AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

JOINT MEETING OF THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY MANAGEMENT ADVISORY COMMITTEE

Monday, July 30, 2007

8:00 a.m.

Holiday Inn Gaithersburg
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Gaithersburg, Maryland

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P A R T I C I P A N T S

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LCDR Cathy A. Miller, M.P.H., Designated Federal Official, Endocrinologic and Metabolic Drugs Advisory Committee

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Arthur J. Moss, M.D.
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David Oakes, Ph.D.
Thomas G. Pickering, M.D., D.Phil.
Peter J. Savage, M.D.
David S. Schade, M.D.
Morris Schambelan, M.D.
John R. Teerlink, M.D.
Gerald Van Belle, Ph.D.

P A R T I C I P A N T S (Continued)

Temporary Members (Non-Voting):

Curt D. Furberg, M.D., Ph.D.

Industry Representatives (Non-Voting):

Steven W. Ryder, M.D.
Annette Stemhagen, Dr.PH.

Guest Speakers (Non-Voting):

David Gordon, M.D., Ph.D., MPH
Robert E. Ratner, M.D.

Consultant (Non-Voting):

Steven Nissen, M.D.

FDA Participants (Non-Voting):

Mark I. Avigan, M.D., C.M.
Gerald Dal Pan, M.D., MHS
Sandra L. Kweder, M.D.
Douglas C. Throckmorton, M.D.
Robert J. Meyer, M.D.
Robert T. O'Neill, Ph.D.
Mary H. Parks, M.D.

C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. ROSEN: Good morning. Welcome, everybody, to the FDA advisory meeting. This is the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. My name is Dr. Clifford Rosen. I am the chairperson today, and today the committees will be discussing cardiovascular ischemic and thrombotic risks of the TZD products, with a particular focus on rosiglitazone, as presented both by the FDA and by the sponsor, GlaxoSmithKline.

Before we get going officially, I would like to read a statement approved by the FDA's Office of the Chief Counsel: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal in today's meeting will be a fair and open forum for discussion of these issues, and individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if they are recognized by me, the chair, and we look forward to a very productive meeting. As chair, I will call on individual people around the room to give their opinions, questions or discussions, as well as the vote, and we will talk about the procedures for the vote in the afternoon session.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask the advisory committee members to take care that their conversations about the topic at hand take place only in the open forum at the meeting, and we are very aware-BI have already been approachedB-that the members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. I would say that also goes for members of the advisory committee. I would absolutely refrain from talking to the media until the end of the meeting. There will be a

press conference and things will be discussed. I will do my best to try to make sure that everything is as clear as possible during the discussions. Also, the committee is reminded to please refrain from discussing the meeting during the break or lunch. We have a couple of additional comments that I need to make.

We have two people, or at least one additional person that needs to be recognized, Dr. Steven Nissen, who is sitting in the front row, has been invited as a guest to attend today's meetings. In the event the committee has specific questions directly related to either Dr. Nissen's meta-analysis, as published in the New England Journal, or if there are specific questions for Takeda's product pioglitazone I may actually ask them to take the microphone. Again, this is at the chair's discretion.

So, I would like to turn it over to Cathy Miller just to give the conflict of interest, and then it will come back to me to introduce the individual panel members.

Conflict of Interest Statement

LCDR MILLER: Thank you. The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest with the following exceptions.

In accordance with 18 USC 208(b)(30, full waivers have been granted to the following participants: Dr. David Schade, for his membership in a competitor's unrelated speaker's bureau, for which he received less than $10,001 per year. Also, for his unrelated consulting for another competitor, for which he receives less than $10,001 per year.

Dr. Morris Schambelan, for his membership in a competitor's complications committee for unrelated products, for which he receives less than

$10,001 per year.

Dr. Thomas Pickering, for his membership in a competitor's unrelated advisory board, for which he receives less than $10,001 per year. Dr. Pickering has also been awarded a waiver under 21 USC 355(n)(4) for owning stock in three competing firms worth between $5,001 to $25,000 in total. This de minimis financial interest falls under 5 CFR part 2640.202 which is covered by a regulatory waiver under 18 USC 208(b)(2).

In accordance with 18 USC 208(b)(10, Dr. John Teerlink has been granted a full waiver for being a blinded endpoint reviewer for a competitor's unrelated study. He receives between $10,001 to $50,000 per year, also for his shares of a health sector mutual fund valued between $50,001 to $100,000.

Lastly, limited waivers under 18 USC 208(b)(3) have been granted to the following participants: Dr. Curt Furberg, for his membership in a data safety monitoring board for an NIH-sponsored study involving rosiglitazone that is

funded by the federal government, the sponsor, and two competing firms. He receives less than $10,001 per year. Dr. Furberg's participation in this meeting will be limited to committee's discussions and deliberations. He will not be allowed to vote on the matters coming before the committees.

Dr. Steven Nissen, for his employer's related research grants with two competing firms for between $100,001 and $300,000 per year per firm, and a related research grant with another competing firm for greater than $200,000 per year. Dr. Nissen's participation in the meeting will be limited to answering questions regarding his meta-analysis of pooled data from clinical studies of rosiglitazone and the associated paper that was published in the June 14, 2007 issue of the New England Journal of Medicine. He will not be allowed to participate in the committee's discussions, deliberations, or vote in the matters coming before the committees.

Waiver documents are available at FDA's dockets web page. Specific instructions as to how

to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guest speaker, there are reported interests that we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Robert Ratner receives research support from GlaxoSmithKline, Merck and Pfizer and is on the advisory board for GlaxoSmithKline, Sanofi-Aventis and Takeda. Dr. Ratner also owns stock in Merck.

Lastly, with respect to FDA's invited industry representatives, we would like to disclose that Dr. Steven Ryder and Dr. Annette Stemhagen are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Their role on this committee is to represent industry interests in general, and not any one particular company. Dr. Ryder is

employed by Pfizer, a competing firm, and Dr. Stemhagen is employed by United Biosource Corporation.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from the discussions and their exclusion will be noted for the record.

With respect to all other participants, we ask that in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

Introductions

DR. ROSEN: Thank you, Cathy. I would like to introduce the advisory committee first and then the FDA panel, sitting to my right. I will start with the advisory committee. Dr. Teerlink, if we could just have a brief one sentence on who you are, and what institution you represent and what your field of interest is.

DR. TEERLINK: I am John Teerlink. I am at University of California, San Francisco, and Director of Heart Failure at the San Francisco VA Medical Center.

DR. SCHAMBELAN: Morris Schambelan, also at UCSF where I am a Professor of Medicine and Chief of Endocrinology at San Francisco General Hospital.

DR. LEVIN: Art Levin, Director, Center for Medical Consumers in New York and a consumer advocate.

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

DR. NELSON: Lewis Nelson, Associate Professor Emergency Medicine, New York University Medical Center.

DR. SCHADE: Dave Schade, Professor of Medicine and Chief of Endocrinology at the University of New Mexico School of Medicine.

DR. SAVAGE: I am Peter Savage, Special Assistant for Clinical Research in the Office of the Director of the National Heart, Lung and Blood

Institute.

DR. PICKERING: Tom Pickering. I am a Professor of Medicine at Columbia Medical College, and my expertise is in hypertension and cardiovascular disease.

LCDR MILLER: Cathy Miller, with the FDA advisors and consultants staff.

DR. ROSEN: Cliff Rosen. I am a clinical endocrinologist and a bone biologist, from Bangor, Maine.

DR. HOLMBOE: I am Eric Holmboe. I am Senior Vice President for Quality Research and Academic Affairs at the American Board of Internal Medicine, and Professor Adjunct at Yale University School of Medicine.

MS. KILLION: Good morning. Rebecca Killion. I am a patient representative and an insulin-requiring diabetic.

DR. GOLDFINE: Allison Goldfine. I am the Assistant Director for Clinical Research at the Joslin Diabetes Center in Boston.

DR. GELLER: Nancy Geller. I am Director

of the Office of Biostatistics Research at the National Heart, Lung and Blood Institute, and I am an expert in clinical trials.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University.

DR. BURMAN: Kenneth Burman, Head of Endocrinology at Washington Hospital Center, and a Professor of Medicine at Georgetown University.

DR. FRADKIN: Judith Fradkin, Director of the Division of Diabetes, Endocrinology and Metabolic Diseases Division of the National Institute of Diabetes and Digestive and Kidney Diseases. Would this be a good time, I just wanted to disclose that although I have no financial interest or income from any pharmaceutical company, GSK does provide study drug and placebo for the TODAY trial, which is funded and administered in my division. Also, NIDDK provides co-funding for the NHLBI ACCORD and BARI 2D trials in which rosiglitazone is the study drug.

DR. ROSEN: Thank you.

DR. LESAR: Timothy Lesar, Director of

Pharmacy, Albany Medical Center in Albany, New York.

DR. HENDERSON: Jessica Henderson, Associate Professor at Western Oregon University, and I am the consumer representative.

