FDA Briefing Document

Readjudication of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes Trial (RECORD)

Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

June 5 - 6, 2013

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this discussion of the results of a readjudication of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, for new drug application (NDA) 21071, AVANDIA (rosiglitazone maleate) tablets, manufactured by GlaxoSmithKline, to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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To: Advisory Committee Panel Members for June 5-6, 2013, advisory committee meeting on the re-adjudication of RECORD trial for Avandia (rosiglitazone)

Introduction

The topic of the cardiovascular safety associated with use of Avandia (rosiglitazone) has been discussed at numerous public meetings, including two joint advisory committee meetings of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Committee (DSARM) held on July 30, 2007 and July 13-14, 2010.

A detailed discussion of the data sources, evaluation and conclusions on the CV safety of rosiglitazone over the course of the past 6+ years is beyond the scope of this Introductory Memo and the reader is referred to memos under Appendices 1 through 6 of this FDA AC background package, including Dr. Woodcock's decisional memo dated September 22, 2010 (signed September 23, 2010), for a more detailed history related to the CV safety of rosiglitazone. This memo will provide a high-level summary of data and outcomes from the 2007 and 2010 AC meetings for the purposes of orienting the reader on preceding events that may be considered in the next two days as panel members are asked to deliberate over the questions/points for discussions included at the end of this memo.

Background

2007 Advisory Committee Meeting

In 2006, FDA received the results of a meta-analysis of 42 controlled clinical trials in patients with T2DM performed by GSK that suggested a concern for CV risk associated with rosiglitazone use in this patient population. FDA requested patient-level data for these 42 trials in order to conduct its own meta-analysis. During FDA's review, a separate meta-analysis of rosiglitazone trials was published in the *New England Journal of Medicine* (NEJM) based on data retrieved by the authors from clinicaltrials.gov.[1] [2] For

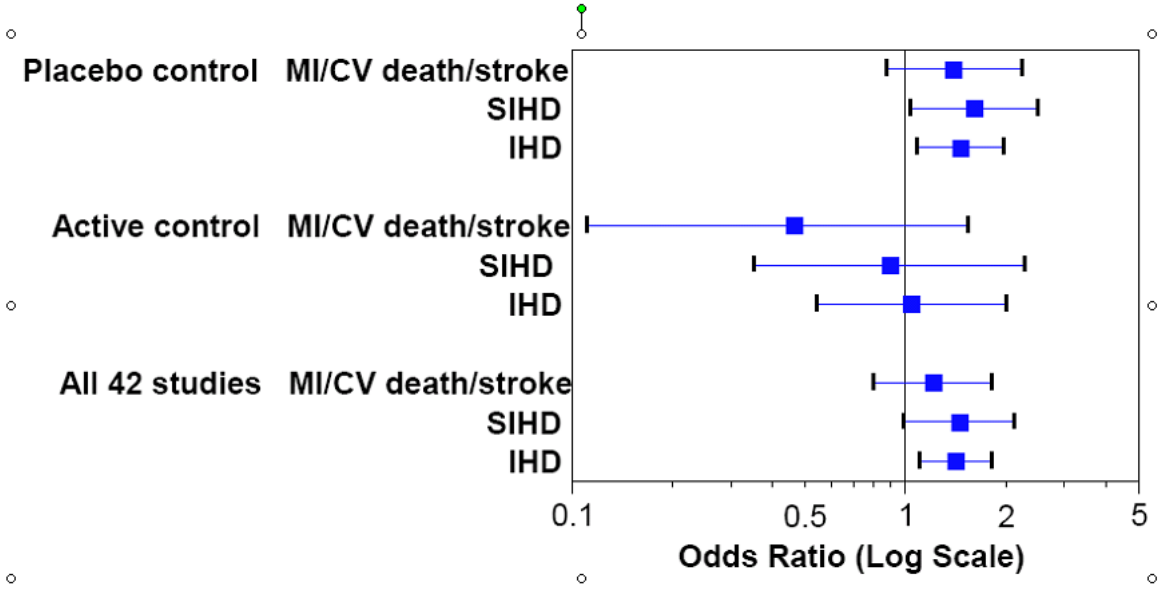
[1] Nissen SE and Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2457-2471.

[2] FDA's meta-analysis of 42 controlled trials included trials that were different from those relied upon in the meta-analysis performed by Nissen and Wolski.

purposes of this Introductory memo, discussion of CV risks based on meta-analyses refer to those analyses performed by FDA.

The patient population across these 42 trials was diverse including treatment-naïve to those on multiple background therapies. The choice of comparators (controls) was placebo, metformin and/or sulfonylureas (SUs). None of these trials was designed to prospectively assess CV risk and the majority of the trials were ≤ 6 months in duration, limiting the ability to evaluate long-term CV risk. Unlike dedicated cardiovascular outcomes trials (CVOTs) with a well-outlined plan for collecting major adverse cardiovascular events (MACE) using established definitions for myocardial infarctions, stroke, and CV death, the trials in these meta-analyses were not initiated with a pre-specified plan for capturing CV events for submission to an independent adjudication committee. Instead, the events reported to investigators as adverse events captured in case reports forms were retrospectively adjudicated, often with non-specific terms (e.g., chest pain without laboratory data) relied upon for defining a CV event. Despite these limitations, the meta-analysis included a large sample size (>14,000 patients), comparable to the sample size of many CVOT, and identified a cardiovascular safety signal. FDA's analysis in 2007 revealed a signal for non-serious or serious myocardial ischemia with an odds ratio of 1.4 (95% CI: 1.1-1.8) (Figure 1).

Figure 1. Ischemic Risk Associated RSG Use in Placebo vs Active-controlled Studies (Slide presented by FDA statistician, Joy Mele, M.S. at July 30, 2007 Advisory Committee)



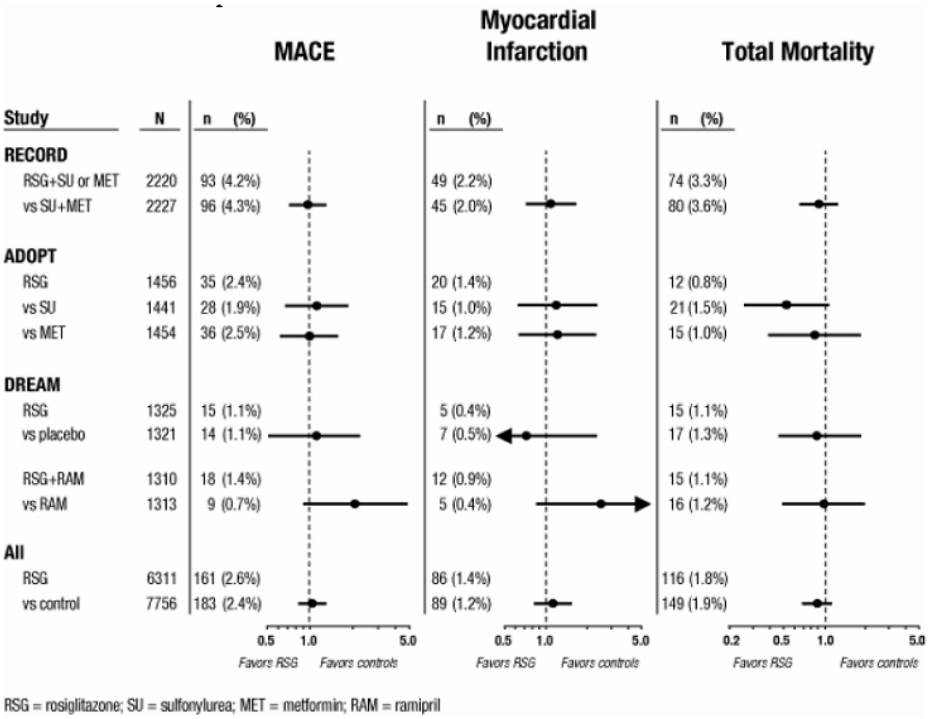
In 2007, FDA also evaluated the CV risk of rosiglitazone in 3 large long-term controlled trials: DREAM,[3] ADOPT,[4] and an interim analysis of RECORD. This database was also comprised of approximately 14,000 patients but minimum duration of treatment was longer at approximately 3 years. With the exception of the RECORD trial, which will be discussed further below, these trials were not designed with a primary objective of evaluating CV risk of rosiglitazone, although DREAM did have an endpoints committee adjudicate for MACE endpoints. FDA's analysis of these 3 trials, combined,

[3] DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) was a double-blind, randomized, 2x2 factorial design trial in 5269 patient with impaired glucose tolerance or impaired fasting glucose. The primary composite endpoint was incident diabetes or all-cause mortality.

[4] ADOPT (A Diabetes Outcomes Progression Trial) was a randomized, double-blind, parallel group trial in 4351 subjects recently diagnosed with T2DM who were previously managed with diet and exercise only. Primary endpoint was time to monotherapy failure.

revealed nonsignificant increases in risk of experiencing MACE or myocardial infarction with rosiglitazone relative to comparators and a nonsignificant decrease in risk of all-cause mortality (Figure 2).

Figure 2. Summary of MACE, MI, and Total Mortality Findings from 3 Long-term, Controlled Trials of Rosiglitazone in 2007



RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril

The CV safety of another marketed thiazolidinedione, pioglitazone, was also discussed in 2007. The cardiovascular outcomes trial PROactive (PROspective pioglitAzon Clinical Trial In macroVascular Events) compared pioglitazone to placebo as add-on to current anti-diabetic therapies in 5,238 patients with T2DM. The primary objective was to demonstrate a risk reduction of pioglitazone on the composite of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, CABG/PTCA, major leg amputations, or peripheral revascularization procedures. Although this primary objective was not met, a late-amendment to the protocol after the trial had been completed added an evaluation of the effect of pioglitazone on MACE and suggested a risk reduction. Pioglitazone products are currently labeled as having 'no increase in mortality or in total macrovascular events, but do not include a CV benefit claim.

At the conclusion of the data presentation and after extensive discussion, the 2007 advisory committee voted as follows on two questions:

1. Do the available data suggest[5] a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus?

   20 voted yes, 3 voted no

[5] In the original question, FDA asked if the available data "support" a conclusion of increased risk. Panel members requested that this question be changed to ask if the available data "suggest" given the inconsistent findings of risk in the meta-analysis subgroups and the long-term controlled trials (please see page 439 of meeting transcript).

2. Does the overall risk-benefit profile of Avandia support its continued marketing in the US?

   22 voted yes, 1 voted no

Following the 2007 AC meeting, the FDA decided that Avandia could continue to be marketed with revised labeling that included a boxed warning and Medication Guide that highlighted the potential risk of myocardial ischemia based on the meta-analysis.

FDA also required that GSK initiate a CVOT to prospectively evaluate the CV risk of rosiglitazone. The Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial was proposed by GSK to meet this requirement. TIDE was an event-driven, multicenter, international, randomized, double-blind, placebo-controlled trial designed to evaluate the effects of rosiglitazone, pioglitazone, or placebo added-on to background anti-diabetic therapies in approximately 11,680 patients with type 2 diabetes. The primary endpoint was the time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (MACE). Secondary endpoints included total mortality, the individual components of the primary endpoint, and a composite of microvascular outcomes.

The trial had two co-primary objectives:

1. A non-inferiority comparison of rosiglitazone versus placebo performed after total follow-up of 4.5 years
2. A superiority comparison of TZDs (rosiglitazone and pioglitazone) versus placebo performed about one year after the non-inferiority comparison

A secondary objective of this trial was to demonstrate noninferiority between rosiglitazone and pioglitazone on the primary composite of MACE. This was the only prospective, randomized CVOT comparing rosiglitazone and pioglitazone.

While TIDE was designed with the primary goal of evaluating the CV risk of rosiglitazone, it also had a secondary research question to compare the effects of long-term supplementation of vitamin D on death and cancer.

TIDE was initiated in 2009. As will be discussed further in this memo, this trial was placed on complete clinical hold on September 23, 2010, following the 2010 AC meeting.

<u>2010 Advisory Committee Meeting</u>

On August 25, 2009, FDA received the completed results of the RECORD trial, which led to the second advisory committee meeting held on July 13 and 14, 2010.

RECORD (*Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes)* was an open-label trial comparing the addition of rosiglitazone to metformin when either one was added on to background sulfonylurea (SU) and the addition of rosiglitazone to SU when either one was added on to background metformin. The primary objective of the trial was to show non-inferiority, defined as the demonstration of the upper bound of a 2-sided 95% CI for the hazard ratio < 1.2, between rosiglitazone combined with either metformin or SU to the combination of metformin and SU on the primary composite endpoint of CV death and CV hospitalizations. The trial was required by the European Medicines Authority (EMA) shortly after rosiglitazone's approval because one of the CV concerns associated with this drug class was congestive heart failure. This trial was not conducted under a U.S. IND.

The trial met its primary objective with an estimated HR of 0.99 and corresponding 95% CI of (0.85, 1.16), excluding an upper margin of 1.2. A non-significant increase in risk of myocardial infarction was

observed in the rosiglitazone arm; but, there was also a non-significant reduction in risk of stroke and all-cause mortality in rosiglitazone users. Multiple analyses were performed to evaluate the impact of loss-to-follow-up, early disclosure of interim data, and differential drop-outs, none of which appeared to modify the overall findings. However, some reviewers inside and outside FDA voiced criticism of the trial's design (e.g., open-label, non-inferiority), choice of primary endpoint (e.g., CV hospitalization) and there were allegations of data mishandling. Doubt was thus cast on the reliability of the RECORD results.

In addition to RECORD, other clinical data sources were reviewed and presented at the 2010 AC meeting including:

- an updated meta-analysis of controlled clinical trials of rosiglitazone (52 trials) performed by FDA;
- comparisons of rosiglitazone to pioglitazone through
    - a review of epidemiologic and observational studies identified in the published literature and a
    - a retrospective cohort study of Medicare claims
- meta-analysis of 29 pioglitazone controlled trials performed by FDA designed to parallel the FDA meta-analysis of rosiglitazone .

While each of these additional data sources contributed to the overall assessment, none was a dedicated cardiovascular outcomes trial designed to prospectively evaluate the CV risk of rosiglitazone, and each data source had limitations.

At the conclusion of the 2-day advisory committee meeting in 2010, panel members were asked 6 voting questions. The questions distinguished between comparative safety data for rosiglitazone and pioglitazone and rosiglitazone and non-TZD diabetes drugs, and further distinguished between ischemic CV risk and mortality. These distinctions were made because the original CV safety signal for rosiglitazone arose from trials comparing rosiglitazone to non-TZD controls (i.e, placebo, metformin or SUs), not pioglitazone, and the CV signal for myocardial ischemia was not consistent with findings on all-cause mortality. Four of the six questions were revised by the committee members at the meeting. Below is a summary of the voting questions as originally written followed by the revised questions (#2, 3, 5, and 6) and the final votes.

VOTING QUESTIONS (ORIGINAL AND REVISE) AND FINAL VOTING RESULTS

2. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
C. I am not able to make a finding A or B.

REVISED QUESTION #2
Considering the available data, do you find that, for rosiglitazone (choose 1):

A. These data are sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
B. These data are not sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.

C. I am not able to make a finding A or B.

VOTING RESULTS:

A. 18
B. 6
C. 9

3. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

REVISED QUESTION #3
Considering the available data, do you find that, for rosiglitazone (choose 1)

A. These data are sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
B. These data are not sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

VOTING RESULTS:

A. 21
B. 3
C. 9

5. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
B. Does not increase the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
C. I am not able to make a finding A or B

REVISED QUESTION #5
Considering the available data, do you find that, for rosiglitazone:

A. These data are sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
B. These data are not sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
C. I am not able to make a finding A or B

VOTING RESULTS:

A. 1
B. 20

C. 12

6. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of mortality in patients with Type 2 diabetes relative to pioglitazone
B. Does not increase the risk for mortality in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

REVISED QUESTION #6
Considering the available data, do you find that, for rosiglitazone (choose 1):

A. These data are sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to pioglitazone
B. These data are not sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 7
B. 12
C. 14

8. Based on the available data, which of the following regulatory actions do you recommend FDA pursue regarding rosiglitazone? Please select only one option or if you wish to abstain, do not vote. (These options are listed from most favorable to rosiglitazone to least favorable to rosiglitazone and do not reflect any prejudgment on the part of FDA.)

