So if you'd like us to present that,

1 we can.

2 DR. BURMAN: I think we'd like that. Thank  
3 you.

4 DR. MAHONEY: It's slide 6. So this is part  
5 of a table from my review. It was a multi-page  
6 table, but this is the page on which this  
7 information is included.

8 So if you look on about the third row or  
9 so -- it's a little hard to read because it's a  
10 PDF -- there's a third row that says, "On statin at  
11 baseline." And then the next line is, "Not on  
12 statin at baseline."

13 You can see that in patients who are not on  
14 statins at baseline, the point estimate for the  
15 hazard ratio is lower than the point estimate for  
16 patients who were on statin at baseline, and that  
17 the p-value for the interaction is .1 something.  
18 And that's for the primary endpoint, which is a  
19 composite of --

20 DR. JENKINS: Karen, can you actually read  
21 the data? Because I'm sure no one can read that on  
22 the slide.

1 DR. MAHONEY: Yes, I can. I'm sorry.

2 So for the patients who were not on statin  
3 at baseline, the point estimate for the hazard  
4 ratio was 0.83 with a confidence interval of 0.71  
5 to 0.97. And for patients who were on statin at  
6 baseline, it was 1.02, with a confidence interval  
7 of 0.84 and 1.22. And the p-value for interaction  
8 was 0.1071.

9 Then the next slide is the post hoc  
10 secondary composite of all-cause mortality and  
11 nonfatal MI, excluding silent MI and stroke. About  
12 a little over halfway down, for patients who were  
13 not on statin at baseline, the point estimate for  
14 the hazard ratio was 0.77, confidence interval  
15 0.64, 0.93. And for patients who were on statin at  
16 baseline, it was 0.97, 0.75, and 1.26 for the  
17 confidence interval. And the value for the  
18 interaction is 0.1547.

19 So that's the information about what the  
20 actual values were in PROactive. And we also have  
21 Dr. Soukup, who is team leader for biometric  
22 safety. And if you like, he can tell us a little



1 bit about how the FDA approaches subgroup analyses  
2 in terms of safety.

3 DR. BURMAN: Sure. Thank you.

4 DR. KONSTAM: While he's coming up, I'm just  
5 curious. Do you have the data on cardiovascular  
6 mortality or all-cause mortality singled out? Or  
7 that's not available? Because I think the biggest  
8 signal that we saw in RECORD, if I'm not mistaken,  
9 was on cardiovascular mortality. So I just wonder  
10 if that's available. It might not be available.

11 DR. MAHONEY: No. I only have it for these  
12 two composites.

13 DR. BURMAN: Thank you.

14 Please state -- thank you.

15 DR. SOUKUP: Yes. I'm Mat Soukup. I'm a  
16 team lead within the Office of Biostatistics at  
17 CDER. There's been a lot of discussions on  
18 subgroups, and I thought it was worthwhile to just  
19 bring in some statistical principles or just  
20 general clinical principles in how we view  
21 subgroups at the agency.

22 The first issue, I think, is we need to

1 provide a distinction between a proper subgroup and  
2 an improper subgroup. A proper subgroup is defined  
3 as a characteristic that's defined at baseline. So  
4 these are things that, statistically, we have  
5 traditional methods where we can explore these and  
6 analyze them in fairly traditional approaches, and  
7 we commonly do so.

8 The improper subgroup are subgroups that are  
9 defined on a characteristic that develops post-  
10 randomization. These are things that are much more  
11 difficult to handle statistically. We have a lot  
12 of caution when we interpret these.

13 There are methods that can handle it, but  
14 these are very difficult to define a priori absent  
15 any data. So I think it is worthwhile, if you're  
16 thinking about subgroups, is there is a big  
17 distinction between those in what we can handle.

18 Then there's now an issue of how do we apply  
19 this? And this is after a trial is complete. When  
20 do we do subgroup analyses? If the trial is  
21 successful, how we apply subgroup analyses is we  
22 look for consistency in findings. We're also

1 looking for differential effects. And I think  
2 that's something that we can think about here.

3 If there's a failed trial, sometimes people  
4 want to look at a subgroup analysis to look at that  
5 to rescue a trial. This is something that I think,  
6 as an agency, we view as hypothesis-generating that  
7 requires replication -- maybe not so relevant here.

8 But one thing we always need to consider  
9 when we're doing a subgroup is the problem of a  
10 chance finding. The chance finding can be either  
11 in a case of a false positive result; it can also  
12 be a false negative. And I think that's important  
13 here.

14 If we don't prespecify looking at a specific  
15 subgroup, we always have this chance of  
16 multiplicity creeping in. So we have to be  
17 concerned about that. And that's when we have to  
18 think about if we're going to interpret the  
19 findings. How much strength do we want to place on  
20 that if there is no multiplicity adjustment?

21 So that's where it gets into this subjective  
22 world where you have to look at the clinical

1       implications and plausibility of the subgroup  
2       finding, as well as you have to think about the  
3       strength of the finding. If it's really obvious,  
4       it's extreme, then I think you can maybe be  
5       reasonably assured. And I think, in the past, the  
6       agency has done that.

7               The last point I want to raise is we're now  
8       looking at a safety trial where the objective was  
9       to show non-excessive risk or noninferiority. And  
10      this is a little bit different than from a trial  
11      designed to show improvement in risk. What you see  
12      here is something around 1 is a very good thing.  
13      If we see a null finding, that's good. It met its  
14      objective.

15             So any time we're going to go to a subgroup  
16      analysis, you're going to see a point estimate  
17      that's going to jump below 1, and you're going to  
18      see one that jumps above 1. It's something you're  
19      going to see.

20             So I don't think we can put a whole lot of  
21      emphasis on the point estimate. I think you should  
22      be cautious with this. And also, in slides that

1       have been presented, there hasn't been a  
2       multiplicity adjustment. So it's just a nominal  
3       95 percent confidence interval. So we need to be a  
4       little bit cautious with some of that.

5               So those are just a couple points I wanted  
6       to raise on subgroup.

7               DR. BURMAN: Those are very good. Thank  
8       you.

9               Yes? Hold on. Yes?

10              DR. TEMPLE: I just wanted to add, this is  
11       not just --

12              DR. BURMAN: Dr. Temple. Yes?

13              DR. TEMPLE: This isn't just FDA thinking.  
14       At least 15 years ago, others have published the  
15       idea of what's a valid subgroup, that is, a  
16       baseline characteristic, and what's not a credible  
17       subgroup. This is in the literature from  
18       experienced trialists.

19              I just want to make one other observation.  
20       Even though we don't depend on them or rely on  
21       them, you will not see a published or labeled  
22       result of a large outcome trial that doesn't show

1 forest plots. Well, forest plots are all subgroup  
2 analyses. They're all based on baseline  
3 characteristics. We would never throw one in with  
4 an after-the-fact characteristic.

5 So you look at those things. But as Mat  
6 said, you don't rely on them because there's  
7 tremendous multiplicity and it's impossible to sort  
8 out.

9 So we look at those things, but you don't  
10 make decisions based on them, with very, very rare  
11 exceptions.

12 DR. BURMAN: Thank you. One clarification  
13 point. Dr. Konstam?

14 DR. KONSTAM: Well, this is usually helpful.  
15 But I for one would love your comments specifically  
16 on this subgroup. So let's nail it down. So we're  
17 dealing with a pre-randomization difference in  
18 baseline use of statin. I believe that this is a  
19 prespecified subgroup in the DCRI analysis. Okay?

20 We're dealing with safety, where the bar is  
21 lower than with efficacy, generally. We're dealing  
22 with an admittedly huge amount of multiplicity but

1 a very low p-value, at least .003, for the  
2 treatment by subgroup interaction with a  
3 qualitative interaction -- that is, one group has a  
4 ratio of less than 1, one group with a hazard ratio  
5 of more than 2.

6 Maybe there's a signal in another drug of  
7 this class. Maybe there isn't. So that's what  
8 we're dealing with. Okay. Take it away. What  
9 should you do with that finding?

10 DR. SOUKUP: I won't go into detail because  
11 I think DCRI is going to present some of the forest  
12 plots, and what you're looking at is probably the  
13 most extreme case. You can look at all-cause  
14 mortality, cardiovascular unknown death, and you  
15 can also look at MACE. And the one is the most  
16 extreme; I can't recall off the top of my head.

17 In terms of prespecification, in honesty, we  
18 saw results from this trial previously. So I think  
19 it's hard to really say it's truly prespecified.  
20 To me, prespecification occurs prior to trial  
21 initiation. And again, there's also not a  
22 multiplicity adjustment, working back from the

1 initial primary objective.

2 So a 95 percent confidence interval, I don't  
3 think, is probably appropriate here. But again,  
4 it's just you're looking at consistency of  
5 findings. So I think you add all that in. You  
6 also see there's not just the baseline medication  
7 use. You can also look at age, gender, these  
8 types. These are other subgroups that were looked  
9 at.

10 So if you look at a whole, you might see one  
11 that is going to be extreme, and that's where it  
12 is. It's difficult to say if it's real or not.  
13 That's where these are really challenging, and  
14 that's where maybe it gets into the clinical  
15 plausibility because it seemed like that's  
16 something real. And we do struggle with it.

17 DR. BURMAN: So do we. Thank you.

18 Let's move now to the GSK/DCRI updates.

19 Thank you. Please introduce yourself.

20 DR. STEWART: We can show this slide. Yes.  
21 It's Dr. Stewart here from GSK. So clearly, the  
22 committee had a lot of questions, and I'll go



1 through these briefly.

2 So we've touched on the statins, and I'll  
3 leave DCRI to go through that. I'll go through the  
4 prespecified sub-analysis in the original and the  
5 one that did change. There were some questions  
6 about event rates across the countries in Europe,  
7 the enrollment by site. There was a question  
8 regarding event rate prior to rescue, and there did  
9 seem to be some confusion. I'll try and clarify  
10 that. And then clearly there were some questions  
11 on the REMS.

12 This is the primary endpoint from the  
13 original RECORD, CV death and CV hospitalization  
14 by prespecified, prior to starting the protocol,  
15 analysis. And the only one that had a p-value of  
16 0.05 was prior IHD. As I said before, there was  
17 nothing on statin.

18 I'm aware the committee have asked about,  
19 well, is it a problem with age? When we looked at  
20 RECORD by those above and below 60, there was no  
21 difference. But given this interaction p-value, we  
22 did originally go and look and say, well, and it's

1     pertinent to the debate -- if you're on statins,  
2     have you had prior IHD? Is there a different  
3     risk/benefit in people who had prior IHD? So we  
4     did look at that population.

5             So this is prior ischemic heart disease  
6     subgroup. And the first thing to note is,  
7     obviously, the people with prior IHD, 30137 and  
8     90138 (indiscernible) represents about 17 percent.  
9     You might say, how did you define prior IHD? This  
10    was based on a tick box in the form, have you had  
11    ischemic heart disease, rather than anything more  
12    definitive. RECORD, in comparison to PROactive,  
13    took a broad population with type 2 diabetes, and  
14    therefore they didn't all have high-risk or high  
15    evidence of previous MIs or heart disease.

16            Then we looked to see whether, given the  
17    slight increase in events of CV death and  
18    hospitalization, 105 versus 88 in prior IHD versus  
19    216 and 235, no prior IHD, whether there was any  
20    imbalance that was leading to that.

21            If you look at deaths, no difference in  
22    all-cause death. Cardiovascular death's the same

1       between rosi and comparator in prior IHD. We  
2       wondered whether there would be more MIs driving  
3       the prior IHD. It was 20 to 19. As has been  
4       consistently shown, there was more heart failure,  
5       17 versus 8.

6               So I thought that would be useful to the  
7       committee. Just to look at the only prespecified  
8       analysis in the original study that had a p-value  
9       of 0.05, we looked at the subgroups.

10              I then want to go into the question about  
11      rate of events by country. There is a long list of  
12      European countries on the bottom there, starting on  
13      your side on the left with Russia, all the way  
14      through to Croatia.

15              The event rate per hundred patient years for  
16      the primary endpoint for rosiglitazone is in  
17      yellow, and the comparator, met/SU, is in blue.  
18      And what you can see is in some countries, there  
19      were higher event rates, as in Russia with the  
20      rosi. And then you look at Ukraine, it was higher  
21      for met/SU.

22              Then someone wanted to know what happened in

1 the U.K. If you look at the U.K. in the middle,  
2 the event rate per hundred patient-years was the  
3 same for rosi and metformin. This just gives you  
4 an idea of the variability.

5 Another question was related to subject  
6 enrollment per site. So were the sites just lots  
7 of sites with one patient? No. When we look at  
8 subjects who enrolled less than two, that was  
9 20 percent. And therefore, you've got 80 percent  
10 of sites who had greater than three subjects, and  
11 more than 60 percent of sites who had more than  
12 five subjects. And I think we know the impact.  
13 More subjects per site tends to give a bit more  
14 reliability than having one or two persons in lots  
15 of sites.

16 Then this is the graph for the primary  
17 endpoint CV death or hospitalization for those  
18 subjects who were on randomized dual therapy prior  
19 to any rescue therapy.

20 So they came in and they were on the four  
21 groups. They were on rosi and metformin, or rosi  
22 and sulfonylurea, or metformin and sulfonylurea, or

1       sulfonylurea and met. And they stayed just on that  
2       dual therapy.

3               So the first thing you see, if you look at  
4       one and two years, the majority of patients stayed  
5       on dual therapy. It was only when you start going  
6       into years 3 and 4 where people were rescued. This  
7       is the data looking at randomization for dual  
8       therapy prior to any initiation. And you can see  
9       the hazard ratio is 1.03.

10              Then there were questions on the REMS about  
11       participation in the survey, comparison of survey  
12       respondents versus REMS enrollees. What were the  
13       examples? Some of the questions. And we're going  
14       to ask Dr. Annette Stemhagen from UBC to take us  
15       through some of the REMS information.

16              DR. STEMHAGEN: Thank you. I'm Annette  
17       Stemhagen. I'm senior vice president of  
18       epidemiology and risk management at United  
19       Biosource Corporation.

20              UBC has been working in the area of  
21       pharmaceutical risk management really since 1999,  
22       and we've been involved in just about half of the

1       REMS with Elements to Assure Safe Use that are in  
2       the marketplace.

3               We are retained by GSK to help design and to  
4       run the rosiglitazone REMS, and I'm going to  
5       provide some data here from the surveys that we do  
6       as part of the assessment for the effectiveness of  
7       the REMS. If I could have the first slide.

8               One question yesterday was just how many  
9       people were surveyed and what do the statistics  
10      look like. So this is the prescriber survey.  
11      There are two time points. We've done the survey  
12      twice.

13              I should say first that the protocol and the  
14      survey are required to be submitted to FDA at least  
15      90 days before they are fielded. So all of that is  
16      specified. There is a full protocol, and the  
17      sample size is determined.

18              In this case, the sample size for physicians  
19      is 150. And we issued invitations, actually, to  
20      all of the prescribers who were enrolled in the  
21      REMS, so there was not a sample selected. Then  
22      those who agreed to participate are shown in the

1     number of respondents screened, and then there's a  
2     very minimal eligibility criteria based on, one,  
3     providing consent; two, that the respondent does  
4     not work for either the sponsor, UBC, or FDA.

5             Then in wave 2, there's also a requirement  
6     that you haven't taken the first survey. You're  
7     only supposed to take it once. And also, there's a  
8     little change in the eligibility that was made  
9     between waves 1 and 2 because there were a large  
10    number of physicians who are enrolled in the REMS  
11    but do not prescribe rosiglitazone or they haven't  
12    yet prescribed rosiglitazone. So the eligibility  
13    criteria of having at least written one  
14    prescription was added, which is why there's a  
15    somewhat larger dropoff for eligibility in wave 2.

16            So the number who completed the survey was  
17    155, and 120 in the second survey. And it's done  
18    both by internet or phone, although -- and I'm  
19    sorry, I think these numbers are reversed -- the  
20    primary mechanism for prescribers is for the  
21    internet.

22            If I could have the next slide, we have a

1 similar slide that shows patients. And here the  
2 eligibility criteria are you do have to be age 18  
3 or over, and we do accept both patients and  
4 caregivers. And then the other eligibility  
5 criteria are the same. Here the sample size was  
6 set at 300, and there are 300 and 305.

7 I should make one comment about the  
8 participation rate because it's not exactly what we  
9 might think of as a participation rate. There's a  
10 very short time window in which the survey is  
11 actually fielded because it has to be analyzed and  
12 delivered to FDA in very specified time frames  
13 based on the REMS.

14 So once the sample size goal is met, the  
15 survey is closed. Anybody who comes in after that  
16 is thanked for their interest and told that we may  
17 contact them again. So the participation rate  
18 certainly could be much higher than that; it's just  
19 once we reach that goal, it's closed.

20 If I could have the next slide. One of the  
21 other things that was asked was about the  
22 questions. And these are the types of questions.



1       There are both true and false, yes and no, some  
2       multiple choice, and there's one open-ended  
3       question that FDA likes at the end in terms of, "Do  
4       you have any questions about the materials?"

5               The survey is constructed so it started with  
6       the screening. Then it looks at key risk messages,  
7       and there might be 15 to 20 questions on key risk  
8       messages. They're set up in terms of various kinds  
9       of messages.

10              There are a number of questions that are  
11       focused on the same key risk message so that you  
12       have more than one that's going to look at your  
13       knowledge of heart attack or heart failure, and so  
14       on. This is just a sample.

15              One of the reasons we do the dichotomous for  
16       many things is because the patients have a much  
17       larger percent of telephone interviews, and it's a  
18       lot harder in a phone interview to have a multiple  
19       choice where you're reading a lot of options to a  
20       patient as opposed to going each option, yes or no.  
21       So that's not necessarily always desirable, but it  
22       makes it logistically more feasible for the phone

1 interviews.

2           These are some of the data in terms of the  
3 prescriber that were referred to in the briefing  
4 book, with the range of understanding rates being  
5 from 99 for some, and then the one that we  
6 mentioned yesterday about the understanding about  
7 patients with New York Heart Association  
8 classification being lower, and also co-  
9 administration with insulin.

10           As GSK mentioned yesterday, there is some  
11 work ongoing with qualitative research with  
12 prescribers to understand what the barriers to  
13 understand for those elements are and why they are  
14 scoring as low as they do.

15           I should say that UBC has conducted more  
16 than 70 of these types of surveys for about 45  
17 different products across a number of different  
18 therapeutic areas, over 11,000 surveys. And we do  
19 find that the key risk message knowledge can range  
20 from 15 percent to 100 percent.

21           The messages are based on whatever the  
22 educational materials that are provided, whether

1       that is the medication guide for patients and the  
2       enrollment form, in this case, the enrollment form  
3       and prescriber overview, and the label for  
4       prescribers. If we could just have the next slide  
5       for one minute.

6               These are similar kinds of things for  
7       patients, looking at some of the questions. And  
8       you'll see again the question about taking with  
9       insulin did also for patients have low scores. And  
10      it was changed between waves 1 and 2. There was  
11      some review and some comments with FDA, actually,  
12      and the wording was changed.

13             It does look like it has improved the level  
14      of understanding of that question. There is still  
15      again low understanding with heart failure, and  
16      similar kinds of research is going on to try to  
17      determine what the reason for that low rate is.

18             I think I had one other slide, if I could,  
19      about the representativeness of the patients. We  
20      did look at the demographic characteristics of the  
21      entire REMS enrolled population, which would be  
22      everybody who was eligible, and then those that

1 completed the survey.

2 I'm not sure if we have the slide at hand,  
3 but in terms of the age distribution, it's very  
4 comparable. In terms of, for prescribers, the  
5 medical specialty of the prescribers, it's  
6 comparable, as you might expect.

7 I believe that answers the questions.

8 DR. BURMAN: Thank you very much to both of  
9 you. Those are very helpful.

10 I believe that brings GSK up to date on the  
11 questions that were remaining. Does DCRI have some  
12 updates as well? Thank you. Please state your  
13 name, of course.

14 DR. MAHAFFEY: Ken Mahaffey from DCRI.  
15 Thank you, Mr. Chairman. There were a few  
16 questions that were asked of us yesterday. I'm  
17 going to answer two or three of them, and then my  
18 colleague, Dr. Bigelow, will take on some of the  
19 statistical ones.

20 Could I please have backup slide number 214?  
21 I believe it was Dr. Suarez, but others as well,  
22 who had questions about the response to the queries

1 by randomized treatment assignment. As you can see  
2 here, remember for death we issued 127 queries.

3 As you would think, there were a few more  
4 queries issued for the rosiglitazone group than the  
5 metformin comparator group because there were more  
6 suspected events in that arm, if you remember the  
7 bar graphs that I showed you yesterday.

8 If you'll also remember, there were  
9 34 percent of the 127 queries for death we did not  
10 get a response for, the "No response" line, and you  
11 can see here that there was similar "No response"  
12 proportions across the two treatment groups.

13 For stroke and MI, you'll remember there  
14 were 70 queries issued; 44 percent of those queries  
15 did not have any response, and you'll see here a  
16 similar response rate by the randomized treatment  
17 assignment. So although a relatively small number  
18 of patients, I think this shows that there was a  
19 response to the queries that was independent of the  
20 randomized treatment assignment.

21 Could I please core slide number 40?

22 Dr. Kaul, you asked us specifically to look

1 at the individual components of the patients that  
2 composed the primary composite endpoint. This was  
3 the core presentation, so these are the data that  
4 you saw yesterday, just to refresh your memory of  
5 the number of cardiovascular deaths, 88 versus 96,  
6 and the MIs, which I think you were particularly  
7 interested in, 68 versus 60.

8 Now may I please have backup slide  
9 number 202, which will show you the first event  
10 that contributed to this primary composite? So you  
11 can see here there were 64 deaths that contributed  
12 to the primary composite in the rosiglitazone arm  
13 and 56 myocardial infarctions that contributed in  
14 the comparator arm.

15 Finally, for the last question that I have,  
16 may I please have backup slide number 213? Several  
17 people were having discussions about the ischemic  
18 heart disease group. Dr. Stewart has already shown  
19 you some of these data.

20 But this is a further breakdown that was not  
21 on his slide of the cause of death by subgroups of  
22 prior ischemic heart disease or not, and then by

1 randomized treatment assignment. And you can see  
2 here specifically, looking at the acute myocardial  
3 infarction events contributing to death, there were  
4 6 versus 6 in the patients with prior ischemic  
5 heart disease, 3 versus 6 in the patients without  
6 prior ischemic heart disease.

7 Relatively small numbers, but a suggestion  
8 that even those patients with the highest risk,  
9 i.e. those with prior ischemic heart disease, there  
10 was not an excess of mortality due to myocardial  
11 infarction with rosiglitazone.

12 Then finally, at the bottom of the slide,  
13 I've added in simply nonfatal myocardial  
14 infarction, looking at the data from our  
15 reanalyses, reevaluation effort, which were very  
16 similar to what Dr. Stewart has shown you already.

17 There was also discussion, finally, about  
18 interaction terms for the relationship between  
19 patients with ischemic heart disease or not, and  
20 various outcomes.

21 When I've looked back through our clinical  
22 study report -- and I apologize, I don't have

1 slides for this -- but both for the primary  
2 composite endpoint, for the endpoint of  
3 cardiovascular mortality, and for mortality alone,  
4 all of the interaction terms for ischemic heart  
5 disease, yes or no, and randomized treatment  
6 assignment were all statistically nonsignificant.

7 I'll ask Dr. Bigelow, then, to come up and  
8 address a couple more of the issues. Thank you.

9 DR. BURMAN: Thank you.

10 DR. BIGELOW: Thank you. Bob Bigelow, DCRI.  
11 I have four issues that I think were left yesterday  
12 that we needed to discuss. The first one was the  
13 definition of the last date of randomized  
14 treatment.

15 The last date of randomized treatment was  
16 when rosiglitazone was stopped in the rosiglitazone  
17 arm, or a sulfonylurea, if it was an add-on, or  
18 metformin, if it was an add-on. The last date of  
19 randomized treatment plus 30 and plus 60 days were  
20 predefined in our SAPs, and this data was  
21 transferred to us from GSK at the time of the  
22 database lock for the mortality report, and it was



1       used to produce those analyses.