DR. KRAMER: Judith Kramer. I am Associate Professor of Medicine at Duke University and the principal investigator of the Duke Center for Education and Research on Therapeutics for Cardiovascular Disease.

DR. FLEGAL: Katherine Flegal, from the Centers for Disease Control and Prevention.

DR. HENNESSY: Good morning. I am Sean Hennessy. I am an epidemiologist at the University of Pennsylvania School of Medicine.

DR. FURBERG: Curt Furberg, Professor of Public Health Sciences, former member of the Drug Safety and Risk Management Advisory Committee.

DR. STEMHAGEN: I am Annette Stemhagen. I am Vice President of Epidemiology and Risk Management at United BioSource Corporation. I am an epidemiologist and I am the industry

representative on the Drug Safety and Risk Management Advisory Committee.

DR. RYDER: Steve Ryder, Pfizer R&D and I am the industry representative on the Endocrine and Metabolic Drugs Advisory Committee.

DR. ROSEN: Thank you, Steve. Dr. Savage has a clarification on a conflict.

DR. SAVAGE: I also wanted to just add, similar to what Dr. Fradkin said, that I have no personal conflict or financial interest in this but the National Heart, Lung and Blood Institute does receive rosiglitazone from GSK for both the ACCORD study, which was in the division I headed until July 1st, and for the BARI 2D study which Dr. Gordon is going to talk about later this morning.

DR. ROSEN: Thank you, Dr. Savage. Before I introduce the FDA, just another housekeeping note. There are two people who have not been able to make it by plane, Dr. David Oakes and Dr. Arthur Moss. We hope to have them on teleconference.

DR. MOSS: This is Dr. Moss. I am on the teleconference.

DR. OAKES: And this is David Oakes.

DR. ROSEN: Welcome. David, just one sentence about who you are and then we will turn it over to Arthur.

DR. OAKES: Yes, I am a professor of biostatistics at the University of Rochester. I have interest in clinical trials, specifically in cardiology and in neurodegenerative disorders. I should, by the way, just make an indication that in terms of conflict of interest, I have received fees totaling less than $10,000 per year from a competitor in the past for unrelated products.

DR. ROSEN: Arthur?

DR. MOSS: Yes, I am Dr. Arthur Moss, Professor of Medicine and Cardiology in Rochester, New York, with particular interest in clinical trials related to coronary disease and long QT syndrome. I have removed myself from any potential conflict of interest that I could identify.

DR. ROSEN: Thank you very much. Mary, could we start down at your end and just have the FDA people introduce themselves? Thank you.

DR. PARKS: I am Dr. Mary Parks. I am the Director for the Division of Metabolism and Endocrinology at FDA.

DR. MEYER: Yes, I am Dr. Robert Meyer and I am the Director of the Office of Drug Evaluation II, which is in the Office of New Drugs in the Center for Drug Evaluation and Research.

DR. KWEDER: I am Sandra Kweder. I am Deputy Director of the Office of New Drugs in CDER.

DR. THROCKMORTON: I am Doug Throckmorton. I am the Deputy Center Director in CDER.

DR. DAL PAN: I am Gerald Dal Pan. I am the Director of the Office of Surveillance and Epidemiology in CDER.

DR. AVIGAN: I am Mark Avigan, Director of Drug Risk Evaluation, Division of the Office of Surveillance and Epidemiology.

DR. O'NEILL: I am Bob O'Neill. I am the Director of the Office of Biostatistics in CDER.

DR. ROSEN: Thank you very much. We do have one additional note. There isn't any room here anymore but there is room in the overflow

room, the Washingtonian Room, which is just down the hall and to the right and then to the left. So, anybody who doesn't have a seat and wants to sit there, there is live video.

All right, I think we are going to get started then. I would like to introduce Dr. Mary Parks, who is the Director of the FDA CDER Division of Metabolism and Endocrine Products, who will give a brief introduction.

Introduction/Background

DR. PARKS: Good morning. Dr. Rosen, members of the advisory committees and invited participants, the FDA has convened this meeting several weeks in advance of the originally planned date to discuss an important public health matter that has garnered much publicity.

The topic for discussion will focus primarily on the drug rosiglitazone or Avandia. This drug is approved for glycemic control of type 2 diabetes, a condition that affects approximately eight percent of adults in the United States and whose incidence is expected to increase with the

rising rate of obesity and the aging population.

This is not some obscure medical disease known only to subspecialists. This is a disease that affects many of us in this room today, whether it be one's own medical condition, the patients that we treat or close friends or a family member with type 2 diabetes. As such, any public health recommendations made today have the potential for far-reaching consequences.

The issue at hand is the finding of an increased risk of myocardial ischemia associated with rosiglitazone therapy from several analyses of the controlled clinical studies for rosiglitazone, the large majority of which were of six months duration or less. While these different analyses have used similar odds ratios, they have not been accompanied by a universal conclusion that this is a definitive finding of increased risk.

Publication of one meta-analysis earlier this year by Dr. Nissen sparked public discussions on the limitations of meta-analyses through several editorials. It is not the focus of today's meeting

to compare and contrast the various analyses of the randomized, controlled data sets. Instead, today's meeting should focus on several clinical databases in addition to the FDA meta-analysis, including several epidemiologic studies and, more importantly, results from long-term controlled clinical studies, some completed and some still underway, in considering whether rosiglitazone is associated with an increased risk of myocardial ischemia.

The data you will hear today from both GSK and the FDA involve not only our own meta-analysis of the clinical trials data set but these other studies. It should be evident that there are many complex issues in evaluating this potential risk with rosiglitazone, issues involving statistics, trial design, patient populations, other interacting or contributing risk factors, duration of exposure, and all this on the backdrop of a complex metabolic disease, diabetes mellitus.

While we have many means of controlling hyperglycemia, the disease is a progressive one for

which one drug is often not adequate, and the choice between which second drug to start remains a debatable one among experts in the field. It is a disease in which there are short-term and long-term complications. It is a disease for which an evaluation of interventions on reducing the risk of complications has not yielded a clear algorithm for disease management. Not surprisingly, such a complex application has generated diverse opinions even within the agency that require this public discussion today to call on expert advice from a panel made up of diabetologists, endocrinologists, drug safety experts, cardiologists, biostatisticians and consumer representatives.

In order to provide all of you with the necessary background material to make informed decisions on the cardiovascular safety of this product, we have assembled the following presentations for the morning: Dr. Robert Ratner, a diabetologist from Georgetown University and MedStar Research Institute, will provide the background presentation on type 2 diabetes, its

complications and management and the benefits of glycemic control. GSK will provide the product history, the basis for their conducting the meta-analysis and other additional data, including the long-term controlled studies.

Some overlap may occur with the FDA presentations which you will hear from Miss Joy Mele, the Office of Biometrics, on the FDA review of the meta-analysis. Dr. Karen Mahone, from the Division of Metabolism Endocrine Products, will present on the long-term controlled clinical trials, followed by Dr. David Gordon, from the NHLBI, who will discuss the ongoing NIH-sponsored study BARI 2D.

From the Office of Surveillance and Epidemiology, you will hear Dr. Kate Gelperin present on observational cohort studies, and Dr. David Graham's analysis of risk/benefits of rosiglitazone.

Finally, you will hear closing remarks from Drs. Meyer and Dal Pan, from the Office of New Drugs and Office of Surveillance and Epidemiology

respectively.

In closing, I would like to thank the many individuals at the FDA and GSK who have invested countless hours in preparing for this advisory committee. It is not exaggeration that many personal and professional interests have been placed on hold by many of us to ensure that this meeting could be held in a timely fashion.

Finally, on behalf of the FDA, I would like to thank each participant in today's advisory committee meeting for your careful review of the background materials. We look forward to your thoughtful discussions and your sound scientific deliberations throughout the day. Thank you very much. Dr. Robert Ratner.

DR. ROSEN: Thank you, Dr. Parks. Dr. Robert Ratner is Vice President for Scientific Affairs for MedStar Research Institute and his topic will be Achieving Diabetes Targets: Where Are We and How Can We Do Better?

Guest Speaker Presentation

Achieving Diabetes Targets:

Where Are We and How Can We Do Better?

DR. RATNER: Mr. Chairman, ladies and gentlemen, it is a great pleasure for me to be here to speak with you.

[Slide]

As Dr. Parks mentioned, my role is to give you a background on where we are with type 2 diabetes. For 70 years scientists and clinicians debated as to whether or not controlling glucose was important at all. It wasn't until 1993, with the publication of the diabetes control and complications trial that we finally had an evidence base that said control mattered. Despite that, what we have seen even since then is an epidemic of diabetes and, with it, and epidemic of complications, 4,100 new cases of diabetes every day; amputations, 230 daily; 55 cases of blindness daily; and 120 cases of renal failure daily, all the number one cause of these morbidities in the U.S.; finally, 810 deaths daily and 60 percent of these are, in fact, due to cardiovascular disease. This is a prevalent disease. It is a growing

disease and it is an expensive disease.