A. Allow continued marketing and revise the current label to remove the boxed warning and other warnings regarding an increased risk of ischemic CV events, or
B. Allow continued marketing and make no changes to the current label, or
C. Allow continued marketing and revise the current label to add additional warnings (e.g., contraindications for certain patient populations, recommendation for second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents); or
D. Allow continued marketing, revise the current label to add additional warnings, and add additional restrictions on use (such as restricting prescribing to certain physicians or requiring special physician and patient education)
E. Withdrawal from the U.S. market

VOTING RESULTS:
A. 0
B. 3
C. 7
D. 10
E. 12
Abstain: 1

9. If rosiglitazone remains on the U.S. market, do you recommend that the TIDE trial be continued in order to provide further data on the comparative CV safety of rosiglitazone, pioglitazone, and standard-of-care management of type 2 diabetes (placebo add-on)?

Vote Yes/No/Abstain

VOTING RESULTS:

YES: 19
NO: 11
ABSTAIN: 2
NON-VOTING: 1 (member departed before meeting adjourned)

Similar to the recommendations made by the AC panel members, recommendations within the Center for Drug Evaluation and Research (CDER) were varied (See Appendices 2-6). On September 23, 2010, Dr. Janet Woodcock,Director of CDER, taking into account the multiple views of several CDER senior managers and that of the AC panel members, finalized her decisional memo (Appendix 1).

Dr. Woodcock acknowledged the "multiple and conflicting signals" of CV risk associated with rosiglitazone and the absence of similar signals with pioglitazone leading to her decision to allow rosiglitazone's continued availability on the market but under a restricted distribution program. However, she also noted that RECORD was the only large, randomized, long-term trial comparing the CV safety of rosiglitazone to other anti-diabetic therapies, most notably metformin and SUs, which were the active controls in the trials included in the meta-analyses. On this basis, her final recommendation included that GSK commission an external organization to re-adjudicate the results from RECORD. While the re-adjudication would not resolve some inherent limitations of the trial (e.g., open-label design), Dr. Woodcock concluded that a separate, blinded adjudication of the data might provide more confidence on the trial results with respect to comparative CV safety of rosiglitazone to the commonly prescribed anti-diabetics, metformin and SUs.

Dr. Woodcock's memo noted that the re-adjudication of RECORD would provide no comparative safety data between rosiglitazone and pioglitazone. However, she concluded that the re-adjudication may provide additional information to allow reconsideration of the regulatory decisions made in 2010, or if new regulatory actions should be considered.

In summary, the regulatory actions taken for rosiglitazone and rosiglitazone-containing products following consideration of the 2010 AC meeting and multiple views within CDER were as follows:

1. Rosiglitazone-containing products would remain on the market but through a restricted distribution plan under a Risk Evaluation and Mitigation Strategy (REMS) which included a Medication Guide and Elements to Assure Safe Use (ETASU).

   A REMS with Elements to Assure Safe Use was approved for rosiglitazone-containing products, Avandia, Avandamet, and Avandaryl on May 18, 2011.

2. Revisions to the product labeling were required as safety labeling changes in accordance with section 505(o)(4) of the Food Drug and Cosmetic Act (FDCA).

   Safety labeling changes to all 3 rosiglitazone product labels were approved on February 3, 2011.

3. The *Thiazolidinedioine Intervention with Vitamin D Evaluation* (TIDE) trial, a cardiovascular outcomes trial initiated in 2009 to investigate the cardiovascular safety of rosiglitazone compared to placebo and pioglitazone, was placed on full clinical hold on September 23, 2010.

   At the 2010 AC meeting, there was considerable debate on the ethics of the TIDE trial. In her decisional memo, Dr. Woodcock stated the following:

While both a majority of the Advisory Committee members and OND recommend continuation of TIDE, I do not believe it should proceed at this time, given the restrictions I have determined are necessary for rosiglitazone and the level of concern about its cardiovascular safety. In many cases, when a drug safety issue arises, conduct of a randomized trial is an appropriate step to resolve the question. However, the results of RECORD, which are currently in question, directly affect the ethics of conducting TIDE. I believe that re-adjudication of RECORD is the appropriate next step, with decisions on whether to conduct further studies or take additional regulatory actions to be based on the results of the re-adjudication and any other data that may become available in the interim. FDA is not rescinding the post-market requirement for the sponsor to study the safety of rosiglitazone compared to pioglitazone, if feasible and appropriate, but is stopping the current trial until all existing information is evaluated, including the data from RECORD, if possible.

4. Glaxo-Smith Kline (GSK) was required to commission an independent re-adjudication of the results of RECORD. The re-adjudication was to proceed in a step-wise fashion with verification first of mortality findings followed by verification of major adverse cardiovascular events (MACE).

   GSK commissioned the Duke Clinical Research Institute (DCRI) to undertake the re-adjudication of RECORD. The methodology and process for re-adjudication performed by DCRI were actively discussed with FDA prior to its initiation.

Purpose of June 5 and 6, 2013 AC Meeting

The purpose of this 2-day AC meeting is to present the re-adjudicated results of RECORD and to determine whether new analyses based on the re-adjudication might modify regulatory decisions made on September 23, 2010 for rosiglitazone-containing products.

At the conclusion of the presentations, AC panel members will be asked to consider several discussion points and voting questions. In order to provide the AC panel members with necessary information to address these discussion points and questions, the FDA presentations and briefing materials will cover:

- Methodology and process of re-adjudication of RECORD
- Statistical analyses of RECORD based on re-adjudicated results
- FDA inspection of DCRI, the contractor who performed the readjudication
- An update on new epidemiologic data since the 2010 AC meeting
- A summary of the meta-analysis of rosiglitazone controlled clinical trials considered during the July 2010 AC meeting
- Drug utilization data for rosiglitazone and rosiglitazone-containing products
- Summary of the REMS program for rosiglitazone and rosiglitazone-containing products

FDA recognizes that parties inside and outside the FDA have strongly held views on the cardiovascular safety of rosiglitazone. Some of these views are expressed by FDA staff in the briefing documents/reviews prepared for this AC and may also be expressed during presentations and comments during the meeting. The views expressed in individual reviews provided in the FDA briefing materials and during presentations/comments at the AC meeting do not necessarily reflect the official position of

the FDA. FDA believes that its decision-making is strongest when it is made following a full consideration of all available data and the perspectives of individual FDA staff involved in the review process on the interpretation of the data and the recommended regulatory actions. FDA also looks forward to hearing the perspectives and advice of the Committee members and other stakeholders during the AC meeting, including during the Open Public Hearing. Therefore, it is important to note that FDA has not reached any final updated conclusions on the CV safety of rosiglitazone based on the readjudication of RECORD and the other new data that will be discussed at the AC meeting. Following the AC meeting, FDA will carefully consider the Committees' deliberations and take appropriate regulatory actions.

Draft Topics for Discussion

1. Based on DCRI's readjudication of the RECORD trial, do you believe the results of this trial provide interpretable data to address the cardiovascular risks of rosiglitazone?

If you believe that RECORD is interpretable, are the overall results concerning that a CV risk exists with rosiglitazone, reassuring that no CV risk exists with rosiglitazone, or neutral with respect to the CV risk of rosiglitazone?

2. Please comment on the MACE results from RECORD. How do you interpret the divergence of risk estimates for the components of MACE (CV death, NFMI, and stroke)?

3. Please comment on conclusions reached from a single outcome trial, such as RECORD, versus the synthesis of multiple controlled trials, such as the meta-analysis of 52 controlled trials presented in 2010 – which data source should be relied upon to provide a more reliable assessment of the cardiovascular risk of rosiglitazone?

4. Are there residual CV safety concerns or new CV safety concerns associated with rosiglitazone use?

5. Do you recommend any additional clinical studies to evaluate the cardiovascular safety of rosiglitazone? For any study you might propose, please describe the feasibility of this study given the current marketing status of rosiglitazone.

6. Rosiglitazone and rosiglitazone-containing products are currently marketed in the U.S. under a REMS with ETASU. Based on the independent readjudicated results of RECORD, do you recommend:

a. removal of the REMS with ETASU
b. continuation of the REMS with ETASU without changes
c. modification of the REMS with ETASU. Please specify what you recommend be modified.
d. withdrawal of rosiglitazone from the market

Endocrine Clinical Review
Blinded Readjudication of All-Cause Mortality and Cardiovascular Mortality
The Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes Trial (RECORD)
Readjudication by the Duke Clinical Research Institute

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6 May 2013

I. Introduction and Background

Avandia® (rosiglitazone maleate), hereafter referred to as RSG, is an oral antidiabetic drug of the thiazolidinedione class. It is an agonist of the peroxisome proliferator-activated receptor (PPAR) gamma. It was originally approved in 1999 for the treatment of patients with type 2 diabetes mellitus. Its current indication is:

"After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of Avandia, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are:

- already taking Avandia, or
- not already taking Avandia and are unable to achieve adequate glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons."

Among the safety concerns for RSG has been a possible increased risk of myocardial ischemic events, such as angina or myocardial infarction. This risk has been discussed at two public Advisory Committee meetings, in 2007 and 2010. The data regarding myocardial infarction risk are conflicting and are not statistically robust, and arise from meta-analyses and observational studies rather than from randomized controlled clinical trials. At the 2010 Advisory Committee meeting, the results of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) Trial were discussed. The RECORD trial was an open-label, randomized, cardiovascular outcomes study comparing rosiglitazone-containing combination therapy with combination metformin/sulfonylurea therapy. This is the only cardiovascular outcomes trial for rosiglitazone. The analyses of the trial conducted by GlaxoSmithKline (GSK, the sponsor) showed no increase in risk for myocardial infarction or death for rosiglitazone versus comparator. However, during the review of RECORD, questions were raised regarding whether all cardiovascular events and deaths were properly captured and interpreted. After the Advisory Committee meeting, Dr. Woodcock, the Director of the Center for Drug Evaluation and Research, made the decision to allow rosiglitazone to remain on the market, but with restricted distribution. Please see Dr. Woodcock's memorandum (DARRTS 23 Sep 2010) for details of her decision and its

basis. GlaxoSmithKline was also required to commission an independent readjudication of the RECORD trial. This readjudication was to be done in two phases. Mortality was to be addressed first. If rosiglitazone was not found to increase mortality, a second phase of readjudication was to address myocardial infarction and stroke. The Duke Clinical Research Institute was contracted to perform the readjudication and has now completed the mortality phase.

This review presents the main findings of the DCRI readjudication of the mortality in RECORD. A significant focus of the review is an attempt to examine how the DCRI readjudication results can be used to address some of the concerns that arose during the 2010 review of RECORD. Please see Sections III.D, III.F and IV for this discussion.

Please see the clinical reviewer's previous review of the RECORD trial for details regarding study design and the results of the original adjudication.

In addition to this clinical review, Dr. Andraca-Carrera is conducting a statistical review, and Dr. Dunnmon is conducting a cardiology consult review. Please refer to their reviews for additional information. Please note that small differences in the numbers of events may exist between the reviews, as datasets were updated during the review process, slightly changing the numbers of events as additional information was gathered by DCRI.

II. Methods of the DCRI Readjudication

The readjudication was performed in accordance with documents submitted by DCRI and reviewed by the Agency:

- A readjudication protocol, submission date 28 Jan 2011
- A clinical events classification charter, dated 2 May 2011 and included in Appendix A of the current report
- An amended readjudication protocol, submission date 24 Jun 2011
- A statistical analysis plan for the mortality phase, submitted 13 Jul 2011

Per the adjudication charter, key specific objectives included:

- Systematic identification of all deaths, all suspected myocardial infarctions and all suspected strokes, using all available data sources by reviewers blinded to patients' treatment assignment.
- Standard preparation of all events for adjudication without filtering of suspected events by persons who have knowledge (or potential knowledge) of patient treatment assignment.
- Adjudication of all events using the original RECORD endpoint definitions and contemporary definitions under development by FDA through the Standardized Data Collection for Cardiovascular Trials Initiative.

The DCRI Clinical Events Classification (CEC) group developed event adjudication pages to capture key data required for "efficient and accurate adjudication" and final analysis of suspected events. The CEC was responsible for systematically identifying,

adjudicating and classifying suspected events while blinded to treatment assignment, as well as being blinded to all glucose-lowering agents. There were no GSK representatives on the CEC committee.

The DCRI received the original RECORD datasets and the event packets used in the original adjudication process. When additional information was needed, requests were sent to the original study sites. Additionally, MediciGlobal, a third party vendor, was employed to search for additional vital status information for patients whose vital status at the end of study had not been clearly documented.

One of the objectives of the readjudication was to define, independently, end-of-follow-up dates. Patients were considered to have completed follow-up if any of the following conditions were met:

- Patient died
- Patient had a face-to-face visit (vital signs recorded) on or after 24 Aug 2008
- Patient had a face-to-face visit in 2008 and a phone visit (a visit with no vital signs recorded) after 24 Aug 2008

By the above conditions, 3843 patients were designated as having completed follow-up. For the remaining 604 patients, which included 127 patients reported in the original RECORD trial to have unknown vital status at study end, the following efforts were made:

- For 344 of these patients, additional source documents had been collected by GSK. DCRI reviewed these documents to determine if data were adequate to determine vital status. For 46 patients, data were inadequate, and MediciGlobal was asked to obtain vital status information.
- For 252 patients, additional documents had not been obtained, and DCRI asked MediciGlobal to obtain vital status information.
- Eight additional deaths were discovered by GSK, and were sent to the DCRI CEC for adjudication.
- If patients had an unknown or partial date of death, their cases were referred to MediciGlobal.

As mentioned, initially, DCRI identified 604 patients for whom follow-up was deemed incomplete for one reason or another. At the end of their efforts, only 21 of these patients required imputation of a death date. For all 21 of these patients, the year of death was found, and for 11 out of these 21, documentation of month of death was also found. Thus, the only imputation required for death dates was for the month of death for ten patients.

The CEC issued 127 queries for additional information regarding deaths. Beyond the above processes, they received additional data for 23 events. Of these, 16/23 events were re-reviewed with no change to the adjudication result. For the other 7/23 events, re-review resulted in a change to the adjudication result from “unknown” to a known cause of death. For the other 104/127 queries, 43 were closed with no response from the site

and 61 were closed with a response from the site that no additional information was available.

Both automated and manual methods were used to identify potential events. The automated methods included:

- screening of all Adverse Experience (AE) and Serious Adverse Experience (SAE) forms from the Case Report Form data fields from the RECORD datasets
- use of a set of prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms, with the set of terms intended to have a low threshold for identification of events
- identification of Death Forms (called Form D) in the RECORD database.

Manual trigger procedures involved review of paper source documents, including:

- unscheduled visit forms
- "Hospitalization or Accident and Emergency Department Visit Endpoint Form"
- source documents used as part of the original RECORD adjudication process
- additional source documents collected as part of the readjudication activities; these documents included discharge summaries, progress notes, lab reports and physician narratives
- investigator verbatim terms
- all SAE and AE forms
- all cases that were sent to the original RECORD Clinical Endpoints Committee, including endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator
- all Death Endpoint Forms
- all Myocardial Infarction/Unstable Angina Endpoint Forms
- all Stroke/TIA (Transient Ischemic Attack) Forms
- all hospitalizations
- all Survival Status Forms
- all "Documentation of Third Party Survival Status" Forms
- all "Tracking Forms for Completely Withdrawn Patients"
- all Study Completion Forms
- any SAEs or AEs that were deleted by RECORD investigators. These were identified from the audit trails of the study's electronic datasets.

Once redacted documents arrived at DCRI, they were checked by CEC administrative personnel to ensure that blinding/redaction was complete before documents were forwarded to adjudicators.

When additional information was requested, DCRI made two attempts to obtain it.

Each event underwent a "Phase 1" review during which two physicians independently adjudicated the event using prespecified event criteria. Each event was reviewed using the original RECORD event classification criteria, and with the new draft definitions based on the FDA's current efforts to develop standardized definitions for endpoint

events in cardiovascular trials. If the reviewers agreed in their classification, the adjudication was considered complete. If they did not agree, the event went to "Phase 2" review.

In "Phase 2" review, an adjudication committee meeting was held with at least three faculty physicians. All areas of disagreement were discussed and a decision made by consensus of the Phase 2 panel.

The charter established two Quality Control (QC) processes- one for the readjudication process and one for the manual trigger process.