2               The second issue that I had on my last was  
3       the discussion of the landmark analyses that came  
4       up during Dr. Mahaffey's presentation. If it was  
5       possible to see one of those slides, it would be  
6       good; otherwise, I can just describe what the  
7       landmark analysis is.

8               DR. BURMAN: Excuse me. Can we get one of  
9       the slides? Do you know which slide?

10              DR. BIGELOW: It was actually one of the  
11       ones from Dr. Bigelow's presentation.

12              DR. MAHONEY: If you'll just pull my  
13       presentation up, I can find the slide number for  
14       you or you can just start scrolling through.

15              DR. SPRUILL: It's slide 43, is the first of  
16       those.

17              DR. BIGELOW: In the landmark analyses, the  
18       analysis is designed to determine if a particular  
19       event in calendar time changes the risk of the  
20       event that's being analyzed in the time to event  
21       analysis.

22              In this particular slide 43, the time to

1 event is for cardiovascular plus unknown cause  
2 mortality, and we're looking at the landmark of  
3 June 5th. So the denominator prior to June 5th  
4 should be everybody who's enrolled in the trial  
5 because their times goes from the date of  
6 randomization up until the landmark.

7 The denominator after June 5th should be  
8 everybody who was still -- on June 5th has not had  
9 an event yet and who was actively being observed  
10 for the event. And so that's how those  
11 denominators are calculated.

12 Are there questions about these particular  
13 denominators or why they are there? They are not  
14 related to treatment; they're simply related to  
15 whether or not a patient is being followed as of  
16 the calendar date shown there.

17 DR. BURMAN: Thank you very much to GSK and  
18 DCRI. Very, very helpful. And we have 20 minutes  
19 before lunch. Maybe we should open the questions  
20 up for any of the issues that were brought up this  
21 afternoon or this morning or yesterday.

22 DR. BIGELOW: I have another issue.

1       Yesterday we also discussed the possibility of  
2       doing missing data simulations for the components  
3       MI and cardiovascular death. We are in progress  
4       doing that. Our normal process is to write up  
5       specifications and then have the specifications  
6       programmed. This involves creating a data set,  
7       and then running the program on the data, and then  
8       QC'ing the results.

9               At this time we do not have results. It is  
10       unlikely that we will have QC'd, ready-to-present  
11       results to show today. I think it would be  
12       counterproductive for us to show things that we  
13       thought were possibly not correct.

14              We would accept a commitment to do these and  
15       submit them to the agency after this meeting, after  
16       we've completed our QC, if the panel so desired.

17              DR. BURMAN: Is the sense of the panel that  
18       that information, even though it would be after the  
19       vote, would be useful? We'll discuss that further.

20              Thank you very much. Very helpful. Is your  
21       presentation done?

22              DR. BIGELOW: I do have one final point.

1 DR. BURMAN: Sure.

2 DR. BIGELOW: It also was discussed  
3 yesterday that we should consider doing time-  
4 dependent covariate analyses based on the reason  
5 for discontinuation of treatment. But we have not  
6 started that effort yet. We would consider such an  
7 analysis to be exploratory since it would be  
8 basically based on an improper subgroup, and so we  
9 have not really initiated that analysis yet.

10 DR. BURMAN: Thank you.

11 Let me open the floor for questions for any  
12 of the FDA, GSK, or DCRI. Dr. Hiatt?

13 DR. HIATT: And the only other residual from  
14 yesterday --

15 DR. BURMAN: Please give your name.

16 DR. HIATT: William Hiatt -- was the true  
17 on-treatment exposure to rosiglitazone, given the  
18 design and some of the informative censoring. And  
19 I realize you probably can't do that, but to take  
20 that back to look at these events and see if that  
21 changed things very much.

22 So just the on-treatment plus 30 or 60, I

1 think, could be on multiple treatments based on the  
2 design of the study.

3 DR. BURMAN: Thank you. I don't think that  
4 requires any -- you don't want any further comment  
5 from the company?

6 DR. HIATT: I just think we're missing an  
7 opportunity that wasn't presented in any of the  
8 material that when you look at drug safety, when  
9 you're actually taking the drug is when you have  
10 the most risk. And the risk is of rosiglitazone,  
11 not of the other add-on therapies that occurred  
12 after that, necessarily.

13 DR. BURMAN: Agreed. Thank you.

14 Dr. Geller?

15 DR. GELLER: I'll try one more time. If I  
16 look at slide 43, I see the number of events before  
17 June 5th, and I see the sample size. And I would  
18 think the denominator after June 5th should be the  
19 original sample size minus the number of people who  
20 had the event, and that's not what it is.

21 DR. BIGELOW: It would also subtract out the  
22 people who were described prior to June 5th. So if

1       you began it the date of randomization and you were  
2       censored without event prior to June 5th, then you  
3       would be subtracted from the denominator for the  
4       June 5th analysis.

5               DR. GELLER: I see. Thank you.

6               DR. BURMAN: Thank you. Dr. Geller, any  
7       other questions in general or for the presenters  
8       this morning?

9               DR. GELLER: (Shakes head negatively.)

10              DR. BURMAN: Dr. Day?

11              DR. DAY: I'd like to thank Annette  
12       Stemhagen for her overview of the methods and  
13       results, things that we've been wondering about.  
14       And that information is entirely appropriate and,  
15       as a matter of fact, necessary for the briefing  
16       document.

17              So in the future, I think that when there  
18       is a REMS and it's relevant to the questions for a  
19       committee, that this type of information be  
20       included. And there were quite a few omissions,  
21       errors, or ambiguities in the briefing document.

22              We still don't know some things. I'm still

1 not clear on how many questions there really were.  
2 In the background material, there was something  
3 about five, and then today there was 15 to 20, and  
4 so on. And we couldn't actually -- oh, and another  
5 discrepancy was we were told yesterday that all the  
6 questions were yes/no/maybe, and Annette clearly  
7 indicated that was a variety of different question  
8 types.

9 So I think just specifying all of that will  
10 enable the committee to understand better what has  
11 been done and what has been found, and we won't  
12 need to spend all the time asking. It's still  
13 difficult, without seeing the questions, to have a  
14 full everyone, but we're in a much better state  
15 now. So thank you for your comments.

16 DR. BURMAN: Thank you.

17 Dr. Proschan?

18 DR. PROSCHAN: So regarding those three  
19 components of the REMS, and as Dr. Kaul pointed  
20 out, it seemed like the dropoff in prescriptions  
21 was precipitous before getting to the REMS phase.

22 But I'm just wondering if any of those three

1 things -- is there one that's much more limiting  
2 than the other? Is there one of those that would  
3 really cause a big dropoff and the other two  
4 wouldn't? Or some idea of that, those  
5 restrictions.

6 DR. BURMAN: Does the FDA want to respond?

7 DR. WEAVER: This is Joyce Weaver. I don't  
8 think that we know that. It's possible that it's  
9 the discussion with the patient. We don't know  
10 really how many times that discussion with the  
11 patient happened, and then they didn't go on to  
12 prescribe the drug, or perhaps the prescriber  
13 preempted that discussion.

14 So those are things also that may have led  
15 to that dropoff besides the actual logistics of  
16 managing the REMS.

17 DR. BURMAN: Thank you.

18 Dr. Kaul?

19 DR. KAUL: Slide 202, backup slide 202. I  
20 just want to make sure if I did the math correctly.  
21 They still don't add up, the individual components,  
22 although I appreciate their updating the data set.



1 DR. BURMAN: This is slide 202 in --

2 DR. KAUL: The DCRI backup. Oh, so  
3 cardiovascular death changed? Okay. That explains  
4 it. Thank you.

5 DR. BURMAN: Dr. Kaul, I'm sorry. Would you  
6 just give what you were thinking?

7 DR. KAUL: I overlooked that the  
8 cardiovascular death had changed from 88 in 96 to  
9 67 and some 60-odd numbers. So that adds up.  
10 Thank you.

11 DR. BURMAN: Thank you.

12 Dr. Suarez-Almazor?

13 DR. SUAREZ-ALMAZOR: Yes. Thank you. I  
14 have a comment and a question. My comment relates  
15 to the trial, and I'd like to commend DCRI for the  
16 adjudication process, which I think was done in a  
17 very robust and thoughtful way; and also, the  
18 analyses that were done by both the sponsors and  
19 the FDA as far as the splicing and subgroup  
20 analyses and looking at the data from every single  
21 perspective.

22 But I think that, unfortunately, that

1 doesn't fix the major flaws that the trial has,  
2 which I think are primarily three. One is the fact  
3 that the trial was not blinded, and that's really a  
4 very important drawback; the other one, that  
5 there's a large number of missing data, even after  
6 trying to contact the different centers. And that  
7 unfortunately has not been solved.

8           Then finally, I think that, again, the main  
9 analysis looked at the same follow-up in person-  
10 years for the two groups when indeed the exposure  
11 to rosi had been shorter because patients had  
12 dropped before, given that they were given insulin  
13 or other reasons for discontinuation that we don't  
14 know.

15           But there was about a 10 percent  
16 differential in discontinuation rates early on. So  
17 although the follow-up was the same for the main  
18 analysis, I know there was a 90-day analysis and so  
19 forth that didn't show any differences. But I  
20 think those are major flaws that cannot be solved  
21 with a readjudication or some of the other analyses  
22 that were done. So that's my comment.

1           My question is in general for the sponsors,  
2           the FDA, and any members in the panel who are  
3           endocrinologists. I'm not an endocrinologist, but  
4           I still cannot see what niche rosi is filling here.

5           I'm not clear that's more beneficial with  
6           respect to glycemic control. I'm not sure there  
7           are differences in some of the potential signals  
8           that are certain, such as heart failure. And I  
9           don't know the data from Actos well enough to know  
10          if the bladder cancer signals are very strong, and  
11          what's the effect size on that, and whether we can  
12          be reassured that Avandia does not have any risk  
13          whatsoever on the development of bladder cancer.

14          So in order for me to understand what role  
15          this drug would play, I would like to get some  
16          answers from anyone who feels they can answer that  
17          question.

18          DR. BURMAN: I'd like to ask any of the  
19          endocrinologists on the panel if they'd like to  
20          respond to that. Is that Dr. Smith coming forward?

21          DR. SMITH: I'll take a crack at it. Robert  
22          Smith. I can absolutely not provide any numbers.

1       So I can't even cite for you, from my memory, the  
2       data regarding bladder cancer in pioglitazone, for  
3       example.

4               But although the number of candidate  
5       patients is likely to be quite small, as a  
6       practicing endocrinologist I could envision  
7       patients who might indeed have a history or a  
8       family history of bladder cancer, or have had a  
9       reaction, an idiosyncratic, perhaps, reaction to  
10      pioglitazone that would make that not appropriate.

11              I could also envision a small number of  
12      patients who might be unable, for various reasons,  
13      to tolerate other oral medications or unable to  
14      tolerate enough of them, since we often use oral  
15      medications in combination, to adequately control  
16      their blood glucose levels.

17              We always have insulin as a therapeutic that  
18      is available beyond oral agents, and that, for most  
19      patients, I would think, would be a potential  
20      option. But again, I could envision patients who  
21      would refuse, and I have patients who will refuse  
22      insulin, whether that's what I might consider to be

1 a good medical decision or not.

2 So having talked all through that, I think  
3 that from an endocrinologist's perspective, the  
4 number of patients who might qualify by all those  
5 criteria as someone who, with knowledge of the risk  
6 and with their own medical/clinical picture that  
7 might modify that risk -- such as whether or not  
8 they had congestive heart failure or a congestive  
9 heart failure history -- I could envision patients  
10 who in fact might make that informed choice, and  
11 their physicians might make that informed choice.

12 I think it would be a small number of  
13 patients. But I wouldn't feel that I could take  
14 the alternative position that there are no patients  
15 who would meet those criteria. And I've provided  
16 you with no numbers; I realize that.

17 DR. SUAREZ-ALMAZOR: Can I ask you, and  
18 maybe some of the other endocrinologists here, how  
19 many patients you have on Avandia right now?

20 DR. SMITH: I have a very small practice at  
21 this point, and I'm not a good person, perhaps, to  
22 really answer thought. I really have no patients

1 on Avandia at this point in my practice.

2 DR. BURMAN: As an endocrinologist, I agree  
3 with your cogent comments. And of course, PPAR  
4 gammas are second-line therapy at best; they're not  
5 first-line therapy for most type 2 diabetics. But  
6 there does seem to be a role for selected patients  
7 of using rosiglitazone versus pioglitazone for the  
8 reasons that you mentioned.

9 Anybody -- yes?

10 DR. SEELY: The other comment I would make  
11 is that when we're treating diabetes, we really do  
12 need drugs that lower blood sugar without causing  
13 hypoglycemia. And there is not a lot that's  
14 available that's actually effective at lowering  
15 blood sugar without causing hyperglycemia.

16 So I agree with Dr. Smith's comments that it  
17 may not be a large group, but when you're dealing  
18 with individual patients, you come up often against  
19 dead ends of what you can do. And it's important  
20 to have options.

21 Patients are very sensitized to the  
22 publicity about pioglitazone and bladder cancer.

1       So they may have had a great-great-grandfather with  
2       bladder cancer, and they may be very adamant that  
3       they won't go on pioglitazone. And the number of  
4       patients who refuse insulin, who will refuse in the  
5       office, is high, and then the number that agree to  
6       take it who actually don't end up taking it is very  
7       high. We really need oral agents for that  
8       population.

9               DR. SUAREZ-ALMAZOR: Is there data, though,  
10       on the bladder cancer with Avandia? I was looking  
11       in PubMed a little bit to see if I could find it,  
12       and I think there is some data also that rosi may  
13       increase bladder cancer. So I don't know if anyone  
14       can answer that. Because if that's the only  
15       difference between the two drugs, and rosi  
16       apparently increases also the risk.

17              DR. BURMAN: Does anyone on the panel want  
18       to comment on that, or the FDA?

19              DR. SUAREZ-ALMAZOR: Maybe the FDA knows?

20              DR. BURMAN: Dr. Hammerschmidt, you had a  
21       comment?

22              DR. HAMMERSCHMIDT: Yes. As a matter of

1 convenience, for perspective, I was operated for  
2 recurrent bladder cancer on the 15th of last month,  
3 so I've been watching this literature with a  
4 certain amount of interest.

5 Kaiser Permanente is doing a long-term  
6 follow-up, comparing people who've been on Avandia,  
7 until they had it stopped recently, and  
8 pioglitazone to try and get a better answer on  
9 this.

10 The meta-analyses have shown that the  
11 incidence of bladder cancer is about twice as high  
12 in people getting pioglitazone, but that still  
13 doesn't add up to a very big number. And when  
14 you look at the specific data, the thing that's  
15 interesting is most of the excess is in people  
16 below 50, who are people who ordinarily are at very  
17 low risk for bladder cancer.

18 Three-quarters of the cancers have been  
19 superficial, either carcinoma in situ or a level 2  
20 or lower. So they're the sort that are usually  
21 cured by curettage.

22 But I think there aren't any data yet about



1       whether a prior history or a family history of  
2       bladder cancer is a problem. There aren't yet any  
3       data about whether these people do less well than  
4       people who have bladder cancer just out in the  
5       community.

6               So it looks as though it's probably a real  
7       signal, but we don't have it very well  
8       characterized yet.

9               DR. BURMAN: Thank you.

10              We only have a minute or two. We're going  
11      to take one last question from Dr. Brittain.

12              DR. BRITTAIN: Yes. My question is for  
13      Dr. Gerstein. Is he still here?

14              DR. BURMAN: Dr. Gerstein?

15              DR. BRITTAIN: Yes. I had hoped to ask this  
16      earlier, but we ran out of time.

17              You proposed or discussed the possibility of  
18      a 10,000-patient trial comparing rosi to placebo,  
19      and originally, the original trial had three arms.  
20      While I definitely agree that a placebo-controlled  
21      trial would be the cleanest way to assess safety,  
22      I'm wondering in practice, if you don't have the

1 three arms, what are you going to have at the end  
2 of the day? And on the other hand, does that just  
3 make it completely not doable?

4 DR. GERSTEIN: I was not proposing a trial  
5 design when I made that comment. I was simply  
6 creating a scenario for the people to respond to  
7 the scenario, which was simple. So if we were  
8 talking about a trial design, it would be a very  
9 different discussion.

10 As I said earlier on, if there was to be a  
11 trial design, I think it would be appropriate to  
12 test superiority and non a placebo for  
13 noninferiority. It really doesn't make that much  
14 sense.

15 DR. BURMAN: Thank you.

16 Maybe one last question. I'm sorry,  
17 Dr. Parks?

18 DR. PARKS: Thank you, Dr. Burman. I just  
19 wanted to revisit the issue of bladder cancer  
20 because you asked what we know between the two  
21 TZDs.

22 I think the difficulty here in being able to

1 dismiss the signal about a cancer in pioglitazone,  
2 as Dr. Hammerschmidt has already talked about, is  
3 about the epi study. But the signal is also  
4 consistently seen across three different databases.

5 So there is a pre-clinical signal, which was  
6 put into the label very early on. I don't know if  
7 it was at the time of approval, but certainly  
8 shortly thereafter.

9 There have been two large clinical trials,  
10 controlled clinical trials, of pioglitazone where  
11 there were numeric imbalances of bladder cancer not  
12 favoring pioglitazone. And they're small numbers.  
13 It's very hard to say conclusively.

14 Then now, also, with the epi study that's  
15 continuing out to at least, I believe, 10 years and  
16 the data I believe Dr. Hammerschmidt is referring  
17 to is at least a five-year analysis, so those  
18 signals haven't gone away.

19 Now, having seen that, we were very  
20 concerned, and we looked at the rosi database as  
21 well, and we're not seeing that same kind of  
22 consistent finding. In fact, what's interesting is

1       that even looking in RECORD, you see that the  
2       bladder cancer signal is not there. There were  
3       6 in rosi versus 5 in comparator.

4               I say this for Dr. Temple. It's something  
5       that Dr. Temple always raises when you look at  
6       RECORD, is that there doesn't seem to be any  
7       acknowledgment that in this controlled trial that  
8       the pancreatic cancer finding was very much leaning  
9       in the other direction, with 2 of rosiglitazone and  
10      13 in that of active control.

11              So going to the bladder cancer signal, we  
12      don't see the same type of consistent finding of  
13      bladder cancer for rosiglitazone as we've seen in  
14      pioglitazone.

15              DR. SUAREZ-ALMAZOR: There's a 2012 study in  
16      the Journal of the National Cancer Institute that  
17      shows risk for both drugs. But I've just found it  
18      now, so I don't know how strong it is. But it's in  
19      thousands of people.

20              DR. BURMAN: Thank you.

21              Maybe for three to five minutes, Dr. van  
22      Belle, you had a question as well?

1 DR. VAN BELLE: I have a question and a  
2 comment. One of the things that I think why we're  
3 here is that we're dealing with a surrogate outcome  
4 as the primary objective of a clinical trial. And  
5 the question is, what is the correlation between  
6 the surrogate outcome, glucose control, and  
7 clinical outcomes? And we don't have the answer  
8 yet.

9 My question was actually going to for  
10 Dr. Gerstein, who lists a whole series of effects  
11 of glucose control or lack of control -- increased  
12 blindness, kidney failure, amputations, chronic  
13 pain, heart attacks, strokes, dementia, cirrhosis,  
14 cancer, falls, erectile dysfunction, frailty, and  
15 accelerated aging.

16 Which of those endpoints correlates best  
17 with a surrogate endpoint like glucose control? Do  
18 you have any idea?

19 DR. BURMAN: Dr. Gerstein?

20 DR. GERSTEIN: In fact, if you look at  
21 epidemiologic analyses, a large number of those  
22 endpoints correlate with the level of glycemia, as

1 measured at least in epidemiologic analyses.

2           So, for instance, cardiovascular disease is  
3 progressively related to higher levels of glucose  
4 levels, related to cardiovascular disease, as do  
5 cancers, in addition to even things that are more  
6 recently identified, such as cognitive decline; and  
7 certainly eye disease, kidney disease, nerve  
8 disease.

9           So really, whenever people look at the  
10 relationship between glucose and chronic  
11 consequences of diabetes, you almost always find  
12 some progressive relationship, with a different  
13 effect size depending on the outcome you're looking  
14 at.

15           DR. BURMAN: Thank you.

16           Before we break for lunch, I think our  
17 schedule will be, we'll come back at 1:00 and  
18 we'll reconvene in this room at 1:00. Take your  
19 belongings with you. Remember not to discuss  
20 issues of the meeting topic amongst yourselves.

21           But in addition, we're going to have  
22 questions and clarification for the committee from

1 1:00 to 1:30. And then we'll go into the four  
2 questions. That will hopefully give us enough time  
3 to discuss those in detail and still end up at a  
4 reasonable time. Thank you.

5 (Whereupon, at 12:03 p.m., a luncheon recess  
6 was taken.)  
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A F T E R N O O N   S E S S I O N

(12:58 p.m.)

DR. BURMAN: Good afternoon. Let's call this meeting to order. Thank you.

This afternoon, of course, is the most important part of the committee meeting, when we discuss the questions and vote on them. And I'd like a sense of the panel, an informal sense, how you'd like to proceed.

So we have four questions that we want to discuss, and want to encourage every member, nonvoting and voting, on the panel to discuss these issues, and then we have a voting question at the end.

There are still some people who did not have their questions or comments addressed from earlier sessions, partly because of time. But it's entirely possible those answers or comments will be taken into account with the discussion that we're going to have on the questions.

So my specific question to the panel is, what is your sense? Would you rather that we spend



1       15 or 20 minutes addressing previous questions, or  
2       potential questions, from the panel, or to go right  
3       into the discussion of the questions themselves, of  
4       which there are four, that we will spend  
5       considerable time on? What are people's views?

6             DR. SEELY: I vote discussion.

7             DR. BURMAN: When you say discussion, do you  
8       mean with --

9             DR. SEELY: Discussion of the questions and  
10       then elaboration of some of the answers during  
11       that.

12            DR. BURMAN: Sure. Does anybody object to  
13       that, or are there any burning questions that you  
14       think might not be answered during the discussion  
15       of the four questions?

16            DR. GELLER: I wonder if we could recommend  
17       suspension of the REMS on condition of undertaking  
18       another clinical trial.

19            DR. BURMAN: That's part of the question, so  
20       I think we'll get to that.

21            DR. GELLER: Well, it's questions 3 and 4,  
22       basically, together.

1 DR. BURMAN: Right. And we'll get there in  
2 a minute, if that's all right.

3 DR. GELLER: I guess my question for now is  
4 whether it was within the FDA's purview to do that  
5 because it's not a "modification" of the REMS, as  
6 was discussed earlier.

7 DR. BURMAN: I can't speak for the FDA, and  
8 maybe they would. But that will come up when we  
9 discuss these individual questions, and we can ask  
10 them that. Is that all right with the FDA?

11 DR. JENKINS: Yes. As I understand the  
12 question we're being asked, could the panel  
13 recommend suspending the REMS on the condition that  
14 the company do another trial. I think those are  
15 two separate actions, but they're clearly related.

16 As I said earlier, we have to conclude that  
17 the REMS is necessary for the safe and effective  
18 use, to ensure that the benefits outweigh the risk  
19 of the drug. So if we conclude, based on the  
20 panel's recommendation, that the REMS is not  
21 necessary, then you can't have a REMS if it doesn't  
22 meet the statutory standard. But we could still,

1 under our authority, require a new study.

2 So they're two separate actions, but clearly  
3 they're related. But it's not really, we'll  
4 suspend the REMS contingent upon the company  
5 agreeing to do another trial. They're independent  
6 actions that are related.

7 DR. GELLER: My concern was whether the  
8 company would be otherwise motivated to do a trial.

9 DR. JENKINS: Well, we have the authority to  
10 require a trial. So if you don't do a required  
11 trial, the companies are subject to monetary and  
12 civil penalties, and subject to having the drug  
13 declared misbranded and withdrawn from the market.