[Slide]

In 2002, 132 billion dollars were spent in the care and management of individuals with diabetes. There is a very important consideration here, 54 billion dollars of this is due to institutional care, the chronic complications of the disease; outpatient care, 20 billion dollars; indirect costs, loss of productivity, 40 billion dollars; and our treatment of diabetes essentially 17 billion dollars.

As we move forward with the epidemic of type 2 diabetes, what we are going to see is an astronomic rise in the direct and indirect costs related to diabetes care.

[Slide]

So, here you are seeing the direct and indirect costs that were demonstrated in that 2002 study and projections to 2010 and 2020, with direct costs ultimately reaching 138 billion dollars and total costs approaching 200 billion dollars.

[Slide]

Much of this increase in cost has been the result of an increase in the micro- and macrovascular complications of the disease. So, here you see a 20-year demonstration of the remarkable increase of end-stage renal disease seen in the United States. Keep in mind that in 1993 we had the publication of the diabetes control and complications trial which definitively demonstrated that controlling blood glucose could reduce the development of renal disease. Despite that, over the ensuing decade one sees a remarkable increase in the relationship between diabetes and end-stage renal disease.

[Slide]

Fortunately, since the publication of the UKPDS in 1998 we actually see a leveling off of the incidence of diabetic end-stage renal disease, and this is in the face of a progressive increase in the prevalence of the disease. We are finally making headway in beginning to control end-stage renal disease related to diabetes.

[Slide]

It is demonstrated most actively right here. You see the flattening of the curve and, in fact, a beginning drop in the adjusted incidence rate for end-stage renal disease. If you simply look at the change from the previous year, we are now actively decreasing the incidence of end-stage renal disease.

[Slide]

Other microvascular complications are also beginning to come under control. Here you see the prevalence of visual impairment by different ages, with the younger group and the older group up here. Though the slope is not very steep, in all age groups there is a progressive decline in visual impairment over the previous decade.

[Slide]

Peripheral vascular disease is also being improved. Despite this little bump here, in about 1994-1996, what you see is a progressive decline, again, in all age groups in the peripheral vascular complications related to diabetes. We are making headway but we are clearly not there yet.

[Slide]

The UKPDS has demonstrated definitively the relationship between glycemic control and complications in patients with type 2 diabetes. The DCCT was exclusively in type 1 diabetes and, though there really wasn't an a priori reason why there ought to be a difference between the two types of diabetes, the UKPDS, in 1998, definitively showed the relationships for type 2 diabetes as well. So, for every one percent decrement in hemoglobin A1c in type 2 diabetes you find a 37 percent decrease in the microvascular endpoints related to diabetes.

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But you also see this relationship, albeit less steep, with macrovascular disease, with a 14 percent decrease in fatal and non-fatal MI for every one percent decrement in A1c and a 12 percent decrease in the incidence of fatal and non-fatal stroke.

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So, when you begin to look at the

relationship of diabetes control and complications, one sees a relationship both with microvascular disease, a rather steep slope, and with myocardial infarction, albeit a less steep slope.

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What can we draw from this information? Hemoglobin A1c is a good biologic correlate to microvascular disease complications. We have waited 70 years for the DCCT to finally show us the relationship, and A1c is the only surrogate we have to see how we are doing with microvascular complications. But what about macrovascular disease? A1c is a less powerful correlate to macrovascular disease, but that is because of the multifactorial nature of the underlying disorder. It doesn't mean that there is no value.

[Slide]

So, if hemoglobin A1c is so important, how are we doing? The answer is not particularly well. This is a public health observation of well over a quarter of a million individuals with diabetes in a community practice. What one sees is that 55

percent of individuals fail to meet the ADA guidelines for therapy which would be a hemoglobin A1c of less than 7 percent. Unfortunately, what you see is that 20 percent are in awful control with hemoglobin A1c levels exceeding 9 percent.

Now, this is a community practice and perhaps we ought to be able to do better. But these are controlled clinical trials where you have very motivated patients; you have very motivated investigators; and at least in DCCT you have unlimited amounts of money in order to bring them under control.

[Slide]

What do we see? We can see that in a controlled clinical trial you can bring hemoglobin A1c's down, and the moment the study ends and patients go back to community-based care the hemoglobin A1c's begin to rise from 7.3 at the very best in DCCT up to 8.1 six years later.

What about in the UKPDS? Initially individuals come under control and then they progressively deteriorate. The natural history of

the disease is this progressive nature of deterioration in beta cell function and perhaps mass. So, it is not surprising that we are not doing great but, in fact, we are doing better.

[Slide]

This is the diabetes physician recognition program from NCQA and the ADA, looking at those specialized practices in diabetes. What one can see is that as you move from 1997 to 2003 the percent of individuals who are in awful control is actually diminishing. We are getting a bit better and, yet, still 8 percent have A1c's in excess of 9.5 percent. We are also getting a greater percentage under good control, with an A1c of less than 7. But even so, in the best of practices less than half are achieving ideal glycemic control.

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Why is this? Why can't we bring glucose levels under control? The first issue is that it is a dynamic state. We can get people under control, as demonstrated here in the ADOPT trial, but if we continue effective therapy ultimately

they fail because the beta cell function deteriorates over time. So, initial success ultimately becomes failure in a large percentage of patients.

[Slide]

Not only that, physicians and patients are reluctant to take the next step. This is called clinical inertia. The simple fact is that when you fail diet only two-thirds are willing to initiate drug therapy. In the clinic basically the patients say, doc, give me another three months. I will follow my diet this time. And three months turns into five years. But the reluctance also occurs when you move from one agent, whether it is sulfonylurea or metformin, to a second agent and the response when you have failed on a combination is abysmal. The simple fact is that patients and physicians are not moving therapy forward, and we will explore some of the reasons why this may be.

[Slide]

None of these drugs are simple or without their complications so that when we begin to talk

about insulin, insulin can control anybody with diabetes. If you give it often enough in sufficient quantity you can bring anybody's glucose levels down. Anybody's. But it may take five or six injections per day and the world's record for the largest quantity of insulin given in a 24-hour period is 144,000 units. But you can do it. The consequences are a very complex regimen that includes a risk of hypoglycemia.

Fortunately, we have no data that would suggest that insulin causes cardiovascular disease or other major complications, other than weight gain. The sulfonylureas cause hypoglycemia, are much simpler than insulin because it is simply a pill, but we have this nagging suspicion of cardiovascular effects of sulfonylureas as well, dating all the way back to the UGDP study in the 1960s and '70s.

Metformin was kept off the market in the United States for 20 years because of a risk of lactic acidosis and it now has become a well-deserved darling of the endocrionologists. It

is simple. It is easy. It is usually well tolerated and the risk of lactic acidosis is relatively mild. There is no risk of hypoglycemia. We only have to deal with the GI side effects.

The alpha-glucosidase inhibitors have no major side effects. They are simply not well tolerated either by the patient or the patient's family.

The glitazones, no risk of hypoglycemia, no risk of lactic acidosis, but clearly a risk of CHF, and you will hear much more about the risk of other forms of cardiovascular disease.

The short-acting insulin secretagogues, repaglinide and nateglinide, cause hypoglycemia. They must be taken several times a day, and have limited efficacy.

And, the data on the incretin mimetics and enhancers is really too short to be able to make any firm claims, but it appears as though they have a very low risk of hypoglycemia, no impact on cardiovascular disease and no impact on lactic acidosis.

[Slide]

One of the major limiting factors in the treatment of diabetes is that, with the exception of metformin, any other drug that we give tends to be associated with weight gain. Now, the new incretin mimetics and enhancers look to be weight neutral or perhaps causing weight loss. But you can see with the traditional medications there is always a substantial weight gain. In fact, if we were to put insulin into this, it would be out here so it has the greatest problem.

[Slide]

So, we begin to find limitations in our ability to institute therapy based on side effects and complexity. As a result, what we find is that even with the simple oral anti-diabetic drugs there is only a 50 percent patient adherence to therapy. Why do patients stop taking medicine? They stop taking medicine because of either side effects or inconvenience or cost. Yet, here 50 percent are stopping. If you look at the lipid-lowering agents, they are very simple. People take those

drugs.

[Slide]

What about insulin? Insulin works. The difficulty is that when you look at insulin adherence in patients with type 2 diabetes, what you find even here is a marked reduction in the adherence rate. It is a very complex regimen, drawing up variable doses of insulin, giving the injections, monitoring glucose and altering the dose dependent upon activity and glucose levels.

[Slide]

So, what have we got? We have data that suggests that glucose control actually can relate to complications. We have good data on insulin, sulfonylureas and metformin with microvascular disease. In direct clinical trials you can demonstrate a reduction in microvascular complications. We don't have that data in microvascular disease for the alpha-glucosidase inhibitors, the glitazones, repaglinide, or nateglinide, or the incretin mimetics and enhancers. One can ask the question is it even

ethical now to do those studies, and that is something that we are going to have to come to grips with.