For the readjudication process Quality Control, a random sample of 5% of the events was selected. Sampling was weighted more heavily toward the early part of the study. The first random sample was generated after 50 mortality events were adjudicated; subsequent samples were generated after 100, 200 and 300 mortality events were adjudicated. The QC reviewers were blinded to the original adjudicated result. Discrepancies between the first DCRI readjudication result and the QC review result were classified as "major" or "minor". A major discrepancy occurred when there was disagreement about whether an event did, or did not, occur. A minor discrepancy occurred when there was agreement on whether an event occurred, but there was disagreement on the date, time, type or evidence. If the Quality Control process identified an issue, several actions were possible, including readjudication of events via the established CEC process, modification of the CEC process, additional CEC reviewer training, removal of a CEC reviewer or supervisor, or continuation of the CEC process without modifications.

For the manual trigger process Quality Control, a random sample of documents that were screened during the manual trigger process were re-screened. Manual trigger process documents reviewed included 5% of those screened by the CEC Coordinator, 5% of those not previously reviewed in the previous QC process, and 5% of subjects not triggered for an endpoint event.

The endpoint definitions used in the original RECORD adjudication may be found beginning on page 321 of the DCRI readjudication study report. The "new" endpoint definitions used in the DCRI readjudication may be found beginning on page 323 of the DCRI readjudication report. The new definitions used by DCRI were based on ongoing work that the Agency and academia are doing to devise standardized definitions of major adverse cardiovascular events to be used in clinical trials. These definitions are in evolution; therefore, the clinical reviewer considered analysis involving the "new" definitions to be a type of sensitivity analysis.

III. Mortality Analyses

III.A. Summary of DCRI Findings

III.A.1. Results of Triggering Process

Please see the Methods section above for the sources used for programmatic and manual triggering for identification of potential death events. The table below summarizes the total numbers of triggers, and their sources.

Table A.1: Triggers for Case Review for All-Cause Mortality

		Total (Total N = 4447)	RSG (Total N = 2220)	MET/SU (Total N = 2227)
All Triggered Cases		419/4447 (9.4%)	200/2220 (9.0%)	219/2227 (9.8%)
Number of Cases Identified by Each Triggering Method	**Programmatic**	396/419 (94.5%)	187/200 (93.5%)	209/219 (95.4%)
	Manual	23/419 (5.5%)	13/200 (6.5%)	10/219 (4.6%)
Sources of Programmatic Triggers[1]	**Adverse Event Form**	328/396 (82.8%)	152/187 (81.3%)	176/209 (84.2%)
	Study continuation/withdrawal form	197/396 (49.7%)	91/187 (48.7%)	106/209 (50.7%)
	Tracking form for withdrawal	42/396 (10.6%)	19/187 (10.2%)	23/209 (11.0%)
	Death form	252/396 (63.6%)	111/187 (59.4%)	141/209 (67.5%)
	Survival status form	4/396 (1.0%)	2/187 (1.1%)	2/209 (1.1%)
	Third party survival form	25/396 (6.3%)	16/187 (8.6%)	9/209 (4.3%)
Sources of Manual Triggers	**CRF**	0	0	0
	Source documents	23/23 (100%)	13/13 (100%)	10/10 (100%)

Source: Sponsor's Table 1.1, pg 71, study report
1 A patient could trigger from more than one source and could be counted in more than one row

Of note in the above table is that the distribution of numbers of patients who triggered, and the sources of triggering, were similar between the RSG and MET/SU groups. The triggering process did not identify evidence of systematic over- or under- identification of potential death events.

Of the 419 triggered cases, 313 were found to be actual deaths, and the remainder were found not to have died.

III.A.2. New Deaths Found After Initiation of DCRI Readjudication Process

In addition to the deaths identified in the original RECORD dataset, 23 other deaths were identified among patients who had been lost to follow-up:

- Eight deaths occurred before 31 Dec 2008, which was the cut-off date for the original study, and for DCRI's primary analysis. Three of these deaths were found by the GSK/Quintiles search effort, three were from IND annual reporting, and two were from the MediciGlobal effort.
- Eleven deaths occurred after 31 Dec 2008. Five of these deaths were found by GSK, one came from IND annual reporting, and five came from the MediciGlobal effort.
- Four deaths occurred on an unknown date. Two of these were from the Quintiles tracking database and 2 were from the MediciGlobal effort.

III.A.3. All Cause Mortality

The primary analysis for the readjudication was all-cause mortality from randomization until date of death. For purposes of this analysis, follow-up for patients who did not die was censored on the date the patient was last known to be alive, on or before 31 Dec 2008. The following table summarizes the primary analysis:

Table III.A.3.a: Primary Analysis: All-Cause Mortality

	RSG N=2220 PY=12953.6	**MET/SU N=2227 PY=12815.0**
Number of patients with event of death (%)	139 (6.3%)	160 (7.2%)
Rate per 100 patient-years (95% CI)	1.07 (0.89, 1.26)	1.25 (1.05, 1.45)
Hazard ratio[1] (95% CI)	0.86 (0.68, 1.08)	
Absolute rate difference per 100 patient-years (95% CI)	-0.18 (-0.44, 0.09)	

Source: Sponsor's Table 3.1, pg 93, study report
1 Hazard ratio from a Cox proportional hazards model stratified by background therapy. Hazard ratio <1 favors RSG

By this analysis, there was no difference between RSG and MET/SU for the rate of death, and the point estimate for the hazard ratio favored RSG.

Analyses by background stratum showed no evidence of an interaction between treatment and background therapy (sponsor's Table 3.2, pg 95, study report). Multiple subgroup analyses also showed no evidence of an interaction by gender, age (<60 or ≥ 60 yrs), duration of diabetes (<6 or ≥ 6 yrs), body mass index (<30 or ≥ 30 kg/m^2), a history of prior heart disease, or baseline hemoglobin A1c (<7.4%, 7.4-<7.8%, 7.8-<8.4%, ≥ 8.4%) (sponsor's Figure 3.3a, pg 98, study report).

The following table displays death by category, including the numbers of patients readjudicated to have death from any cause, cardiovascular death, noncardiovascular death, and death due to unknown cause.

Table III.A.3.b: Summary of Readjudicated Deaths (Original Definition)		
Cause of Death	**RSG N=2220 n (%)**	**MET/SU N=2227 n (%)**
All-Cause	147 (6.6)	166 (7.5)
Cardiovascular	34 (1.5)	42 (1.9)
Noncardiovascular	51 (2.3)	66 (3.0)
Unknown Cause	62 (2.8)	58 (2.6)
Source: Sponsor's Table 1.2, pg 72, study report		

The percentage of patients who died from any cause, from a cardiovascular cause, and from noncardiovascular causes, was similar between treatment groups, with a numerically smaller percentage of deaths in the RSG group compared to the MET/SU group.

During the review process for the original RECORD submission, discussion occurred regarding the noninferiority design of the trial, and whether an "intention-to-treat" (ITT) or "as-treated" approach was more appropriate. Some advocated an "as-treated" approach, using only time on randomized therapy, rather than the ITT approach that had been prespecified for the primary analysis.

For the DCRI readjudication, analyses were performed using last date of randomized treatment, plus either 30 or 60 days. These analyses are displayed in the following table.

Table III.A.3.c: All-Cause Mortality, on Randomized Treatment, Plus Either 30 or 60 Days				
	LDRT Plus 30 Days		**LDRT Plus 60 Days**	
	RSG N=2220 PY=10918.8	**MET/SU N=2227 PY=10289.4**	**RSG N=2220 PY=10982.6**	**MET/SU N=2227 PY=10368.5**
Number of patients with death (%)	57 (2.6%)	70 (3.1%)	69 (3.1%)	83 (3.7%)
Rate per 100 PY (95% CI)	0.52 (0.38, 0.66)	0.68 (0.52, 0.84)	0.63 (0.48, 0.78)	0.80 (0.62, 0.98)
Hazard ratio (95% CI)	0.76 (0.54, 1.08)		0.78 (0.57, 1.07)	
Absolute rate difference per 100 PY (95% CI)	-0.16 (-0.37, 0.06)		-0.17 (-0.40, 0.06)	
Source: Sponsor's Tables 8.1 (pg 122) and 11.1 (pg 143), study report **LDRT = last day of randomized treatment**				

With censoring by these methods, there was no evidence of a treatment effect.

Subgroup analyses were performed for the same categories as those used for the primary analysis. All but one subgroup showed no evidence of an interaction. For the LDRT + 30 days analysis, for patients with a prior history of heart disease, the hazard ratio was 1.27 (95% CI 0.67, 2.41) not favoring RSG, while for those without a prior history of

heart disease, the HR was 0.62 (0.41, 0.95), favoring RSG (p value 0.072). A similar result was seen for the LDRT + 60 days analysis (pg 34, study report). However, as mentioned earlier, this was not seen for the primary analysis for all-cause mortality.

III.A.4. Cardiovascular Death Plus Death From Unknown Cause

In the original RECORD analyses, deaths due to unknown cause were counted as cardiovascular deaths. The following table displays the results of the DCRI readjudication analysis of cardiovascular mortality plus unknown cause mortality.

Table III.A.4.a: Cardiovascular Plus Unknown Cause Mortality, Original Definitions

	RSG N=2220 PY=12953.6	**MET/SU N=2227 PY=12815.0**
Number of patients with event of cardiovascular death or death due to unknown cause (%)	88 (4.0)	96 (4.3)
Rate per 100 patient-years (95% CI)	0.68 (0.53, 0.83)	0.75 (0.59, 0.90)
Hazard ratio[1] (95% CI)	0.90 (0.68, 1.21)	
Absolute rate difference per 100 patient-years (95% CI)	-0.07 (-0.28, 0.14)	

Source: Sponsor's Table 5.1, pg 109, study report
1 Hazard ratio from a Cox proportional hazards model stratified by background therapy. Hazard ratio <1 favors RSG

By this analysis, there was no difference between RSG and MET/SU for the rate of cardiovascular plus unknown cause death, and the point estimate for the hazard ratio favored RSG.

The following table summarizes cardiovascular mortality by subclassification of cardiovascular cause of death.

Table III.A.4.b: Summary of Cardiovascular Deaths by Subclassification of Cardiovascular Cause of Death (Original Definitions, Deaths Occurring On or Before 31 Dec 2008 Original Trial Cut-Off Date)

Cardiovascular Cause of Death	**RSG N=2220 n (%)**	**MET/SU N=2227 n (%)**
Any cardiovascular cause	34 (1.5)	42 (1.9)
Heart failure or cardiogenic shock	9 (0.4)	1 (<0.1)
Acute myocardial infarction	8 (0.4)	12 (0.5)
Sudden cardiac death	14 (0.6)	15 (0.7)
Acute vascular event	1 (<0.1))	12 (0.5)
Other cardiovascular cause	2 (0.1)	2 (0.1)

Source: Sponsor's Table 1.5, pg 86, study report

There were numerically more deaths due to heart failure among RSG-treated patients than among comparator-treated patients. For overall CV mortality, and for specific

cardiovascular causes other than heart failure, the percentage of patients was similar between treatment groups, with slightly numerically fewer deaths among RSG-treated patients than among comparator-treated patients. Of particular note is death due to acute myocardial infarction. A primary concern regarding the cardiovascular safety of rosiglitazone has been whether it increases the risk of myocardial infarction; in the readjudication, there was not evidence that it increased the risk of death due to acute myocardial infarction.

A variety of subgroup analyses were performed, and in general, there was no evidence of interactions. However, there was evidence of an interaction by baseline statin use. Using the "new FDA definitions", among patients using statins at baseline, the hazard ratio was 2.29 (95% CI 1.16, 4.54), not favoring RSG, while for patients not using statins at baseline, the HR was 0.72 (0.52, 1.00), favoring RSG (p-value 0.003). This was also noted in analyses which included time on randomized therapy plus either 30 or 60 days (pages 33 and 35 of study report). Neither the endocrine clinical reviewer nor DCRI have been able to propose a mechanistic explanation for this observation.

The original RECORD subclassifications for cardiovascular causes of death included a category of "acute vascular event", but did not have a specific subcategory of death due to stroke. The DCRI readjudication added separate analyses using new definitions, which did include a subclassification of death by stroke. There were no deaths due to stroke among RSG-treated patients, and 6 deaths due to stroke among patients in the MET/SU comparator group.

As for total mortality, analyses were performed for cardiovascular mortality using last date of randomized treatment, plus either 30 or 60 days. These analyses are displayed in the following table.

Table III.A.4.c: Cardiovascular Mortality Plus Mortality of Unknown Cause, on Randomized Treatment, Plus Either 30 or 60 Days

	LDRT Plus 30 Days		**LDRT Plus 60 Days**	
	RSG N=2220 PY=10918.8	**MET/SU N=2227 PY=10289.4**	**RSG N=2220 PY=10982.6**	**MET/SU N=2227 PY=10368.5**
Number of patients with CV death or death due to unknown cause (%)	34 (1.5)	43 (1.9)	41 (1.8)	44 (2.0)
Rate per 100 PY (95% CI)	0.31 (0.20, 0.42)	0.42 (0.29, 0.55)	0.37 (0.25, 0.49)	0.42 (0.29, 0.55)
Hazard ratio (95% CI)	0.74 (0.47, 1.16)		0.87 (0.57, 1.34)	
Absolute rate difference per 100 PY (95% CI)	-0.11 (-0.27, 0.06)		-0.05 (-0.23, 0.12)	

Source: Sponsor's Tables 10.1 (pg 136) and 12.1 (pg 150), study report
LDRT = last day of randomized treatment

With censoring by these methods, there was no evidence of a treatment effect.

To assess the impact of classifying deaths of unknown cause as cardiovascular in the main analyses of cardiovascular mortality, DCRI also did analyses of CV mortality that did not include these deaths.

Table III.A.4.d: Cardiovascular Mortality, Not Including Deaths Due to Unknown Cause

	RSG N=2220 PY=12953.6	MET/SU N=2227 PY=12815.0
Number of patients with event of cardiovascular death (%)	34 (1.5)	42 (1.9)
Rate per 100 patient-years (95% CI)	0.26 (0.17, 0.36)	0.33 (0.22, 0.43)
Hazard ratio[1] (95% CI)	0.80 (0.51, 1.25)	
Absolute rate difference per 100 patient-years (95% CI)	-0.07 (-0.20, 0.07)	

Source: Sponsor's Table 15.1, pg 167, study report
1 Hazard ratio from a Cox proportional hazards model stratified by background therapy. Hazard ratio <1 favors RSG

Results of these analyses are consistent with those of the analyses of cardiovascular mortality which included deaths due to unknown cause. Analyses by background treatment (pg 169, study report), and by subgroup (pg 37, study report), were also consistent.

III.A.5: "Landmark" Analyses

In addition to the other types of sensitivity analyses already presented, DCRI examined the effects of two "landmark" events.

III.A.5.a. Impact of Amendment 7 of the Original RECORD Protocol

Amendment 7 (dated 27 Feb 2006) of the original RECORD protocol instituted a tracking substudy to collect endpoint data from withdrawn patients who consented to enter the tracking substudy. To assess the impact of this amendment, DCRI conducted landmark analyses prior to and after Amendment 7, as summarized in the following tables.

Table III.A.5.a.(1): Impact of Amendment 7: Total Mortality Before and After 27 Feb 2006 (Date of Amendment 7)

	Before 27 Feb 2006		After 27 Feb 2006	
	RSG N=2220 PY=7449.1	**MET/SU N=2227 PY=7387.8**	**RSG N=2220 PY=5501.8**	**MET/SU N=2227 PY=5427.2**
Number of patients with death (%)	66/2220 (3.0)	73/2227 (3.3)	73/2104 (3.5)	87/2091 (4.2)
Rate per 100 PY (95% CI)	0.89 (0.67, 1.10)	0.99 (0.76, 1.22)	1.33 (1.02, 1.64)	1.60 (1.26, 1.94)
Hazard ratio (95% CI)	0.90 (0.64, 1.25)		0.83 (0.60, 1.13)	
Absolute rate difference per 100 PY (95% CI)	-0.10 (-0.42, 0.21)		-0.28 (-0.74, 0.18)	

Source: Sponsor's Tables 16.1 (pg 170) and 17.1 (pg 173), study report

For total mortality, hazard ratios and absolute rate differences before and after Amendment 7 were similar, as were upper and lower bounds of the confidence intervals for these measures. There was no evidence of a treatment effect, either before or after the amendment.