14 There obviously are considerations of  
15 whether the company would choose just to withdraw  
16 the application if they were required to do another  
17 trial. But that's speculation that I can't get  
18 into right now because I don't know what their  
19 response would be.

20 DR. BURMAN: Thank you.

21 Any other quick questions before we move to  
22 the official four questions? Please state your

1 name.

2 DR. WOODS: Mark Woods. Just a quick  
3 question for perhaps the sponsors or Dr. Gerstein.

4 I was looking at the E.U. investigations  
5 website and noticed that while TIDE was stopped in  
6 the U.S., Canada, and a lot of the world. It  
7 actually has continued to accumulate patients in  
8 certain countries. It looked like the Netherlands,  
9 Denmark, France, and Ireland.

10 Is that true, or is that just an error in  
11 the thing that I was looking at?

12 DR. GERSTEIN: No. There is no truth  
13 whatsoever to that. Within approximately 60 to  
14 90 days of being informed that the trial was  
15 suspended by Dr. Woodcock, every single patient in  
16 the world had been withdrawn in an orderly and  
17 careful fashion and had discussions with them. So  
18 maybe it's a different TIDE trial, but it's  
19 certainly not this one.

20 DR. BURMAN: Thank you. And since  
21 Dr. Gerstein is at the microphone, he's got to  
22 leave in a few minutes. Does anybody else have any

1 specific questions for him?

2 (No response.)

3 DR. BURMAN: No? Thank you, Dr. Gerstein.

4 Before we go to our official four questions,  
5 does anyone have any other points of clarification?

6 (No response.)

7 **Committee Discussion and Vote**

8 DR. BURMAN: All right. We will now proceed  
9 with the questions to the committee and panel  
10 discussion. I would like to remind public  
11 observers that while this meeting is open for  
12 public observation, public attendees may not  
13 participate except at the specific request of the  
14 panel.

15 I would like to solicit all possible  
16 comments and questions from all committee members,  
17 voting and nonvoting. If we look at these  
18 questions as an overview, there are four questions.  
19 We want full discussion on each of them.

20 The fourth one is the only voting question,  
21 and after the vote we will go around the table for  
22 each of the, I believe, 26 or 27 members who are

1       voting and ask their view on that. So that will  
2       take some time.

3               If I look at an overview of the agenda, we  
4       should spend 30 to 35 minutes on each of the  
5       discussion questions, and maybe 45 to 60 minutes on  
6       the voting question, if we start now. That seems  
7       like a reasonable plan. Does that meet with  
8       everyone's approval?

9               Here's the question, just to get everyone in  
10      the right frame of mind. I'll read quickly.

11              At the July 13-14, 2010 joint meeting of  
12      the Endocrinologic and Metabolic Drugs Advisory  
13      Committee and the Drug Safety and Risk Management  
14      Advisory Committee, questions were raised about the  
15      reliability and interpretability of the results  
16      from the Rosiglitazone Evaluated for Cardiovascular  
17      Outcomes and Regulation of Glycemia in Diabetes,  
18      the so-called RECORD trial.

19              As part of the regulatory actions taken by  
20      FDA in September 2010, CDER required  
21      GlaxoSmithKline to commission a readjudication of  
22      the RECORD trial to determine if the results could

1       be relied upon for the assessment of cardiovascular  
2       safety for rosiglitazone.

3               Based on the readjudication conducted by  
4       the Duke Clinical Research Institute and other  
5       presentations and discussions at this meeting,  
6       please discuss if the results of RECORD are  
7       reliable and interpretable.

8               In your discussion, please comment on  
9       questions related but not limited to: trial  
10      design; trial conduct; informative censoring; the  
11      conduct of the readjudication; and the reliability  
12      and interpretability of the various CV endpoints  
13      assessed, for example mortality, nonfatal  
14      myocardial infarction, and nonfatal stroke.

15              I think it would be fine for an individual  
16      to discuss several of those subcategories at the  
17      same time. I open the floor up for discussion. I  
18      believe the first is Dr. Heckbert.

19              DR. HECKBERT: Yes. Susan Heckbert. Thank  
20      you. I'll just indicate my thoughts on this  
21      discussion question. After the presentations we  
22      have heard, I don't have remaining concerns about

1 the conduct of the readjudication of the RECORD  
2 trial.

3 I conclude that the RECORD trial found  
4 noninferiority for the primary endpoint, but that  
5 the trial had many important limitations that have  
6 been discussed extensively, and they include  
7 its open label design; it's a relatively small size  
8 for a cardiovascular trial; the choice of a weak  
9 primary endpoint for a noninferiority study; the  
10 provision for investigator option in referring  
11 potential events for adjudication; and a fairly  
12 large amount of missing data for key outcomes.

13 So thus I conclude that the RECORD trial  
14 does not provide the randomized, double-blind,  
15 long-term clinical outcomes trial result that we  
16 would like to have. And so therefore, its results  
17 need to be considered together with the data from  
18 the meta-analysis of the short-term trials, the  
19 observational studies of rosi versus the non-TZD  
20 drugs, and the observational studies of rosi versus  
21 pio.

22 So I think we have to consider that body of



1 evidence together. I don't feel like we have the  
2 long-term outcome trial definitive answer that we  
3 would wish that we had.

4 DR. BURMAN: Thank you.

5 Dr. Brittain?

6 DR. BRITTAIN: I agree with what Dr.  
7 Heckbert said. Just in terms of the various  
8 outcomes, endpoints, I'm pretty comfortable with  
9 the all-cause mortality endpoint, certainly in  
10 terms of ascertainment of that, although there's  
11 still the potential that the lack of blind led to  
12 difference in patients management, so we can't  
13 untangle that aspect of it.

14 I think the MACE endpoint, there's more  
15 uncertainty with that, both because there's a lot  
16 of deaths that were not clearly determined to be  
17 cardiovascular or not. So there's that  
18 uncertainty. That was a lot more missing data, and  
19 because off the lack of blind, a lot more  
20 uncertainty about whether endpoints are being  
21 captured completely.

22 I did think, however -- and of course then

1       it also has the problem of the potential for  
2       patient -- differences in the management because of  
3       the lack of blind. I found the simulation somewhat  
4       helpful, that they did where they said if you had a  
5       hazard ratio of 1.5 for the person-years that were  
6       missing, then I think they came up with a hazard  
7       ratio of about 1 overall.

8               But again, that doesn't take care of all the  
9       problems. It doesn't take of the issue of  
10      the -- that doesn't address the uncertainty in the  
11      cardiovascular heart of the mortality assessment  
12      and the potential for differential patient  
13      management, differential reasons for dropout in the  
14      groups.

15             So I think, on balance, it's somewhat  
16      reassuring, the results. But I definitely have the  
17      same feeling that Dr. Heckbert noted, that I still  
18      think -- this doesn't mean that we now ignore the  
19      meta-analysis. I think the meta-analysis has a lot  
20      of strengths. It has comparisons to placebo, which  
21      I think, to me, is the more natural comparison.  
22      And it's blinded.

1           Especially in terms of perhaps the all-cause  
2 mortality, which was noted yesterday, everyone felt  
3 comfortable, seemingly felt comfortable about the  
4 all-cause mortality for the RECORD study. But you  
5 could maybe make that same comment about that for  
6 the meta-analysis because even though those studies  
7 weren't designed as cardiovascular outcome trials,  
8 they should be able to get the mortality right.

9           DR. BURMAN: Thank you.

10          Dr. Konstam?

11          DR. KONSTAM: Thanks. I do think that the  
12 DCRI readjudication process went a long way toward  
13 helping us markedly reduce some of the concerns  
14 that were raised in 2010, specifically vis-a-vis  
15 ascertainment of events, and bias, and even  
16 potential malfeasance on the part of ascertainment  
17 and delivery of events for adjudication. I no  
18 longer have those concerns.

19          I think there still is potential bias. But  
20 in my mind, generally speaking, in 2010 I felt that  
21 including look to RECORD at all for any useful  
22 information. I don't feel that way at this point.

1           I think there were a number of very  
2 thoughtful memos in the briefing document. I'll  
3 specifically call attention to Dr. Unger's memo and  
4 Dr. Temple's memo. And I really agree with much of  
5 what they said in there.

6           So generally speaking, I think we still have  
7 significant concerns about RECORD, specifically its  
8 open label, very complex protocol, undoubtedly some  
9 complex post-randomization imbalances, some of  
10 which we might be able to know, some of which we  
11 will never know; and missingness, as other people  
12 have said, with regard to not so much the -- I not  
13 as concerned with the missingness on vital status,  
14 but as Sanjay has pointed out and others, that  
15 there is still concern about missingness related to  
16 the MACE endpoint. I'm not overly concerned, but  
17 there is still some concern.

18           So generally speaking, I think there is as  
19 much useful information now in RECORD as there is  
20 in some of the other sources, such as the meta-  
21 analysis that we've been looking at and the  
22 observational data.

1           Specifically, I feel we can give a lot of  
2           credence to the mortality endpoint, both all-cause  
3           and the cardiovascular mortality endpoints. I  
4           think those findings are extremely helpful in  
5           influencing our overall thinking, and to some  
6           extent the other endpoints as well.

7           DR. BURMAN: Thank you.

8           Dr. Seely?

9           DR. SEELY: I think the readjudication by  
10          Duke really struck a chord with me in terms of that  
11          GSK had really done a good job of carrying out the  
12          study in terms of the very limited number of  
13          discrepancies that were raised in the  
14          readjudication when a study is that incredibly  
15          large.

16          So I felt that the conduct of the  
17          readjudication was up to par, and that it helped  
18          reinforce that the original data that GSK had  
19          provided was up to par as well.

20          I think we're answering some of the issues  
21          with number 2 when we're talking about this. I  
22          think when you're looking for potential harm, that

1 an open label study is a big problem, especially  
2 when there's been a lot of publicity about one of  
3 the labels.

4 For that reason, I think it is important,  
5 as has been mentioned, that we don't consider the  
6 randomized trial as definitive since it was open  
7 label, but we use it in consideration with the  
8 other studies.

9 DR. BURMAN: Thank you.

10 Dr. Hiatt?

11 DR. HIATT: A couple of additional thoughts.

12 In terms of having certainty about the events, I  
13 agree with the rest of the panel. I think that  
14 issue has been resolved by the DCRI review. I  
15 won't go over the design issues; they've already  
16 been stated. The conduct seemed, therefore, to be  
17 reasonable.

18 What I would like to focus on is informative  
19 censoring and missing data. I think the question  
20 in my mind is how much could that have changed the  
21 signal? And there were simulations run for the  
22 missing data, which demonstrated that it would take

1 an extreme imbalance to change the primary results.

2 In terms of informative censoring and the  
3 earlier discontinuation on the rosiglitazone arm, I  
4 don't know how much error there would be there. I  
5 was struck by the 60 patients who discontinued  
6 because of heart failure versus 30 or 29 in the  
7 other arm.

8 But numerically, I don't think that could  
9 have changed the story much, either. If you were  
10 to add informative censoring plus missing data  
11 extremes, how much would that change things? And I  
12 don't know, but I'm guessing that it wouldn't  
13 change things a lot.

14 So then when you go back to the DCRI final  
15 results, which confirm the initial RECORD results,  
16 I did want to make a couple comments, that the MACE  
17 endpoint, which is the primary guidance endpoint,  
18 had an upper bound of 1.17. So that's well below  
19 the threshold for a post-approval endpoint.  
20 All-cause mortality, which I think in this  
21 situation is an estimate of net clinical benefit,  
22 had an upper bound of 1.08. So those bounds are

1 well below thresholds of concern.

2 The only one that goes above that is the MI  
3 risk, which is at 1.59 as the upper bound. And I  
4 don't think we've completely resolved that issue at  
5 all. But you have to ask yourself that it's a  
6 component of an irreversible harm endpoint, and so  
7 if the MI endpoint was a little worse and the  
8 stroke endpoint a little better, is it the  
9 totality? Is it the MACE? Which is, I think,  
10 reassuring.

11 So overall, I think the RECORD study does  
12 inform us in terms of is there a strong signal to  
13 retain a huge amount of concern about this drug. I  
14 think it helps resolve that.

15 DR. BURMAN: Thank you.

16 Dr. Kaul?

17 DR. KAUL: Thank you. I too did not have  
18 any issues with the conduct of the readjudication.  
19 I think they did a very good job. It was very  
20 comprehensive and informative. But the key  
21 question is, was that readjudication process  
22 equipped to address some of the key concerns that



1       were raised? And I think that's acknowledged by  
2       the DCRI readjudicators themselves, that it was not  
3       equipped to answer all. Some, but not all.

4               With regards to the trial design issue,  
5       the design only allows us an assessment of the  
6       comparative safety of rosiglitazone versus the  
7       metformin/sulfonylurea combination. It does not  
8       allow a true assessment of cardiovascular safety.

9               The results of RECORD, which is an active  
10      controlled trial, are not dissimilar from the  
11      results of the FDA meta-analysis focusing on active  
12      controlled trials. The signal was only discernible  
13      in placebo-controlled trials. So the issue still  
14      remains whether this drug is definitively proven to  
15      be safe from a cardiovascular point of view.

16              The informative censoring is an important  
17      issue, as Dr. Hiatt has already brought out. And  
18      if you look at the MI hazard in the subgroup that  
19      was on statins at baseline, the confidence limits  
20      stretch from 0.95 to 2.67, which means that it is  
21      possible that you can have a hazard ratio of up to  
22      2.7 that can -- it's conceivable to see a subset of

1 patients where you can have a hazard ratio of 2.67.

2 So in those patients that had missing data  
3 on MI, an imbalance of up to 2.5- to threefold is  
4 going to convert a nonsignificant hazard into a  
5 significant hazard. That's how I interpret it.

6 So the task to the DCRI investigators is to  
7 do those simulation studies, quality controlled and  
8 all of that, to see what is the likelihood of  
9 having a threefold increase in the hazard in the  
10 patients that had missing MI data.

11 I think I'm going to stop there. Thank you.

12 DR. BURMAN: Thank you.

13 Ms. Killion?

14 MS. KILLION: Rebecca Killion. I was on  
15 the initial panel in 2007 when we first dealt with  
16 Avandia. And at that time, I expressed my concern  
17 that we were jumping the gun based on information  
18 from a meta-analysis that I thought was inadequate  
19 to enable us to make the decisions we were being  
20 asked to make at that time.

21 I realize that RECORD still has some  
22 inherent weaknesses, as do many studies -- maybe

1       this might have a few more -- that we wish we could  
2       have done differently. But based on the DCRI  
3       readjudication, which I think was conducted with  
4       rigor and integrity, that went a long way to me to  
5       validate the sponsor's initial data, which is  
6       something that questions had been raised about.

7               That also tells me that my concerns that we  
8       were jumping the gun in terms of all the actions  
9       that followed were not unfounded. So the  
10      information that I received in this meeting with  
11      respect to the readjudication really did a lot to  
12      reassure me in terms of the initial data that we  
13      were looking at.

14             DR. BURMAN: Thank you.

15             Dr. Proschan?

16             DR. PROSCHAN: I agree with a lot of what's  
17      already been said. Just concerning the informative  
18      censoring, I think it would be a big concern if  
19      patients who had heart failure were withdrawn from  
20      the study because that would be a very bizarre  
21      thing to do.

22             We heard from Dr. Marciniak that that was

1 the case, but we also heard from the company that  
2 that was not really the case. They weren't  
3 considered withdrawn from the study, just not  
4 receiving drug any more, which makes me feel a lot  
5 better because there's a huge difference,  
6 obviously, between those two situations, withdrawn  
7 from drug and withdrawn from further follow-up.

8 I do also think it's interesting,  
9 though -- and the readjudication did go a long way  
10 to making me feel better about the RECORD trial.  
11 But I still think it's interesting, the interaction  
12 with statins.

13 I don't think that you can quite dismiss  
14 it as a multiplicity issue. I do agree that  
15 multiplicity is a big issue and that it could  
16 explain that. However, when you look at those  
17 confidence intervals, the intervals themselves  
18 were completely separate.

19 Non-statisticians think, oh, well, if the  
20 two intervals are separate, then there's a  
21 significant interaction. If there's overlap, there  
22 isn't. And that's not true. You can have overlap

1 and still have a significant interaction. So when  
2 there's no overlap, then that tells you that  
3 there's pretty strong interaction.

4 Also, I think I remember from that picture,  
5 it looked like one interval -- it's not just that  
6 the point was to the left of unity. The entire  
7 interval was to the left of unity. And the other  
8 entire interval was to the right of unity.

9 So to me, that's a little bit more difficult  
10 to dismiss as a multiplicity issue. And so I think  
11 that is an intriguing finding, and I'm not sure  
12 what to make of it. But I'm not sure that that's  
13 just a multiplicity issue, either.

14 DR. BURMAN: Thank you.

15 Dr. Smith?

16 DR. SMITH: Yes. I also concur with the  
17 essence of what others have expressed, to just very  
18 briefly state that it's the strength or the  
19 reassurance in the strength of the RECORD study  
20 data based on the reanalysis, and the recognition  
21 of the persistent limitations in that study that  
22 fundamentally lie in its design. So I'm not going

1 to go through that again because others have.

2 I was intending and will make a further  
3 remark about the statin subgroup because I think  
4 it's important, at least, to have that clear in our  
5 thinking in the record on this. I guess where I am  
6 with the statin data is that I think that they are  
7 of substantial interest, and I wouldn't want to say  
8 more than that.

9 I think the level of that interest is  
10 increased somewhat by the fact that these hazard  
11 ratios were increased for patients on statins and  
12 RSG, both for cardiovascular mortality and for MACE  
13 data.

14 It's the magnitude of the effect for the  
15 hazard ratio, particularly for the cardiovascular  
16 death data, and the fact that a weaker observation,  
17 that with at least some pioglitazone data, that  
18 numerically things go in the same direction,  
19 although those were very much smaller magnitude  
20 effects and perhaps not hardly worthy of mention.

21 So I think those findings are of substantial  
22 interest. I do think it's clear that they emerged

1 as part of observations on multiple endpoints made  
2 post hoc, and I think there's as much we don't know  
3 about potential, either the role of chance for  
4 multiple determinations or co-varying endpoints  
5 that might be responsible for all or part of what's  
6 observed with the statins.

7 So to bring that all together, I feel that  
8 it's an interesting finding. I don't feel that  
9 it's something that motivates a much more powerful  
10 effort to resolve that as an obligation from having  
11 made that observation.

12 DR. BURMAN: Thank you.

13 Dr. van Belle?

14 DR. VAN BELLE: I agree with a lot of what  
15 was said by the earlier speakers. Just a couple  
16 comments on the design and the analysis.

17 With respect to the design, we heard this  
18 morning that there were 65 centers that had two  
19 subjects or fewer. It's not clear how the  
20 randomization would be conducted in that case. So  
21 I have some concerns about those centers that had  
22 two or three or four subjects. And there were

1       probably about 70 or 80 centers like that.

2               On the other hand, if you just do a rough  
3       back-of-the-envelope calculation, those centers  
4       constitute less than one-tenth of the total sample  
5       size. So my guess is it's not going to matter very  
6       much. But nevertheless, it would be worthwhile  
7       looking at.

8               The second thing is with respect to the  
9       analysis. I mentioned yesterday the possibility of  
10      doing a random effects model with centers as one of  
11      the effects on either centers or countries. I  
12      don't know. I still don't know whether that was  
13      done or not.

14              But that would also have implications with  
15      respect to the simulations because you could  
16      simulate a non-zero center effect of treatment and  
17      then see how robust those results are with respect  
18      to that effect.

19              So I don't know the answer to that. But my  
20      thinking is that it's probably not going to make  
21      too much of an effect. So my bottom line is that  
22      the study readjudication was done reasonably well,



1       and I'm fairly satisfied with it.

2               DR. BURMAN:   Thank you.

3               Dr. Flegal?

4               DR. FLEGAL:   Yes.   I agree with many of the  
5       things that have already been said.   I actually  
6       wonder, in terms of the 2010 meeting, if we had not  
7       had so much uncertainty about RECORD, if we had had  
8       the results of the readjudication then, if our  
9       deliberations would have been a little different.

10              But I feel about the statin issue that these  
11       are concerning.   But I also worry about partly  
12       having to do with all the many sites and the  
13       possibilities of some kind of confounding by all  
14       these different countries with different standards  
15       of medical care, with different mortality rates,  
16       and whether somehow there is some kind of  
17       confounding with the statin categories in some way.

18              So I agree with the other speaker that this  
19       is concerning, but I don't know quite how far we  
20       can go with it.   So it's really something to keep  
21       an eye on, but not maybe something to make a  
22       determination of some kind about at the moment.

1 DR. BURMAN: Thank you.

2 Dr. Moss?

3 DR. MOSS: First, let me say I think that  
4 holding this meeting has been very important in  
5 view of the decisions that were made in 2010, and I  
6 want to congratulate the FDA on bringing this  
7 meeting to fruition. It's been controversial  
8 but it's, I think, extremely important.

9 I think we generally agree that RECORD was a  
10 less than perfect trial. But for a large clinical  
11 trial, the available findings, I think, are still  
12 valuable and informative. The biggest concern, I  
13 think, does relate to open label. I think the DCRI  
14 did an outstanding job.

15 The most important thing in this type of a  
16 trial from my standpoint is all-cause mortality.  
17 And all-cause mortality was, if anything, reduced  
18 in a direction, but it certainly was not in any way  
19 increased.

20 I find no substantial information or  
21 evidence that rosiglitazone is unsafe. If we look  
22 at the MI question, I find it difficult to take the

1 MI out of context and not do an analysis where it's  
2 MI or death, whichever comes first in the analysis,  
3 since these are covariates or concomitant  
4 conditions.

5 So if you're going to look at death as a  
6 single endpoint, that's the important thing. If  
7 you look at MI as a single endpoint when the death  
8 is not increased, I find that difficult. So I'm  
9 not willing to put very much evidence on that.

10 The statin question is secondary. It wasn't  
11 prespecified in any way. And I'm surprised there  
12 were not adjustments made for what would be very  
13 significant imbalances. What are the indications  
14 for statins, and how did this relate to a lot of  
15 covariates, age and gender and a number of other  
16 things, including the history of prior MI that was  
17 touched upon, et cetera? So I find it an  
18 interesting observation, but not enough to warrant  
19 any major concern.

20 I think one of the striking things that was  
21 mentioned earlier in a favorable sense was that  
22 this drug lowers blood sugar significantly and

1        meaningfully without product hyperglycemia. And  
2        therefore, I think this drug has a real potential  
3        use.

4                It seems to be almost unique, and at least  
5        at the present time we don't have any evidence that  
6        there is any associated cancer of the bladder. And  
7        if one looks at all of the usual adverses that lead  
8        to a drug's withdrawal, such as bone marrow  
9        suppression, advancing kidney disease, liver  
10       disease, unspecified or unusual allergies, that  
11       hasn't shown up, either in the clinical use, which  
12       was quite substantial for a long period of time, as  
13       well as in the RECORD trial itself.

14               The post hoc development or concern about  
15       bone fractures from other studies just has to be  
16       looked at. Every drug on the market that I know of  
17       has some adverse effects. And we just have a huge  
18       experience with this drug, and I don't see that any  
19       of the adverse effects that have been talked about  
20       are substantial. So I just make these comments at  
21       this time.

22               DR. BURMAN: Thank you very much.

1 Dr. Spruill?

2 DR. SPRUILL: I agree with most of the  
3 comments that have already been made and said. My  
4 only comments at this point, as I said yesterday  
5 and I tried to point out yesterday, is that all of  
6 the sites in the clinical trials were outside of  
7 the United States of America. And I would have  
8 felt better if we had some clinical trials  
9 conducted in the U.S.

10 I ponder if there would be a difference if  
11 we had a clinical trial here and the outcomes, in  
12 terms of cardiovascular deaths, MIs, and bladder  
13 cancer. And so while I agree with what was said  
14 earlier, I still have reservations about the  
15 clinical trial only occurring in countries of  
16 America.