What about the relationship of therapy to cardiovascular disease? Can we impact cardiovascular outcomes? Well, with insulin you have the DIGAMI study, and DIGAMI 1 suggested, yes, insulin can reduce cardiovascular outcomes. The difficulty is that DIGAMI 2, with all of its problems, failed to reinforce that finding.

For sulfonylureas we have absolutely no data suggesting we can minimize cardiovascular disease and, to the contrary, some data that would suggest that we increase it.

Metformin, well, again a question mark yes. If you look at the UKPDS metformin analysis, they did, in fact, get a statistically significant reduction in the development of cardiovascular disease but that was a post hoc analysis. Not only that, if metformin was added to sulfonylureas they actually had an increase in cardiovascular disease over and above the sulfonylureas alone so we remain

with a question mark.

The interesting issue is that the only drug used in the treatment of diabetes which has a study that shows a remarkable reduction in cardiovascular events is acerbose, in the STOP-NIDDM trial where myocardial infarction was significantly decreased. But they only had 14 cases in the entire study. So, it is unclear as to how well that is going to be replicated.

So, the issue is if we have cardiovascular outcomes as our primary indication for therapy, we have no drugs to treat diabetes and that becomes a problem. Our drug therapy isn't adequate. We really need to have a broad spectrum of drugs in order to be able to pick and choose what is best for the individual patient.

[Slide]

So, why do we need new therapies for type 2 diabetes? We are in the midst of an epidemic and soon our entire medical system is going to be swamped. Hemoglobin A1c is a well validated short-term target that gives our patients and gives

physicians guidelines on whether they are going in the right direction.

Having said that, we are still not meeting our glycemic targets, and at least in part that is because current therapies have limited efficacy, marked complexity and unacceptable side effects either to patients or to physicians, and ultimately any therapy must be acceptable to the patient and to the healthcare provider because if it stays on the shelf and doesn't get utilized it doesn't work.

[Slide]

So, what should drive diabetes drug development and approval? Clearly, safety. That ha to be the first consideration. First do no harm whether it is hepatic, cardiovascular, hypoglycemic. However, as we are looking at safety let us balance these safety features with the realization that diabetes is a serious disease with serious complications. We have to look at efficacy. But efficacy goes to glycemic control and risk factor reduction, both. We have to look at side effects because this is what is going to be

limiting the utilization by our patients and, in particular weight gain, and simplicity and availability for patient acceptability is what we need to do.

[Slide]

Now, the argument can be that we can't do all of this because it is too expensive. Well, this is an economic analysis of a health plan simply looking at the relationship of costs by virtue of hemoglobin A1c achieved. Whether you are looking at diabetes alone or diabetes complicated by hypertension and heart disease, as the hemoglobin A1c rises from 6 to 10 costs continue to go up. It costs more to take care of a patient who is in bad control than a patient in good control.

[Slide]

Now, this could be a circular argument. So, the question is, is it cost effective to treat diabetes? The only way we can rally do that analysis is through computer modeling and looking at comparison therapies. This was done by the CDC and published in JAMA four years ago.

If you look at hypertension therapy, it is clearly very cost effective, actually cost savings when it comes to quality adjusted life years gained. But take a look at glycemic control versus lipid control. In the CDC's computer model it is more cost effective to take diabetes down to a hemoglobin less than 7 than it is to take LDLs down to less than 100. So, we do have the opportunities. We do have cost motivations to spend more up front on therapy before we have to spend the money later on complications. I thank you very much.

DR. ROSEN: Thank you, Dr. Ratner. We are going to move on to the sponsor presentation. I would just like to introduce this by saying that we want to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. You have already heard about a couple of exceptions.

The presentations today by the sponsors will be limited to 70 minutes and then we will have

15 minutes of questions from the committee. During the discussion period the panel members will be recognized by myself, and if there are further questions this afternoon for the sponsor we may get back to the sponsor at that time. So, I would like to introduce Dr. Krall from GlaxoSmithKline.

GlaxoSmithKline Presentation

Introduction

DR. KRALL: Mr. Chairman, members of the committees, members of the FDA, good morning.

[Slide]

My name is Ronald Krall. I am Senior Vice President and Chief Medical Office of GlaxoSmithKline. On behalf of GSK, I wish to thank the FDA and the committees for the opportunity to present, and especially to thank the members of the committees in advance for what I know will be your thoughtful and thorough deliberations.

[Slide]

Our formal presentation will be in three parts. After my introduction Dr. Murray Stewart, an endocrinologist and diabetologist, will review

with you the data on the cardiovascular safety of rosiglitazone. I will return to conclude, after which our team will answer your questions. I will be speaking for about 20 minutes now, Dr. Stewart for about 35. I will take another 10 minutes at the end and we will, Mr. Chairman, adhere to our time schedule.

[Slide]

Why are we here today? Over the past year three meta-analyses of primarily short-term rosiglitazone trials, our own, one done by the FDA and one done by Drs. Nissen and Wolski, have reported an increase in myocardial infarction and cardiovascular mortality. All three of these analyses were performed on largely the same set of studies and, despite some methodological differences, all raised the same questions.

[Slide]

These are the questions that we will address today. Is there an increase in cardiovascular mortality associated with rosiglitazone? Is there an increase in myocardial

infarction associated with rosiglitazone?

Now, before I go on to tell you how we have addressed these questions, I would like to acknowledge that one of the questions that you will be asked to discuss this afternoon is about the quality of these meta-analyses. First, these analyses are subject to the limitation of all meta-analyses. They are not always right. LeLorier published a review of meta-analyses in 1997 that showed only 65 percent of meta-analyses were confirmed by subsequent clinical trials.

[Slide]

Robust analyses share certain characteristics. Their trials have the same or at least similar objectives. Their patient populations are similar, especially with regard to those factors that may influence the endpoint of the meta-analysis. The endpoint of the meta-analysis is the primary endpoint of the trials. The meta-analysis event is well defined and reliably captured in the trials. Within the component trials there is no bias in allocation to

treatment with respect to the meta-analysis endpoint. Finally, the number of events is sufficiently large. Usually 200 events are considered a minimum.

The three meta-analyses that we will discuss today fall short on all of these points. Dr. Stewart will have more to say about the limitations of the GSK meta-analysis which, by the way, in this presentation we refer to as the integrated clinical trial analysis or ICT. When Dr. Stewart presents the data he will discuss some of the limitations. Suffice it to say that it has always been our point of view that all three analyses have substantial limitations and can only generate hypotheses.

[Slide]

Knowing these limitations, we sought better evidence to answer the questions the integrated trial analysis posed. We have assumed that if the hypothesis raised by the integrated trial analysis were true, the signal should be clear in these better sources of evidence.

The first place we have looked for evidence is in large, long-term prospective outcome studies. There were three and I will describe these in a minute. Additionally, we have looked for evidence of increased cardiovascular risk in the real-life use of rosiglitazone. We have carried out three different epidemiology studies in more than 1.3 million diabetic lives. We have examined the data from a study in a high cardiovascular risk population. Finally, there are four other ongoing studies. While we can't analyze these studies, their data safety monitoring boards can assess whether the level of cardiovascular risk seen in the integrated trial analysis is present and, if so, whether those trials should continue.

Dr. Stewart will review with you the design of the epidemiology study in the high cardiovascular risk patients when he presents their data. Let me now review for you the salient features of the key long-term clinical trials, how the events were identified in those trials, and describe the endpoints that we will consider.

First the trials. There were three, RECORD, ADOPT and DREAM.

[Slide]

RECORD is an active control study of cardiovascular outcomes in a patient population requiring oral anti-diabetic treatment, combination oral anti-diabetic treatment. It is being conducted in just under 4,500 patients over six years, and the endpoint is cardiovascular hospitalization or death and includes heart failure. This composite endpoint was selected because the interest was one of understanding the consequences of cardiac events.

[Slide]

The other components of the MACE endpoint are collected and adjudicated, and can be assessed though, admittedly, with lower power. Because the study anticipates progression of disease and the need for insulin therapy, it was impractical to blind the treatments in the trial, similar to the landmark UKPDS study which has been a rock-solid basis of evidence for diabetes management. What is

important is that adjudication of the events in RECORD is performed by an expert assessment panel blind to treatment. We do not believe that the knowledge of treatment in this trial has somehow differentially affected collection or reporting of events.

In your briefing documents you have the interim analysis for RECORD and, therefore, know that the actual number of cardiovascular events is lower than originally anticipated. Unless the trial is extended or the event rate increases, it may not be achieve the non-inferiority margin for the primary endpoint. However, there are more events in RECORD than in the 42 trials of the integrated trial analysis. And, because of its randomized and controlled design and the adjudication of events, it remains the best source of evidence for rosiglitazone's cardiovascular profile. We may have less certainty than planned but that doesn't mean we have none.

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ADOPT was a study testing durability of

glycemic control in patients newly requiring single-drug therapy. More than 4,000 patients participated. Its mean follow-up was approximately four years. Cardiovascular events in ADOPT were not adjudicated. They were identified from the reported adverse events.