Table III.A.5.a.(2): Impact of Amendment 7: Cardiovascular Death Plus Death Due to Unknown Cause Before and After 27 Feb 2006 (Date of Amendment 7)

	Before 27 Feb 2006		After 27 Feb 2006	
	RSG N=2220 PY=7449.1	**MET/SU N=2227 PY=7387.8**	**RSG N=2220 PY=5501.8**	**MET/SU N=2227 PY=5427.2**
Number of patients with CV death or death due to unknown cause (%)	34/2220 (1.5)	43/2227 (1.9)	54/2104 (2.6)	53/2091 (2.5)
Rate per 100 PY (95% CI)	0.46 (0.30, 0.61)	0.58 (0.40, 0.76)	0.98 (0.71, 1.25)	0.98 (0.71, 1.24)
Hazard ratio (95% CI)	0.79 (0.50, 1.24)		1.00 (0.69, 1.46)	
Absolute rate difference per 100 PY (95% CI)	-0.13 (-0.36, 0.11)		0.00 (-0.37, 0.38)	

Source: Sponsor's Tables 18.1 (pg 176) and 19.1 (pg 179), study report

For cardiovascular plus unknown cause mortality, hazard ratios and absolute rate differences, before and after Amendment 7, were essentially identical. There was no evidence of a treatment effect, either before or after the amendment.

III.A.5.b. Impact of Published Interim Report

During the initial controversy regarding the cardiovascular safety of rosiglitazone, Home et al (Home 2007) published an interim analysis of the RECORD trial. Questions arose regarding whether this interim publication could have affected the subsequent conduct or

outcome of the trial. In order to assess for this, DCRI performed analyses of total mortality and cardiovascular mortality before and after 5 Jun 2007, the date of publication of the interim analysis.

Table III.A.5.b.(1): Impact of Interim Analysis Publication: Total Mortality Before and After 5 Jun 2007 (Date of Interim Publication)

	Before 5 Jun 2007		After 5 Jun 2007	
	RSG N=2220 PY=10091.7	**MET/SU N=2227 PY=10009.9**	**RSG N=2220 PY=2862.9**	**MET/SU N=2227 PY=2807.5**
Number of patients with death (%)	97/2220 (4.4)	114/2227 (5.1)	42/2057 (2.0)	46/2032 (2.3)
Rate per 100 PY (95% CI)	0.96 (0.76, 1.16)	1.14 (0.92, 1.35)	1.47 (1.02, 1.92)	1.64 (1.16, 2.12)
Hazard ratio (95% CI)	0.84 (0.64, 1.10)		0.89 (0.59, 1.35)	
Absolute rate difference per 100 PY (95% CI)	-0.18 (-0.47, 0.11)		-0.17 (-0.83, 0.48)	

Source: Sponsor's Tables 20.1 (pg 182) and 21.1 (pg 185), study report

For total mortality, hazard ratios and absolute rate differences before and after the interim publication were similar between treatment groups. There was no evidence of a treatment effect, either before or after the amendment. As was noted in the original RECORD review, the incidence and rate per 100 PY of events was somewhat lower in both groups after interim, without a difference between treatment groups. The reason for this difference was not entirely clear, but a possible contributing factor was an increased rate of withdrawal (without a primary event) in both treatment groups after the interim publication. Prior to the interim publication, withdrawal without a primary event occurred at a rate of 1.9 withdrawals per 100 PY, while after the interim publication, the rate was 2.5/100 PY.

Table III.A.5.b.(2): Impact of Interim Analysis Publication: Cardiovascular Mortality Plus Unknown Cause Mortality Before and After 5 Jun 2007 (Date of Interim Publication)

	Before 5 Jun 2007		After 5 Jun 2007	
	RSG N=2220 PY=10091.7	**MET/SU N=2227 PY=10009.9**	**RSG N=2220 PY=2862.9**	**MET/SU N=2227 PY=2807.5**
Number of patients with cardiovascular death or death due to unknown cause (%)	55/2220 (2.5)	68/2227 (3.1)	33/2057 (1.6)	28/2032 (1.4)
Rate per 100 PY (95% CI)	0.55 (0.40, 0.69)	0.68 (0.51, 0.85)	1.15 (0.75, 1.55)	1.00 (0.62, 1.37)
Hazard ratio (95% CI)	0.80 (0.56, 1.14)		1.15 (0.70, 1.90)	
Absolute rate difference per 100 PY (95% CI)	-0.13 (-0.36, 0.09)		0.16 (-0.39, 0.70)	

Source: Sponsor's Tables 22.1 (pg 188) and 23.1 (pg 191), study report

Both before and after the published interim analysis, there was no statistical evidence of a treatment effect. Prior to the published analysis, the point estimate for the hazard ratio favored RSG, while after the interim, it favored MET/SU. Since the difference was not statistically significant during either time period, it is difficult to make much of this observation. It is possible that there was stimulated reporting of events in the RSG arm after the large amount of negative publicity regarding rosiglitazone at the time. It is perhaps noteworthy that this observation does not suggest a fraudulent attempt (as has been alleged by some) to suppress event-reporting for RSG-treated patients after the interim publication.

III.B. Deaths Due to Unknown Cause

In the DCRI readjudication, there were 120 deaths (62 RSG, 58 MET/SU) which were adjudicated as having been due to unknown cause. In the original RECORD adjudication, there were 61 deaths (28 RSG, 33 MET/SU) which were adjudicated as having been due to unknown cause.

Because of this difference between the original adjudication and the DCRI readjudication, the clinical reviewer explored this area further.

The following table lists all patients who were adjudicated as having death due to unknown cause, for both the DCRI readjudication and the original RECORD adjudication.

Table III.B.1: Patients Who Were Listed as Having Unknown Cause of Death by DCRI and/or Original GSK Adjudication, With Treatment Assignment

Patient ID	DCRI Unk?	GSK Unk?	Tx
18106	y	SSU	SU + MET
18122	y		SU + MET
18195	y		SU + RSG
18227		y	MET + SU
18278	y		MET + SU
18285		y	MET + SU
18337	y		SU + MET
18342	y		SU + RSG
18451	y		MET + SU
18454	y		MET + RSG
18497	y		MET + RSG
18504	y		SU + MET
18514		y	SU + MET
18654		y	MET + SU
18775	y	y	SU + RSG
18787	y		SU + MET
18796	y	SSU	SU + MET
18831		y	SU + RSG
18836	y		MET + SU
18886		y	SU + RSG
18890	y	y	SU + RSG
18997		y	SU + MET
19039	y	y	MET + SU
19110	y	SSU	SU + RSG
19115	y	SSU	MET + SU
19119	y	TSS	SU + MET
19390	y	SSU	MET + RSG
19452	y	SSU	SU + MET
19516	y		MET + SU
19544		y	SU + MET
19545	y	y	MET + RSG
19562	y	y	SU + MET
19615	y		SU + RSG
19731	y	y	MET + RSG
19734	y	y	MET + SU
19735	y	SSU	MET + RSG
20058	y		MET + SU
20074	y		SU + RSG
20099	y		SU + RSG
20111	y	y	MET +SU
20164	y		SU + MET
20230	y		SU + MET
20235	y	y	SU + RSG
20600	y	y	SU + RSG
20616	y		SU + RSG
20721	y		SU + RSG
20757	y	y	SU + RSG
20830	y		SU + RSG

Table III.B.1: Patients Who Were Listed as Having Unknown Cause of Death by DCRI and/or Original GSK Adjudication, With Treatment Assignment			
Patient ID	**DCRI Unk?**	**GSK Unk?**	**Tx**
20839		y	MET + RSG
20930	y	After study end	MET + RSG
20945	y	y	MET + RSG
21013	y		MET + SU
21027	y	SSU	MET + RSG
21102	y	SSU	SU + MET
21153	y		SU + MET
21165		y	SU + RSG
21201	y	y	MET + SU
21250	y	y	SU + MET
21294	y		SU + RSG
21358	y		SU + RSG
21380	y	SSU	SU + MET
21441	y	y	MET + SU
21508	y		SU + MET
21523	y		MET + RSG
21567	y	y	SU + RSG
21612	y	SSU	SU + RSG
21695	y		MET + RSG
29119	y		SU + MET
29190	y		SU + RSG
29198	y	y	SU + MET
29261	y	y	SU + RSG
29342	y	y	SU + MET
29440	y		SU + MET
29551		y	SU + MET
29570	y	y	SU + MET
29583	y		MET + RSG
29605	y	y	MET + SU
29609		y	SU + RSG
29652	y	y	SU + RSG
29685		y	SU + MET
29696	y		MET + RSG
29895	y	SSU	SU + RSG
29971	y		SU + MET
30009	y	y	SU + MET
30145	y	y	MET + SU
30327	y		SU + RSG
30340	y	SSU	MET + RSG
30436	y	y	SU + MET
30540		y	MET + SU
30757	y	y	SU + RSG
30881		y	MET + RSG
31183	y		SU + MET
31184	y	y	SU + RSG
31204	y	y	SU + MET
31223	y		MET + SU
31237	y	SSU	MET + RSG

Table III.B.1: Patients Who Were Listed as Having Unknown Cause of Death by DCRI and/or Original GSK Adjudication, With Treatment Assignment

Patient ID	DCRI Unk?	GSK Unk?	Tx
31241	y	Death not reported in orig study report	SU + MET
31283	y	y	MET + RSG
31298	y	y	MET + SU
31316	y		SU + MET
31362		y	SU + MET
31389	y		MET + RSG
31452	y	y	SU + MET
31496	y		SU + RSG
31553	y		MET + SU
31598	y	y	SU + RSG
31729	y	SSU	MET + RSG
31860	y		SU + MET
31868		y	MET + SU
37825	y	y	SU + RSG
38069	y		MET + RSG
38093	y	SSU	MET + RSG
38409	y		MET + RSG
38468	y		SU + RSG
38533		y	MET + RSG
38561	y	y	MET + RSG
38912	y	SSU	SU + MET
38938	y	SSU	SU + MET
39112	y		MET + SU
39115	y	y	MET + RSG
39170	y		SU + RSG
43620	y		MET + RSG
43676	y	y	SU + MET
43686	y	SSU	SU + RSG
43786	y		SU + MET
43821	y		MET + SU
43885	y		MET + RSG
97520	y	SSU	SU + MET
97573		y	SU + MET
97603	y		SU + RSG
97622	y	y	SU + RSG
97744	y		SU + MET
97862	y	y	MET + RSG
97914	y	y	SU + MET
97947		y	MET + RSG
97954		y	SU + MET
98059	y	SSU	SU + RSG
98159	y	SSU	SU + MET
98236		y	MET + SU
98343	y	SSU	SU + RSG
98460	y		SU + MET
98463	y	SSU	MET + SU

Source: NDA 21071, 20 Dec 2011 submission, study report, Listing 3.0, beg pg 226; NDA 21071, 27 Aug 2009 submission, dataset cvendpt

The 61 deaths due to unknown cause that were noted in the original RECORD study report were not a perfect subset of the 120 deaths due to unknown cause in the DCRI readjudication. Of the 120 deaths due to unknown cause in the DCRI readjudication, 80 deaths had not been adjudicated as due to unknown cause in the original RECORD adjudication. These 80 deaths were evenly distributed between the RSG group (41 deaths) and the comparator group (39 deaths). This relatively even distribution is not suggestive of a systematic process in the original RECORD adjudication of assignment of cause of death in cases where data were actually insufficient.

When one examines the cases which were readjudicated by DCRI as due to unknown cause, but which had not been adjudicated as due to unknown cause in the original adjudication, a common reason for this is that the deaths had been identified in the original RECORD study through the Survival Status Update, which collected survival status only, but did not collect all information necessary to determine cause of death. Beyond this, the reason for the remaining difference in the number of cases adjudicated by DCRI vs those in the original adjudication is unknown. Per the charter, DCRI developed its own adjudication forms. It is possible that these new forms, and the consciousness of the readjudicators of expected scrutiny of their adjudication process, could have been associated with increased stringency in the requirements for events to meet definitions for cause of death. This could have resulted in more deaths being found to have insufficient data to meet a definition, and less use of adjudicator judgment for cases that appeared to be due to a particular cause but for which certain data were missing.

When examining the 61 deaths which were originally adjudicated as having been due to unknown cause, in 22 of these cases in the DCRI readjudication, the death was not adjudicated as being due to unknown cause, i.e. a cause of death was assigned by DCRI. Among these 22 cases, 8 patients were in the RSG group, and 14 were in the comparator group. Of the 8 deaths in the RSG group, DCRI adjudicated 4 as cardiovascular deaths, and 4 as non-cardiovascular deaths. Of the 14 deaths in the comparator group, DCRI adjudicated 8 as cardiovascular and 6 as non-cardiovascular deaths. The following table displays these cases.

Table III.B.2: Cardiovascular vs Noncardiovascular Death Among Patients Originally Adjudicated as Having Unknown Cause of Death, but Readjudicated as Having Known Cause of Death by DCRI

Patient ID	Treatment Assignment	Death CV or Non-CV by DCRI?
18227	MET + SU	CV
18285	MET + SU	Non-CV
18654	MET + SU	Non-CV
30540	MET + SU	CV
31868	MET + SU	Non-CV
98236	MET + SU	CV
18514	SU + MET	Non-CV
18997	SU + MET	CV
19544	SU + MET	CV
29551	SU + MET	CV
29685	SU + MET	CV
31362	SU + MET	Non-CV
97573	SU + MET	CV
97954	SU + MET	Non-CV
20839	MET + RSG	Non-CV
30881	MET + RSG	Non-CV
38533	MET + RSG	Non-CV
97947	MET + RSG	CV
18831	SU + RSG	Non-CV
18886	SU + RSG	CV
21165	SU + RSG	CV
29609	SU + RSG	CV

Source: Listing 3.0, beg pg 226, study report

This relatively even distribution is not suggestive of deliberate misclassification in the original adjudication process, and is not weighted toward differing assignment away from either CV or non-CV deaths.

III.C. Results of the DCRI Quality Control Process

For the quality control process, the lead (blinded) statistician randomly selected 25 adjudicated death events. These events were then adjudicated by the DCRI CEC Committee. Of the 25 events, in 14 cases, the QC result matched the original DCRI readjudication result. For 11 events, the QC result did not match on all variables:

- For six events, there was a minor discrepancy regarding date/time.
- For three events, there was a minor discrepancy regarding death subclassification. For example there was agreement that the death was a cardiovascular death, but the subclassification of type of CV death differed between the original DCRI readjudications and the QC readjudication.
- For two events, there was a major discrepancy between the QC and original readjudication regarding death classification. These events were re-reviewed and reconciled by the DCRI CEC Committee, and the adjudication result was updated in the database.

The study report does not detail the actual cases, or what the discrepancies were. This information has been requested from the sponsor. These differences perhaps illustrate the inherent variability in adjudication processes. Even when adjudication is conducted under the most stringent conditions, individual adjudicators may differ in their conclusions.

III.D. Use of DCRI Information to Address Concerns from the Original RECORD Review

During the original review of RECORD prior to the 2010 Advisory Committee meeting, a consultant from the Division of Cardiorenal Products expressed concerns regarding study conduct and other matters, and requested additional information regarding approximately 475 patients. His concerns, particularly his allegations of trial misconduct, contributed in part to the decision to request an independent readjudication of RECORD. Some of his concerns were somewhat speculative and probably cannot be addressed by this readjudication or by other means. Overall, the readjudication process addresses his concerns in a major way, in that it examines whether highly qualified adjudicators, working under a rigorously-defined blinded process, would come up with analysis results similar to those found in the original adjudication. This review also attempts to use the readjudication results to address his concerns in other ways.

For the current review, the endocrine clinical reviewer identified the patient ID numbers for those patients mentioned above. The following table includes the subset of those patients who died, and who were among those patients for whom the 2010 Cardiorenal consultant expressed some type of concern and requested additional records. The table includes the concern expressed (if the concern was documented), the original adjudication result for cause of death, and the DCRI results for adjudicated cause of death. Most of the concerns expressed did not relate directly to adjudicated cause of death. However, since these were cases for which the 2010 Cardiorenal consultant had some type of concern regarding study conduct or other matters, each of the cases was examined to observe how often the adjudicated cause of death differed between the original study report and the DCRI adjudication. This process was not intended to examine the 2010 Cardiorenal consultant's interpretation of individual cases, but was rather intended to identify a population of cases for which there appeared to be heightened concern for problems, and to examine the outcome of the DCRI readjudication compared to the original RECORD adjudication, for this enriched population. It should be noted that it was not always possible to identify accurately the concerns that led to the 2010 Cardiorenal consultant's information requests, but the clinical reviewer has attempted to identify the concern when possible.