17 DR. BURMAN: Thank you. I have a few  
18 comments as well. Thank you all for your cogent  
19 comments.

20 I tried to follow, as you did, what  
21 Dr. Hamburg's advice was, to follow the science  
22 where it leads and the rest will fall into place.

1 And of course, the goal of science in this case is  
2 truth.

3 In reality, however, in general and with  
4 respect to the evaluation of the safety and  
5 efficacy of medications, we are always approaching  
6 truth, and we have to weigh the problems with a  
7 trial, such as in this case, and render a judgment  
8 whether the problems are sufficient to limit or  
9 abrogate the possible benefits.

10 My view in this instance is that the  
11 problems are not inconsequential but the results  
12 still have validity, especially since they are  
13 concordant with other data, including previous  
14 trials, literature review, and some meta-analysis.

15 There is no compelling evidence that the  
16 trial had misconduct. There were multiple issues  
17 uncovered, but in my view overall they involved a  
18 relatively few number of patients. The informative  
19 censoring -- there is no compelling evidence that  
20 informative censoring significantly affected the  
21 results, in my view.

22 I am impressed with the performance of the

1 DCSI group with regard to reviewing the data and  
2 attempting to obtain all relevant information. Of  
3 course, they did not totally succeed, but they  
4 added to the data set originally obtained in a  
5 meaningful way.

6 There is no evidence in my view that there  
7 was bias or misconduct. On the contrary, they  
8 appeared to cooperate with the FDA and also went to  
9 great lengths to try and obtain all data sets.

10 They of course could only readjudicate  
11 information that was given to them. The  
12 readjudication process showed comparable results  
13 with regard to overall and CV mortality as compared  
14 to the original RECORD analysis. Numerous  
15 sensitivity analyses were performed, and  
16 rosiglitazone does, of course, separately cause an  
17 increased rate of congestive heart failure.

18 There are, as mentioned, problems with the  
19 adjudication process, including loss of follow-up  
20 data and original data access. But strengths  
21 include predefined endpoints, adjudicators were  
22 blinded, and triggers were employed.

1           Although there are possible minor issues  
2           that have been raised, the conduct of the Duke  
3           Clinical Research Institute seems to me to be  
4           appropriate. There have been confirmatory  
5           independent reviews of the DCRI data and conduct,  
6           for example by the FDA, and handling of the data  
7           seems appropriate and consistent with previous  
8           studies.

9           With regard to the reliability and  
10          interpretability of the various endpoints, there  
11          was no compelling evidence of a treatment effect on  
12          all-cause mortality or CV mortality. The results  
13          of the primary analyses and sensitivity analysis  
14          showed the readjudication outcomes were consistent  
15          with the original RECORD results. It did not show  
16          statistically significant differences between the  
17          two groups for the primary composite outcomes of CV  
18          death, MI, or stroke.

19          The original data has issues with collection  
20          and interpretation. However, I feel the results  
21          are reliable. The RECORD study and the  
22          readjudication process gave results that are



1 plausible and congruent with the previous studies,  
2 and multiple analyses were performed to strengthen  
3 the data.

4 Does anybody have any other comments on  
5 question 1?

6 (No response.)

7 DR. BURMAN: Thank you very much for your  
8 input. Very appreciative, very informative. Could  
9 we go to question 2?

10 Question 2 is shorter. Please comment on  
11 how each of the following clinical data sources  
12 should be weight in the overall consideration of CV  
13 evaluation for rosiglitazone, with regard to  
14 observational studies, FDA's meta-analysis of 52  
15 rosiglitazone controlled clinical trials, and with  
16 regard to cardiovascular outcome trial, RECORD,  
17 which we have been discussing.

18 I open the floor up for discussion.

19 Dr. Brittain?

20 DR. BRITTAIN: I guess I said some of this  
21 already in the first question. But I do  
22 think -- I'm not going to put a lot of weight on

1 the observational studies. But I do think the  
2 meta-analysis -- I don't know. I don't know that I  
3 would weight it the same as the RECORD, but maybe  
4 pretty close. I don't see it as black and white  
5 that the RECORD is better than meta-analysis.

6 As I said, the meta-analysis is based on  
7 blinded data. It has a lot of placebo information.  
8 And as a few people have already mentioned, the  
9 results seem somewhat different in the placebo  
10 comparisons than they do in the comparisons to the  
11 active drugs.

12 Also, there's an interesting consistency  
13 between -- even though the point estimates are  
14 different in the meta-analysis than the RECORD,  
15 there's some consistency. Stroke looks better in  
16 the rosi group and the MI looks worse in the rosi  
17 group in both sets of data.

18 To some extent, if they -- first of all,  
19 I don't really know that they are different.  
20 Statistically, I think, if you did an analysis, the  
21 results are probably not statistically  
22 significantly different from each other between the

1 meta-analysis results and the RECORD. So it could  
2 just be noise, statistical noise, in the difference  
3 in the point estimates. But it also could be that  
4 they're really answering different questions.

5 The meta-analysis data is primarily placebo  
6 data, I believe -- I mean comparison to  
7 placebo -- and it also is very much short-term  
8 trial data. So it could be perhaps answering a  
9 different question than the RECORD data, and that's  
10 why the estimates look different.

11 But anyway, I do think that both are very  
12 valid. And somehow, you could either say they're  
13 really measuring the same thing and combine them.  
14 One thing is, however, that the number of person-  
15 years in the meta-analysis is quite a bit lower  
16 than the number of person-years in RECORD. So in  
17 that sense, RECORD provides more precise  
18 information.

19 But I still think both sources of  
20 information are valid and should be considered.

21 DR. BURMAN: Thank you.

22 Dr. Kaul?

1 DR. KAUL: Thank you. When we talk about  
2 the totality of evidence, I like to split that into  
3 three components. One is the hierarchy of  
4 evidence, the other one is the quantity of the  
5 evidence, and the third is the quality of the  
6 evidence. So I'm going to talk specifically about  
7 these three things.

8 In the hierarchy of evidence, randomized,  
9 controlled, double-blind superiority trials are  
10 very pinnacle, followed by randomized,  
11 noninferiority assessments, and they rest on some  
12 shaky platform. And when you factor in the open  
13 label nature, it makes it even shakier.

14 There's a sort of a perverse incentive that  
15 you get rewarded for sloppiness. So the sloppier  
16 the trial conduct, the more likely you're going to  
17 achieve noninferiority.

18 Followed by -- a well-done meta-analysis can  
19 be informative. And when I say well-done  
20 meta-analysis, I'm talking about trials that are  
21 designed for the specific outcome of interest,  
22 prespecified, and where we talk about p-values of

1 .01 and .001, not p-values of .05, followed then by  
2 observational studies.

3 So in terms of the quantitative assessment  
4 of the evidence pertaining to rosiglitazone, when  
5 you look at RECORD, it excludes a hazard ratio of  
6 1.3 for all outcomes except myocardial infarction,  
7 as Dr. Hiatt already brought that up. But there's  
8 a favorable lean on mortality. And we'll all agree  
9 that mortality is insensitive to bias. So that's  
10 at least somewhat reassuring.

11 The meta-analyses -- the original meta-  
12 analysis for MI danced around a p-value of .05.  
13 The FDA meta-analysis failed to exclude a hazard  
14 ratio of 1.3 for MACE. But the question remains,  
15 were there an adequate number of events? There  
16 were a total of 109 events, less than one-third of  
17 the over 300 events observed in the RECORD.

18 With respect to epidemiologic studies, there  
19 are weak associations with all studies showing an  
20 odds ratio of less than 2, and most of them showing  
21 less than 1.5. And I think questions have already  
22 been raised whether these effect sizes allow a

1       reliable assessment of safety.

2               In terms of qualitative assessment, I think  
3       with RECORD there's a large exposure. There were  
4       319 MACE events, blinded adjudication, consistent  
5       intention-to-treat, and per-protocol analyses. But  
6       we are obviously burdened by challenges in study  
7       design, conduct, and analysis which some may argue  
8       does not provide reassuring estimates.

9               The meta-analyses results are inconsistent  
10       and provide fragile evidence. They are hampered by  
11       methodologic limitations. Results are not reliable  
12       or replicable. And essentially, they're good for  
13       raising questions, not settling them.

14              For epidemiologic studies, there are  
15       inherent limitations, the confounding bias. The  
16       meta-analysis pooled these observation studies, and  
17       I'm not a big fan of pooling observational studies.  
18       I completely agree with the FDA statisticians'  
19       approach of not providing a pooled estimate.

20              But the more interesting point was that the  
21       primary hypothesis of increased MI risk was not  
22       validated. There's only one study where it was

1       prespecified, the David Graham study, and it failed  
2       to validate that.

3               The three high quality observational studies  
4       that I consider to be high quality are the  
5       Winkelmayer, the David Graham, and the Juurlink  
6       studies. In all three of these studies, the MI  
7       risk was not confirmed.

8               So again, these are hypothesis-generating at  
9       best. So when you look at, overall, the totality  
10      of evidence, it is not sufficient enough to either  
11      implicate or exonerate rosiglitazone versus  
12      cardiovascular risk. And I find that when you have  
13      such insufficient data, they are not adequate  
14      platform for making regulatory decisions or  
15      clinical guideline recommendations.

16              I believe that when you have such  
17      uncertainty in data, we should all be allowed to  
18      exercise clinical judgment. I do not believe that  
19      the FDA has a greater obligation to protect and  
20      promote public health than the individual  
21      physicians. These are judgment calls, and we  
22      should all be allowed to make judgment calls in the

1 face of uncertainty. Thank you.

2 DR. BURMAN: Thank you.

3 Dr. Konstam?

4 DR. KONSTAM: Yes, thanks. First off, with  
5 regard to all of these outlines of evidence, just  
6 to say again, I actually agree with Dr. Gerstein's  
7 analysis about what we know and how little we know.  
8 And I really don't think we actually knew anything  
9 in 2010, and I don't think we know anything now.

10 I think it's a matter of degree of concern  
11 and degree of certainty. And I think we have to  
12 have a relatively low bar for safety. So that's  
13 really what this is about. It's not about  
14 achieving certainty because it's not here in any of  
15 these data sets.

16 So having said that as an intro, I would say  
17 that each of these three lines of evidence need to  
18 be taken into account with our current decision-  
19 making. And that's a big difference for me  
20 compared to 2010, where I felt personally that I  
21 had to completely disregard RECORD.

22 Based on what we were told at that time, I



1        didn't feel like there was anything that I could  
2        usefully glean out of RECORD. And I think that's  
3        changed by the reanalysis by DCRI. I do think it's  
4        a very useful data set that adds information and  
5        should be combined with the other sources.

6                So I think each of the sources provides  
7        information, I think starting with the meta-  
8        analyses. And each of them is flawed. Each of the  
9        sources of information has information. Each of  
10       the sources is flawed.

11               The meta-analyses, we know the flaws. And  
12       yet I feel there is a concern that still exists  
13       specifically with regard to the placebo-controlled  
14       aspects of the meta-analysis and MI that is not  
15       alleviated by any other source of information since  
16       RECORD has no placebo-controlled information.

17               Now, one can ask, and this has been raised,  
18       how useful is placebo-controlled data in patients  
19       where you may have to add therapy for glycemic  
20       control? I think that's a very good point. And I  
21       think we need to understand that.

22               What does it mean if there is in fact excess

1 MI, for example, or MACE within placebo-controlled  
2 trials? Let's say that's real, and let's say it's  
3 not true compared to sulfonylureas and metformin,  
4 for example. What would that mean?

5 I think we should really understand that.  
6 It could be that particularly with small trials,  
7 where you're looking at short-term events, it could  
8 be that increasing glycemic control in the short  
9 term drives some short-term events that may not be  
10 true in the longer term.

11 It really would be helpful to try to  
12 understand that and not dismiss that finding with  
13 regard to the placebo-controlled data. So I think  
14 there still are some lingering concerns with regard  
15 to the meta-analysis.

16 I think with regard to observational  
17 studies, I feel like, generally speaking, I would  
18 have completely dismissed all of the observational  
19 findings that I've seen, except for the fact that  
20 with the series of better performed pio versus rosi  
21 observational analyses, where there seems to be a  
22 consistent excess of mortality -- which again is

1 not disputed by RECORD, which didn't have a pio  
2 group -- I still am concerned about that,  
3 particularly in that setting, where it seems like  
4 the baseline characteristics of those populations  
5 is so, so similar.

6 I think that's an extraordinary circumstance  
7 with regard to observational data. And I think  
8 when we decide what drug we're going to use, that's  
9 a pretty strong indication to me that pio might be  
10 a better choice than rosiglitazone.

11 With regard to RECORD, I think in particular  
12 the mortality data are very credible and, I think,  
13 very reassuring that they're on the correct side of  
14 unity. And I believe that should significantly  
15 influence our overall thinking.

16 I will remark about the statin thing again.  
17 There's nothing proven by that subgroup finding,  
18 but it's worrisome to me. I think for the  
19 cardiovascular death, it's a large magnitude  
20 interaction for a prespecified assessment. And  
21 it's a qualitative interaction.

22 I would urge the FDA to do whatever it can

1 to explore other databases to see whether there's  
2 some reason for substantiation there because if  
3 that is a real finding, it could be a hugely  
4 important finding. I don't know that it's true,  
5 but I'd urge the FDA to do whatever it can to  
6 further explore that.

7 So generally speaking, I think we do have  
8 useful -- compared to where we were in 2010, I  
9 think mostly we have more and credible information  
10 from RECORD than we had before.

11 DR. BURMAN: Thank you.

12 Dr. Heckbert?

13 DR. HECKBERT: Yes. Susan Heckbert. If the  
14 sponsor had conducted an appropriate randomized,  
15 controlled, blinded clinical outcomes trial at an  
16 appropriate time earlier in the natural history of  
17 the use of this drug, then I would give its results  
18 prominence over all of the other things that we're  
19 considering -- the meta-analysis, the observational  
20 studies, and so on.

21 But we don't have that. And I think even  
22 when the RECORD trial was started, it would not

1       have met FDA standards for a long-term  
2       cardiovascular outcomes trial, and thus, its  
3       results aren't definitive.

4               So like others who have spoken, I feel that  
5       we have to consider the results both of RECORD, of  
6       the meta-analysis of short-term trials, and the  
7       observational studies, and in particular, those of  
8       rosiglitazone versus pioglitazone, as Dr. Konstam  
9       mentioned.

10              In considering all those together, I feel  
11       that we are still dealing with a cardiovascular  
12       safety signal regarding rosiglitazone. And I am  
13       not convinced even by, I think, what was a very  
14       nicely done readjudication. Those do not allay all  
15       my concerns about that trial, and I don't think we  
16       can rely entirely on the RECORD trial to help us  
17       make decisions today.

18              DR. BURMAN: Dr. Hiatt?

19              DR. HIATT: The only thing I'd like to  
20       emphasize in addition to what Dr. Konstam and  
21       others have said is that the prior data to RECORD,  
22       given its weaknesses, the FDA meta-analysis did

1 illustrate, I think, an interesting finding that  
2 Dr. Kaul has already brought up, which is that  
3 compared with placebo-controlled trials,  
4 rosiglitazone did have a signal for MACE events.

5 Therefore, to me the real challenge with the  
6 data, including RECORD, is that there's active  
7 controls that we don't know how they all stack up  
8 against placebo.

9 So if you're trying to make a decision based  
10 on a noninferiority design, you have to have a lot  
11 of certainty about what your active comparator  
12 does. And when you don't know that, then you're  
13 comparing two unknowns to one another.

14 So how do we know if basically every drug  
15 we're getting for diabetes is really safe? Because  
16 there's just a paucity of placebo-controlled  
17 evidence. And therefore, I think the consequence  
18 of what happened in 2010, in my mind the most  
19 concerning thing, is that a really well-designed  
20 trial, the TIDE trial, was put on hold.

21 I think that if you look at the design, a  
22 couple things to emphasize. It had a placebo arm,

1 and it had a superiority hypothesis. And those are  
2 two things that would have added a lot of really  
3 important information to this field.

4 Now, I understand the FDA had a lot of  
5 concern. And of course, that's what you do with  
6 concern is you put things on hold. So I'm not  
7 necessarily directly faulting the FDA for making  
8 that decision.

9 But the unfortunate consequence is that a  
10 trial that might have really told us a lot, not  
11 just about this drug class but about cardiac risk  
12 in treating diabetes because of a placebo control  
13 and a superiority design, was taken off the table.  
14 And I don't know if that can be resurrected. Maybe  
15 we'll discuss that later today.

16 But the answer to that question could have  
17 been in progress. And so I think that's the real  
18 consequence of what happened here, is that we're  
19 still left with uncertainty. The active control,  
20 metformin, based on the United Kingdom Prospective  
21 Diabetes Trial, might look favorable but  
22 sulfonylureas may not. So one might ask the

1 question, should we have two different subgroup  
2 comparisons? I wouldn't want to go there.

3 The only way to answer this question is to  
4 have a placebo control, and that opportunity was  
5 lost. So the information based on what we see,  
6 including RECORD, today leaves me with that great  
7 degree of uncertainty. I don't see a signal from  
8 RECORD. But I don't know what that means in the  
9 context of what the active control arms were.

10 DR. BURMAN: Thank you.

11 Dr. Smith?

12 DR. SMITH: Since I've put my hand up, there  
13 have been so many things said that I agree with  
14 that I don't really need to make any extended  
15 comment.

16 I felt that Dr. Heckbert perhaps stated best  
17 where my feelings are about the question for  
18 discussion, what has to do with the strength of  
19 these different study formats.

20 Just to make that very brief, I guess I  
21 think they're all flawed. I understand the data  
22 better from the RECORD study, and I find a greater



1 confidence and reliability on that study, but it's  
2 flawed in design.

3 I am unwilling to write off the meta-  
4 analysis data because the RECORD data are different  
5 and it's a randomized, controlled study because of  
6 the problems that it presents. And so I in a sense  
7 weigh them equally, or relatively equally, in terms  
8 of trying to figure out where we really are.

9 DR. BURMAN: Thank you. Dr. Temple, did you  
10 have a comment?

11 DR. TEMPLE: Actually, I had one for  
12 Dr. Hiatt. In long-term diabetes studies, you  
13 don't usually like to let one group have much worse  
14 hemoglobin A1c. So I don't know what the TIDE  
15 study did, but my bet would be that the placebo  
16 group would have gotten something.

17 They wouldn't have gotten rosi or pio, but  
18 they would have gotten something to help control  
19 their blood sugar, which means it's not exactly a  
20 placebo-controlled trial. And if you did leave  
21 them with much worse hemoglobin A1c, wouldn't that  
22 make you nervous about the results of this trial?

1       Because maybe that's what's driving any difference  
2       you see.

3               DR. HIATT:   If you believe Alc would  
4       confound the results.

5               DR. TEMPLE:   Well, I believe it might -- no,  
6       so far it hasn't shown much on these endpoints.  
7       But then that's another problem.

8               DR. BURMAN:   Thank you.

9               Dr. Kaul, you have a follow-up?

10              DR. KAUL:   If I may just respond to  
11       Dr. Smith's comments.   Actually, the results of the  
12       FDA meta-analysis, active controlled treatments,  
13       are exactly the same as that of the RECORD.   I  
14       don't know whether that reassures you or not.

15              If you look at the MACE endpoint, FDA meta-  
16       analysis, active controlled, hazard ratio 1.05,  
17       going from .48 to 2.34; RECORD .95, going from .78  
18       to 1.17.   MI, 1, going from .36 to 2.82.   RECORD,  
19       1.13, from .80 to 1.59.

20              If you just focus on the FDA meta-analysis,  
21       which in my opinion is a high quality meta-  
22       analysis, the results are similar.

1 DR. BURMAN: Thank you.

2 Dr. Proschan?

3 DR. PROSCHAN: Yes. I think there's no  
4 question that the observational studies are at the  
5 bottom of the totem pole in terms of convincing us  
6 because of the potential biases.

7 Then the weighing of the meta-analysis  
8 versus RECORD, I do think an important point that's  
9 been brought up several times is that the meta-  
10 analysis gives you a chance to look at versus  
11 placebo and RECORD, of course, doesn't.

12 I hate to think about this, but it may be  
13 that there are several diabetes drugs that are  
14 worse than placebo; if you ever did a very large  
15 trial to see that, you might see it. And then the  
16 question is, well, how should you act? Should you  
17 be okay with rosiglitazone if it's no worse than  
18 the other drugs that are being prescribed for  
19 diabetes? Knowing that they could potentially be  
20 harmful as well.

21 So I do think that the meta-analysis versus  
22 the RECORD trial are a little bit different. They

1 give you different pieces of information.

2 If you're just talking about versus other  
3 diabetes drugs, there's no question I would put  
4 RECORD ahead of the meta-analysis. And I would  
5 probably put it at least twice as influential as  
6 the meta-analysis. But because it contains  
7 information that isn't in RECORD, I think it's  
8 closer than that.

9 DR. BURMAN: Thank you.

10 Dr. Jenkins and Dr. Mahoney, either one, or  
11 both? Jenkins first.

12 DR. JENKINS: Dr. Kaul said earlier, as he  
13 was giving his hierarchy of evidence, he talked  
14 about a meta-analysis of trials that were  
15 prespecified and designed to assess the endpoint in  
16 question.

17 The trials that were in this meta-analysis  
18 were not prespecified in design to look at  
19 cardiovascular events. So I'm interested in asking  
20 the committee, as they're weighing the down sides  
21 of the open label design of RECORD versus the fact  
22 that the meta-analysis is based on trials that

1 really weren't intended to be looking at  
2 cardiovascular endpoints. Most of the endpoints  
3 were not adjudicated by an independent committee

4 So can you just comment on how you weigh  
5 those factors of open label randomized trial versus  
6 meta-analysis of trials that weren't specified to  
7 assess the endpoint of concern.

8 DR. BURMAN: Thank you. And Dr. Mahoney,  
9 did you have an additional comment as well?

10 DR. MAHONEY: I just want to clarify one  
11 thing about what we mean by a placebo-controlled  
12 trial. Among the trials that are included the  
13 meta-analysis, the vast majority of them are not  
14 placebo-controlled trials in which you had  
15 monotherapy of rosiglitazone versus placebo. Most  
16 of them are add-on trials, and also, rescue was  
17 permitted.

18 So the patients who were in the placebo arm  
19 were, for the most part, getting attempts at good  
20 glycemic control. So I just want to make that one  
21 clarification. They're not classical placebo-  
22 controlled trials.

1 DR. BURMAN: Thank you.

2 Dr. van Belle?

3 DR. VAN BELLE: With respect to these  
4 observational studies, I would agree with Dr. Kaul  
5 with one caution, that when we're talking about  
6 safety, that barriers are a little lower than when  
7 it comes to efficacy. So I think that's one point  
8 that I'd like to make.

9 The second point, that Dr. Unger made, that  
10 these are fishing expeditions, well, that's not  
11 quite true. The later studies presumably were  
12 prompted by the earlier studies. So you could take  
13 the later studies as being somewhat confirmatory of  
14 the earlier studies.

15 So when I look at that -- and this is the  
16 question I asked yesterday -- what do we know now  
17 in terms of the observational studies that we  
18 didn't know before? Let's look at all-cause  
19 mortality.

20 What I did was looked at the data from the  
21 FDA, the meta-analyses. There were two studies out  
22 of two that showed the lower confidence bound on

1 the effect to be 1 or greater. In the 2013  
2 analysis, there are 5 out of 6. And it depends a  
3 little bit on how you count, whether you count the  
4 Graham study in that or not.

5 But to my mind there are at least two more  
6 studies that indicate -- that confirm -- the signal  
7 that was suggested by the earlier studies. So  
8 that's really quite important to me. And the same  
9 thing goes for heart failure, stroke, and acute MI,  
10 are roughly the same in terms of proportions of  
11 studies.

12 So then you get the question, well, what are  
13 we going to do about the potential contradiction  
14 between the RECORD study and the observational  
15 studies, the meta-analysis? And I'm still trying  
16 to struggle with that.