[Slide]

DREAM was a trial in patients with impaired glucose tolerance, studying the effects of rosiglitazone, ramipril and the combination in delaying progression to frank diabetes. More than 5,000 patients participated and mean follow-up was more than three years. Cardiovascular events in this trial were adjudicated. Because these patients were very early in their disease, it is not surprising that the cardiovascular event rates in the trial were low.

In total, these three prospective, randomized trials included more than 14,000 patients. They represent a body of evidence as large as the integrated trial analysis.

[Slide]

Let me now turn to how the events were collected and classified. Cardiovascular events were identified in different ways in the different trials. At the lowest level events were collected as part of routine adverse event reporting, an adverse event being any untoward medical occurrence. In this case there is no systematic questioning for cardiovascular events and no systematic collection of the relevant information about any event that is called cardiovascular. This was how cases were identified for the integrated trial analysis and for ADOPT.

It is possible to improve upon case definition when cases are found through routine adverse event reporting by external, independent, blinded classification of events after the study. We have called this post-study adjudication. It is a higher level of case definition. It approximates standard in-stream adjudication, but fundamentally it depends on the quality of the data as they were originally collected.

Because of our concerns about the accuracy

of case definition, especially for myocardial infarction, we have recently commissioned this kind of review for the integrated trial analysis and ADOPT. This allows us to compare similarly defined cases across the three large outcome studies, RECORD, DREAM and ADOPT. These are new results and Dr. Stewart will review them for you.

In-stream adjudicated events represent the highest level of certainty of case definition. Investigators are given specific instructions to identify cases and an independent committee reviews each case blind to treatment during the conduct of the trial. The committee has the ability to seek additional information or clarification in order to make its classifications. This was the approach used in RECORD and DREAM.

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Finally, here are the endpoints that we will discuss. Dr. Stewart will start with the most inclusive endpoint, the one that was the subject of the original integrated trial analysis, myocardial ischemia. He will then focus on the harder MACE

endpoints of myocardial infarction, stroke and cardiovascular mortality.

[Slide]

Here is what Dr. Stewart will tell you. Regarding cardiovascular mortality, the long-term trials RECORD, ADOPT and DREAM provide no evidence of increased cardiovascular mortality.

[Slide]

Regarding myocardial infarction, among the sources of evidence we used to test the hypothesis raised by the integrated trial analysis, the number of myocardial infarctions is small. The data are inconsistent and there is no overall evidence that rosiglitazone is different from other oral anti-diabetic agents. Importantly, Dr. Stewart will share new data from a large epidemiology study that rosiglitazone is not different from pioglitazone. He will also show you that in the long-term outcome studies there are fewer strokes in patients treated with rosiglitazone. Now I would like to introduce Dr. Stewart.

Review of Data

DR. STEWART: Thank you, Dr. Krall.

[Slide]

Mr. Chairman, it gives me pleasure to present the data on the cardiovascular safety of rosiglitazone to this committee.

[Slide]

As Dr. Krall has just said, this part of the presentation will show the data on the following endpoints. I will begin with myocardial ischemia which was the endpoint determined in the integrated clinical trial analysis. Following that, I will concentration on the three well-recognized hard endpoints of MACE. These are commonly used in cardiovascular outcome studies and these are myocardial infarction, stroke and cardiovascular mortality. I will also present data at the end of my presentation for all the long-term data combined for each of the MACE endpoints and its composite.

[Slide]

One of the reasons myocardial ischemia was chosen as an endpoint in the integrated clinical

trial analysis was due to the observation of a small excess of ischemic events when rosiglitazone was added to insulin. It was, therefore, very important to determine whether there was an increase in myocardial ischemia when rosi was used in different combinations in other studies.

[Slide]

The integrated clinical trial analysis combined data from 42 double-blind, controlled studies. These studies were primarily designed for glycemic efficacy, not to assess cardiovascular events. The studies were heterogeneous and included studies in drug-naive patients, monotherapy patients, combination with other oral anti-diabetic agents and insulin. The studies also examined the range of patients, from those with minimal risk factors to those with known chronic heart disease, and also included the study in patients with known heart failure. The mean duration of the study was six months and the majority were placebo controlled.

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The adverse event definitions for myocardial ischemia that were considered in the ICT data set were very broad and inclusive. This was done to ensure all events were captured. It was also done in order to minimize the risk of missing a potential signal and to maximize the number of events to help identify patient groups who may be at risk. AEs included, for example, unadjudicated cardiac chest pain through to death. It is important to note that some symptoms of ischemia, such as chest discomfort and dyspnea, are also symptoms of heart failure. Given the well-known fluid-related effects, this may have led to some reporting bias by investigators.

The more definitive endpoints of myocardial infarction and cardiovascular death are included, but these will be also discussed separately. This is important as myocardial ischemia or angina is often short-lived and reversible, whereas myocardial infarction leads to permanent myocardial damage and long-term clinical sequelae.

[Slide]

ADOPT is an additional source of data on myocardial ischemia. The data captured in ADOPT is based on adverse event reports from investigators for angina, myocardial infarction and coronary artery disease.

[Slide]

This slide shows the summary events of myocardial ischemia. The format of the next few slides will be similar so I will take you through this. From left to right the sources of data will be listed, followed by the treatment and number of subjects assigned to that treatment. The next column is the number of patients with events. Inclusion of rate per 100 patient-years is important as this takes into account the different denominators, the fact that studies are of different duration and, therefore, allows comparison across the different studies. It also demonstrates the absolute event rate. The final column shows the hazard ratios and the confidence intervals.

The data from the ICT shows more events with rosiglitazone, 171 cases versus 85 in the comparator. But note that there are more patients in the rosiglitazone group, 8,600 versus 5,600, which is why it is important to look at the rate per 100 patient-years, which is 4.1 versus 3.1. This gives a hazard ratio of 1.3 with confidence intervals from 1.01 to 1.7.

In contrast, the ADOPT data shows a hazard ratio for rosiglitazone or metformin of 0.99 and rosiglitazone versus SU of 1.18. It is important to note that the numbers here are patients randomized. There were a number of dropouts in the SU arm and this may reflect the fact that there were more dropouts for hypoglycemia and monotherapy failure.

There is a difference between ICT and ADOPT. This may reflect both the heterogeneity of the population and the studies included in the ICT data set, such as studies including patients on insulin and patients with heart failure that were not included in the ADOPT study.

There are a umber of other differences in ICT and ADOPT. ICT consists largely of short-term studies, 70 percent of which were against placebo, whereas ADOPT is a long-term study of four to six years and directly compares rosiglitazone against the two most commonly used anti-diabetic agents.

The difference between active and controlled studies, placebo-controlled, is discussed in the FDA briefing document and I will not discuss this much further. However, it is interesting that the increase in cardiovascular events in short-term studies with placebo is not a new phenomenon in diabetes.

[Slide]

The data for other oral agents has shown discrepancies between short- and long-term studies. The data here is taken from the summary basis of approval. In particular note that for metformin in short-term studies there were more cardiovascular events, 128 verus 80 per 1,000 patient-years, an observation that generated some debate at the time of approval for metformin. However, as you heard

earlier, in the long-term study, the UKPDS, over ten years metformin was shown to decrease myocardial infarction and mortality in an obese subset.

The data from glimepiride show more deaths in the control, although clearly the numbers are small. But as you have heard already, there have been concerns regarding the cardiovascular safety of sulfonylureas dating back to the UGDP and even in the UKPDS. The long-term data on sulfonylureas only showed avoidance of excess risk.

The data on pioglitazone is interesting. The data presented in the FDA briefing document showed more cardiovascular events in the pioglitazone group compared to placebo in the first six months of the PROactive study, whereas in the same study, by study end there was a neutral to trend for benefit in macrovascular outcomes.

The reason for this difference for oral anti-diabetic agents in the short-term studies is unclear. This may be due to the fact that studies are not designed to assess cardiovascular outcomes

and that the number of events is generally low. What is clear, however, is that short-term studies don't always predict long-term outcomes. Returning to the data with rosiglitazone, although there appears to be more myocardial ischemia in the ICT analysis, this is not borne out in ADOPT.

[Slide]

So, in conclusion, in contrast to the ICT data where there was an increase in myocardial ischemia, the ADOPT study against comparators showed no increase in myocardial ischemia both in the short and long term. As part of ongoing pharmacovigilance, GSK has explored the adverse event reporting system, the AER system. We did this to look for any signal of increased myocardial ischemia with rosiglitazone, and found no disproportionate reporting for events of myocardial ischemia for either rosiglitazone or pioglitazone, and the details of the postmarketing surveillance are in the briefing document.

[Slide]

I would now like to move to the first of

the three hard cardiovascular endpoints, myocardial infarction. This is a more robust endpoint with a diagnosis of important consequences to patients.

[Slide]

In addition to ICT, evidence to assess the risk of myocardial infarction with rosiglitazone comes from a wide range of sources. The most important is RECORD interim analysis where events are defined using in-stream adjudication by an endpoint committee that was blinded to treatment.