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
18106	MET + RSG	Hospitalization adjudicated as "unknown, insufficient data". Possible heart failure hospitalization adjudicated as non-CV. Death captured via survival status update after patient withdrawn from CV follow-up. Revised CRF submitted by GSK during FDA review.	Deaths captured via survival status update not adjud	Unk	Undeterm
18107	SU + MET	Many annotations on SAE CRF	Cause of death acute vascular event	Cause of death acute vascular event	Cause of death "other CV-periph vascular disease"
18122	SU + MET	Death adjudicated as non-CV	Non-CV	Unk	Undeterm
18124	MET + RSG	Death adjudicated as non-CV	Non-CV	Non-CV	Non-CV
18143	MET + RSG	Death adjudicated as non-CV	Non-CV	Non-CV	Non-CV
18172	MET + SU	Death adjudicated as non-CV. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review.	Non-CV	Non-CV	Non-CV
18195	SU + RSG	Death adjudicated as non-CV	Non-CV	Unk	Undeterm
18215	MET + RSG	Pulmonary edema event adjudicated as pneumonia and non-CV death.	Non-CV	Non-CV	Non-CV
18221	SU + MET	Death adjudicated as non-CV. Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Non-CV	Non-CV	Non-CV
18227	MET + SU	Initial cause of death unknown. Info re possible subarachnoid bleed submitted later; death readjudicated as unknown cause. Many annotations on SAE CRF.	Unk death (insuff data)	Acute vascular event	Other CV-cerebral bleed from ruptured aneurysm
18257	SU + RSG	Death adjudicated as non-CV. Many annotations on SAE CRF.	Cause of death non-CV.	Cause of death non-CV.	Cause of death non-CV.

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
18285	MET + SU	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unknown (insuff data)	Cause of death non-CV	Cause of death non-CV
18296	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18307	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18332	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18337	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
18388	SU + MET	Hospitalization for "collapse", during which 3V CAD found, not adjudicated as CV. Little info on subsequent death. Death captured via survival status update after patient withdrawn from CV follow-up. Many annotations on SAE CRF.	Deaths captured via survival status update not adjud	Cause of death acute vascular event	Cause of death stroke
18418	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18488	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18497	MET + RSG	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
18498	MET + SU	Arrhythmia during hosp for cholecystitis; arrhythmia type not specified. Diabetes drug names not redacted from some forms in adjud dossier. CEC record contains 2 reviewer adjud forms, but not full committee adjud form.	Cause of death "other CV death-multiorgan failure"	Cause of death "other CV death-complications of CABG"	Cause of death acute MI
18502	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18504	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Non-CV	Unk	Undeterm
18521	SU + MET	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Cause of death MI	Cause of death acute MI	Cause of death acute MI

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
18660	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18675	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18769	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18786	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18787	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
18796	SU + MET	Death captured via survival status update after patient withdrawn from CV follow-up. Little documentation regarding death; withdrawal date unknown. Many annotations on SAE CRF.	Deaths captured via survival status update not adjud	Unk	Undeterm
18805	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18912	MET + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Cause of death MI	Cause of death acute MI	Cause of death acute MI
18950	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
18995	MET + SU	Death adjudicated as non-CV. Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
19079	SU + RSG	Deletion of SAE and possible MI by investigator. Revised CV adjudication form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review. Many annotations on SAE CRF.	Unk death (insuff data)	Cause of death heart failure or cardiogenic shock	Cause of death heart failure or cardiogenic shock
19110	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up. Many annotations on SAE CRF.	Deaths captured via survival status update not adjud	Unk	Undeterm
19115	MET + SU	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
19119	SU + MET	Discrepancy for last CV follow-up date between dataset and CRF	Deaths found via tracking substudy not adjud	Cause of death unk	Cause of death undeterm
19134	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19204	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19269	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19338	SU + RSG	Hospitalization adjudicated as "unknown, insufficient data". Hospitalization with reported suspected MI had discharge diagnosis of hyperkalemia. Death adjudicated as non-CV.	Death non-CV	Death non-CV	Death non-CV
19350	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19353	MET + RSG	Hospitalization adjudicated as "unknown, insufficient data" (endpoint E22590-499). Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (endpoint E22589-499).	Cause of death heart failure	Cause of death acute MI	Cause of death acute MI
19390	MET + RSG	In datasets, date of death earlier than date of end of vital status follow-up. Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
19437[1]	SU + RSG	Hospitalized for heart failure; discharge summary mentions suspected MI; MI endpoint not adjudicated.	Cause of death heart failure.	Cause of death heart failure or cardiogenic shock	Cause of death heart failure or cardiogenic shock
19438	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19450	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Patient did not die	Patient did not die

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
19452	SU + MET	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E17642-198 and E27188-198). Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
19481	SU + MET	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Sudden death	Sudden cardiac death	Sudden cardiac death
19545	MET + RSG	Hospitalization adjudicated as "unknown, insufficient data" (endpoint E21513-665). Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E21504-665 and E21514-665).	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
19677	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19720	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19731[1]	MET + RSG	2 events close in time; one not adjudicated. Death adjudicated as "unknown" although reportedly admitted for ventricular arrhythmias.	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
19734[1]	MET + SU	3.5 year delay in subm of death event from site to study monitor. Two death tracking forms.	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
19735	MET + RSG	Revised CV adjudication form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review. Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
19825	MET + RSG	Delay in adjudication of a hospitalization	Cause of death acute vascular event	Cause of death heart failure or cardiogenic shock	Cause of death heart failure or cardiogenic shock

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
19950	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
19978	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
20011	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
20046	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
20100	SU + MET	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E16000-279 and E16769-279). Death adjudicated as non-CV.	Cause of death non-CV.	Cause of death non-CV.	Cause of death non-CV.
20164	SU + MET	Event detected by endpoint sweep.	Cause of death heart failure	Cause of death unk	Cause of death undeterm
20230	SU + MET	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
20235	SU + RSG	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
20623	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
20694	SU + RSG	Hospitalization adjudicated as "unknown, insufficient data". Revised CRF submitted by GSK during FDA review.	Cause of death MI	Cause of death acute MI	Cause of death acute MI
20766	MET + SU	Autopsy report of pulmonary embolism with suspicion of myocardial infarction. MI not referred for adjudication.	Cause of death acute vascular event	Cause of death acute vascular event	Cause of death "other CV-pulmonary embolism"
20773	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
20839[1]	MET + RSG	Pt with GI bleed transferred to ICU with chest pain and died. Adjudicated non-CV death due to inadequate documentation.	Cause of death unk (insuff data)	Cause of death non-CV	Cause of death non-CV
20841	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
20892	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
20930[1]	MET + RSG	Event of "collapse" attributed to atrial fibrillation; not sent for adjudication.	Death not reported in orig study (died [redacted], after study end date)	Cause of death unk	Cause of death undeterm
21027	MET + RSG	Death captured via survival status update after patient withdrawn from CV follow-up. Many annotations on SAE CRF.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
21093	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
21102	SU + MET	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
21153	SU + MET	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
21178	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21210	MET + SU	Endpoint for which adjudication forms were not provided.	Cause of death acute vascular event.	Cause of death acute vascular event.	Cause of death stroke
21250	SU + MET	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
21261	MET + RSG	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
21292	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21365	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21368	SU + RSG	Hospitalizations for digit amputation and peripheral artery disease not sent for adjudication. Death adjudicated as non-CV. Question regarding imputation process for unknown exact date of death.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
21380	SU + MET	Death captured via survival status update after patient withdrawn from CV follow-up. Death listed in dataset but not in other documents.	Deaths captured via survival status update not adjud	Unk	Undeterm
21395	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21483	MET + SU	Hospitalization adjudicated as "unknown, insufficient data" (2 endpoints- E20804-685 and E20805-685).	Cause of death acute vascular event	Cause of death acute vascular event	Cause of death stroke
21486	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21503	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21508	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death unk	Cause of death undeterm
21523	MET + RSG	Hospitalization adjudicated as "unknown, insufficient data". Death adjudicated as non-CV.	Cause of death non-CV	Cause of death unk	Cause of death undeterm
21527	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
21589	SU + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Cause of death MI	Cause of death acute MI	Cause of death acute MI
21612	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
29079	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29094	MET + RSG	One CEC reviewer said cause of death MI; 2nd CEC reviewer said cause "sudden death". Full CEC called it "cardiac arrest".	Cause of death "other CV death, cardiac arrest"	Cause of death sudden cardiac death	Cause of death sudden cardiac death
29136	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29323	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
29331	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29440	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV.	Cause of death unk	Cause of death undeterm
29518	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29563	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29570	SU + MET	Hospitalization adjudicated as "unknown, insufficient data" (endpoint E20876-682). Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (endpoint E19768-682).	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
29582	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29583	MET + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom. Death adjudicated as non-CV.	Cause of death non-CV	Cause of death unk	Cause of death undeterm
29620	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
29696	MET + RSG	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
29749	MET + RSG	Revised CV adjudication form submitted by GSK during FDA review.	Cause of death "Other CV death-multiorgan failure"	Cause of death acute MI	Cause of death acute MI
29895	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up. Many annotations on SAE CRF.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
29971	SU + MET	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
29985	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
30009	SU + MET	Revised CRF submitted by GSK during FDA review.	Cause of death unk	Cause of death unk	Cause of death undeterm

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
30035	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
30094	SU + MET	Death adjudicated as non-CV. Revised CV adjudication form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review.	Death non-CV	Death non-CV	Death non-CV
30165	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
30340	MET + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
30359	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
30491	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
30540	MET + SU	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unk (insuff data)	Cause of death sudden cardiac death	Cause of death sudden cardiac death
30754	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
30757	SU + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (4 endpoints- E19742-686, E19746-686, E19755-686 and E20853-686).	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
31000	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
31183	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31184	SU + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
31209	MET + RSG	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
31237	MET + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
31241[1]	SU + MET	Delay in subm of event to CEC	Death not reported in orig study (died)	Cause of death unk	Cause of death undeterm
31294	SU + RSG	In datasets, date of death earlier than date of end of vital status follow-up. Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Non-CV	Non-CV
31302	MET + SU	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E20340-687 and E20342-687).	Cause of death MI	Cause of death acute MI	Cause of death acute MI
31316	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31389	MET + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E22848-827 and E22849-827). Death adjudicated as non-CV.	Cause of death non-CV.	Cause of death unk	Cause of death undeterm
31413	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
31496	SU + RSG	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31515	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
31553	MET + SU	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31598	SU + RSG	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
31725	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
31729	MET + RSG	Discrepancy for last CV follow-up date between dataset and CRF. Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
31741	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
31756	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
31785	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
31868	MET + SU	Reported lung cancer death with little documentation	Unk death (insuff data)	Non-CV	Non-CV
32017	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
37303	SU + MET	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
37660	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38013	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38039	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38040	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38056	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38067	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38069	MET + RSG	Had 6 endpoints referred; 3 readjudicated by full CEC as non-CV	Cause of death heart failure	Cause of death unk	Cause of death undeterm
38093	MET + RSG	Death captured via survival status update after patient withdrawn from CV follow-up. Revised CRF submitted by GSK during FDA review.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
38125	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38333	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
38458	MET + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom. Death adjudicated as non-CV.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
38468	SU + RSG	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
38483	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38489	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
38582	SU + MET	Hospitalization adjudicated as "unknown, insufficient data". Death adjudicated as non-CV.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
38912	SU + MET	Death captured via survival status update after patient withdrawn from CV follow-up. In datasets, date of death earlier than date of end of vital status follow-up. Data query form regarding death not located.	Deaths captured via survival status update not adjud	Unk	Undeterm
38923	SU + RSG	Hospitalization adjudicated as "unknown, insufficient data". Death adjudicated as non-CV. Revised CV adjudication form submitted by GSK during FDA review.	Cause of death non-CV.	Cause of death non-CV.	Cause of death non-CV.
38938	SU + MET	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
39115	MET + RSG	Revised CRF submitted by GSK during FDA review.	Cause of death unk (insuff data)	Cause of death unk	Cause of death undeterm
43567	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
43614	MET + RSG	Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review.	Cause of death "other CV death-multiorgan failure"	Cause of death "other CV- peri-CABG/AVR complications"	Cause of death "other CV- peri-CABG/AVR complications"
43653	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
43686	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
43907	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
97520	SU + MET	In datasets, date of death earlier than date of end of vital status follow-up. Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
97580	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
97660	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
97742	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
97811	MET + SU	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
97858	MET + SU	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
97954	SU + MET	Question regarding whether autopsy in drowning death followed up appropriately	Unk death (insuff data)	Non-CV	Non-CV
97991	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
98047	SU + RSG	Death adjudicated as non-CV. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review.	Cause of death non-CV.	Cause of death non-CV.	Cause of death non-CV.
98059	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
98159	SU + MET	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E17711-205 and E27195-205). Revised CV adjudication form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review. Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Cause of death unk	Cause of death undeterm
98161	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV
98256	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
98276[1]	SU + RSG	15 month delay in transmission of event to CEC	Cause of death "Other CV death-pulmonary embolism"	Cause of death acute vascular event	Cause of death "other CV-pulmonary embolism"
98287	SU + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
98343	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
98435	MET + RSG	Death adjudicated as non-CV.	Non-CV	Non-CV	Non-CV
98463	MET + SU	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Unk	Undeterm
98472	MET + SU	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death non-CV	Cause of death non-CV

Table III.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD

Pt ID	Tx	Concern(s)	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def

Sources: Inspection report, Dr. Khin U, NDA 21070, DARRTS 11 Jun 2010. NDA 21071 submissions from 25 Aug 2009; 8, 10 and 11 Dec 2009; 2 and 5 Feb 2010; 1, 23 and 24 Mar 2010; 13 Apr 2010; 25 and 26 May 2010; 4, 8, 9 and 15 Jun 2010; and 20 Dec 2011.
Abbreviations: 3V = 3 vessel; Adjud = adjudication; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CEC = Clinical Endpoints Committee; CEVA = Quintiles Clinical Event Validation and Adjudication center; CRF = case report form; CV = cardiovascular; Def = definition; GI = gastrointestinal; hosp = hospitalization; ICU = intensive care unit; ID = identification; insuff = insufficient; MET = metformin; MI = myocardial infarction; Orig = original; periph = peripheral; Pt = patient; Readjud = readjudication; RSG = rosiglitazone; SAE = serious adverse event; SU = sulfonylurea; subm = submission; Undeterm = undetermined; Unk = unknown
1 Case was cited on form FDA-483 during inspection

The following table is a subset of the table above; this following table includes only those cases for which the adjudicated cause of death differed between the original adjudication and the readjudication.