17 Three points. One is that, clearly,  
18 clinical trials have a very strong patient  
19 selection item, whereas the observational studies  
20 may just take patients as they occur in clinical  
21 practice.

22 Secondly, in terms of the RECORD study, the

1 heterogeneity is still a concern to me, and we  
2 really don't have an answer to that.

3 Then finally, a former colleague of ours  
4 here, Gordon Pledger, used to say that clinical  
5 trials do not reflect clinical practice, and I  
6 think that that is quite true. So maybe part of  
7 what we're seeing in terms of the difference is a  
8 reflection of clinical trials versus clinical  
9 practice. Thank you.

10 DR. BURMAN: Thank you.

11 Dr. Proschan, you had a point of  
12 clarification?

13 DR. PROSCHAN: Yes. Just a comment about  
14 the question about looking at trials that weren't  
15 designed to answer the question versus ones that  
16 were. I really think that that's pretty much of a  
17 non-issue. And the reason is, we do that all the  
18 time in clinical trials. In clinical trials, we  
19 have multiple centers. They weren't designed to  
20 answer the question in each separate center. And  
21 we have no qualms about combining the different  
22 centers.



1           So I really don't think that's the issue, is  
2 whether they were designed with enough people. Of  
3 course they weren't doesn't with enough people to  
4 answer the question, and that's part of the reason  
5 you're doing a meta-analysis.

6           So to me, that's not -- the more important  
7 issue with meta-analysis to me is the fact that you  
8 do know the answer, perhaps, ahead of time, and  
9 then that can influence which trials you include  
10 and which you don't. But the fact that they  
11 weren't designed to answer the question doesn't  
12 bother me.

13           DR. BURMAN: Thank you.

14           Dr. Kaul, you had a point of clarification?

15           DR. KAUL: I was just going to respond to  
16 Dr. Jenkins's question, which I think was addressed  
17 to me.

18           I agree with you that that might be viewed  
19 as a potential weakness, that the trials were not  
20 designed prospectively for cardiovascular results,  
21 with no disrespect to Dr. Proschan.

22           But I think when I said that the FDA meta-

1     analysis is a high quality meta-analysis, I meant  
2     that it only included randomized, double-blind  
3     trials that were confined to diabetics and had  
4     patient-level data. And the long-term trials  
5     greater than two years' follow-up were excluded,  
6     which automatically excluded the hypothesis-  
7     generating trial from the meta-analysis, which was  
8     the DREAM study.

9             It focused on a clinically relevant  
10     endpoint, which was MACE. And the meta-analysis  
11     was stratified by trial to maintain the within-  
12     trial randomization method that the used; the exact  
13     odds ratio permits that. All other meta-analyses  
14     did not do that, and that was one limitation.

15            The FDA in their analysis conducted an  
16     appropriate sensitivity analysis, including risk  
17     differences that allows inclusion of zero event  
18     trials. And in the most updated meta-analysis,  
19     they even considered a Bayesian fixed effects  
20     model. I wish they had chosen a Bayesian  
21     hierarchical model, which would allow random  
22     effects to be analyzed.

1           So I think, based on those criteria, the FDA  
2 meta-analysis is a high quality meta-analysis, but  
3 the weaknesses remain. One weakness is that none  
4 of these trials were prospectively designed to  
5 address cardiovascular outcomes. Results were  
6 known prior to the statistical plan, so that  
7 renders it observational. So that's why it's  
8 hypothesis-generating.

9           Yes, events were not adjudicated by a  
10 blinded clinical endpoint committee, but that's a  
11 minor concern because we are looking at hard  
12 outcomes. And if an adjudication process has a  
13 role to play, and nobody knows it better than Dr.  
14 Mahaffey, it's for untangling events that are  
15 unclear, not for hard endpoints. So it's not a  
16 major issue there.

17           Yes, they didn't make adjustments for  
18 multiplicity, and there were insufficient number of  
19 events to even meet the diabetes cardiovascular  
20 guidance requirement. But regardless, of all the  
21 meta-analyses that I have seen published on this  
22 topic, the FDA meta-analysis meets the criteria of

1 a high quality meta-analysis.

2 DR. BURMAN: Thank you.

3 Dr. Jenkins, did you want to respond or  
4 comment?

5 DR. JENKINS: No. I wasn't making a point.  
6 I was just asking for the committee to opine  
7 because that's part of what we're having to weigh  
8 here. We have the RECORD trial, which normally you  
9 would think the randomized trial would be the gold  
10 standard. But it was not blinded and it was a  
11 noninferiority. So those are limitations.

12 I just was picking up on Dr. Kaul's comment  
13 earlier about his preferred meta-analysis would be  
14 of trials that were designed to assess the endpoint  
15 of interest. And I think it's been useful to hear  
16 a couple of different perspectives on how you weigh  
17 those factors in the hierarchy of evidence.

18 DR. BURMAN: Thank you.

19 Dr. Temple, you had a comment as well?

20 DR. TEMPLE: Yes. This is for Dr. Kaul and  
21 others, too. I assume reservations about what the  
22 studies were designed to do are not as applicable

1 to the mortality result because that pretty much  
2 speaks for itself, which is a phenomenon here, too.  
3 So on that one, the meta-analysis is pretty  
4 striking. It's a nearly twofold increase.

5 I also assume, although I can't tell from  
6 everybody's comment, that people are not so worried  
7 about the unblinding with respect to the mortality  
8 finding in RECORD because death is death, as  
9 somebody said the other day.

10 So it is striking that the results on the  
11 meta-analysis and the results on RECORD are quite  
12 strikingly different. And I just wondered what  
13 people make of that. I don't think the fact that  
14 one had placebo-controlled trials and the other  
15 didn't really explains that very well. I just  
16 wondered what people thought.

17 DR. BURMAN: Thank you.

18 DR. TEMPLE: Oh, I'm also interested in  
19 whether people really do mean that they are not  
20 particularly worried about assessment bias or  
21 anything like that when it comes to the mortality  
22 findings in RECORD. Am I right in assuming that

1       that's what everybody means?

2               DR. KAUL: I have the data here. I don't  
3       see a twofold increase in mortality. The endpoint  
4       with the highest estimate was MI, with 1.8.  
5       Mortality all-cause death was 1.38. Am I missing  
6       something?

7               DR. TEMPLE: Maybe I'm thinking of an  
8       earlier one. Okay. Sorry.

9               DR. BRITTAIN: I think maybe you're  
10      referring to the placebo portion of the meta-  
11      analysis there. I think it's about -- depending on  
12      which one you look at, maybe it's close to 2 for  
13      all-cause mortality. I thought that was the case.

14              DR. BURMAN: That was Dr. Brittain. Thank  
15      you.

16              DR. KONSTAM: Can I just -- I think that's  
17      the problem, Bob, isn't it, that there's no placebo  
18      in RECORD. So that sort of sits there and is  
19      unanswered. And again, there may be flaws in the  
20      meta-analysis anyway, and it may be post hoc  
21      conclusion. But still, I don't think that goes  
22      away. I don't think that goes away with RECORD.

1 DR. BURMAN: Thank you.

2 Dr. Suarez, you had a comment and point of  
3 clarification as well?

4 DR. SUAREZ-ALMAZOR: Yes. I think because  
5 of the various flaws that we have already discussed  
6 with relation to RECORD, we need to take the  
7 evidence all together and the totality of the  
8 evidence, including the observational studies.

9 I think one of the differences may also be  
10 related to the populations as they enter the  
11 studies. Usually in clinical trials you have a  
12 more -- even if they are outcome trials, you have a  
13 more restricted population than what you would have  
14 in observational studies, where you have everyone  
15 with all the comorbidities and so forth. So that  
16 can explain some of the results.

17 But in my view, there is deficiencies in the  
18 data, but that's what we have. So if I had to  
19 summarize what I see, I think there are three  
20 different aspects. If we look at mortality and we  
21 look at stroke, I think the data are still very,  
22 very uncertain, so we can't really say anything

1       about mortality or stroke.

2               If we look at MI, I think the signal is  
3       there and it's almost in every single study,  
4       observational or not. And it's there in RECORD as  
5       well, although it's nonsignificant. But there's a  
6       15 percent increase in MI risk, and the sample size  
7       is smaller than what you see in observational  
8       studies. But the signal is consistent across every  
9       single study.

10              The third aspect is a comparison within  
11       class. And I think that almost every study has  
12       shown that pio is better than rosi. And I still  
13       fail to see a single advantage why someone would  
14       want to use rosi other than bladder cancer, which  
15       we haven't reviewed in detail. But I'm not  
16       absolutely convinced that rosi does not cause  
17       bladder cancer in the same way from the data I've  
18       been reviewing while we were talking. So that's my  
19       summary of the data.

20              DR. BURMAN: Thank you.

21              Ms. Killion?

22              MS. KILLION: Thank you. I wanted initially



1 to thank Dr. Kaul for his answer to this question  
2 and his recommendation that in the face of  
3 uncertainty, we come down on the side of judgment.

4 To answer why patients might actually want  
5 rosiglitazone and not pioglitazone, I'm taking a  
6 step back in my perspective as a patient. And as a  
7 patient, Dr. Gerstein's presentation today really  
8 resonated with me because I think that in terms of  
9 treatment, in terms of dealing with the disease,  
10 there's always a tension between what we know and  
11 what we fear. And what we fear tends to overpower  
12 what we know, so we have to be very, very careful  
13 because it's very difficult to rehabilitate a drug,  
14 any drug, once it's been through a process like  
15 this.

16 We may or may not be able to assess the harm  
17 of a particular therapy to the degree of certainty  
18 that we would like, but it's much more difficult to  
19 assess what we can't know. And one of the things  
20 that we can't know is, what is the harm to patients  
21 who will not have access to a therapy that is best  
22 suited to them, or patients are forced off a

1       therapy that is working for them onto a different  
2       drug?

3               So these are the kind of choices that we're  
4       making here. And we need to be cognizant of the  
5       fact that drugs are not interchangeable, and  
6       neither are patients. So diabetics are a very  
7       diverse population. It's a very heterogeneous  
8       population.

9               They have a disease that lasts their  
10       lifetime. It's progressive. It changes over the  
11       course of their life. And how do you measure the  
12       harm that may occur when access to therapies are  
13       restricted without a very clear signal? Thank you.

14              DR. BURMAN: Thank you.

15              Dr. Phillips?

16              DR. PHILLIPS: I think you addressed a lot  
17       of the things that I was feeling, too. And the  
18       questions for both the clinician and a patient are  
19       looking at what's important to them.

20              The bottom line, I think there's two major  
21       issues. One is mortality, death versus no death,  
22       and the other is quality of life. And certainly

1 the MACE endpoint addresses the quality of life  
2 issues with things like stroke and cardiovascular  
3 events that could be debilitating.

4 The bottom line that I get from looking at  
5 all the data, and I think you need to look at all  
6 of it in its totality, is, as Dr. Gerstein said  
7 earlier this morning, we've got a whole lot of  
8 uncertainty. And the uncertainty as far as life  
9 prolongation and reduced mortality is, it might be  
10 a little bit to this much better; it might be a  
11 little bit to this much worse.

12 I think you need to look at potential  
13 cardiovascular signals within the context of that  
14 overall mortality and quality of life. So I think  
15 we don't know what we don't know, and there's still  
16 a whole lot that we don't know.

17 But I think a lot of the concerns and  
18 signals -- the concerns that were present in 2010  
19 have resolved to more uncertainty without the fears  
20 that there were significant errors or problems that  
21 were leading to that uncertainty.

22 DR. BURMAN: Thank you.

1           We have about 20 more minutes. Dr. Geller?

2           DR. GELLER: I actually would like to  
3 address the third question.

4           DR. BURMAN: I'm sorry. Address what?

5           DR. GELLER: The third question. The third  
6 item on the discussion list.

7           DR. BURMAN: We're going to get there next.

8           DR. GELLER: So in my ideal world, I'd like  
9 to see the TIDE trial done. But I don't know that  
10 that's feasible. TIDE was supposed to have 16,000  
11 patients. Now, in Dr. Gerstein's presentation, he  
12 was talking about a trial of 10,000 comparing  
13 rosiglitazone to placebo. I don't think 10,000 is  
14 necessary. I'm not sure where that number came  
15 from.

16           The TIDE trial was supposed to deal with  
17 patients who had high cardiovascular risk but were  
18 previously untreated diabetics, so I think that's  
19 why the sample size was so large.

20           So I think one could insist upon a better  
21 RECORD. It would be a superiority trial which was  
22 placebo-controlled and blinded, double-blinded,

1 with matching HbA1c goals in the two arms. And  
2 that answers the question of whether there's other  
3 drugs that have adequate control over glucose but  
4 not the same toxicity profile.

5 The data should go to an independent data  
6 coordinating center. There should be large sites  
7 accruing patients, and a good chunk of them should  
8 be from North America, respecting the fact that  
9 Dr. Gerstein comes from Canada.

10 DR. BURMAN: Dr. Geller, these are all  
11 excellent comments. We're still on question 2.

12 DR. GELLER: I thought you said I should go  
13 ahead and talk about question 3.

14 DR. BURMAN: Well, I don't want to cut off  
15 if you're in the middle.

16 DR. GELLER: I'm sorry.

17 DR. BURMAN: No, I'm sorry, too. You're in  
18 the middle.

19 DR. GELLER: How should I --

20 DR. BURMAN: Why don't you please finish,  
21 and we'll go on.

22 DR. GELLER: All right. So the primary

1 endpoint should be MACE. The component should be  
2 secondary endpoints. Of course, total mortality  
3 must be a secondary endpoint. And I would like to  
4 motivate the company to undertake this trial by  
5 agreeing to suspend the REMS if they undertake the  
6 trial.

7 I understand these are two separate issues,  
8 but I'm not sure they'll undertake the trial if  
9 they don't have to.

10 DR. BURMAN: Thank you. We will get back to  
11 you in a minute when we finish up question 2. I  
12 apologize for any misunderstanding.

13 I think we still have several  
14 people -- Dr. Morrato, who had some comments, for  
15 one?

16 DR. MORRATO: Yes. I wanted to get back to  
17 the question that Drs. Jenkins and Temple had asked  
18 because for me, when I'm considering whether or  
19 not, in the meta-analyses, these were prospectively  
20 designed, the point I think you were getting to is  
21 the ascertainment of the endpoints, and were they  
22 consistently collected, and so forth.

1           So for me -- you asked it open-ended -- I  
2       would affirm that yes, it's less of a risk with  
3       mortality, and more of the concern is with the MI.

4           The degree to which we're talking about the  
5       MI being the signal, then that becomes more of a  
6       concern to the degree to which there's consistency  
7       and rigor in how those events were collected. I  
8       know we didn't get to discuss that data today, but  
9       that would be one thing I would look at.

10          To your question around what do you do with  
11       the disparate mortality results, I went back, and  
12       the point estimates, if you look at all-cause  
13       death, for example, and I think the meta-analysis  
14       data that you had quoted, Dr. Temple, in your memo  
15       last time was using I guess the one that was  
16       preferred by biometrics. So that was an odds ratio  
17       of 1.38. Right? That's compared to maybe the  
18       RECORD of .086.

19          But if you look at the confidence intervals  
20       of those, they are overlapping. So the point  
21       estimates may make it look like they're more  
22       disparate results, but maybe, in totality, if you

1 look at it, they're more similar than maybe  
2 dissimilar.

3 You see similar things, I think, with the  
4 point estimates for MACE as well as MI. RECORD  
5 brings it back down more to the null in terms of  
6 the odds ratio, but there are overlapping  
7 confidence intervals. So that's where I would get  
8 into wanting to better understand how are those  
9 endpoints ascertained, and how did that vary versus  
10 how RECORD was doing it.

11 DR. BURMAN: Thank you.

12 Dr. Hammerschmidt?

13 DR. HAMMERSCHMIDT: Yes. I think most of  
14 the points that I would make directly to the  
15 question have already been made. But I also want  
16 to point out that there are other sources of  
17 information that we have to think about because  
18 they provide context, things like pathophysiologic  
19 plausibility of things and research that may be  
20 coming down the pike.

21 I'd specifically address the FASO (ph)  
22 conclusion that rosiglitazone is much better with



1       respect to bladder cancer by pointing out that in  
2       animal models, where you deliberately induce  
3       bladder cancer with nitrosamine, rosiglitazone  
4       doubles the incidence of bladder cancer.

5               So there's quite a bit of evidence in animal  
6       studies that rosiglitazone may do the same thing,  
7       but may do it with a longer time interval or at a  
8       different dosing. So I think we have to be a  
9       little bit careful to pay attention to what's going  
10      on in the rest of the data universe, not just in  
11      the clinical trials.

12             DR. BURMAN: Thank you.

13             Dr. Moss?

14             DR. MOSS: I wasn't planning on responding  
15      to that particular question as I have another  
16      point. But I think one has to be very careful with  
17      animal studies that very frequently they are not  
18      consistent with what we find in clinical studies in  
19      many different diseases. So I think one has to be  
20      careful on that.

21             The only point I want to make is that the  
22      sponsor has been criticized for not conducting a

1 placebo-controlled trial when it was designed. I  
2 disagree with that because I don't think one could  
3 have done a placebo-controlled trial because there  
4 were already two existing drugs or more on the  
5 market that have been accepted; so that it's very  
6 unlikely that this would have ever gotten through  
7 our human investigation committee with a placebo-  
8 controlled trial when there are existing  
9 medications that are prescribed routinely to reduce  
10 the incidence of hyperglycemia and all its  
11 complications.

12 So this criticism of the RECORD trial, I  
13 think the only real criticism was that it was not  
14 blinded. But in terms of placebo control, I don't  
15 see how that could have been done.

16 DR. BURMAN: Thank you. Thank you all for  
17 your excellent comments.

18 My thoughts are similar. There obviously is  
19 a difference of opinion regarding the ranking of  
20 the hierarchy of studies. It's agreed, of course,  
21 that placebo, randomized, controlled, double-blind  
22 studies are at the top of the list, although on

1 fairness, some groups put meta-analysis at the  
2 highest level.

3 There is debate in some questioners whether  
4 observational studies or meta-analysis should be  
5 ranked higher. In my view, after reviewing the  
6 relevant literature, the putative higher ranking  
7 of a meta-analysis depends on the quality of the  
8 included studies.

9 Therefore, I'm not sure I can make a general  
10 statement regarding the hierarchy and its priority.  
11 However, when applied to the present discussion, I  
12 rank observational studies and the RECORD CV  
13 outcome trials higher than the meta-analysis.

14 I rank RECORD higher in particular given the  
15 clinical trial nature of the study, the large  
16 number of patients involved, and because of the  
17 adjudicated results. I do agree with consideration  
18 of each type of data, but giving higher priority to  
19 RECORD. There are flaws, of course, with each of  
20 the studies we are discussing.

21 I did review an article by Dr. Garg  
22 published in 2008, where he reviewed the

1 limitations of meta-analysis and emphasized that  
2 meta-analyses in general have many potential  
3 limitations that we've talked about, that they  
4 depend totally on the quality and analysis of the  
5 original studies. Combining studies of various  
6 duration and quality is problematic. And, for  
7 example, 58 percent of it 86 renal meta-analyses  
8 had substantial flaws, at least in their opinion.

9 The literature is replete with examples of  
10 meta-analysis giving variable, misleading, or  
11 inappropriate results. The examples include the  
12 use of magnesium in the post-MI setting. Laurier,  
13 et al., compared 12 RCTs with 19 previous meta-  
14 analyses. Approximately 35 percent of the time,  
15 the randomized trial results were not correctly  
16 predicted by the meta-analysis. Tiotropium and  
17 cefepime probably represent additional examples.

18 So with that, I think, unless there's any  
19 other comments or questions, we'll move to  
20 question 3. Dr. Hiatt, did you have a question?  
21 No. Okay, no problem.

22 Based on the totality of available data,

1     please recommend if any additional clinical trial  
2     or trials should be conducted to evaluate the CV  
3     safety of rosiglitazone. For any trial you might  
4     propose, please describe the objectives of such a  
5     trial, discuss the feasibility of conducting such a  
6     trial, and discuss the ethics of conducting such a  
7     trial.

8             I'd like to ask Dr. Geller to follow up. I  
9     apologize for the miscommunication before, but we  
10    certainly appreciate your comments.

11            DR. GELLER: I think I've heard expressions  
12    of considerable uncertainty, and I think the best  
13    way to resolve that would be with another trial. I  
14    proposed the skeleton of a design, and I'll just  
15    repeat some of it.

16            Placebo-controlled, double-blinded, with  
17    matching HbA1c goals. The data go to an  
18    independent data coordinating center. There's  
19    prompt blinded endpoint review, including review of  
20    all hospitalizations.

21            There are North American sites included, a  
22    substantial number of them. And the centers accrue

1 more than a couple of patients; they should be  
2 large centers. Primary outcome should be MACE.  
3 Components should be secondaries. Total mortality  
4 should be secondary.

5 I think regarding the ethics, I think there  
6 really is clinical equipoise because we just don't  
7 know. And the feasibility, I think, is somewhat of  
8 an issue, and I think the FDA would have to make a  
9 statement that they consider this very important to  
10 do. And I think the REMS would have to be  
11 suspended in order to conduct such a trial. But I  
12 think we need it because we don't know the answer  
13 now.

14 Otherwise, we'll have a drug on the market,  
15 even if in a very limited way, for which we really  
16 don't have a good handle on the safety. And that's  
17 really not a good idea for the American public.

18 DR. BURMAN: Dr. Heckbert?

19 DR. HECKBERT: Yes. I'd make the comment  
20 that rosiglitazone was approved in 1999. So  
21 there's been a really long delay in getting  
22 definitive information about its effects on major

1       cardiovascular outcomes, and we still don't have  
2       it now.

3               If a large, long-term, randomized, double-  
4       blinded trial had been conducted soon after its  
5       approval when there really was equipoise, we might  
6       have the answer now.

7               As much as I would like to see the kind of  
8       trial you're talking about, based on Dr. Gerstein's  
9       presentation, at this point my take is that it may  
10      well not be feasible to conduct the kind of trial  
11      that would provide the information that we want and  
12      that patients deserve to have.

13              DR. BURMAN: Thank you.

14              Dr. Hiatt?

15              DR. HIATT: It's been an interesting  
16      journey, starting this process over a decade ago  
17      with the Cardiorenal Division, where the only level  
18      of evidence accepted for making decisions was  
19      clinical evidence, to now serving a division that  
20      historically would approve drugs based on  
21      surrogates such as LDL cholesterol or hemoglobin  
22      A1c.

1           That changed a lot, I understand, in  
2   2010 -- I wasn't at that meeting -- with the RECORD  
3   trial results and the concern about data integrity,  
4   and the signal leading to a guidance that now  
5   requires cardiovascular outcome trials to rule out  
6   a safety concern, not necessarily to show that  
7   lowered A1c is clinically beneficial from a  
8   cardiovascular perspective.

9           Then the irony for me is that, in fact, this  
10   sponsor took that responsibility on and designed  
11   what I still think is a pretty good trial that got  
12   put on hold. And so we're kind of left in a  
13   quandary.

14           In this situation, I think, based on the  
15   evidence we're seeing today, that it would be  
16   ethical certainly to run a trial. I think if  
17   background therapy was managed, that placebo should  
18   be included.

19           I think that, to Dr. Temple's comment  
20   earlier, there may be several things that could  
21   alter a MACE endpoint that are obvious, such as use  
22   of statins has been discussed extensively in this



1 meeting; perhaps blood pressure control.

2 I don't put a lot of weight on the  
3 cardiovascular benefits of lowered A1c, but the  
4 design might be a little challenged in making sure  
5 that those background therapies are properly  
6 regulated.

7 In addition, if glycemic control were  
8 different between arms, it could unblind the study.  
9 So in my mind, that might be a bigger concern than  
10 whether it might actually alter the primary  
11 endpoint.

12 So I think such a trial, testing a  
13 superiority hypothesis to truly try to get at truly  
14 the cardiovascular benefit of treating blood sugar  
15 and diabetes, would be extremely important.  
16 Whether it's feasible or not, though, in this  
17 particular case, I can see where that would be  
18 extremely challenging.