In ADOPT myocardial infarction was defined using investigator reports. In an effort to address the weakness of this type report, GSK recently commissioned a post-study adjudication event of two external cardiologists. They followed predefined criteria and they reviewed all the SAEs from both ADOPT and the ICT data set. This was done in a blinded manner and events were categorized into three categories, definite MI, unconfirmed MI and cardiovascular death which included sudden death and fatal myocardial infarction. The two cardiologists are with us here

today and are prepared to answer detailed questions about the adjudication.

For both DREAM and a study in high risk patients events were adjudicated in-stream. Three large epidemiological studies also formed a very useful source of information. For these events myocardial infarction was confirmed using ICD-9 codes which were validated by medical charts and medical records.

[Slide]

The ICT, as did other meta-analyses conducted in this data set, raised a very important question of whether there are more cases of myocardial infarction with rosiglitazone. The data shown in this slide are based on the SAE reports that have not been adjudicated. The results show 45 cases with rosiglitazone compared with 20 in the control group, giving a hazard ratio of 1.59. Again, please note the larger number of patients in the rosiglitazone treatment group. The rate per 100 patient-years is 1.09 for rosiglitazone and for the comparator is 0.75.

In RECORD overall there are more events of myocardial infarction than in any other data source. There were six more myocardial infarctions in rosiglitazone, 43 cases versus 37 cases in the active comparator group where there was matching for glycemia. This gave a hazard ratio of 1.16 with confidence intervals from 0.75 to 1.8. I would now like to point out what this means in absolute terms, and 0.52 minus 0.45 gives a difference of 0.07 per 100 patient-years which, if real, would represent less than one event per 1,000 patient-years.

In ADOPT, which compared rosiglitazone to the gold standard metformin, there were four more cases on rosiglitazone, 24 versus 20 in metformin, giving a hazard ratio of 1.23. There were fewer cases of myocardial infarction in the glimepiride comparator arm which may be explained in part, as I mentioned earlier, that there were more withdrawals in this arm.

In DREAM, as expected given the patient population, these were non-diabetics, the overall

event rate was much lower than in RECORD, 0.12 versus 0.52 per 100 patient-years. The comparisons shown here are versus placebo. There was no difference in event of myocardial infarction between rosiglitazone and placebo. There were more events in the rosiglitazone and ramipril combination as compared to placebo and FDA have commented on this in their briefing document. A review of data from ADOPT and ICT does not confirm this observation but we agree it warrants further investigation.

[Slide]

So, overall what does this data show in clinical trials? There is no statistical difference between rosiglitazone and active comparator. The numbers are small and it is difficult to reach a definitive conclusion. Therefore, it is important to look at other sources of information.

When comparing events from different studies it is important that event definition is consistent. In ICT and ADOPT the definition of

myocardial infarction included non-fatal, fatal MI and sudden death. This was not the case for RECORD and DREAM which did not include sudden death in the definition of myocardial infarction. Sudden death is important as some MIs may present as sudden death. For completeness, I will now show you data combining myocardial infarction with sudden death.

[Slide]

Here are the summary of events across the data sources for myocardial infarction combined with sudden death. As a reminder, the data from ICT and ADOPT are unchanged and therefore shaded, leaving the new data showing the results in addition of sudden death for RECORD and DREAM.

[Slide]

In RECORD events increased from 43 to 49 and in the control group from 37 to 45, giving a hazard ratio changing from 1.16 to 1.09. This gives an absolute difference in event rates of 0.05 per 100 patient-years.

[Slide]

Adding sudden death to DREAM had little

impact, changing in events from 5, 11, 3 and 6 to 5, 12, 5 and 7, with no real appreciable change in the hazard ratios. Therefore, adding in sudden death did not change the overall conclusions for myocardial infarction.

[Slide]

Previously I noted that the data from the ICT and ADOPT for myocardial infarction which have been shown thus far are based on unadjudicated serious adverse event records, not adjudicated as in RECORD and DREAM. As a reminder, two external cardiologists reviewed the SAEs from ADOPT and ICT. They followed predefined criteria and events were characterized into definite MI, unconfirmed MI or CV death. The definitions are shown on the following slide.

[Slide]

Non-fatal Mi was broken into definite MI and non-confirmed MI. For definite MI the criteria included symptoms accompanied by either ECG changes and/or enzyme changes. For the non-confirmed MI the clinical course was likely to represent acute

MI but just insufficient information was available to make the diagnosis.

[Slide]

Now we will look at the effect of adjudicating events in ADOPT and ICT using the confirmed cases of myocardial infarction. The data from RECORD and DREAM have not changed and therefore are shaded. Adjudicating events in ICT changed the cases from 45 to 24 for rosiglitazone and 20 to 11 in the comparator, with no appreciable change in the hazard ratio, 1.59 to 1.53.

[Slide]

For ADOPT the cases changed from 24, 20 and 14 to 12, 12 and 11. This reduced the hazard ratio from 1.23 for rosiglitazone versus met to 1.03, and for rosiglitazone versus SU from 1.52 to 1.0. This adjudication did not appreciably change the overall conclusions but I think demonstrates the fragility of the estimates when the number of events is low.

[Slide]

For completeness, I will now show the data

for adjudication in both the confirmed and non-confirmed cases. The original numbers in the ICT for rosiglitazone were 45 and the comparator is 20. These changed to 36 and 18, with a hazard ratio changing from 1.59 to 1.47.

For ADOPT the original numbers changed from 24, 20 and 14 to 20, 17 and 15. The hazard ratio changed from 1.23 to 1.21 in the rosi-met comparison and 1.52 to 1.2 for the rosi versus glimepiride comparison.

[Slide]

In summary, following adjudication there were still more cases of myocardial infarction in the ICT data set. But for ADOPT, where the difference was 24 versus 20 cases, there was no longer any difference between the groups. As with myocardial ischemia, there is a difference between data in short and placebo-controlled studies compared to controlled studies in the long term where there are active comparators.

If, as suggested by the ITC analysis, rosiglitazone does cause an increase in MI one

might expect the fact to be exaggerated in a high risk population. I will now review data from a recently published study conducted in a population at high risk of myocardial infarction.

[Slide]

This study in high risk patients was a 12-month, randomized, double-blind study in 200 obese subjects with underlying coronary artery disease who were undergoing percutaneous coronary intervention. The patients in the study had to have one or more risk factors, hypertension, dyslipidemia or dysglycemia. The majority were non-diabetic subjects. Of these subjects, more than 35 percent had a previous MI; 20 percent previous cardiac surgery; and 50 percent had a history of angina. This is in contrast to RECORD and ADOPT where there was less than 5 percent of subjects with a prior MI.

The primary endpoint of the study was progression of carotid intima media thickness. The results showed no difference in ICT progression between rosiglitazone and placebo. In this study

the key cardiovascular events were adjudicated and the data is shown on the following slide.

[Slide]

This study is small, with about 100 patients in each group. The event rate is higher, 5-10 percent compared with the event rate in ADOPT and RECORD, which was less than 1 percent. Overall, the results show fewer events in the rosiglitazone group compared to the placebo group across all the MACE endpoints, the composite and the individual components of death, myocardial infarction and stroke.

[Slide]

What if we look at things another way? If rosiglitazone is associated with a small increase in myocardial infarction one would expect to see it in a real-world setting where there are likely to be a high number and rate of myocardial infarction. If the signal seen in ITC is real, it is important to see if it is present in real-world clinical experience which is represented by large epidemiological studies. GSK has conducted three

large epidemiology studies in three managed care databases using two different methodologies. I will now review the results of these studies.

[Slide]

The data I am going to show you is from three very large managed care databases. The IHC had over 800,000 diabetic patients, Ingenix, 33,000 and PharMetrics, 400,000. Head-to-head comparisons were conducted for rosiglitazone versus other anti-diabetic agents including pioglitazone.

The IHC study is a nested case control study and both Ingenix and PharMetrics are cohort studies. In the cohort studies propensity scoring, which captures and accounts for the large number of patient characteristics and risk factors, was used. This was done to minimize collection bias that may be introduced by physician's choice of therapy. The endpoints of the studies are hospitalization for myocardial infarction or coronary revascularization. Myocardial infarction and coronary revascularization as primary hospital discharge diagnoses are considered reliable

endpoints, and these were validated against the medical records. The data are similar for both endpoints and I will present the data only for myocardial infarction.

Sudden death was not part of this analysis and is not captured in managed care databases. There is no reason, however, to believe that the pattern of events should be different from those in myocardial infarction.

[Slide]

The results from the nested case control study, where each case of myocardial infarction was matched to three control subjects, are shown here. The likelihood of myocardial infarction in subjects exposed to rosiglitazone is not different from those exposed to other anti-diabetic agents, with an odds ratio of 1.02. The results for pioglitazone compared to other oral anti-diabetic agents give an odds ratio of 0.9.

[Slide]

The cohort studies provide more robust data compared to case control studies as they

account for time of exposure to therapy. Cohort designs also adjust for baseline risk factors by propensity scoring and minimize confounding by indication. These cohort studies will be discussed next.