Table III.D.2: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD: Cases Where Adjudicated Cause of Death Differed Between Original Study Report and DCRI Readjudication (Original Definitions)

Pt ID	Tx	Concern	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
18122	SU + MET	Death adjudicated as non-CV	Non-CV	Unk	Undeterm
18195	SU + RSG	Death adjudicated as non-CV	Non-CV	Unk	Undeterm
18227	MET + SU	Initial cause of death unknown. Info re possible subarachnoid bleed submitted later; death readjudicated as unknown cause. Many annotations on SAE CRF.	Unk death (insuff data)	Acute vascular event	Other CV-cerebral bleed from ruptured aneurysm
18285	MET + SU	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unknown (insuff data)	Cause of death non-CV	Cause of death non-CV
18337	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
18497	MET + RSG	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm

Table III.D.2: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD: Cases Where Adjudicated Cause of Death Differed Between Original Study Report and DCRI Readjudication (Original Definitions)

Pt ID	Tx	Concern	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
18498	MET + SU	Arrhythmia during hosp for cholecystitis; arrhythmia type not specified. Diabetes drug names not redacted from some forms in adjud dossier. CEC record contains 2 reviewer adjud forms, but not full committee adjud form.	Cause of death "other CV death-multiorgan failure"	Cause of death "other CV death-complications of CABG"	Cause of death acute MI
18504	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Non-CV	Unk	Undeterm
18787	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
19079	SU + RSG	Deletion of SAE and possible MI by investigator. Revised CV adjudication form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review. Many annotations on SAE CRF.	Unk death (insuff data)	Cause of death heart failure or cardiogenic shock	Cause of death heart failure or cardiogenic shock
19353	MET + RSG	Hospitalization adjudicated as "unknown, insufficient data" (endpoint E22590-499). Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (endpoint E22589-499).	Cause of death heart failure	Cause of death acute MI	Cause of death acute MI
19450	SU + RSG	Death captured via survival status update after patient withdrawn from CV follow-up.	Deaths captured via survival status update not adjud	Patient did not die	Patient did not die
19481	SU + MET	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom.	Sudden death	Sudden cardiac death	Sudden cardiac death
19825	MET + RSG	Delay in adjudication of a hospitalization	Cause of death acute vascular event	Cause of death heart failure or cardiogenic shock	Cause of death heart failure or cardiogenic shock

Table III.D.2: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD: Cases Where Adjudicated Cause of Death Differed Between Original Study Report and DCRI Readjudication (Original Definitions)

Pt ID	Tx	Concern	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
20164	SU + MET	Event detected by endpoint sweep.	Cause of death heart failure	Cause of death unk	Cause of death undeterm
20230	SU + MET	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
20839	MET + RSG	Pt with GI bleed transferred to ICU with chest pain and died. Adjudicated non-CV death due to inadequate documentation.	Cause of death unk (insuff data)	Cause of death non-CV	Cause of death non-CV
21153	SU + MET	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
21508	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV	Cause of death unk	Cause of death undeterm
21523	MET + RSG	Hospitalization adjudicated as "unknown, insufficient data". Death adjudicated as non-CV.	Cause of death non-CV	Cause of death unk	Cause of death undeterm
29094	MET + RSG	One CEC reviewer said cause of death MI; 2nd CEC reviewer said cause "sudden death". Full CEC called it "cardiac arrest".	Cause of death "other CV death, cardiac arrest"	Cause of death sudden cardiac death	Cause of death sudden cardiac death
29440	SU + MET	Death adjudicated as non-CV. Endpoint for which adjudication forms were not provided.	Cause of death non-CV.	Cause of death unk	Cause of death undeterm
29583	MET + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom. Death adjudicated as non-CV.	Cause of death non-CV.	Cause of death unk	Cause of death undeterm
29696	MET + RSG	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm
29749	MET + RSG	Revised CV adjudication form submitted by GSK during FDA review.	Cause of death "Other CV death-multiorgan failure"	Cause of death acute MI	Cause of death acute MI
29971	SU + MET	Death adjudicated as non-CV.	Non-CV	Cause of death unk	Cause of death undeterm

Table III.D.2: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original Review of RECORD: Cases Where Adjudicated Cause of Death Differed Between Original Study Report and DCRI Readjudication (Original Definitions)

Pt ID	Tx	Concern	Original Adjud Result	Duke Readjud with Orig Def	Duke Readjud with "New FDA" Def
30540	MET + SU	Hospitalization adjudicated as "unknown, insufficient data".	Cause of death unk (insuff data)	Cause of death sudden cardiac death	Cause of death sudden cardiac death
31183	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31241	SU + MET	Delay in subm of event to CEC	Death not reported in orig study (died)	Cause of death unk	Cause of death undeterm
31316	SU + MET	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31389	MET + RSG	Hospitalization adjudicated as nonurgent CV procedure or nonspecific symptom (2 endpoints- E22848-827 and E22849-827). Death adjudicated as non-CV.	Cause of death non-CV.	Cause of death unk	Cause of death undeterm
31496	SU + RSG	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31553	MET + SU	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
31868	MET + SU	Reported lung cancer death with little documentation	Unk death (insuff data)	Non-CV	Non-CV
38069	MET + RSG	Had 6 endpoints referred; 3 readjudicated by full CEC as non-CV	Cause of death heart failure	Cause of death unk	Cause of death undeterm
38468	SU + RSG	Death adjudicated as non-CV.	Non-CV	Unk	Undeterm
43614	MET + RSG	Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review.	Cause of death "other CV death-multiorgan failure"	Cause of death "other CV- peri-CABG/AVR complications"	Cause of death "other CV- peri-CABG/AVR complications"
97954	SU + MET	Question regarding whether autopsy in drowning death followed up appropriately	Unk death (insuff data)	Non-CV	Non-CV
98276	SU + RSG	15 month delay in transmission of event to CEC	Cause of death "Other CV death-pulmonary embolism"	Cause of death acute vascular event	Cause of death "other CV-pulmonary embolism"

Source: Table II.D.1 above

In the above table, there are 39 cases for which there was not agreement between the original adjudication and the DCRI readjudication for cause of death. Eighteen of these cases were patients randomized to rosiglitazone and 21 were patients randomized to comparator.

The following table summarizes the type of non-agreement by treatment assignment from the above table.

Table III.D.3: Cases of Concern from Original RECORD Review: Reasons for Non-Agreement on Cause of Death Between Original Adjudication and DCRI Readjudication

Reason for Non-Agreement	Number of Cases with This Type of Non-Agreement	
	RSG	Comp
Original adjud "non-CV"; DCRI readjud "unk"	8[1]	12[2]
Original adjud "unk"; DCRI readjud "non-CV"	1[2]	3[1]
Original adjud "unk"; DCRI readjud "heart failure or cardiogenic shock"	1[3]	
Original adjud "unk"; DCRI readjud "sudden cardiac death"		1[4]
Original adjud "unk"; DCRI readjud "acute vascular event"		1[4]
Original adjud "heart failure"; DCRI readjud "acute myocardial infarction"	1[3]	
Original adjud "heart failure"; DCRI readjud "unk"	1[6]	1[4]
Original adjud "acute vascular event"; DCRI readjud "heart failure or cardiogenic shock"	1[3]	
Original adjud "other CV death- multiorgan failure"; DCRI readjud "other CV death- peri-CABG/AVR complications"	1[6]	
Original adjud "other CV death- multiorgan failure"; DCRI readjud "other CV death- complications of CABG"		1[6]
Original adjud "other CV death- multiorgan failure"; DCRI readjud "acute myocardial infarction"	1[3]	
Original adjud "other CV death- cardiac arrest"; DCRI readjud "sudden cardiac death"	1[6]	
Original adjud "other CV death- pulmonary embolism"; DCRI readjud "acute vascular event"	1[6]	
Original adjud "sudden death"; DCRI readjud "sudden cardiac death"		1[6]
Original "death" captured via survival status update and not adjudicated; DCRI "patient did not die"	1[5]	
Original report did not include death; DCRI readjud death with cause "unk"		1[4]

Source: Table III.D.2 above
1 Readjudication does not favor rosiglitazone, because deaths of unknown cause were counted as cardiovascular deaths, and thus if the original adjudication had called these deaths "unknown", the rate of CV death for RSG would have been somewhat higher. This would have affected both the primary endpoint and the endpoint of CV death.
2 Readjudication favors rosiglitazone, because deaths of unknown cause were counted as cardiovascular deaths, and thus if the original adjudication had called these deaths "unknown", the rate of CV death for comparator would have been somewhat higher. This would have affected both the primary endpoint and the endpoint of CV death.
3 Readjudication does not favor rosiglitazone. Would not have increased the rate of CV death or altered the primary endpoint for RSG, but would have been unfavorable for another reason. For example, the change of cause of death might have increased the rate of death from MI or HF for RSG.
4 Readjudication favors rosiglitazone. Would not have increased the rate of CV death for comparator, but would have been unfavorable to comparator, and thus favorable to RSG, for another reason. For example, the readjudicated cause of death might be more clearly a cardiovascular cause. In one case, a new death was noted.
5 Readjudication favors rosiglitazone because a patient who was previously thought dead actually did not die.
6 No clear reason why this readjudication change would be either favorable or unfavorable to RSG

In the above table, each reason for non-agreement has been classified according to whether the change would have been favorable to RSG, unfavorable to RSG, or would not clearly have been either favorable or unfavorable, with respect to the outcomes of

analyses. Please see the footnotes to the table regarding these classifications. Based on these classifications, the readjudication resulted in a potentially more favorable outcome for RSG in 18 cases, in a potentially less favorable outcome for RSG in 15 cases, and appeared to be neither favorable nor unfavorable in 6 cases. This observation is somewhat reassuring, because these cases were identified by the 2010 Cardiorenal consultant as cases for which he had concerns, and during the original review cycle additional information was requested from GSK for these cases. Thus, one might have expected the subjects in this table to be a highly enriched population of "problem cases" for which trial conduct problems could have occurred. It appears, however, that there was not evidence of systematic favorable adjudication decisions, even in this previously suspect population.

In the 2010 Cardiorenal consultant's consult, on page 95 (Table 4), he provided eight case examples of "failures to refer events for adjudication". He also cited three (or perhaps four) of these same cases as having had "extreme mishandling of events" (cases begin pg 27 of consult). Because the 2010 Cardiorenal consultant did not use the patient identification numbers for these cases of interest, it was initially difficult to determine precisely to which cases his consult referred. However, it appeared that the patient identification numbers had been provided to the inspection team for the 2010 inspection, and the patient ID numbers below were therefore extracted from those records. The events which were cited were primarily nonfatal events, and therefore one cannot compare the 2010 Cardiorenal consultant's readjudication with that of DCRI. However, five of these eight patients did have deaths, and one can compare the outcomes of the original death adjudication with that of DCRI:

Table III.D.4: Outcomes of Adjudication and Readjudication for Deaths in Cases Identified in Original Cardiology Consult as Having Had "Failure to Refer Events for Adjudication[1]" or "Extreme Mishandling of Events[2]"

Patient ID	Treatment	Orig Cause of Death Adjudication	DCRI Cause of Death Adjudication
18215	MET + RSG	Non-CV	Non-CV
19079	SU + RSG	Unk death (insuff data)	Heart failure or cardiogenic shock
19338	SU + RSG	Non-CV	Non-CV
20930	MET + RSG	Death occurred after end of study[3]	Unk
21368	SU + RSG	Non-CV	Non-CV

1 Source: Cardiorenal consult, DARRTS 15 Jun 2010, pg 95, Table 4
2 Source: Cardiorenal consult, DARRTS 15 Jun 2010, cases begin pg 27
3 Death occurred [redacted] study cutoff 31 Dec 2008

Of note in this table is the observation that, although the 2010 Cardiorenal consultant identified these cases as extreme cases of concern, in only one of the cases was there non-agreement on cause of death between the original adjudication and the DCRI readjudication. Patient 19079 was originally adjudicated as having death of unknown cause due to insufficient data, but the DCRI readjudication was that of death due to heart failure or cardiogenic shock. This readjudication in this case would not have changed the

outcome of the rate of CV death, because unknown deaths were counted as CV deaths, but it would have slightly increased the rate of heart failure death for RSG.

In his consult, the 2010 Cardiorenal consultant discussed a concern regarding dates of end of cardiovascular follow-up. He cited several cases where he felt that the actual date of end of cardiovascular follow-up differed from the date that was used in analyses.

In order to address this concern, DCRI used four different approaches to derive last follow-up dates:

- "Parsimonious" approach: Defined the last known alive date as the last date of a documented face-to-face visit at which one or more vital signs were recorded on the VITALS module of the CRF. Patients with a last known alive date after 24 Aug 2008 were considered to have completed survival follow-up.
- "Primary analysis approach": For patients who, based on the parsimonious approach, had not completed survival follow-up, the primary analysis approach (which was used for the primary analysis) added follow-up information for two additional types of patients. Patients were added who had a vital sign face-to-face in 2008 and a phone visit after 24 Aug 2008. Patients were also added who had an updated last known alive date based on DCRI reviews of case report forms (CRFs) or associated documents.
- "Primary analysis plus test and reported patient events follow-up" approach: This approach added patients using dates for electrocardiograms, lab tests, microvascular endpoints, adverse events and fractures reported in the electronic database.
- "Primary analysis plus test and patient event dates plus survival status and third party survival data collected with RECORD" approach: For patients whose vital status after 24 Aug 2008 could not be determined by the rules described in the first three approaches above, vital status was updated from Survival Status Update and third party search conducted as part of the RECORD study.

As mentioned above, the primary analysis was conducted using the "primary analysis" approach. To assess the possible impact of censoring follow-up end date derivation, analyses for overall mortality and CV mortality were repeated using the three approaches other than the "primary analysis" approach.

The following table summarizes the mean follow-up, and the percentage of patients with incomplete follow-up, for each approach.

Table III.D.5: Mean Years of Follow-Up and Percentage of Patients with Incomplete Follow-Up Using Four Methods of Derivation of End of Follow-Up				
Approach to Derivation of End of Follow-Up	**Yrs of Follow-Up**		**Patients With Incomplete Follow-Up n (%)**	
	RSG Mean (SD)	**MET/SU Mean (SD)**	**RSG N=2220 n (%)**	**MET/SU N=2227 n (%)**
Parsimonious	5.5 (1.5)	5.4 (1.6)	308 (13.9)	350 (15.7)
Primary	5.8 (1.1)	5.8 (1.2)	85 (3.8)	115 (5.2)
Primary + Test and Event Dates	5.8 (1.1)	5.8 (1.2)	83 (3.7)	114 (5.1)
Primary + Test and Event Dates + Survival Status and Third Party Survival Data	5.9 (1.0)	5.8 (1.2)	50 (2.3)	82 (3.7)
Source: Sponsor's Table 2.1, pg 88, study report				

With each approach, the mean duration of follow-up was similar between the rosiglitazone and comparator groups. Median data, and data by strata, were also presented in the source tables (sponsor Tables 2.1, 2.1a, and 2.1b, pages 88-90 of study report) and were also similar between groups. With each approach, there was a somewhat higher percentage of patients in the MET/SU group who had incomplete follow-up by the definition used in the given approach.

The following table presents all-cause mortality results using the four approaches for derivation of end of follow-up.

Table III.D.6: All-Cause Mortality Analyses Using Four Methods of Derivation of End of Follow-Up

Approach to Derivation of End of Follow-Up	# Pts Who Died		Rate per 100 PY		HR (95%CI)	Absolute Rate Difference per 100 PY (95%CI)
	RSG N=2220 n(%)	MET/SU N=2227 n(%)	RSG Rate (95%CI)	MET/SU Rate (95%CI)		
Parsimonious	139 (6.3)	160 (7.2)	1.14 (0.94, 1.33)	1.32 (1.11, 1.53)	0.86 (0.68, 1.08)	-0.18 (-0.47, 0.10)
Primary	139 (6.3)	160 (7.2)	1.07 (0.89, 1.26)	1.25 (1.05, 1.45)	0.86 (0.68, 1.08)	-0.18 (-0.44, 0.09)
Primary + Test and Event Dates	139 (6.3)	160 (7.2)	1.07 (0.89, 1.26)	1.25 (1.05, 1.45)	0.86 (0.68, 1.08)	-0.18 (-0.44, 0.09)
Primary + Test and Event Dates + Survival Status and Third Party Survival Data	139 (6.3)	160 (7.2)	1.06 (0.88, 1.25)	1.24 (1.04, 1.44)	0.86 (0.68, 1.08)	-0.18 (-0.44, 0.09)

Source: Sponsor's Tables 2 (pg 48), 3.1 (pg 93), 24.1 (pg 194), 26.1 (pg 200) and 28.1 (pg 206)

Although, as expected, the parsimonious approach had a shorter mean follow-up time for both treatment groups, all four approaches resulted in similar hazard ratios and absolute rate differences.

The following table presents cardiovascular plus unknown cause mortality results using the four approaches to derivation of end of follow-up.

Table III.D.7: Cardiovascular Plus Unknown Cause Mortality Analyses Using Four Methods of Derivation of End of Follow-Up

Approach to Derivation of End of Follow-Up	# Pts With CV or Unk Cause Death		Rate per 100 PY		HR (95%CI)	Absolute Rate Difference per 100 PY (95%CI)
	RSG N=2220 n(%)	MET/SU N=2227 n(%)	RSG Rate (95%CI)	MET/SU Rate (95%CI)		
Parsimonious	88 (4.0)	96 (4.3)	0.72 (0.56, 0.87)	0.79 (0.63, 0.96)	0.90 (0.68, 1.21)	-0.07 (-0.30, 0.15)
Primary	88 (4.0)	96 (4.3)	0.68 (0.53, 0.83)	0.75 (0.59, 0.90)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)
Primary + Test and Event Dates	88 (4.0)	96 (4.3)	0.68 (0.53, 0.83)	0.75 (0.59, 0.90)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)
Primary + Test and Event Dates + Survival Status and Third Party Survival Data	88 (4.0)	96 (4.3)	0.67 (0.53, 0.82)	0.74 (0.59, 0.90)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)

Source: Sponsor's Tables 2 (pg 48), 5.1 (pg 109), 25.1 (pg 197), 27.1 (pg 203) and 29.1 (pg 209)
For these analyses, DCRI used the "new FDA" definitions

All four approaches resulted in similar hazard ratios and absolute rate differences. Each approach was also analyzed by background stratum (MET or SU), and there was no difference between strata (sponsor's Tables 2.1a and 3.1b, pages 89-90 of study report).