19 As we saw earlier, the drug class is falling  
20 off in terms of prescriptions; that there are a  
21 number of new options coming online, and therefore,  
22 that may not be feasible. And so I think what's

1       being discussed today has a lot to do, or has more  
2       to do, perhaps, with other drugs coming along than  
3       with rosiglitazone, per se.

4               But should the sponsor get a signal that  
5       this committee is really interested in that  
6       information, it would be awfully nice if they took  
7       it on because I think all the challenges we've been  
8       faced with decision-making today could be resolved  
9       with a properly designed trial.

10              DR. BURMAN: Thank you.

11              Dr. Konstam?

12              DR. KONSTAM: Yes. I also would like to see  
13       a trial. I'm reflecting back to 2010, and my  
14       feelings at that time, I actually think technically  
15       we were in equipoise, but I think that the  
16       overwhelming amount of evidence of concern was such  
17       that I think the FDA's actions were appropriate at  
18       that time.

19              My own feeling was that it was very  
20       difficult for me to justify the ethics of a trial  
21       where you basically, in my mind, were telling a  
22       patient, there is a strong weight of evidence

1       indicating that this drug is harmful. We want you  
2       to participate in a trial to find out whether  
3       that's true or not. And I guess I have a lot of  
4       trouble with the ethics of that.

5               Now, what's different now? I think what's  
6       different now is that the results of the  
7       readjudication of RECORD in my mind has moved the  
8       needle. I think the fact that there's no adverse  
9       signal with mortality, and in fact a nice trend in  
10      the right direction, really to me is a positive and  
11      one that might be legitimately held up to a patient  
12      as a possibility that it might in fact be  
13      substantiated in the trial. So I think that we're  
14      more toward true equipoise now from that in general  
15      than we were in 2010.

16             So what would be the trial? First off, it  
17      may be extremely difficult to do this trial. I'm  
18      not sure what GSK's position on this is. I'm not  
19      sure that they will agree to do the trial, as  
20      opposed to just allowing the drug to disappear at  
21      this point. I asked them that question. I haven't  
22      heard an answer from them.

1           I think there are a lot of problems,  
2 perhaps. But I think nevertheless, that aside, I'd  
3 like to see the trial. I like a lot of the things  
4 that Nancy said. I thought that the TIDE trial,  
5 with no comment on the vitamin D issue, I think the  
6 rosi/ pio/placebo idea I liked.

7           I would like to see a head-to-head  
8 comparison of rosiglitazone and pioglitazone. I  
9 think there's a significant hypothesis posed by the  
10 observational data in that regard. I think that's  
11 been challenged. I think that's a very legitimate  
12 issue to be tested. So I wouldn't be opposed to a  
13 three-way randomization there.

14           I agree with Dr. Hiatt's issues about what  
15 do you do with placebo, and what happens if you  
16 wind up with significant imbalance in glycemic  
17 control? That would be a problem. I think you  
18 have to have some boundaries of similarity in  
19 glycemic control across the groups for it to be  
20 meaningful.

21           The endpoints of interest are all-cause  
22 mortality, cardiovascular mortality, and MACE. I

1       don't know which should be the primary, but I think  
2       that there should be some degree of power, some  
3       substantial degree of power, to test each one of  
4       those endpoints.

5               DR. BURMAN: Thank you.

6               Dr. van Belle?

7               DR. VAN BELLE: Well, I think the train has  
8       left the station, and I don't think this study is  
9       feasible any more, given the length of time that  
10      the current product will still be on the market.

11              I also think that there are lots of other  
12      medications in the pipeline right now in clinical  
13      trials, and I think that's probably where the  
14      action's going to be.

15              I also think, getting back to my earlier  
16      comment about the surrogate outcome, a TIDE-like  
17      study should have been required by the FDA at the  
18      time that Avandia was approved. And I think that  
19      that would have been the way that we would have  
20      solved the whole problem of the clinical efficacy  
21      of this particular drug.

22              I would hope that the FDA in the future

1 would think more carefully about requiring the  
2 clinical efficacy trials to be started concurrently  
3 with medications that are approved on the basis of  
4 a surrogate outcome.

5 DR. BURMAN: Thank you.

6 Dr. Day?

7 DR. DAY: Just a brief comment about having  
8 a new clinical trial and requiring that the REMS be  
9 removed. I think you are referring to the  
10 restriction on prescribing.

11 There are other parts of the REMS that are  
12 in there, such as the medication guide, that I  
13 don't think people would support getting rid of  
14 that. So we need to be more specific about what  
15 parts would be suspended, in your view.

16 DR. GELLER: I think the REMS itself means  
17 the limited access, and that's the part we'd have  
18 to remove. But I think that means removing the  
19 REMS, although I agree with you that the  
20 educational material should be required.

21 DR. BURMAN: Thank you.

22 Dr. Kaul?

1 DR. KAUL: Thank you. I just would like  
2 to remind the committee that at the 2010 panel,  
3 19 people voted yes to allow the TIDE trial  
4 continue to enroll, 11 voted no, 2 abstained, and  
5 one left before the vote was cast. There was no  
6 question regarding readjudication that was asked of  
7 the committee at that time.

8 In June of 2011, shortly after it was  
9 suggested, the REMS program, my colleague  
10 Dr. George Diamond and I wrote that, "The TIDE  
11 trial was recently put on clinical hold by the FDA  
12 pending readjudication of RECORD trial data. In  
13 our opinion, it is scientifically imperative that  
14 the TIDE trial be resumed once the FDA is reassured  
15 that the RECORD trial yields valid inferences."

16 Perhaps it was the idealist in both of us  
17 that articulated those statements. However, from  
18 ethical and economic perspective, challenging  
19 questions remained regarding the necessity and  
20 practicality of such within-class and outside-class  
21 comparative effect on those trials.

22 So the idealist in me still would want the

1 TIDE trial to be conducted for non-scientific  
2 reasons. I think restoring faith in the process is  
3 not a trivial consideration. Regaining the  
4 goodwill of the stakeholders should be an important  
5 consideration for the sponsor as well.

6 But the pragmatist in me realizes that all  
7 the stars have to be aligned for this to happen.  
8 The regulators have to lift the restricted  
9 distribution component of the REMS. The ethics  
10 committees have to agree. The informed consent has  
11 to be written in such a manner that it is not  
12 confusing and burdensome for enrolling patients.  
13 And the sponsor has to provide the necessary  
14 resources for this trial to happen.

15 Is that feasible? The answer, in my mind,  
16 I'm not so sure.

17 DR. BURMAN: Thank you.

18 Dr. Proschan?

19 DR. PROSCHAN: Yes. I think the biggest  
20 reason not to recommend a new trial is, do you  
21 really want to come back in 2017 and hear the  
22 results?



1 (Laughter.)

2 DR. PROSCHAN: No. I'm being facetious.

3 But I do think that we have to figure out what the  
4 question is. Are we trying to show that it's safer  
5 than placebo, or are we trying to show that it's  
6 safer than other diabetes drugs? And those  
7 questions are very different.

8 Ideally, to me the only reason to do another  
9 trial would be to try and assess it against placebo  
10 because I'm satisfied that versus other diabetes  
11 drugs, it's okay. So the only reason to do another  
12 trial would be to assess it against placebo.

13 But I don't think that's feasible. First of  
14 all, I think there are ethical problems. But I  
15 also think there's a huge issue of the fact that  
16 there would be differential rescue medication to  
17 get people down to the right HbA1c level.

18 So I don't think it'll be particularly  
19 informative unless -- and from the ethical  
20 standpoint, perhaps you could do a short-duration  
21 trial, and so maybe that's the solution, is to do a  
22 whole bunch of tiny, short-duration trials, none of

1       which by themselves would be considered unethical,  
2       and then you do a meta-analysis of all these  
3       different trials that are considered ethical. It  
4       doesn't matter that together they're unethical.

5               (Laughter.)

6               DR. PROSCHAN: So I just don't think you can  
7       do another trial that would be meaningful and shed  
8       much light.

9               DR. BURMAN: Thank you.

10              Dr. Suarez?

11              DR. SUAREZ-ALMAZOR: Yes. I think it  
12       wouldn't be feasible, and I also think it wouldn't  
13       be ethical. For patients right now, there's only  
14       3,000 patients in the U.S. that are taking this  
15       drug. RECORD has close to 5,000 patients.

16              So even if every single patient wanted to be  
17       enrolled, I don't think we would get the numbers  
18       because there's a reason why physicians, even  
19       though there is a REMS, are not putting patients in  
20       this drug. So I don't think they would be eligible  
21       because we would see higher numbers.

22              I don't think it's ethical -- it's been

1       mentioned already -- because there are other drugs  
2       that are coming down the pipeline where there are  
3       clinical trials. And I think it's not fair to the  
4       patients to enroll them in a trial where we are not  
5       really trying to see if they are going to improve.

6               We just want to make sure that there's no  
7       more risk for MI because of our scientific  
8       curiosity, to some degree, which is healthy, but  
9       I don't think it's fair to the patient. It doesn't  
10      seem to me that it would be ethical at this point.

11             DR. BURMAN: Thank you.

12             Dr. Rasmussen?

13             DR. RASMUSSEN: I just want to make a few  
14      points to bring into perspective what would be  
15      required and how we likely would end up sitting  
16      here again in maybe not four years, but maybe six  
17      or seven years to discuss how a design or a trial  
18      conducted according to standards today has excluded  
19      an excess risk of 30 percent with reasonable  
20      assurance. And that's with a primary endpoint of  
21      MACE, not of myocardial infarctions or strokes or  
22      any of the individual components, but just the

1       totality of it.

2               Something like that requires something in  
3       the order of 10,000 patients followed for five  
4       years, with a placebo control added to standard of  
5       care, meaning that there are confounding factors  
6       that would have to be taken into ACC again.

7               So I think if this was imposed and if it was  
8       feasible, I think it's very likely that we would  
9       end up in a similar situation as we are today. So  
10      I think the committee has to come to terms with the  
11      fact that we're already today accepting a residual  
12      risk that we allow drugs for the treatment of  
13      diabetes to enter the market with, and that  
14      rosiglitazone shouldn't necessarily be held to a  
15      higher standard.

16              DR. BURMAN: Thank you.

17              Dr. Budnitz?

18              DR. BUDNITZ: Again, I'm not going to  
19      address the feasibility of conducting a safety  
20      trial of rosi. But just as a practical matter, as  
21      I read the goals of the rosi REMS, it's to restrict  
22      access because of potential increased risk of MI.

1           So I don't know how a trial that doesn't  
2     have MI as an endpoint is going to address changing  
3     this REMS because we still wouldn't know  
4     specifically for MI at the end of just a MACE or  
5     death trial.

6           Also, I guess this a comment about specific  
7     safety-focused trials. A few things that just came  
8     up in analysis of RECORD is the importance of per-  
9     protocol treatment. Hopefully, it would not be  
10    such an issue because it would maybe have it a  
11    U.S.-based trial, so we wouldn't have this issue of  
12    people coming off rosi for insulin. But that  
13    should be part of the primary analysis.

14           Then finally, this issue of incomplete  
15    ascertainment, which biases to the null when you  
16    don't do that. That's okay, I guess, for an  
17    efficacy trial. But for a safety trial, that  
18    becomes more of an issue. So three practical  
19    matters if we do consider another trial.

20           DR. BURMAN: Thank you.

21           Dr. Moss?

22           DR. MOSS: Throughout all these discussions,

1 we haven't heard a comment about a phase 4 clinical  
2 trial. So let us just for a moment say that the  
3 decision is to remove the REMS and allow the drug  
4 back on the market, but to encourage the FDA to  
5 really carry out an enhanced, improved phase 4  
6 trial.

7 This is something they have been  
8 progressively involved in. And I would appreciate  
9 Dr. Temple's comments on this as to whether he  
10 thinks this has relevance and whether it could  
11 contribute to answering some of the questions that  
12 have been raised throughout the past two days.  
13 Thank you.

14 DR. BURMAN: Dr. Temple?

15 DR. TEMPLE: Thank you, I guess. Well, the  
16 phase 4 trial is the sort of thing we've been  
17 talking about. Just for context, as everybody  
18 knows, every new drug for glycemic control has a  
19 noninferiority-type safety study against something  
20 else. Could be a placebo. Could be a mixture of  
21 things. Could be a lot of things. So we really  
22 believe in trying to characterize the

1       cardiovascular risk.

2               One could say, and people have said this,  
3       that you sort of have that study from RECORD, if  
4       you believe the readjudication well enough. The  
5       issue in TIDE was how the two members of the same  
6       class compare. That is not something we usually  
7       ask people to do, but obviously, it's an  
8       interesting question given the epidemiologic  
9       studies and stuff like that.

10              We have limited capacity, in my view, under  
11       law to insist on comparative studies of that kind.  
12       Maybe if there's a hint of a problem or a hint of a  
13       benefit, maybe we could figure out how to do it.  
14       But it's not something FDA usually does, insisting  
15       on comparative data, not that people aren't  
16       interested in it.

17              So what we could require and insist on, I  
18       think, remains to be determined and I wouldn't be  
19       able to say right off the bat. But like everyone  
20       else, I'd be really interested in the result of  
21       TIDE, at least partly because of the epi studies.  
22       I'm skeptical of modest effect sizes in an

1 epidemiologic study, but they do go the same way a  
2 lot of times so it's tempting to think about.

3 But I don't know. Other people might want  
4 to comment on that. Whether we could require  
5 something like that seems uncertain to me.

6 DR. MOSS: Let me just make a point. I  
7 wasn't thinking of the TIDE trial as an example. I  
8 was actually thinking of if rosiglitazone were to  
9 be re-released, if you will, could one do an  
10 adequate phase 4 trial that might answer some of  
11 these questions?

12 DR. TEMPLE: John's asking, do you mean  
13 could we require further observational data under  
14 Medicare or something like that?

15 DR. MOSS: Yes. But intense observational  
16 information at a much higher level than what exists  
17 at the present time.

18 DR. TEMPLE: Yes. I have to say my  
19 reservation about that, but other people need to  
20 comment, is we're looking for hazard ratios in the  
21 1.2, 1.1 range. And I continue to be skeptical  
22 about the capacity of epi studies to do that, and



1 I'm not alone; epidemiologists say that all the  
2 time, too, although they don't entirely mean it  
3 because they do studies that have those kinds of  
4 risks. I'm not sure.

5 Cost-wise it's much easier to do than a lot  
6 of other things. But I don't know.

7 Gerald, do you have any thoughts on that?

8 MR. DAL PAN: So if I understand you  
9 correctly, you're saying if the product were  
10 returned to market, it would be prescribed more  
11 widely, one could follow the people to whom it's  
12 prescribed, and measure outcomes in a prospective  
13 way.

14 I think the issue there is that people would  
15 not be receiving treatment randomly, and all the  
16 biases that go into selection of patients to have  
17 one treatment or another would be there.

18 So when you end up comparing a rate of  
19 whatever outcome you're interested in, in the  
20 rosiglitazone group versus whatever comparator you  
21 choose, and the comparator patients would have to  
22 be followed with equal rigor to make a comparison,

1 to even begin to make a comparison, you're still  
2 left with all those biases that are problematic in  
3 observational studies in general.

4 So I think that's why the preferred approach  
5 is a randomized, double-blind, controlled clinical  
6 trial.

7 DR. MOSS: Well, let me just say I still  
8 believe in the randomized, placebo-controlled  
9 design trials. But it seems to me that with the  
10 availability of complex statistics and  
11 biostatistics, if designed properly and  
12 prospectively set up, that one could answer these  
13 questions and correct for these issues.

14 As I say, I think the randomized clinical  
15 trial is the right way to go. But I think it's  
16 impractical that one's going to do that with a  
17 placebo control, et cetera.

18 So the question comes up as to whether a  
19 good phase 4 clinical trial, well thought out, with  
20 involvement of appropriate complex multivariate  
21 statistics, would answer the question. And I think  
22 it could. But it would take a certain degree of

1 design and development to do right.

2 But I think that this may be something  
3 that's going to come up more and more in the future  
4 because many drugs are going to be compared against  
5 existing drugs, and you're not going to have the  
6 placebo control. So I think that this is maybe a  
7 stepwise question for FDA.

8 DR. TEMPLE: Dr. Moss, what particular  
9 comparison would be of most interest to you, do you  
10 think? You didn't mean against pio particularly.

11 DR. MOSS: Well, I think the issues that  
12 have been raised about the safety concerns I think  
13 are problematic, and when viewed in the light of  
14 what appears to be a reduction in mortality from  
15 the existing RECORD trial.

16 So it seems to me that one could look at a  
17 few of the major endpoints that have been raised  
18 here, the secondary endpoints, which I consider  
19 secondary to the primary endpoint of mortality. So  
20 I think that myocardial infarction -- I've not been  
21 convinced that the definition of heart failure was  
22 a good definition. It's a fluid retention

1 definition.

2 So I think that one could really improve  
3 considerably on the criteria used for these  
4 endpoints and carry out and imaginative and  
5 prospective well-designed study, a phase 4 trial.

6 DR. TEMPLE: But the comparison would be  
7 with some other particular or some other group of  
8 oral hypoglycemics, not particularly pio? I just  
9 want -- right?

10 DR. MOSS: That is correct. I think there  
11 are enough patients with diabetes that it would be  
12 easy to get a large number of patients taking any  
13 one of three or four drugs. So I think that this  
14 could be done, and there's plenty of patients  
15 available to do such studies.

16 DR. TEMPLE: One could probably also argue  
17 that the attractiveness of it might come from the  
18 favorable lean on mortality effects. That might  
19 make people interested in doing a study like that  
20 to see if it was true.

21 DR. MOSS: That seems reasonable.

22 DR. BURMAN: Thank you.

1           Dr. Proschan, did you have a clarification  
2           or comment?

3           DR. PROSCHAN: I was just going to comment  
4           that I think the non-statisticians have a lot more  
5           confidence than the statisticians in the ability of  
6           complex statistical models to fix problems.

7           DR. MOSS: I guess it depends upon the  
8           statisticians with whom one works.

9           DR. BURMAN: Thank you.

10          Dr. Smith? You're fine?

11          DR. SMITH: (Nods head affirmatively.)

12          DR. BURMAN: Anybody else have any other  
13          comments?

14          (No response.)

15          DR. BURMAN: I'd like to just have a quick  
16          comment. It certainly agrees with what already has  
17          been discussed, although of course there seems to  
18          be a discordance among people who want a trial and  
19          people who don't.

20          My comment is in an ideal world it would be  
21          appropriate to recommend additional clinical trials  
22          to evaluate the safety of rosiglitazone. However,

1 in the real world, this would seem difficult and  
2 perhaps impossible.

3 Indeed, as mentioned, there are ethical  
4 issues that arise, especially given the goal, which  
5 would be safety. A clinical trial would help to  
6 definitively resolve the issues raised.

7 If it could be performed logistically and  
8 financially, I would recommend efforts be made to  
9 try and perform this study. If the study could not  
10 be performed, given the amount of data collected  
11 and analyzed, it seems reasonable to establish a  
12 registry to monitor patients to help ensure the  
13 agent is safe, assuming it remains on the market.

14 Thank you. Dr. Cooke, you had a comment as  
15 well? No?

16 Any other comments on that issue?

17 (No response.)

18 DR. BURMAN: Then we will move to the voting  
19 question in a second. But I would like to ask the  
20 FDA specifically if there are any specific issues  
21 that you feel should be addressed regarding the  
22 first three questions that haven't been addressed

1       that might help you in your deliberations.

2               We were asked if there's going to be a  
3       break. I think it's better just to go forward, and  
4       if somebody has to leave to do something, please  
5       do.

6               Let me just see -- does the FDA have any  
7       specific other issues they want raised? Dr. Parks,  
8       I'm sorry, I didn't see you.

9               DR. PARKS: I just have one question, I  
10      guess, for those members who actually recommend a  
11      trial. Is there a time frame that they would like  
12      to see this done and completed in?

13              DR. BURMAN: A time frame for the trial?  
14      Does anyone have any comments on that? Dr. Geller?

15              DR. GELLER: As soon as possible.

16              DR. BURMAN: And of course, it depends on  
17      how long the trial is, et cetera.

18              Anybody else have any other comments in  
19      regard to that?

20              (No response.)

21              DR. BURMAN: Any other issues from the FDA  
22      that you'd like to bring up?

1 (No response.)

2 DR. BURMAN: Anybody else have any other  
3 questions or comments before we move on? Dr. Kaul?

4 DR. KAUL: I just had one clarifying  
5 question of the FDA. And perhaps this might be the  
6 elephant in the room, and apologies for bringing it  
7 up.

8 If the FDA deems that the cardiovascular  
9 risk is no longer a concern, is it going to go back  
10 and revisit the diabetes guidance? Because the  
11 cardiovascular risk was the motivation behind the  
12 guidance.

13 DR. ROSEBRAUGH: I think that's a really  
14 interesting question, but I don't think it's the  
15 topic of this meeting. So we're not going to go  
16 down that alley right now.

17 (Laughter.)

18 DR. KAUL: But it is an elephant in the  
19 room.

20 DR. BURMAN: Thank you.

21 Dr. Rosebraugh? No?

22 Dr. Phillips?



1 DR. PHILLIPS: I just had a clarifying  
2 question. In your closing comments, you suggested  
3 a registry, I think, in a summary of the other  
4 discussion. And I think a registry would be a  
5 potential component of voting for either option A  
6 or potentially B or C.

7 So I guess I wonder how we should factor  
8 that -- maybe have that discussion after we have  
9 the vote, or as part of the discussion going around  
10 the room? Or do you have any directions for us as  
11 we vote on how we might consider that possibility?

12 DR. BURMAN: Thank you. I think it should  
13 be brought up in your explanation afterward. And  
14 the concept originally came from the letter from  
15 American College of Cardiology, who noted at least  
16 two large-scale registries that seemed effective.

17 Dr. Morrato?

18 DR. MORRATO: I think it might help with  
19 just some clarification as it relates to how we  
20 interpret -- and maybe you were getting at this,  
21 too, Dr. Phillips -- how we interpret REMS ETASU.  
22 I don't know if this is the right time.

1 I'm interpreting, based on the slide I think  
2 Dr. Jenkins showed earlier that the REMS can be a  
3 medication guide, they can be Elements of Safe Use,  
4 and there can be a communication/education plan.

5 Should we be thinking of it in those terms  
6 when we vote on removal/continuation/modification?  
7 Or like some panel members have raised, they've  
8 focused on the element of safe use which related to  
9 restricted distribution, informed consent,  
10 et cetera?

11 DR. BURMAN: I would ask the FDA to respond  
12 to that if they'd like to.

13 MR. DAL PAN: As Dr. Morrato mentioned,  
14 there's three big components to a REMS, and each  
15 can be done a little bit differently from one REMS  
16 to the next.

17 The first is information for patients, and  
18 that would be a medication guide or in some cases a  
19 different mechanism called the patient package  
20 insert, but basically a medication guide.

21 I'll note that we can require a mediation  
22 guide independent of a REMS, and so we would likely

1       continue a medication guide. It need not be an  
2       element of the REMS for it to be in full effect.  
3       So that's the first big bucket, if you will, which  
4       is information toward patients.

5               Communication plans are information to  
6       healthcare professionals. So they're mutually  
7       exclusive categories, the first two. The first is  
8       to patients. The second is a communication plan to  
9       healthcare professionals.

10              The third are any number of six different  
11       Elements to Assure Safe Use. There's a few of them  
12       here. And for practical purposes, we've built in  
13       the communication to healthcare professionals into  
14       those elements.

15              Some of these elements are dependent on the  
16       others. And maybe Dr. Weaver could explain how  
17       these elements -- let me just read them again from  
18       slide 5 from her presentation. One is --

19              DR. SEELY: Could you put up the slide?  
20       That would help.

21              MR. DAL PAN: Sure. If we could put up  
22       slide 5 from Dr. Weaver's presentation. So there

1       they are. And maybe Dr. Weaver could explain how  
2       these three elements interact with each other.