[Slide]

These are the results for myocardial infarction from the Ingenix study. The data displayed are bar graphs on the left in rate per 100 patient-years for rosiglitazone used as monotherapy, dual therapy or combination with insulin. The number of events of myocardial infarction are included in brackets. On the right are forest plots showing the point estimates for hazard ratio and 95 percent confidence intervals. Any point to the right of 1 favors the comparator, and to the left of 1 favors rosiglitazone.

Over 300 cases of myocardial infarction are captured in this study, which is higher than the number of cases of myocardial infarction in the ICT data set. The hazard ratios for rosiglitazone in monotherapy, dual combination and combination

with insulin are all close to 1, with confidence intervals overlapping 1. For monotherapy and dual therapy comparisons, the risk of myocardial infarction in rosiglitazone users lies somewhere between the risk associated with sulfonylurea at the high risk and metformin at the lower risk.

The risk of MI is similar with insulin, but overall there is no difference in the risk of myocardial infarction in rosiglitazone compared to other oral anti-diabetic agents. The hazard ratio for all rosiglitazone comparators is 0.92, with tight confidence intervals from 0.73 to 1.16.

[Slide]

Here are the results for myocardial infarction from the PharMetrics study. Note that a marked consistent pattern is seen with Ingenix. It is important to note that the PharMetrics database represents data from 80 different managed care organizations in the U.S. and there is no overlap in the managed care organizations captured by PharMetrics and Ingenix. The number of events is very high, over 2,000 events, and there is very

little difference across the groups when comparing rosiglitazone to other anti-diabetic agents, including metformin, sulfonylurea and insulin. In this study the hazard ratio for all rosiglitazone versus comparators is 1.06.

[Slide]

Now I will present head-to-head data comparing rosiglitazone to pioglitazone. Importantly, when comparing agents from the same class in an observational cohort study the election bias by physicians will be minimized. It is important to look in such a large database with PharMetrics because this included over 57,000 rosiglitazone users, 51,00 on pioglitazone and over 1,800 cases of myocardial infarction. If the risk of myocardial infarction is different between the agents you might expect to see it in such a large study.

The data show that for monotherapy the hazard ratio was 0.78 for comparing rosiglitazone to pioglitazone. In dual combinations the hazard ratio comparing rosiglitazone plus metformin versus

pioglitazone plus metformin is 1.01. The hazard ratio for comparing rosiglitazone plus SU versus pioglitazone plus SU is 1.22, and in combination with insulin the hazard ratio is 1.02. For all rosiglitazone versus all pioglitazone the hazard ratio was 1.07, with confidence intervals from 0.89 to 1.27. Therefore, overall there is no difference between pioglitazone and rosiglitazone whether used as monotherapy, dual therapy or in combination with insulin from the PharMetrics study.

[Slide]

In conclusion, there are three large well-defined database studies utilizing different methodologies, case control and cohort studies, and capturing data from different managed care organizations throughout the United States of America. The three studies show consistent results in a total of over 1.35 million diabetic patients. The risk of myocardial infarction is similar for rosiglitazone compared to other anti-diabetic agents. In particular, the risk of myocardial infarction is no different between rosiglitazone

and pioglitazone.

[Slide]

We have looked across a wide number of data sources from clinical trials to observational studies and with regard to myocardial infarction the conclusions are as follows, the number of myocardial infarctions in the clinical trials is small. The data are inconsistent, and overall there is no evidence that rosiglitazone is different from other oral anti-diabetic agents.

[Slide]

I would now like to discuss the data for another of the key cardiovascular endpoints of MACE, and that is stroke.

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The data on stroke from the RECORD interim have been adjudicated by the clinical endpoint committee which includes a specialist neurologist as well as a cardiologist on the panel. The data from ADOPT was collected using SAE investigator reports. Finally, the data collected in DREAM had in-stream adjudication.

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Data from the ICT showed fewer events in the rosiglitazone group, 13 cases as compared to the control group, 18 cases. This gives a hazard ratio of 0.48 with confidence intervals less than 1, 0.23 to 0.98. In RECORD the number of cases is greater than in other data sources and the number of events are similar to the number of events of myocardial infarction. The data, again, show fewer cases with rosiglitazone, 29 versus 38 cases in the active comparators, giving a hazard ratio of 0.76. In ADOPT one again sees similar number of strokes with rosiglitazone compared with metformin or sulfonylurea. In DREAM the number of events was very low. The rate per 100 patient-years is 0.12, lower than in RECORD, 0.35. However, here there were more events in rosiglitazone compared to placebo, five versus 3, giving a hazard ratio of 1.66 with wide confidence intervals, 0.4 to 6.93.

[Slide]

In conclusion, across the data sources there were fewer strokes observed with

rosiglitazone than compared to active comparators, in contrast to the data seen for myocardial infarction.

[Slide]

I have shown you data on myocardial ischemia, the broadly defined endpoint, myocardial infarction, the more clinically important endpoint, and stroke. Now I will review data on the most definitive of the MACE endpoints, cardiovascular mortality.

[Slide]

The data on cardiovascular mortality was adjudicated for RECORD and DREAM and the data from ADOPT is from investigator-reported SAEs. In addition, ADOPT data for CV mortality was also adjudicated by external cardiology experts.

[Slide]

The integrated clinical trial raised an important question, does rosiglitazone increase cardiovascular mortality? This is based on 18 deaths in the rosiglitazone group compared to 7 deaths in the control group, which gave a hazard

ratio of 1.91, confidence intervals of 0.79 to 4.64. In contrast to this concerning number, the results from the RECORD interim showed fewer deaths with rosiglitazone, with 29 deaths in the active comparator group which had 35 deaths, giving a hazard ratio of 0.83 with confidence intervals from 0.51 to 1.36. The absolute difference in events is 0.07 per 100 patient-years which, if real, would represent 7 fewer deaths per 10,000 patient-years.

The number of CV deaths in RECORD is higher than in any other clinical trial data source. Furthermore, the events were adjudicated and RECORD was specifically designed to look at cardiovascular safety, with cardiovascular death being one of the key endpoints of the primary endpoint. The data from RECORD is probably the most robust data to conclude on cardiovascular death. In ADOPT there were fewer deaths than in RECORD. There is no difference across the treatment groups.

The data from DREAM has also a low event rate compared to RECORD. The data show no

difference across the groups, with 5 cases on rosiglitazone, 5 in placebo, 5 with ramipril and 7 with ramipril and rosiglitazone.

[Slide]

As with myocardial infarction, an external cardiologist adjudicated the events of cardiovascular mortality in the ICT and ADOPT data set.

[Slide]

Here are the definitions. Fatal myocardial infarction was defined as death or hospitalized following acute MI or within 30 days. Sudden death was defined as death that occurred unexpectedly or death without prior symptoms. Other cardiovascular death included death due to an identified cardiovascular cause.

[Slide]

The data on this slide shows the results of adjudication. The data from RECORD and DREAM, which were previously adjudicated, don't change and are therefore shaded out. The data from the ICT changed the numbers from 18 with rosiglitazone to

19 and 7 from comparators to 8, with no appreciable difference in the hazard ratio, 1.91 to 1.68.

[Slide]

In ADOPT the adjudication changed the numbers of CV deaths from 5, 4 and 8 to 6, 8 and 12, with a hazard for rosiglitazone versus either metformin or sulfonylurea less than 1.

The adjudication did not change the overall conclusions that, in contrast to the ICT data set, there are fewer deaths in the long-term data sources when rosiglitazone is compared to active comparators.

[Slide]

As one would expect, for all-cause mortality, the most compelling endpoint, it is very important to examine the data for this endpoint which, of course, does not need adjudication. The ICT data showed more deaths with rosiglitazone, 23 versus 9 in the control, with a hazard ratio of 1.8, 0.82 to 3.92. Again, in contrast to the ICT and RECORD which had substantially more events, there were fewer cases, 74 with rosiglitazone

versus 80 cases in the active comparator group of metformin and sulfonylurea, giving a hazard ratio of 0.92, confidence intervals of 0.67 to 1.27.

In ADOPT, as in RECORD, there were fewer deaths with rosiglitazone than metformin, 12 versus 15, with a hazard ratio of 0.82. For rosiglitazone versus sulfonylurea, 12 versus 21, giving a hazard ratio of 0.51. In DREAM there was no difference in death across the groups. [Slide]

In conclusion, there is no increase in cardiovascular death with rosiglitazone compared to active comparators, and this is confirmed with no increase in mortality from any cause.

[Slide]

I will now present the separate components of MACE across each of the data sources. For completeness, I would like to present the MACE endpoint itself.

Some might well ask what happens when data from the long-term studies are combined. I will present estimates for both the relative and absolute risk for rosiglitazone compared from MACE

and its components from the three long-term studies.

We acknowledge the concerns expressed by the FDA in their briefing document about combining short- and long-term studies. Accepting this concern regarding combining short- and long-term trials, we have conducted this analysis. It is available but does not materially change the conclusions and, therefore, I will only present the combination data from the long-term studies, RECORD, ADOPT and DREAM.