Similar results for these four approaches are not suggestive of informative censoring, but cannot rule it out entirely.

III.E. Comparison Between Original RECORD Adjudication and DCRI Readjudication Results

The following tables display the original RECORD adjudication results and the DCRI readjudication results.

Table III.E.1: Total Mortality, Original Adjudication and DCRI Readjudication Results

	Original Adjudication		DCRI Readjudication	
	RSG N=2220 PY=12272	MET/SU N=2227 PY=12338	RSG N=2220 PY=12815	MET/SU N=2227 PY=12953
Number of patients with death (%)	136 (6.1)	157 (7.0)	139 (6.3)	160 (7.2)
Rate per 100 PY (95% CI)	1.05 (0.88, 1.24)	1.22 (1.04, 1.43)	1.07 (0.89, 1.26)	1.25 (1.05, 1.45)
Hazard ratio (95% CI)	0.86 (0.68, 1.08)		0.86 (0.68, 1.08)	
Absolute rate difference per 100 PY (95% CI)	-0.17 (-0.43, 0.09)		-0.18 (-0.44, 0.09)	

Source: Sponsor's Tables 2 (pg 48), and 3.1 (pg 93), current study report; and Table 81, pg 181, original RECORD study report (27 Aug 2009)

For total mortality, analysis results from the DCRI readjudication were highly similar to those in the original RECORD adjudication.

Table III.E.2: Cardiovascular Mortality Plus Death Due to Unknown Cause, Original Adjudication and DCRI Readjudication Results

	Original Adjudication		DCRI Readjudication	
	RSG N=2220 PY=12272	MET/SU N=2227 PY=12338	RSG N=2220 PY=12815	MET/SU N=2227 PY=12953
Number of patients with cardiovascular death or death due to unknown cause (%)	60 (2.7)	71 (3.2)	88 (4.0)	96 (4.3)
Rate per 100 PY (95% CI)	0.49 (0.37, 0.63)	0.58 (0.45, 0.73)	0.68 (0.53, 0.83)	0.75 (0.59, 0.90)
Hazard ratio (95% CI)	0.84 (0.59, 1.18)		0.90 (0.68, 1.21)	
Absolute rate difference per 100 PY (95% CI)	-0.09 (-0.27, 0.09)		-0.07 (-0.28, 0.14)	

Source: Sponsor's Tables 2 (pg 48) and 5.1 (pg 109), current study report; and Table 76, pg 176, original RECORD study report (27 Aug 2009)

For cardiovascular death, including death due to unknown cause, hazard ratios and absolute rate differences did not detect a treatment difference in either adjudication process. Because more deaths were classified as due to unknown cause in the DCRI readjudication (see discussion above), overall numbers of cardiovascular + unknown deaths were somewhat higher in the DCRI analyses, but the distribution between RSG and MET/SU was similar, and thus hazard ratios and rate differences were similar between the original adjudication and the DCRI readjudication.

When excluding deaths due to unknown cause from cardiovascular deaths, the numbers of CV deaths by treatment group were similar between the original adjudication and the DCRI readjudication.

Table III.E.3: Cardiovascular Deaths Excluding Deaths Due to Unknown Cause, Original RECORD Adjudication and DCRI Readjudication Results

	RSG N=2220 n (%)	MET/SU N=2227 n (%)	Raw Ratio RSG:MET/SU
Original adjudication	32 (1.4%)	38 (1.7%)	0.84
DCRI readjudication	34 (1.5%)	42 (1.9%)	0.81

Source: Sponsor's Table 2, pg 49, current study report; and Table 53, pg 147, original RECORD study report (27 Aug 2009)

III.F. Unsolicited Memorandum from Dr. Marciniak, 15 May 2012

On 15 May 2012, Dr. Thomas Marciniak entered an unsolicited memorandum regarding the DCRI readjudication. During the review cycle for the original RECORD resubmission, Dr. Marciniak had made allegations of trial misconduct which were not substantiated by the reviews of others and by an extensive inspection of study coordinating centers and clinical sites, specifically targeting cases of concern to Dr. Marciniak. His concerns regarding the trial *design* were generally also identified by other reviewers as limitations to the usefulness of RECORD to evaluate the cardiovascular safety of rosiglitazone, but his concerns regarding trial *misconduct* were not substantiated.

In his memorandum of 15 May 2012, Dr. Marciniak expresses several concerns, which are discussed below.

Dr. Marciniak states that "the readjudication cannot address many of the trial design flaws documented previously". I concur that the readjudication does not change the fact that the trial had an open-label, active control, noninferiority design.

He also states that "the readjudication is not independent". His primary lines of reasoning for this statement appear to be that GlaxoSmithKline was financially responsible for the costs of the readjudication, and some of the DCRI personnel had received financial compensation of one kind or another from GlaxoSmithKline in the past. While it is true that Dr. Mahaffey, the principal investigator for the readjudication, does disclose on the DCRI website that he had received compensation for "consulting or other services", it should be noted that GSK was one of 24 companies so listed by Dr. Mahaffey, and if one reads the site carefully, one can see that it appears that the compensation was primarily for his participation in Continuing Medical Education activities, rather than as any kind of direct compensation. I do not concur that the fact that GSK, rather than the taxpayer, was held financially responsible for the costs of the readjudication means that the readjudication was therefore not independent. The sponsor of the drug involved should be the party that takes on the costs associated with safety concerns. A readjudication process such as this likely cost millions of dollars. The DCRI

has an impeccable reputation for integrity, and it is implausible that they would risk that reputation for any one contract. Their services are in high demand, largely because of their record of thorough scientific and ethical processes. Continued demand for their services is dependent on continuation of their high standards for rigor and independence.

Dr. Marciniak expresses concern that the study data were supplied to DCRI by GSK, and that redaction of treatment assignment was performed by GSK. These processes were unavoidable; GSK owns the data and had to be the party to provide them. Dr. Marciniak implies that, rather than limiting the redacted items to those specified in the charter, GSK could have redacted other information and hidden adverse event data.

For Dr. Marciniak's memorandum, as well as for his original consultation, some aspects of his input (such as those on trial design limitations) are useful and objective, but his allegations of trial misconduct, and in this case, readjudication misconduct, appear unsubstantiated and do not appear to have been reached through a balanced and objective review process. Regrettably, the case reviews in his original consult were not blinded; although he states that some type of blinding occurred, it appears that he himself did the redactions, then followed with his own review. This is not an acceptable review procedure if one wants to put forth one's review work as blinded. Furthermore, from the earliest meetings in the original RECORD review process, Dr. Marciniak was openly discussing specific patients, including their patient identification numbers and treatment assignments. Therefore, from the earliest stages, his review was unblinded. Nevertheless, his allegations during the original review cycle were taken quite seriously, and extensive inspections focused heavily on cases provided by Dr. Marciniak as examples of possible trial misconduct. The inspection team did not find evidence of misconduct or fraud.

In summary, the endocrine clinical reviewer concurs that the DCRI review cannot address some of the trial design limitations of the original trial. However, as above, the clinical reviewer does not concur that there is evidence that DCRI did not conduct the readjudication in an independent fashion.

IV. Discussion of Limitations and Strengths of Readjudication

IV.A. What the DCRI Readjudication Can and Cannot Address

Overall, it appears that DCRI's readjudication procedures and execution were rigorous. The FDA Office of Scientific Investigations conducted a site inspection at DCRI and confirmed that pre-specified readjudication procedures were followed appropriately; please refer to the OSI briefing document for details. However, even the best-conducted readjudication cannot address all concerns that were raised in the original review. Please see the clinical reviewer's original RECORD briefing document, which discusses these limitations in greater detail (DARRTS, 15 Jun 2010, beginning pg 89).

Concerns that cannot be addressed include the following:

IV.A.1. Trial design issues

As with the original RECORD review, the ability to use alternative analyses to address some of the trial design issues was limited.

Because the study was open-label, one could not entirely rule out bias due to providers and patients having knowledge of treatment assignment. Although DCRI readjudicators and statisticians were blinded to treatment assignment, the original open-label nature of the trial remained. During the trial, patients and caregivers knew which medications were being given.

The trial used a noninferiority design; concerns existed regarding factors that can reduce assay sensitivity with this design, including factors such as compliance with study medication, diagnostic criteria for endpoints, and the possibility of biased assessment of the endpoint. As mentioned above, alternative analyses using last date of randomized therapy may address this to some degree, but the concern remains.

The complexity of the adverse event reporting process was another design issue which the DCRI readjudication cannot address. However, this affects mortality analyses somewhat less than those for nonfatal events, as "dead or alive" is somewhat easier to determine.

Another issue was some expected asymmetry in the use of insulin between groups due to restrictions in Europe at the time of trial design on co-administration of insulin with RSG. To some extent, this issue was addressed by the analyses that used the last date of randomized treatment plus either 30 or 60 days.

IV.A.2. Concerns that Could be Addressed by the DCRI Review

IV.A.2.a. Allegations that There was Widespread Incorrect Interpretation of Adverse Events

During the original RECORD review process, assertions were made that numerous adverse events had been incorrectly interpreted, perhaps with bias in favor in rosiglitazone. This was one of the major factors that contributed to a lack of confidence in the trial's results. The DCRI readjudication analysis results, however, were highly similar to those from the original RECORD trial. There were some cases where a different conclusion was reached regarding specific cause of death, or whether there was sufficient information to determine exact cause of death. This is expected; indeed, it would be highly suspicious if perfect agreement occurred. Overall, however, the primary analysis and numerous secondary and sensitivity analyses had highly similar results to those from the original RECORD study report.

IV.A.2.b. Concern that a Large Percentage of Patients Were Not Taking Original Randomized Therapy at End of Study

As with the original study, this concern was addressed by DCRI using analyses utilizing last date of randomized therapy (see Tables III.A.3.c and III.A.4.c and accompanying discussion).

IV.A.2.c. Concerns Regarding Percentage of Patients Lost to Follow-Up, and Determination of Dates of Last Follow-Up

The DCRI process made a strong and concerted effort to identify the vital status of patients who were deemed to have incomplete follow-up, with DCRI using records that they obtained and the services of MediciGlobal. In this effort, they were quite successful. Initially, DCRI identified 604 patients for whom follow-up was deemed incomplete for one reason or another. At the end of their efforts, only 21 of these patients required imputation of a death date. For all 21 of these patients, the year of death was found, and for 11 out of these 21, documentation of month of death was also found. Thus, the only imputation required for death dates was for the month of death for ten patients.

As discussed earlier, DCRI addressed concerns regarding last date of follow-up by doing analyses using four different methods of defining last date of follow-up. All methods yielded highly similar results (See Tables III.D.6 and III.D.7 and accompanying discussion).

IV.A.2.d. Potential Effect of Publicity and the Published Interim Analysis

This was addressed by DCRI through their landmark analyses of mortality, by treatment group, before and after the interim publication (see Tables III.A.5.b.(1) and III.A.5.b.(2) and accompanying discussion).

IV.A.2.e. Underascertainment

The DCRI process attempted to address this by an extensive automated and manual triggering process, by record review, by requests for additional information from sites, and by use of MediciGlobal for additional patient follow-up. The triggering process identified many records for examination. Additional record requests and MediciGlobal efforts had limited success. At this point, several years out from the end of an international trial, it is unsurprising that little additional information appears to exist. In the end, eight additional deaths were identified that occurred before the trial cut-off; analyses using these deaths were highly similar to the original RECORD analyses.

IV.A.2.f. Inclusion of Deaths with Inadequate Data as Cardiovascular Deaths

This was addressed by examining cardiovascular death, excluding deaths due to unknown cause (see Table III.E.3).

IV.B. Strengths of the DCRI Readjudication

As discussed above, the DCRI readjudication process could address some limitations identified in the original RECORD review, and could not address others. There were several strengths to the DCRI readjudication process that are of note:

- Multiple meetings occurred between DCRI and the Agency to refine readjudication procedures. DCRI asked many questions and requested feedback multiple times in order to address as many concerns as possible.
- All procedures for the readjudication process were predefined, and no charter violations were noted.
- DCRI is highly experienced in clinical trial procedures and cardiovascular event adjudication.
- There were no GSK representatives on the CEC committee.
- Careful attention was paid to redaction of treatment assignments from records, and to blinding of adjudicators.
- In addition to being blinded to treatment assignment, adjudication reviewers were blinded to all glucose-lowering agents.
- Both electronic and manual triggers were used to identify potential events.
- Manual trigger procedures were extensive.
- Manual trigger procedures included review of all cases that were sent to the original RECORD Clinical Endpoints Committee, including endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator. There had been concern during the original RECORD review in this area, particularly about cases that were "deleted" by the investigator
- The numbers of triggered cases, and the sources of triggering, were similar between the RSG and MET/SU groups. The triggering process, which was extensive, did not identify evidence of systematic over- or under- identification of potential death events.
- A systematic effort was made to identify events that had been deleted by investigators, by reviewing the audit trails of the study's electronic datasets.
- Repeated efforts were made to obtain missing data.
- A separate contractor, MediciGlobal, was hired to track down patients who were lost to follow-up.
- Quality control checks were prespecified and conducted.

V. Summary

The Duke Clinical Research Institute has conducted a well-planned and comprehensive readjudication of the RECORD trial mortality data. Their analyses showed highly similar results for overall mortality, and separately for cardiovascular mortality, when compared to the original RECORD adjudication results. No treatment effect was demonstrated; point estimates for hazard ratios favored rosiglitazone and confidence intervals included 1. Numerous sensitivity analyses were conducted. As was noted in the original RECORD adjudication, there were numerically more heart failure deaths among RSG-treated patients than among MET/SU-treated patients (9 RSG heart failure deaths vs 1 with MET/SU). The number of deaths due to myocardial infarction was similar between treatment groups (8 RSG vs 12 MET/SU). There were no deaths due to stroke among

RSG-treated patients, and 6 deaths due to stroke among patients in the MET/SU comparator group.

This readjudication addressed a major concern raised during the original RECORD review, namely an allegation that there was widespread and potentially biased misinterpretation of adverse events. In general, analyses reached highly similar conclusions. As expected, readjudication did not reach the exact same conclusion as the original adjudication in every case. However, the differences were equally distributed between treatment groups, without evidence of systematic misclassification. Efforts were made to address several other concerns, including strong efforts at maximum ascertainment and follow-up. Some concerns related to trial design cannot be addressed by a readjudication effort.

Overall, the readjudication supports the previous observation that, in this trial, rosiglitazone was not associated with increased all-cause mortality or increased cardiovascular mortality.

In a site inspection at DCRI, the FDA Division of Scientific Investigations confirmed that readjudication procedures were followed as specified in the charter.

The review will now proceed to the blinded readjudication of major adverse cardiovascular events (MACE), which DCRI completed after their mortality readjudication effort.

Previously, a well-designed, large cardiovascular outcomes trial (TIDE) of the safety of rosiglitazone had been initiated, but was placed on clinical hold. In the end, the only way to answer the questions regarding the cardiovascular safety of rosiglitazone may be to resume this trial, or to design and execute a new cardiovascular outcomes trial. However, there are many potential difficulties with conducting such a trial, including the negative publicity surrounding rosiglitazone, the extremely low clinical use of the drug right now, the current restricted prescribing program, and the short remaining patent life of the innovator product.

VI. Reference

Home P et al 2007. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. NEJM 357:28-38

Endocrine Clinical Review
Blinded Readjudication of Major Adverse Cardiovascular Events
The Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes Trial (RECORD)
Readjudication by the Duke Clinical Research Institute

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8 May 2013

I. Introduction and Background

This document continues the review of a blinded readjudication, conducted by the Duke Clinical Research Institute (DCRI), of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes Trial (RECORD) trial. GlaxoSmithKline, the sponsor of Avandia®, has a postmarketing requirement to commission an independent blinded readjudication of the RECORD trial, due to concerns expressed about whether all cardiovascular events in that trial were properly captured and interpreted. This readjudication was to be conducted in two phases; mortality, followed by major adverse cardiovascular events. Please see the mortality phase review for further background discussion, a discussion of DCRI's methods, and results of the mortality review. This document includes review of the readjudication of major adverse cardiovascular events.