3               DR. WEAVER: The one that makes it difficult  
4       to remove without destroying the whole REMS is the  
5       certified pharmacies because the certified  
6       pharmacies make sure that the other stakeholders  
7       are enrolled. So if you remove that, then just  
8       logistically it's hard to actually implement a REMS  
9       because there's no mechanism to do it.

10              In terms of the other two, we do have some  
11       REMS that have certified prescribers without  
12       certifying the patients. In those cases, it's more  
13       often that maybe it's something that's used in the  
14       hospital that would be part of their informed  
15       consent in the hospital, or maybe it's something  
16       that for some other reason is more difficult to  
17       understand.

18              So in that case we might have prescribers  
19       certified without having the patients certified.  
20       In this case, it seems like if you think that the  
21       risk is there, that you would want both to have the  
22       information.

1 DR. BURMAN: Thank you.

2 Dr. Konstam?

3 DR. KONSTAM: I'm sort of still confused.  
4 So you started out saying that, if I understand you  
5 right, to have elements to assure safe use of some  
6 sort, you have to have certified pharmacies. You  
7 couldn't remove that and have an effective program  
8 of this type.

9 DR. WEAVER: It's just that logistically  
10 it's difficult to implement because it's at the  
11 dispensing site that they do the checks to be sure  
12 that the other parts of the REMS have been  
13 completed. And so it's the pharmacy that makes  
14 sure that the prescriber is certified, that the  
15 patient is certified, and they don't dispense the  
16 drug unless that is the case.

17 DR. KONSTAM: But if you eliminated provider  
18 certification and patient certification --

19 DR. WEAVER: Then there's almost no point in  
20 the --

21 DR. KONSTAM: -- then there would be also no  
22 reason to have pharmacy certification.

1 DR. WEAVER: That's correct. That's  
2 correct.

3 DR. KONSTAM: So there are three components.  
4 You just mentioned three components of REMS,  
5 although we also just heard that you can have a  
6 medication guide that's not part of a REMS, which  
7 is confusing.

8 DR. WEAVER: Right. Medication guides, we  
9 use them to communicate risk to patients. They're  
10 actually covered in other parts of the regs  
11 that -- we use them if a patient needs information  
12 to consider taking the drug or to continue taking  
13 the drug or for monitoring. That can be done, and  
14 historically has mostly been done, outside of a  
15 REMS.

16 DR. KONSTAM: Right. So could you have a  
17 REMS that just consisted of a medication guide and  
18 a communication strategy without the Elements to  
19 Assure Safe Use?

20 DR. WEAVER: You can have that. I'll warn  
21 you, though, that we have less success  
22 communicating to prescribers when it's not

1 mandatory. So if we're relying on them to read a  
2 communication from us, absorb it, and act on it, it  
3 generally doesn't work as well.

4 DR. KONSTAM: And the only way to do that is  
5 with the Elements to Assure Safe Use?

6 DR. WEAVER: That's what forces them to go  
7 through the process, yes.

8 DR. BURMAN: Mr. Dal Pan?

9 MR. DAL PAN: Sure. So if you go through,  
10 I think for the purposes of the voting question, I  
11 think our intent was to assume that we would retain  
12 a medication guide.

13 So when you vote on the REMS Elements to  
14 Assure Safe Use, what you're really voting on is,  
15 should we continue the restrictions or not? Or  
16 should we modify the restrictions, either lighten  
17 them up or make them tighter? Or can we replace  
18 the restrictions with some communication plan that  
19 doesn't link the ability to prescribe to having  
20 satisfied the requirements of the Elements to  
21 Assure Safe Use?

22 So I think when you go around and discuss

1 the question, you can state your views on those.  
2 If anybody feels strongly that there should not be  
3 a medication guide, we'd want to hear that. But I  
4 think that we're assuming that if we're going to go  
5 forward with patient information, continue a  
6 medication guide. And it's really what should be  
7 done about the restrictions.

8 DR. BURMAN: Thank you.

9 Dr. Morrato?

10 DR. MORRATO: That was very helpful. Is it  
11 fair to say if the medication guide is part of the  
12 REMS, that that also carries with it some  
13 evaluation opportunity, as opposed to when  
14 it's -- so if we were to do a communication plan  
15 and the medication guide, you could build in an  
16 evaluation assessment?

17 MR. DAL PAN: You're correct. When a  
18 medication guide is part of a REMS, the part of the  
19 REMS statute that requires assessments allows us to  
20 request a medication guide assessment. If it's not  
21 part of the REMS, we can't ask for those  
22 assessments.



1 DR. DAY: You said we cannot ask? If it's  
2 not part of the REMS, we cannot ask for assessment?

3 MR. DAL PAN: That's correct. It's only  
4 when it's part of a REMS can we ask for an  
5 assessment.

6 DR. BURMAN: Thank you.

7 Dr. Cooke? Okay.

8 Dr. Proschan?

9 DR. PROSCHAN: I still don't know exactly  
10 what I'm supposed to be considering when I'm  
11 thinking about safety of rosiglitazone. I'm still  
12 trying to figure out whether I should be -- and  
13 it's relevant to this question -- I'm still trying  
14 to figure out whether I should be satisfied if I  
15 think it's as safe as other diabetes drugs.

16 There's no question that lowering HbA1c  
17 helps with microvascular disease. So you could  
18 argue that someone's always going to get some  
19 diabetes drug. And so if you believe that, then it  
20 seems like the relevant comparison is rosiglitazone  
21 versus other diabetes drugs. But I don't know what  
22 the official -- I would imagine that the official

1 position we're supposed to take is relative to  
2 placebo. Is that right?

3 DR. TEMPLE: No. When you evaluate the  
4 safety of a drug, you always have in mind what the  
5 alternatives are. So even a very poorly tolerated  
6 drug might be acceptable if the alternatives were  
7 lousy. So you weigh that.

8 But in this case, you had studies that  
9 suggested an increased heart attack rate and an  
10 increased mortality when you used this as compared  
11 to when you used something else. So that would  
12 trouble you, and that's why you have the ETASU. If  
13 you no longer believed that, you might not worry  
14 about that.

15 If there were no drugs for diabetes at all,  
16 you'd accept all kinds of toxicity. Troglitazone  
17 would come back. But there were alternatives, rosi  
18 and pio. So troglitazone went away even though the  
19 net benefit in the absence of anything would  
20 probably still be favorable.

21 We regularly take drugs that work off the  
22 market if they're worse than other members of the

1 class or if they have extra risks that aren't  
2 justified by some advantage. So you're allowed to  
3 think of what's in the marketplace.

4 DR. BURMAN: Thank you.

5 Dr. Jenkins?

6 DR. JENKINS: Just to add to that, for  
7 approval of a drug we don't have a comparative  
8 efficacy standard. But we always consider the  
9 benefits and risks relative to the available  
10 therapy.

11 The same is true when we're considering  
12 whether a drug can remain on the market or requires  
13 restrictions. You're always considering the  
14 disease you're treating, the available options, how  
15 the drug in question weighs against the benefits  
16 and risks of those other alternatives.

17 So no, you don't just have to factor in how  
18 the drug compares to placebo. You look at it  
19 versus the armamentarium that's available for that  
20 disease as well as the seriousness of the disease,  
21 and then some people would even argue you weigh the  
22 value of alternative treatments. We heard some

1 people may respond to one better than the other.

2 So all those things come into play as we're  
3 making safety decisions about REMS, staying on the  
4 market, et cetera.

5 DR. TEMPLE: And we sometimes make a drug a  
6 second-line drug -- use only if something else  
7 fails -- or a third-line drug. There's all kinds  
8 of things like that that allow you to take those  
9 matters into consideration.

10 DR. BURMAN: Thank you.

11 Dr. Seely?

12 DR. SEELY: I don't have any questions.

13 DR. BURMAN: Dr. Hammerschmidt?

14 DR. HAMMERSCHMIDT: I think I'm going to be  
15 asking a question that probably is running through  
16 people's minds a little bit now, which would be  
17 what one would vote if one thought one certain  
18 thing, which is, if one felt that we should  
19 continue to have an information program and should  
20 have some sort of a data accumulation program, some  
21 sort of a database on people who get the drug, and  
22 want to be able to evaluate whether those programs

1 are having any effect, we would then have to vote  
2 to retain the REMS? Is that correct?

3 DR. JENKINS: I think you would vote for C,  
4 modification.

5 DR. HAMMERSCHMIDT: That's what I was  
6 asking. So that's a strategy we could not ADOPT  
7 outside of a REMS. Correct?

8 DR. JENKINS: Well, the three options are to  
9 remove the REMS with ETASU completely, keep it  
10 without any changes, and the third option is to  
11 continue to have a REMS but change it. And we  
12 specifically ask you to say how you would change  
13 it.

14 So we're not saying how you can recommend  
15 changes if you vote that option. You could say,  
16 get rid of all the ETASU but keep the medication  
17 guide and add a communication plan. You remember I  
18 mentioned earlier that there were basically three  
19 big buckets of elements for a REMS, medication  
20 guide, communication plan and ETASU.

21 So I think in the scenario you just  
22 described, you would vote C and then specify how

1       you would change things.

2               DR. BURMAN:   Thank you.

3               Dr. Geller?

4               DR. GELLER:   I think my question was just  
5 answered.   Thank you.

6               DR. BURMAN:   Thank you.

7               Anybody else have any clarifying questions  
8 in general or to the FDA before we bring up the  
9 vote?

10              (No response.)

11              DR. BURMAN:   No?   Thank you very much.   Then  
12 we will proceed on some general guidelines before I  
13 read the question.

14              We'll be using an electronic voting system  
15 for this meeting.   Once we begin the vote, the  
16 buttons will start flashing and will continue to  
17 flash even after you have entered your vote.

18              Please press the button firmly that  
19 corresponds to your vote.   If you are unsure of  
20 your vote or you wish to change your vote, you may  
21 press the corresponding button until the vote is  
22 closed.

1           After everyone has completed their vote, the  
2       vote will be locked in. The vote will then be  
3       displayed on the screen. The DFO will read the  
4       vote from the screen into the record.

5           Next we will go around the room, and each  
6       individual who voted will state their name and vote  
7       into the record. You should also state the reason  
8       why you voted as you did.

9           The voting question I'll read for everyone  
10      while you consider it. The voting question:

11           Rosiglitazone and rosiglitazone-containing  
12      products are currently marketed in the U.S. under a  
13      Risk Evaluation and Mitigation Strategy, REMS, with  
14      Elements to Assure Safe Use, ETASU. Based on  
15      the totality of available data, including the  
16      readjudicated results of RECORD, do you recommend:

17           A. Removal of the REMS ETASU;

18           B. Continuation of the REMS ETASU without  
19      changes;

20           C. Modification of the REMS ETASU -- please  
21      specify what you recommend be modified; or

22           D. Withdrawal of rosiglitazone from the

1 market.

2           You will see on your panels letters A, B, C,  
3 and D, which obviously correspond to the voting  
4 question. Are we ready to vote? Then please  
5 register your vote.

6           (Vote taken.)

7           DR. BURMAN: Everyone has voted. The vote  
8 is now complete.

9           DR. DOAN: 7 A; 5 B, 13 C, and 1 D.

10          DR. BURMAN: Thank you. We'll go around the  
11 table. It's 3:15. Excuse me?

12          DR. FELNER: For Felner it has A. I thought  
13 I hit B. It should be B. Sorry, I was incorrect.

14          (Multiple panel members advise vote was  
15 recorded incorrectly.)

16          (Laughter.)

17          DR. BURMAN: Let me ask the FDA.

18          We've been advised to take a five-minute  
19 break. Think about the issues, and we will fix the  
20 system.

21          (Pause.)

22          DR. BURMAN: I've been advised it's been



1 fixed, so we're going to move right back to the  
2 question. I've read the question, and you know the  
3 answers are A, B, C, and D. And it's pretty  
4 obvious on the boards, A, B, C, and D. And just  
5 for the record, I'll read it one more time.

6 Rosiglitazone and rosiglitazone-containing  
7 products are currently marketed in the U.S. under a  
8 REMS with Elements to Assure Safe Use, ETASU.  
9 Based on the totality of available data, including  
10 the readjudicated results of RECORD, do you  
11 recommend:

12 A. Removal of the REMS ETASU;

13 B. Continuation of the REMS ETASU without  
14 changes;

15 C. Modification of the REMS ETASU. Please  
16 specify what you recommend be modified; or

17 D. Withdrawal of rosiglitazone from the  
18 market.

19 Please cast your vote.

20 (Vote retaken.)

21 DR. BURMAN: Everyone has voted and the vote  
22 is now complete. Let me be clear. The votes have

1       been recorded? Everybody has cast their vote?

2       Okay. Thank you.

3               DR. DOAN: Seven A, 5 B, 13 C, and 1 D.

4               DR. BURMAN: Could you repeat that? I think  
5       we're forced into a five-minute break. We'll come  
6       back at 3:30.

7               (Whereupon, a brief recess was taken.)

8               DR. BURMAN: Please take your seats. I  
9       apologize for any technology issues.

10              What we'd like to do, they've double-checked  
11      the system and checked the seating arrangements.  
12      So we're going to try the electronic vote one more  
13      time. If that doesn't seem to work, then we'll go  
14      to a more modern technique of just writing it out.

15              (Laughter.)

16              DR. BURMAN: The previous votes that were  
17      read into the record will be amended. Correct.

18              So are you ready for the vote? Then one  
19      more time, just for the record -- I think I'll get  
20      it right this time.

21              Rosiglitazone and rosiglitazone-containing  
22      products are currently marketed in the U.S. under a

1 REMS with ETASU. Based on the totality of  
2 available data, including the readjudicated results  
3 of RECORD, do you recommend:

4 A. Removal of the REMS ETASU;

5 B. Continuation of the REMS ETASU without  
6 changes;

7 C. Modification of the REMS ETASU. Please  
8 specify what you recommend be modified; and

9 D. Withdrawal of rosiglitazone from the  
10 market.

11 Please press the correct button.

12 (Vote retaken again.)

13 DR. BURMAN: All of the votes have been  
14 collected. Everyone has voted. The vote is now  
15 complete.

16 LCDR REESE: This is Cicely Reese. The  
17 votes are the same, and so we're going to rely on  
18 the paper count. So we're going to move to that.  
19 Thank you.

20 DR. BURMAN: Okay. Sorry about that. So  
21 we'll go back, and all the votes will be amended.  
22 This will be the paper vote. So what we'd like to

1 do is put your name on it with the letter for your  
2 vote, covered, of course. Pass them down and we  
3 will take care of it. Make sure there are no  
4 hanging chads. Don't forget to put your name on  
5 it.

6 (Paper vote taken.)

7 DR. JENKINS: Dr. Burman, there's been a  
8 suggestion that maybe DCRI could readjudicate the  
9 votes.

10 (Laughter.)

11 DR. KAUL: Dr. Mahaffey, what's the bill  
12 going to be?

13 DR. BURMAN: This will take a minute.

14 (Votes counted.)

15 DR. BURMAN: The votes have been in.  
16 They've been double-checked and confirmed. The  
17 numbers will be displayed on the board, and then  
18 we'll give the specific names to make sure they  
19 correspond.

20 DR. DOAN: I have 7 A; 5 B; 13 C; and 1 D.

21 DR. BURMAN: Could you read those one more  
22 time?

1 DR. DOAN: 7 A; 5 B; 13 C; and 1 D.

2 DR. BURMAN: So those are the similar  
3 numbers we've seen before.

4 (Laughter.)

5 DR. BURMAN: But I trust this vote.

6 Minh, are you going to display the names of  
7 the people and what they voted? That's the  
8 display. Would you please read it in one more  
9 time?

10 DR. DOAN: We have 7 A; 5 B; 13 C; and 1 D.

11 DR. BURMAN: Thank you. And do you have the  
12 names and who voted? I'll ask the FDA, do you  
13 agree that we should read in the names and the  
14 vote?

15 DR. JENKINS: I think that would be good,  
16 Dr. Burman. I think we should read the names of  
17 who voted and then go around the room just to be  
18 sure.

19 DR. BURMAN: Thank you. Let's do that.  
20 Would you read in the names, please, and the vote?  
21 Cicely, would you read in the names and the vote?

22 LCDR REESE: Letter A is Hiatt, Oakes,

1       Proschan, Killion, Stanley, Cooke, and Seely. B is  
2       Heckbert, Smith, Suarez-Almazor, van Belle, Felner.  
3       C is Flegal, Day, Moss, Konstam, Kaul, Marjorie  
4       Shaw Phillips, Morrato, Dan Budnitz, Brittain,  
5       Woods, Hammerschmidt, Geller, Burman. And D is  
6       Spruill.

7               DR. BURMAN: Dr. Day?

8               DR. DAY: Traditionally, when we go around  
9       the room, we go around the table like this.

10              DR. BURMAN: We're going to.

11              DR. DAY: But would it be possible to amend  
12       that so we can hear from all the As, and then all  
13       the Bs, and all the Cs, and then the D? It might  
14       be more easy to process and understand. No?

15              DR. BURMAN: I don't know. There is a  
16       separate issue, and that is some people indicated  
17       they have to leave. But now that the vote is in,  
18       so what is the sense of the group? To just go  
19       around?

20              PANEL MEMBERS: Yes.

21              DR. BURMAN: Go around. But if it's all  
22       right with the group, I will ask if there's

1 anyone -- what is it, it's 3:40 -- if there's  
2 anyone that has to leave before we go around.

3 (No response.)

4 DR. BURMAN: Just go around? Okay. It  
5 doesn't matter to me where we start. Do you want  
6 to start on this side? Dr. Geller?

7 DR. GELLER: I voted for C, but I'm not  
8 quite sure how to modify the REMS. I'd like to  
9 make the drug more available, and I don't quite  
10 know how to do that other than certifying more  
11 pharmacies for distribution.

12 DR. BURMAN: When you go around, please give  
13 your name and your vote. I may not have heard if  
14 you gave your vote.

15 DR. GELLER: I voted for C. Geller.

16 DR. BURMAN: Thank you.

17 Dr. van Belle?

18 DR. VAN BELLE: Gerald van Belle. B. I  
19 followed the advice of that famous statistician,  
20 Yogi Berra. He said, "I made the wrong mistake."  
21 And I'm trying to avoid making the wrong mistake.

22 So I asked myself, what new evidence has

1       been presented that was not available in 2010? The  
2       RECORD results are robust. This was already noted  
3       in 2010. We do have an updated meta-analysis,  
4       which I think does indicate a continuing concern  
5       about safety.

6               Dr. Woodcock in her memo of 2010 also  
7       stressed the aspect of prudence, that we have to  
8       be careful when it comes to safety. There's no  
9       evidence of clinical efficacy other than the  
10      reduction of glucose. Alternative medicines are  
11      available, and I decided to stay with the current  
12      restrictions. Thank you.

13             DR. BURMAN: Dr. Oakes?

14             DR. OAKES: David Oakes. I voted A. In  
15      2010, I voted for increased warnings but not  
16      drastic reductions in the availability of the drug,  
17      which was what was eventually adopted.

18             Looking through the REMS just now, I felt  
19      that it seems to presuppose known risks and to be a  
20      protection against known risks. I feel there are  
21      certainly signals of possible risks. We've heard  
22      in these two days a lot of disagreement about



1       whether those risks are real, and if so, what the  
2       magnitude of them is.

3               I think we're in a state -- I wouldn't call  
4       it equipoise, but a state of uncertainty. And it  
5       seemed to me that the kind of prescriptions of the  
6       REMS are probably not appropriate, were really  
7       designed for a situation where there was more clear  
8       knowledge, assumed knowledge, of the situation.

9               I suspect, however, as I think one of my  
10       colleagues said a little while ago, that the train  
11       may have already left the station in this, and  
12       point out that the decrease in the number of  
13       prescriptions really predated the introduction of  
14       the REMS.

15               So I'm not sure what the practical results  
16       of this will be, but I do think, looking at the  
17       kind of discussion we've had over these last two  
18       days and looking at the way the REMS is set up,  
19       right now it does not strike me as an appropriate  
20       procedure.

21               DR. BURMAN: Thank you.

22               Dr. Proschan?

1 DR. PROSCHAN: I'm Michael Proschan. Before  
2 I give my answer, I just want to point out we may  
3 still have some problems here because I don't  
4 Dr. van Belle's name on that -- oh, it says Belle.  
5 Okay. Sorry.

6 MALE VOICE: He's been demoted.

7 DR. PROSCHAN: Okay. So I voted for A  
8 because I'm reassured by the data from RECORD that  
9 at least compared to other anti-diabetic drugs, I  
10 don't see a safety concern. And I don't know what  
11 the answer is with respect to placebo for any anti-  
12 diabetic drug, really. But I was reassured that at  
13 least it's not worse than other anti-diabetes drugs  
14 on the market.

15 DR. BURMAN: Thank you.

16 Dr. Hammerschmidt?

17 DR. HAMMERSCHMIDT: Yes. Dale  
18 Hammerschmidt. I voted C, as you might have  
19 guessed from the procedural question I asked just  
20 before we voted. And it's because I'm considerably  
21 reassured by the readjudication and so on that the  
22 magnitude of the possible risk we're talking about

1       here is not very great, and that the conditions of  
2       the REMS were more severe than we needed to address  
3       the situation.

4               But I thought it was probably still good to  
5       retain an information structure. It was good to  
6       consider having a registry of the patients who get  
7       the drug. And if we're going to do that, we need  
8       to be able to evaluate it. So I thought C was more  
9       appropriate than A.

10              MS. KILLION: Rebecca Killion. I voted A.  
11       In 2010, I voted for something that eventually  
12       ended up being the REMS, although I'm not sure I  
13       was aware at that time that it was going to be  
14       something that was so stringent.

15              But the reason that I voted for it is  
16       because I thought that given the level of  
17       uncertainty that we had at that time, that more  
18       physician education and patient education would be  
19       an appropriate way to go.

20              What I was surprised to learn today in the  
21       FDA's presentation is that the population that I  
22       thought would probably be the one least likely to

1       be taking Avandia under the REMS, even though you  
2       had such a drastic reduction in the number of  
3       patients taking it, was exactly the population,  
4       i.e. the elderly population, that I thought would  
5       not be taking Avandia. So I wasn't sure what all  
6       that patient and physician education amounted to.

7               So given the level of -- well, the more  
8       comfort that we have with the RECORD results now,  
9       and what I think is the failure of the REMS to  
10      address what I thought would be the highest issue,  
11      I don't see a need for it at all. And that's why I  
12      voted for its removal.

13             I think our charge here in terms of drug  
14      safety is to be cautious. But an over-abundance of  
15      caution is not a neutral position; it actually can  
16      be detrimental to patients by suppressing the  
17      availability of effective drugs and limiting their  
18      choice. So I think our charge here is to be safe  
19      but to be sane.

20             DR. FELNER: Eric Felner. I voted B. In  
21      2010, I also voted B, although it wasn't the same  
22      choice, and I didn't want the label changed but to

1 keep the black box warning. And the main reason I  
2 chose that was because I didn't think that the  
3 signal was impressive enough to just pull the drug  
4 from the market.

5 Back in looking at my comments, the main  
6 reason is I wanted to see the TIDE study be  
7 performed so we could learn some information. And  
8 what was nice today or these last two days, even  
9 though I didn't say a whole lot, I got to hear a  
10 lot of people wanting to have had that study done  
11 and know some of that information today.

12 Obviously, I think it's a little too late to  
13 do that study or repeat that study. And with the  
14 DCRI and GSK really doing a good job, or at least  
15 DCRI doing a good job with the adjudication,  
16 showing that GSK did a good job with the study, I  
17 think it leaves us in a more difficult position  
18 with what to do with this drug.

19 There are some patients -- we heard from a  
20 man who takes the drug and probably has benefit  
21 from it. And there are probably a few patients  
22 that would benefit from the drug in place of

1 pioglitazone, specifically those that have bladder  
2 cancer or a history or risk for bladder cancer, and  
3 maybe sensitivity issues or allergic reaction to  
4 pio.