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The data is presented as summary of MACE events for the combinations of RECORD, ADOPT and DREAM using confirmed adjudicated events. In addition to the normal parameters, I have included a column on the right-hand side which provides the rate difference per per 100 patient-years and its confidence intervals. This is important as it allows an evaluation of absolute difference in risk, which complements the hazard ratio which is the measure of relative risk.

The point estimates are consistently near the null, near zero. The confidence intervals all include zero with reasonable precision. This demonstrates that across these clinical trials involving 14,000 patients rosiglitazone is not associated with an increase in major adverse cardiovascular events, MACE.

[Slide]

In conclusion, having considered the following endpoints, the totality of the data show, one, there was no increase in the broadly defined endpoint of myocardial ischemia in the long-term comparator study ADOPT. For myocardial infarction, the more clinically important endpoint, the data are inconsistent and there is no overall evidence that rosiglitazone is different from other oral anti-diabetic agents, including pioglitazone. For stroke across the data sources, fewer strokes are observed with rosiglitazone. And for cardiovascular mortality, rosiglitazone is not associated with an increase in cardiovascular or all-cause mortality.

I would now like to hand back to Dr. Krall for concluding comments.

Conclusions

DR. KRALL: Thank you, Dr. Stewart.

[Slide]

The data that Dr. Stewart has just reviewed with you are not the only data that we will have to inform our understanding of the cardiovascular profile of rosiglitazone. Rosiglitazone is being used in four ongoing cardiovascular outcome studies and one IV study that assesses adjudicated cardiovascular endpoints. What are these studies?

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The first of these studies is ACCORD. It is sponsored by NHLBI. It tests the combination of intensive lipid therapy, blood pressure and glycemic control on cardiovascular outcomes. It is expected to have approximately 2,000 rosiglitazone-treated patients. The primary outcome measure is MACE.

The second of these studies is BARI-2D,

also an NHLBI-sponsored trial. It is a trail in a high risk population comparing insulin providing insulin sensitizing regimens in patients undergoing elective revascularization or medical therapy. You will hear more about this trial from Dr. Gordon later this morning.

VADT is a VA-sponsored trial comparing conventional versus intensive glycemic control on cardiovascular outcomes. Patients are at moderate cardiovascular risk. Approximately 1,100 rosiglitazone-treated patients are expected. The primary endpoint is a broad composite endpoint, shown on the slide, that is similar to PROactive but unlike PROactive, includes heart failure.

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APPROACH is a GSK-sponsored study comparing the effects of rosiglitazone and glipazide on the progression of atherosclerosis as assessed by IVUS and QCA. The patient population is higher risk, one that is admitted for cardiac catheterization or PCI. Three hundred rosiglitazone patients will be treated and the out

is change in plaque volume.

Finally, this is RECORD. You have heard about its design, seen the interim analysis, and know that the study continues unaltered.

As you would expect, each of these trials has a data safety monitoring board. Each of these boards has recently met and, in full knowledge of the results of the integrated clinical trial analysis, decided to continue their trial unaltered. We find these actions reassuring.

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These studies will begin to report results next year, in 2008, as you can see on this slide. In total, they will add some 22,000 patient-years and 550 MACE events to the database on rosiglitazone cardiovascular safety.

[Slide]

We started this presentation, ladies and gentlemen, with two questions: Is there an increase in the risk of cardiovascular mortality and/or myocardial infarction associated with rosiglitazone? I think the data that Dr. Stewart

has just reviewed with you provides substantial evidence to answer these questions.

Let me tackle cardiovascular mortality first. I believe the data from the three outcome studies, RECORD, ADOPT and DREAM, showing a hazard ratio below 1, albeit with confidence intervals that span 1, along with the decisions of the data safety monitoring boards, tell us that rosiglitazone is not difference from metformin and sulfonylurea. This is an important conclusion because it helps us put any hypothetical risk in the context of the treatment of type 2 diabetes. It is not tenable to not treat patients and it is very important to know that rosiglitazone does not increase mortality compared to the most commonly used oral anti-diabetic drugs. It is also reassuring because whatever we might conclude is happening with myocardial ischemia or infarction or stroke, these data tell us that those events aren't resulting in excess mortality.

What about myocardial infarction? The evidence we shared with you today I believe casts

significant doubt on the reality and potential magnitude of any increased risk, but it doesn't dispel it completely. The three outcome studies neither confirm nor dispel an increased risk of myocardial infarction associated with rosiglitazone. On the other hand, all the other evidence contradicts the hypothesis. The absence of a signal in the high risk population study, the three independent epidemiology studies that show rosiglitazone is no different from metformin, sulfonylureas and pioglitazone, the finding of fewer strokes, usually stroke and MI go in the same direction, and the decisions of the safety monitoring boards of the ongoing studies.

Of particular relevance to our discussion today is the PharMetrics epidemiology study that compares rosiglitazone and pioglitazone. This comparison is as close as one can get to clinical trial robustness for an observational study. The confounds associated with the treatment decision must be nearly eliminated when comparing two agents with the same mode of action and indications. I

remind you that the point estimates of the hazard ratios comparing rosiglitazone and pioglitazone in this study, both in mono and combination therapy, bracket 1.

While I recognize these data are new and that the FDA does not yet have the full data set, I believe the committee should pay particular attention to this study, and Dr. Walker, who is the principal investigator, is here to answer any questions about it.

So, in view of the inconclusive nature of the evidence for myocardial infarction associated with the use of rosiglitazone, what should be the way forward? In answering that question we need to first and foremost remember our first conclusion, rosiglitazone does not increase the risk of cardiovascular mortality or all-cause mortality in diabetes patients.

Second, we need to also remember that the other commonly used oral anti-diabetic drugs show a numerical increase in cardiovascular events in short-term studies, with the reality that the

mechanism and magnitude of which are today unknown and unexplained.

Third, we need to acknowledge that rosiglitazone has the most comprehensive prospective, controlled, clinical safety database among currently available oral anti-diabetic drugs. In other words, we know more about rosiglitazone's safety in general than most currently available drugs.

Finally, we have five ongoing trials, four of which are large, long-term outcome trials, three in high risk populations that will read out in the next 18 to 24 months and that will undoubtedly alone or as a group help us resolve any current uncertainty about the risk of myocardial infarction associated with the use of rosiglitazone.

Another important factor in informing a decision regarding rosiglitazone is, of course, the need to treat diabetes patients to help them control their glycemia both in the short and the long term. In the short term, hyperglycemia manifests as fatigue, infections, polyurea,

polydipsia and, in the extreme, coma. We must not minimize the benefits of treating hyperglycemia.

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In the long term, over 10-12 years the UKPDS study has clearly established the benefit of controlling glycemia. You heard about this from Dr. Ratner earlier this morning. A one percent decrease in hemoglobin A1c resulted in 20-35 percent reductions in microvascular disease and about a 15 percent reduction in macrovascular disease, myocardial infarction. Not treating diabetes patients, therefore, is not an option.

[Slide]

Unfortunately, most patients do not remain controlled on their first drug. That is the progressive nature of the disease and, again, you heard about this from Dr. Ratner. Long-term control of glycemia requires the combination of various oral anti-diabetic drugs and, as you can see on this slide, half of the patients treated today in the United States are on combination therapy. The failure over time to sustain glycemic

control is a real shortcoming of currently available drugs. In that regard, rosiglitazone has uniquely demonstrated superiority to both SU and metformin in sustained glycemic control.

[Slide]

These data are from the published results of the ADOPT study. They show hemoglobin A1c over time for rosiglitazone in yellow, metformin in green and glyburide in blue. As Dr. Ratner explained earlier this morning, you can see that while all three decrease hemoglobin A1c in the short term, over time rosiglitazone sustains that decrease better than the other two.

[Slide]

This slide is taken from table 2 of the FDA briefing document. Patients and physicians need good oral anti-diabetic medicines to both initiate therapy and combine when monotherapy fails. The choice of oral anti-diabetic agents is limited essentially to five classes, six medicines in five classes, and each has its strengths and shortcomings. Sulfonylureas aren't suitable for

the elderly and for others for whom hyperglycemia represents a risk. They cause fluid retention and there is a probable cardiac ischemic risk for at least some members of the class. Metformin, about 30 percent of patients can't take metformin because of its GI side effects, lactic acidosis and its contraindications in renal failure. Acerbose, the alpha-glucosidase inhibitor, is infrequently used because of its modest efficacy. There are two thiazolidinediones, rosiglitazone and pioglitazone. Both share the effects of fluid retention, heart failure and fractures. Concerns about myocardial ischemia and infarction are the subject of our discussion today. Bladder cancer is a concern for pioglitazone. Sitagliptin, the first of the DPPIVs, is of course very new and there is an understandable absence of long-term efficacy and safety data. In short, none of these drugs is perfect but all are important and rosiglitazone is an important choice.

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So, in view of the inconclusive nature of