5           So I think the drug has a spot. But it  
6 still looks like that rosiglitazone is less safe  
7 than pioglitazone. I think it looks that way, and  
8 so I think removing anything from the REMS would  
9 keep us from learning anything that we could learn.  
10 So I think at this point I'd just keep it as it is.

11           DR. COOKE: David Cooke. I voted A. The  
12 decision about whether a medication should be  
13 available or not obviously is a balance between the  
14 risks and the benefits. And in this case, as in  
15 many cases, there's uncertainty both about the  
16 risks and the benefits. I think we've obviously  
17 been discussing the uncertainty of the risks in  
18 this case.

19           But I think in large part due to the  
20 mortality data in the RECORD study, a relatively  
21 longer-term look at this medication, I think the  
22 data and concern about the safety of it at this

1 point is not sufficient to justify the restrictions  
2 that were placed on it.

3 I think the ongoing question about whether  
4 there is greater safety or greater benefit of  
5 pioglitazone versus rosiglitazone is an open one.  
6 And given the lack of truly controlled studies with  
7 cardiovascular and outcome studies, I think it's  
8 premature to prejudge that. So again, for those  
9 reasons, I voted to remove the REMS restrictions.

10 DR. STANLEY: This is Charles Stanley. I  
11 voted A. I was torn between voting for A or voting  
12 for D to withdraw rosiglitazone from the market  
13 because I think this is a drug that's been severely  
14 tainted in this process. And at this point it's  
15 only being used by a few thousand people. It's  
16 really an orphan drug, and I'm not quite sure  
17 whether anybody has any great interest in seeing it  
18 continue.

19 But I felt that the REMS was an appropriate  
20 requirement back before the RECORD study had been  
21 readjudicated. I feel that the readjudication has  
22 made us more comfortable that the RECORD study not

1       showing severe risks makes it unnecessary to  
2       continue with the REMS.

3               But I don't foresee that this is going to  
4       really increase the number of patients on this drug  
5       very much.

6               DR. WOODS:   Mark Woods, and I voted C.  
7       While the RECORD trial helped reassure us in some  
8       respects, I guess it also introduced some new  
9       questions in my mind.   For example, I think the  
10      statin issue is one that is very much in the air,  
11      and given the number of diabetic patients that will  
12      end up on statins, I guess I have some lingering  
13      concerns about toxicity.

14              I think this drug lacks a clear niche.   I  
15      think the availability of alternative agents as  
16      well as new topic entities is very helpful.   But  
17      granted, I do believe they're a very small subset  
18      of patients that potentially need to have access to  
19      this drug, and the current REMS program affords us  
20      a way that will hopefully ensure prescribers are  
21      competent to prescribe the drug, and that patients  
22      are fully aware of the potential risks.



1           I don't know if this can be done through  
2       REMS. But I guess if it could be somehow  
3       constructed so that we could get outcomes data on  
4       these patients, especially as relates to adverse  
5       events, that would be potentially very helpful.

6           I'm skeptical, given where we are probably  
7       in the patent life of this drug, that we're  
8       probably going to see a lot of new studies. But I  
9       guess that will be for the sponsor to figure out.

10           DR. SUAREZ-ALMAZOR: Suarez-Almazor. I  
11       voted B. I felt that there were consistent signals  
12       for MI in the observational data and also in the  
13       RECORD trial, although they did not achieve  
14       statistical significance.

15           I did not see clear benefit of this drug  
16       over the other in the class. But I hear what the  
17       patient who presented and my colleagues in  
18       endocrinology said, that there might be a small  
19       proportion of patients for whom this drug may be  
20       necessary because they have no other options or  
21       that's their preferred drug of treatment.

22           I think the REMS has been successful in

1 decreasing the use, and that's why I voted B.

2 DR. PHILLIPS: I'm Marjorie Shaw Phillips,  
3 and I actually agonized a bit between A and C. I  
4 voted for C because I think there's some elements,  
5 particularly the communication plan and some  
6 ongoing follow-up, that are beneficial.

7 I do think there's a large level of  
8 uncertainty, but it's uncertainty versus some  
9 really known risks or very strong signals. I  
10 question whether the severe restrictions in the  
11 forms of requiring certification of prescribers and  
12 certification of patients are really necessary,  
13 considering the changes in practice patterns that  
14 have happened that have happened over the last few  
15 years.

16 But I do think, as has already been said,  
17 that it's valuable to be able to track patient  
18 understanding of risk/benefit and make sure that  
19 there's a public communication plan around that.

20 In terms of registry, just registering and  
21 following patients on this one drug is not going to  
22 provide us really anything in the way of useful

1 information, as has been pointed out by FDA,  
2 because of the size of the signal.

3 But I believe the use of robust registry  
4 data, such as the platform of the American College  
5 of Cardiology has designed, that really enrolls  
6 patients across a wide range of real-world  
7 experience is going to -- and in a better-designed  
8 format might give us the real-world performance  
9 data and outcomes that we need over time to start  
10 answering some of those very complex questions.

11 DR. SMITH: I'm Robert Smith. I voted B.  
12 I still think there is unresolved concern about an  
13 adverse cardiovascular effect or effects. But I  
14 very much don't wish to deprive qualifying patients  
15 of rosiglitazone as an option, even in this  
16 context.

17 I would ideally like to see a well-designed  
18 cardiovascular outcomes trial, as we've discussed.  
19 But I don't see this as feasible, also for the  
20 reasons we discussed. Operatively, the use of the  
21 drug is now in the range of an orphan drug, and I  
22 would anticipate that if something like B is

1 followed, that this situation will continue.

2 I would encourage the FDA to consider some  
3 form of registry-type approach so that we're not in  
4 a situation of not monitoring or not looking fairly  
5 vigorously for adverse cardiovascular effects of  
6 the drug. And I think I feel a little bit more  
7 strongly about this because of, for example, the  
8 concerns that have been raised about statins. So  
9 that's my position.

10 DR. BURMAN: Thank you. Let me just ask the  
11 panel one more time, logistically is everyone okay  
12 in terms of time in terms of planes? No? So we're  
13 okay. Thank you.

14 DR. HIATT: William Hiatt. I voted A. In  
15 trying to assess the risk, my mental averaging  
16 across the RECORD trial and the meta-analyses led  
17 me to council that if there is a signal, it's  
18 nonfatal MI, but that in general this drug doesn't  
19 look any different than any other diabetes drug in  
20 terms of cardiac risk.

21 So that said, it seems to me that if we want  
22 to move forward and learn something, that the

1 majority voting to retain a REMS program  
2 essentially negates the opportunity for a  
3 randomized, controlled clinical trial because I  
4 think it affects the perception of the ethics of  
5 doing such a trial. And since I'm favor of those  
6 kinds of things, I voted A.

7 DR. SEELY: Ellen Seely. I voted A. In  
8 terms of the data we've been presented and we've  
9 been reading, I'm not convinced that there is no  
10 cardiovascular risk associated with rosiglitazone.  
11 But I don't think we have data that supports there  
12 is a cardiovascular risk.

13 Based on that, I voted for removal of the  
14 REMS. I, like Dr. Hiatt, feel strongly that we  
15 should position this drug to be able to be studied  
16 in a randomized clinical trial. And I don't think  
17 you can be, at the same time, endorsing a  
18 randomized clinical trial of a drug that is at this  
19 level of restriction.

20 I'm also concerned about the postulation of  
21 using the REMS as a tracking mechanism of adverse  
22 events because I think unless you have a tracking

1 mechanism for all the other diabetes drugs as well,  
2 you're going to get really biased results that are  
3 going to muddle the situation even further.

4 DR. BRITTAIN: I'm Erica Brittain. I voted  
5 C. I think there remains considerable uncertainty  
6 about the cardiovascular safety of the drug.

7 While the RECORD results are somewhat  
8 reassuring, the meta-analysis results for the  
9 placebo are still of concern. But I do favor  
10 loosening the restrictions. I don't feel qualified  
11 to describe how, but I want the very limited number  
12 of patients who are appropriate for the drug to  
13 have relatively easy access, but still some  
14 guaranteed information for them.

15 Now, on the other hand, I very much support  
16 the trial, potentially the three-arm trial along  
17 the lines of TIDE. And if it's true, as others  
18 have stated, that in order for that to be done, it  
19 would not be appropriate to continue the REMS, then  
20 I would support eliminating the REMS. I feel much  
21 more strongly about having the trial done than  
22 continuing the REMS.

1 DR. BURMAN: Thank you. Ken Burman. I  
2 voted C. I wavered between A and C, and I  
3 recommend modification of the REMS ETASU. I do not  
4 recommend complete removal, given remaining  
5 concerns regarding RECORD and also meta-analysis  
6 results.

7 My recommendation would be that patients be  
8 informed of the possible but largely unproven risk  
9 of RSG, so patient communication. I think there  
10 should be prescriber information given and  
11 marketed, but I don't think the prescriber needs to  
12 have specific REMS certification.

13 I think it would be appropriate to continue  
14 having only certified pharmacies prescribe  
15 rosiglitazone, as this system allows close  
16 monitoring and evaluation but does not seem to  
17 impose a significant burden to patients. I also do  
18 not think prescribers must officially determine  
19 that they are unable to achieve glycemic control on  
20 other medications.

21 DR. SPRUILL: This is going to be  
22 interesting. I'm Ida Spruill. I'm the only person

1       that voted to remove the drug from the market. I'm  
2       going to try to respond to this from the lens of  
3       both a person who has lived with diabetes for over  
4       five years, who was on Avandia and was taken off by  
5       my endocrinologist, and I have a strong family  
6       history of family members who have diabetes. I am  
7       not comfortable, as a nurse educator and clinician,  
8       prescribing the drug to my family members and then  
9       to other people as well.

10           I'm also concerned about the health literacy  
11       in this country and health equity; and in terms of  
12       the RECORD trial, what was presented in these from  
13       the surveys, the level of inconsistencies in terms  
14       of what the providers and the patients did and did  
15       not know.

16           I've spent two days listening to a vast  
17       amount of data. I was not here in 2009 nor 2010.  
18       And so what I've heard thus far is still to me  
19       inconclusive.

20           Additionally, there are over 26 million  
21       people in this country that have diabetes, and we  
22       have over eight classifications of diabetes



1       medicine, which translates into about over 20 meds.  
2       So people have options.

3               I am not comfortable, and I said earlier  
4       looking at data, that we try to generalize to a  
5       population here that was done in sites outside of  
6       this country. And so my concern is trying to use  
7       that data to generalize to this particular  
8       population, which may not speak to the factors  
9       that cause people in this country to have diabetes.

10              I'm not comfortable saying that what I've  
11       learned in the past two days changed my mind about  
12       whether or not we should have information from  
13       clinical trials here for people in this country who  
14       suffer with diabetes on a daily basis.

15              So I voted no. I didn't vote for C because  
16       I think adding additional information for patients  
17       is a burden for both providers and the patients and  
18       the prescription at the pharmacist.

19              So that's probably about the last thing I  
20       would say. I'll go on record as being the only  
21       person who said to take it off the market. It's  
22       been too long, too much, too late, and I think the

1 media has had a fair day in terms of making Avandia  
2 the bad boy on the market.

3 DR. KAUL: I'm Sanjay Kaul, and I voted  
4 for C. In 2010, I voted for allowing continued  
5 marketing and revising the current label to add  
6 additional warnings. The reason was that I was  
7 neither reassured nor concerned about the RECORD  
8 data. Notwithstanding the outstanding work,  
9 comprehensive work, the DCRI readjudication  
10 reconfirmed my uncertainty.

11 I also debated between the choice of A,  
12 removing it, and C. And ultimately, I voted for C  
13 because I think there are some unresolved issues,  
14 particularly certain subsets, high-risk  
15 subsets -- for example, ischemic heart disease.

16 I'm not quite sure whether the interaction  
17 that we see with four drugs -- the nitrates, the  
18 ACE inhibitors, the insulin, and now statins -- may  
19 be a reflection of the underlying risk of the  
20 patient population.

21 Patients who have ischemic heart disease are  
22 more likely to be on statins, nitrates, and ACE

1 inhibitors. And patients with longstanding history  
2 of diabetes, and therefore presence of  
3 macrovascular disease, including ischemic heart  
4 disease, are more likely to be on insulin.

5 So I think it's a good opportunity to  
6 committee those uncertainties to the patients in  
7 the form of a communication plan and a medication  
8 guidance, and to have some sort of a process by  
9 which we can collect the information, evaluate, and  
10 see there are no sudden spikes in the use of  
11 rosiglitazone.

12 If, somehow, magically the stars are aligned  
13 and it is feasible to conduct the desired trial,  
14 and the only way the FDA will allow that is to  
15 remove the REMS, then I will be in favor of  
16 removing the REMS. Thank you.

17 DR. KONSTAM: Marv Konstam, and I voted C.  
18 The difference between now and 2010 is the  
19 readjudication of RECORD. And those results do not  
20 remove my concern about the cardiovascular safety  
21 of rosiglitazone, but in my mind they move the  
22 needle in a direction that seems to me is

1       appropriate to shift the burden of decision-making  
2       for prescribing this drug to the physician and in  
3       terms of interpreting the entirety of the data.

4               I think if we learn one thing from today's  
5       deliberations it is that if we take a large group  
6       of intelligent folks who carefully study all of the  
7       data, they come to a spectrum of conclusions about  
8       what the totality of the data shows.

9               I think that spectrum is all within the  
10      realm of acceptability. And to me, that states  
11      that we ought to be shifting the burden back to the  
12      physician to look at the entirety of the data. So  
13      that's really basically what I believe.

14              In terms of what that translates to  
15      specifically, I don't really understand all of the  
16      options here with regard to the REMS. I do feel  
17      like we should continue with the medication guide,  
18      a communications strategy.

19              It may be possible in my mind to eliminate  
20      the ETASU program or at least to soften it in a way  
21      that simply shifts the burden to the physician to  
22      use his or her judgment based on the totality of

1 the data.

2 DR. MOSS: Art Moss from Rochester. I was  
3 torn between A and C, and I came voting for C  
4 because there were some minor signals, but they  
5 were really uncertain. I do think it's important  
6 to continue and in fact make the drug a little bit  
7 more available.

8 I also wanted to give the FDA time to make  
9 appropriate changes in the REMS ETASU. And I think  
10 that it's advisable to have a stepwise approach,  
11 and I think we're going to get information from the  
12 endocrinologists in practice that will influence  
13 the FDA.

14 So I think it's a stepwise approach. And  
15 it's reasonable to think that there will be more  
16 availability of the drug, but gradually. Thank  
17 you.

18 DR. FLEGAL: Katherine Flegal. I also voted  
19 for C, although I also vacillated between A and C.  
20 I think Avandia still has its place. I think the  
21 REMS could be softened; on the other hand, if  
22 having the REMS at all would prevent further data

1 collection or the trial, I would say we could do  
2 without the REMS.

3 But I think a communications strategy and  
4 a medication strategy is still appropriate, maybe  
5 because my views are a little bit tainted by the  
6 history of this drug.

7 DR. HECKBERT: Susan Heckbert, and I voted  
8 B. Based on the results that we heard at this  
9 meeting presented in the briefing materials and  
10 that we heard here, none of the conclusions from  
11 the July 2010 meeting have changed, neither from  
12 the RECORD trial nor the meta-analysis of the  
13 short-term trials nor from the observational  
14 studies. No new results suggested any unique  
15 benefits of rosiglitazone, and no results for  
16 effects on CV endpoints have changed.

17 So that explains my vote, and I don't see  
18 any reason to change the current approval status  
19 for the drug. And I voted to keep the REMS ETASU  
20 in place as it is because it seems to be reasonably  
21 effective at dealing with the cardiovascular safety  
22 signal that I believe is still present.

1 DR. BUDNITZ: Dan Budnitz. I voted for C,  
2 and vacillated a little bit between C and D. In  
3 terms of suggestions, I would suggest keeping the  
4 ETASU components in place, just updating the  
5 medication guide and communications to include  
6 findings from the readjudicated RECORD study, as  
7 well as other more recent meta-analyses.

8 These data were not convincing to me to  
9 dispel the potential for increased risk of MI. But  
10 I think with the ETASU components, it really can be  
11 made up to the physician and patient to make that  
12 determination.

13 I do think there are good alternatives. On  
14 the other hand, I did not want to completely remove  
15 it from the market for individual patients where it  
16 might be appropriate, as described by folks here.

17 DR. MORRATO: Elaine Morrato, and I voted C.  
18 Many FDA advisory committee meetings the DSaRM  
19 members get to participate in typically focus on  
20 whether or not to escalate risk management. So I  
21 thought it was refreshing that when we were  
22 presented new information, that we could also

1 consider the de-escalation of risk management.

2 Back in 2010, I felt that was great  
3 uncertainty about the credibility of the RECORD  
4 data, and therefore how to weigh its findings  
5 relative to the meta-analysis and observational  
6 data. For that reason, I voted for increased  
7 warnings and the need to ensure informed patient-  
8 physician decision-making, and in fact, that's  
9 largely what happened with the REMS.

10 So the new data today was the adjudication  
11 of the RECORD study, which I felt demonstrated  
12 rosiglitazone's noninferiority to active  
13 comparators with regard to all-cause mortality and  
14 the cardiovascular outcomes.

15 Importantly, as one FDA reviewer concluded,  
16 there is no convincing evidence for systemic,  
17 systematic, or intentional manipulation of the  
18 data. So considering this new information, I voted  
19 in favor of relaxing the REMS but not removing the  
20 REMS.

21 I would eliminate the requirement for the  
22 mandatory prescriber certification, the documented



1 informed consent, and the requirement for  
2 distribution through a specialty pharmacy. I  
3 believe this level of restricted distribution is  
4 overly burdensome and not warranted now.

5 The REMS evaluation data showed relatively  
6 high knowledge of the risks among current  
7 prescribers and patients, and I believe that  
8 relaxing the REMS helps put rosiglitazone's REMS  
9 on a more even playing field with other drugs with  
10 similar levels of risks. I think this is important  
11 for public transparency and to ensure consistency  
12 across drugs that many stakeholders talk about the  
13 undue burden.

14 My other modification would be to add a  
15 formal communication plan to healthcare  
16 professionals, and this might have two objectives.  
17 One, obviously, is to summarize the collective  
18 understanding of the cardiovascular risk.

19 But I think it's also important that it's an  
20 opportunity to educate clinicians on REMS to some  
21 degree and why the REMS ETASU requirements might be  
22 being relaxed. I think this is important because

1       REMS are still relatively new. And how we think of  
2       them in the context of a drug's life cycle is  
3       important.

4               I recommend keeping the med guide and  
5       communication plan within a REMS as opposed to not  
6       simply because I think it's important to look at  
7       the evaluation during this transition period.  
8       However, I think the communication plan could be  
9       something that's a one-time communication, not  
10      necessarily ongoing.

11             Then I just wanted to add one last comment,  
12      that as Dr. Day had also discussed, I was  
13      disappointed with the initial evidence that was  
14      presented by both the sponsor and FDA to support  
15      the conclusion that there was "good knowledge"  
16      regarding potential risk of MI.

17             It was presented in a qualitative manner,  
18      and I think there was a missed opportunity. So I  
19      was very thankful that Dr. Stemhagen gave her  
20      presentation of the survey studies. I think it  
21      would have been nice to have had that in briefing  
22      materials.

1           I think we should be striving to use the  
2       same scientific rigor that we're accustomed to  
3       seeing in briefing materials for trial data and  
4       epidemiology studies when reviewing these kinds of  
5       data, so specifically survey design, the  
6       methodology, the sampling scheme, the instrument,  
7       prespecified measures of success, response rates,  
8       tabular reporting of the numeric findings, and then  
9       consideration of nonresponder bias when  
10      interpreting the results.

11           This is the standard that's used when these  
12      kinds of data are presented in a scientific  
13      publication, and I think it's important that we  
14      use that same rigor and presentation in briefing  
15      materials in future REMS assessments. Thank you.

16           DR. DAY: Ruth Day. I voted for C,  
17      modification of the REMS. And Dr. Morrato and I  
18      have discussed the presentation of the methods and  
19      results for the REMS and are in complete agreement.  
20      So I echo that.

21           I am open to lightening the REMS in a  
22      variety of ways that have already been mentioned.

1       One in addition would be the lightening up of all  
2       of the intense monitoring of everything about the  
3       restrictive part of the program. A huge amount of  
4       time and energy is going into that; I think that  
5       could be lightened a bit.

6               In terms of the patient education part, at  
7       the time of enrollment, I would like to see  
8       something about their true understanding about  
9       whatever the key message is supposed to be, whether  
10      it's MI or whatever is going to go forward, instead  
11      of having a meta-cognitive question saying, yes, I  
12      understand; a couple of questions and then that is  
13      part of their enrollment. And if they don't get  
14      those in, then they would have more of a  
15      conversation with their provider.

16              So I would like to see that included as well  
17      in order to have true informed consent. Informed  
18      consent is not just reading something at someone,  
19      but in order to have more informed consent.

20              I was hoping that someone would suggest  
21      something about or talk a little more about  
22      decision-making on the physician's end. And it did

1       come up at the end of this table a little while  
2       ago, but it was more in terms of, well, let's send  
3       it back to the physicians and other prescribers and  
4       let them do it.

5               I would not be opposed, however, at the  
6       time of the registration or certification of the  
7       prescriber that they had a couple of scenario  
8       questions; if you had a patient with X, Y, and Z,  
9       would it be all right to prescribe this drug,  
10      et cetera. I would not be opposed to that,  
11      although I know it would be very unpopular among  
12      some in this room and elsewhere. Thank you.

13             DR. BURMAN: Thank you. I would note for  
14      the record that the individual votes and comments  
15      confirmed the record of the results that we have.

16             I would ask the FDA if they have any other  
17      final questions or comments.

18             DR. JENKINS: Dr. Burman, first I'd like to  
19      thank you and the members of the committee for,  
20      really, an outstanding discussion of a very  
21      complicated issue. Far from being a waste of time  
22      and resources, I think this has been a fabulously

1 productive meeting. We've heard a wide range of  
2 perspectives on the data.

3 I think it illustrates that this is not an  
4 easy decision on the benefit/risk, given the data  
5 and a lot of the uncertainties. I think it's been  
6 very valuable to have that discussion in the public  
7 forum in a very professional and respectful manner.

8 I really appreciate your chairing the  
9 committee, the committee members' preparation, and  
10 your time for being here; the public speakers; and  
11 I'd like to congratulate all of my colleagues from  
12 the FDA on their presentations. They've done a lot  
13 of work, and I think it really showed in the  
14 quality of what they presented. They don't always  
15 agree, but I think they always work hard to try to  
16 get to the right answer for the patients.

17 So you've given us a lot to think about, and  
18 we're going to need to take some time to go back  
19 and consider all the recommendations. I always  
20 tell the media, it's not just the vote, and in  
21 fact, it's more important than the vote, is to hear  
22 why you voted the way you voted. We always analyze

1       carefully what you said about your choices and why  
2       you went that direction.

3               So we will be taking all this information  
4       back, having internal discussions, and of course at  
5       some point we'll have to have discussions with the  
6       sponsor about any changes that might be proposed to  
7       the marketing status of rosiglitazone.

8               So again, thank you very much. I think it  
9       was a very productive two-day meeting, and I really  
10      appreciate the time and effort you've all put into  
11      making it such a productive meeting. So thank you.

12              DR. BURMAN: Thank you.

13              Any other comments?

14              (No response.)

15                                      **Adjournment**

16              DR. BURMAN: Then I personally would like  
17      to thank the FDA for all the support and work they  
18      gave, not only to me but to the panel. And I won't  
19      single out individual members, but everyone that we  
20      work with has been excellent. I wanted to thank  
21      the sponsor for excellent presentations; the OPH  
22      speakers, which were very helpful; and the

1 consultants as well.

2 If there are no objections, I would move to  
3 adjourn the meeting. So moved. The meeting is  
4 adjourned. Thank you all.

5 (Whereupon, at 4:20 p.m., the meeting was  
6 adjourned.)

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