A significant focus of this review is an attempt to examine how the DCRI readjudication results can be used to address some of the concerns that arose during the 2010 review of RECORD. Please see Sections II.D and III for this discussion.

Dr. Preston Dunnmon is conducting a cardiology consult review, and Dr. Eugenio Andraca-Carrera is conducting a statistical review. Their reviews will be in separate documents.

The key specific objectives of the DCRI readjudication were:

- Systematic identification of all deaths, all suspected myocardial infarction (MI), and all suspected stroke events using all possible data sources while blinded to patient level treatment assignment.
- Standard preparation of all events for adjudication without filtering of suspected events by site or central personnel with knowledge or potential knowledge of patient level treatment assignment.
- Adjudication of all events using the original RECORD endpoint definitions and contemporary definitions under development by FDA (Standardized Data Collection for Cardiovascular Trials Initiative).
- Independent definition of study follow-up phases and derivation of dates last observed without event for patients who were not reported to die or experience MI or stroke.

- Statistical analysis of the mortality and nonfatal MI and nonfatal stroke outcomes by treatment assignment as well as a series of complementary analyses to evaluate and understand potential confounders and data limitations in the original analyses.

Extensive procedures were in place for database transfers, redaction of treatment assignment, redaction of concomitant diabetes medication, and readjudicator blinding. For the MACE phase of the readjudication process, these procedures are documented in the main body of the study report (beginning page 22), and in Appendix C (beginning page 431 of the study report). The report details the process, points in the process where problems were identified, and procedures followed to address problems. The clinical reviewer and the Office of Scientific Investigations have reviewed these procedures, and adherence to data integrity and blinding appears to have been stringent. In a process where many thousands of redactions of treatment assignment are needed, occasional misses are expected; indeed, a claim of perfect redaction would arouse suspicion. The DCRI had procedures in place to handle cases of missed redaction, and followed procedures well. Please see the review from the Division of Scientific Investigations for details. Across both the mortality and MACE readjudication processes, the Division of Scientific Investigation's inspection noted that procedures were followed well except for isolated cases of missed redaction; only one of these cases (a concomitant medication of insulin was not redacted) actually went to adjudication prior to the redaction error being noted. However, the originally designated readjudicator noted the missed concomitant insulin redaction, and returned the file; it was properly redacted and then sent for readjudication by a different readjudicator. In general, when adjudication occurs in a clinical trial, redaction occurs for the study drug and comparator, but often not for concomitant medications. However, in the DCRI readjudication process, a decision was made to redact all concomitant diabetes medication names as well. This was appropriate, because concomitant use of insulin was not permitted in the rosiglitazone arm, and thus, if an adjudicator saw a concomitant medication of insulin, it could result in unblinding. Conversely, nonredaction of other kinds of concomitant diabetes medications could also give some indication of treatment assignment, and thus the charter called for redaction of all diabetes medications.

Sources used by DCRI during the MACE readjudication included:
- original RECORD dataset
- original RECORD paper case report forms
- original RECORD serious adverse event forms
- source documents contained in the original RECORD event packets
- original RECORD review queries and query responses
- responses from GSK to DCRI Clinical Events Committee (CEC) queries
- responses from study sites to DCRI CEC queries
- electrocardiograms (ECGs) from study site files and ECG substudy files
- correspondence from GSK
- correspondence from MediciGlobal

II. Analyses of Major Adverse Cardiovascular Events

The original RECORD endpoint definitions, and the version of the definitions (draft Standardized Data Collection for Cardiovascular Trials Initiative) used for complementary analyses may be found in Appendices VI.B and VI.C below.

In general, when DCRI reported analyses using both the original RECORD definitions and the "new FDA" definitions, the clinical reviewer has presented those which used the original definitions, as these would be expected to allow the most comparability between the original adjudication and the DCRI readjudication. The clinical reviewer considered the analyses using the "new FDA" definitions to be exploratory. For a number of the complementary/exploratory analyses, DCRI presented only analysis results with the "new FDA" definitions rather than the original RECORD definitions; when that was the case, the "new FDA" definitions are included, and the review specifies this. The "new FDA" definitions, while not in use at the time RECORD was conducted, continue to be refined and are being used in new cardiovascular outcomes trials of diabetes drugs.

II.A. Summary of DCRI Findings

II.A.1. Results of Triggering Process

Please see the Methods section (section II) of the mortality readjudication review for a description of the sources used for programmatic and manual triggering for identification of potential MACEs. The table below summarizes the total numbers of triggers, and their sources, for myocardial infarctions (MIs) and strokes.

Table II.A.1: Triggers for Case Review for Myocardial Infarction and Stroke

		Myocardial Infarction			Stroke		
		Total (Total N = 4447)	**RSG (Total N = 2220)**	**MET/SU (Total N = 2227)**	**Total (Total N = 4447)**	**RSG (Total N = 2220)**	**MET/SU (Total N = 2227)**
All Triggered Cases	**Number of Patients Who Triggered for At Least One Event**	916/4447 (20.6%)	484/2220 (21.8%)	432/2227 (19.4%)	364/4447 (8.2%)	168/2220 (7.6%)	196/2227 (8.8%)
	Number of Patients Who Triggered for Only One Event[2]	589/916 (64.3%)	296/484 (61.2%)	293/432 (67.8%)	315/364 (86.5%)	150/168 (89.3%)	165/196 (84.2%)
	Number of Patients Who Triggered for Two or More Events[3]	327/916 (35.7%)	188/484 (38.8%)	139/432 (32.2%)	49/364 (13.5%)	18/168 (10.7%)	31/196 (15.8%)
	Total Number of Potential Events Triggered[4]	1477	813	664	423	193	230
Number of Cases Identified by Each	**Programmatic**	1428/1477 (96.7%)	792/813 (97.4%)	636/664 (95.8%)	395/423 (93.4%)	176/193 (91.2%)	219/230 (95.2%)

Table II.A.1: Triggers for Case Review for Myocardial Infarction and Stroke

		Myocardial Infarction			Stroke		
		Total (Total N = 4447)	**RSG (Total N = 2220)**	**MET/SU (Total N = 2227)**	**Total (Total N = 4447)**	**RSG (Total N = 2220)**	**MET/SU (Total N = 2227)**
Triggering Method[5]							
	Manual	49/1447 (3.3%)	21/813 (2.6%)	28/664 (4.2%)	28/423 (6.6%)	17/193 (8.8%)	11/230 (4.8%)
Sources of Programmatic Triggers[1]	**Adverse Event Form**	1407/1428 (98.5%)	778/792 (98.2%)	629/636 (98.9%)	391/395 (99.0%)	176/176 (100%)	215/219 (98.2%)
	Invasive Cardiovascular Procedure/ Amputation Endpoint Form	241/1428 (16.9%)	114/792 (14.4%)	127/636 (20.0%)	14/395 (3.5%)	2/176 (1.1%)	12/219 (5.5%)
Sources of Manual Triggers	**CRF**	25/49 (51.0%)	8/21 (38.1%)	17/28 (60.7%)	7/28 (25.0%)	4/17 (23.5%)	3/11 (27.3%)
	Source Documents	24/49 (49.0%)	13/21 (61.9%)	11/28 (39.3%)	21/28 (75.0%)	13/17 (76.5%)	8/11 (72.7%)

Sources: Sponsor's Table 1.1 (pg 106), 1.1a (pg 107), and 1.1b (pg 108), MACE readjudication report.
1 A patient could trigger from more than one source and could be counted in more than one row.
2 In the columns for myocardial infarction, this specifies the number of patients who had one, and no more than one, event review triggers for myocardial infarction. In the columns for stroke, this specifies the number of patients who had one, and no more than one, event review triggers for stroke.
3 In the columns for myocardial infarction, this specifies the number of patients who had two or more event review triggers for myocardial infarction. In the columns for stroke, this specifies the number of patients who had two or more event review triggers for stroke.
4 In the columns for myocardial infarction, this it the total number of potential MI events triggered, and in the stroke columns, this is the total number of potential stroke events triggered. A patient may have had more than one event triggered for review.
5 This denotes the percentage of the total number of triggered events that came from each triggering method (programmatic or manual). In each column, programmatic + manual = 100%. All events went to readjudication, whether triggered programmatically or manually.

Among all triggered events, the proportions of programmatic and manually triggered MIs and strokes appeared evenly distributed between RSG and MET/SU.

A total of 70 CEC queries were issued for MI and stroke events: 31 were closed with no response from the site; 20 were closed with a response from the site that no additional data were available; and 19 were closed with additional data received. Of these 19 with additional data received, only two resulted in a changed adjudication result: one from MI "yes" to "no", and one from MI "no" to "yes". The DCRI reported that efforts to obtain additional information were challenged by multiple factors, including closure of some research sites, lack of current Institutional Review Board approval, national regulations preventing additional follow-up, and the long period of time since the initial trial.

In all, a total of 1896 MI and stroke triggers were adjudicated per the process described in the charter (Appendix A of study report, beginning page 400 of study report, and beginning page 11 of charter). These procedures are summarized in the clinical review of the mortality phase.

Each event underwent a "Phase 1" review during which two physicians independently adjudicated the event using prespecified event criteria. Each event was reviewed using the original RECORD event classification criteria, and with new definitions based on the FDA's current efforts to develop standardized definitions for endpoint events in cardiovascular trials. If the reviewers agreed in their classification, the adjudication was considered complete. If they did not agree, the event went to "Phase 2" review.

In "Phase 2" review, an adjudication committee meeting was held with at least three faculty physicians. All areas of disagreement were discussed and a decision made by consensus of the Phase 2 panel.

All 1896 MI and stroke triggers went to Phase 1 review. Of these, 151 events required adjudication at a Phase 2 committee meeting.

II.A.2. Updated Information on Follow-up Time

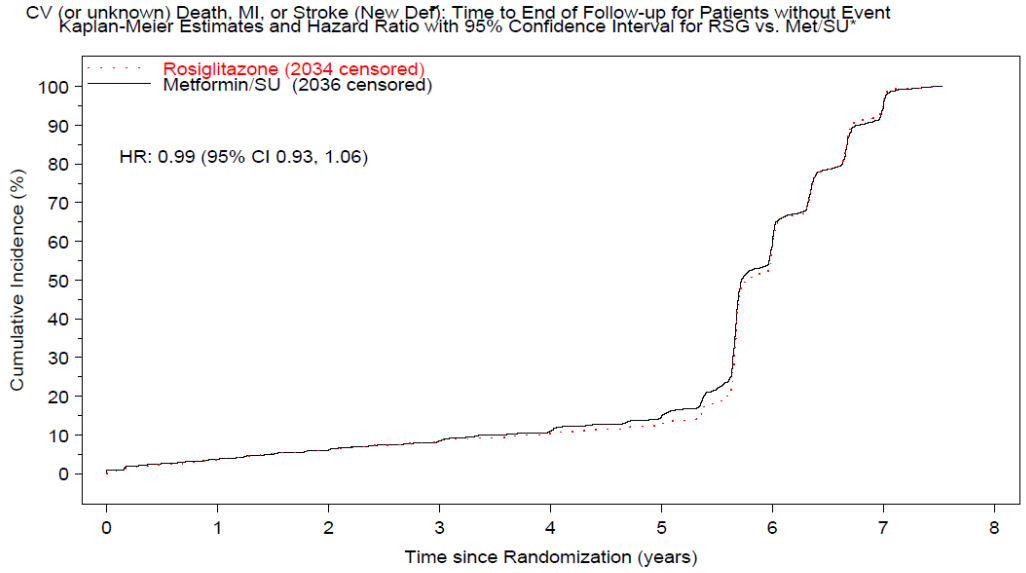
Please see the clinical review of the mortality phase for details of numbers and analyses of total mortality. After completion of the mortality report, DCRI continued to search for vital status and other information related to total mortality. MediciGlobal did not find any additional deaths which occurred before 31 Dec 2008. Additional information for one previously known death resulted in a change from the initial readjudication of cause of death as "unknown" to "cardiovascular". An additional 64 person-years of follow-up were obtained for a total of 24 patients. This additional information would not have changed the main results of the original DCRI mortality readjudication analyses. The following table is updated to reflect the slight changes related to this additional information.

Table II.A.2: Mean Years of Follow-Up and Percentage of Patients with Incomplete Follow-up Using Four Methods of Derivation of End of Follow-up				
Approach to Derivation of End of Follow-up	**Yrs of Follow-up**		**Patients With Incomplete Follow-up n (%)**	
	RSG Mean (SD)	MET/SU Mean (SD)	RSG n (%) N=2220	MET/SU n (%) N=2227
Parsimonious	5.5 (1.5)	5.4 (1.6)	308 (13.9)	349 (15.7)
Primary	5.8 (1.1)	5.8 (1.2)	74 (3.3)	102 (4.6)
Primary + Test and Event Dates	5.9 (1.1)	5.8 (1.2)	74 (3.3)	101 (4.5)
Primary + Test and Event Dates + Survival Status and Third Party Survival Data	5.9 (1.0)	5.8 (1.2)	44 (2.0)	73 (3.3)
Source: Sponsor's Table 2.1, pg 442, study report				

In the original RECORD study publication (Home 2009), mean follow-up duration was stated as 5.5 years, with a reported 12,338 person-years in the RSG group, and 12,272 person-years in the MET/SU group. In the DCRI readjudication process, follow-up duration for the composite of CV (or unknown cause) death, MI or stroke was 11,913 person-years for RSG and 11,808 for MET/SU (Table 2.1b, pg 119 of study report). In the DCRI report, derivation of follow-up period for MI and stroke was done similarly to that described in the mortality readjudication review, using the parsimonious approach. If a patient was determined to have at least one MI, the last follow-up date for that endpoint was the date of first occurrence of MI, and follow-up was considered uncensored. If a patient did not have an MI, follow-up for this endpoint was censored at the date of the last study visit at which any measurements (blood pressure, heart rate, or weight) were recorded on the VITALS module of the CRF. A similar approach was used for stroke. The rationale used for this parsimonious approach (rather than allowing follow-up to be documented by the presence of laboratory results, phone call records, reports of adverse events in the database, ECGs, third party survival status information, etc) was that, when there was not evidence that a patient was actually seen face-to-face, there may have been a greater chance for a nonfatal event to remain undetected. Thus, the total person-years were 3-4% lower using this parsimonious approach compared to that used in the original RECORD review, which included time to types of patient contact other than face-to-face visits. In the DCRI readjudication, total person-years of follow-up were similar between the RSG and MET/SU groups (<1% difference).

In order to assess the possibility of informative censoring by treatment arm, DCRI performed a Kaplan Meier analysis for time from randomization to end of follow-up for patients without an event of CV (or unknown cause) death, MI or stroke, and separately for the components of MI and stroke, using the "new FDA" definitions. The following figures depict those analyses.

Figure II.A.2.a:

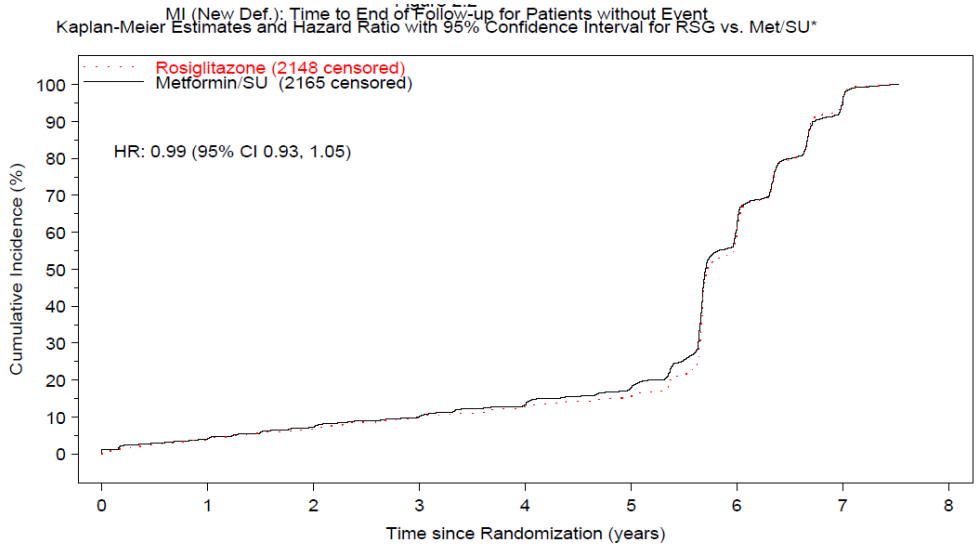


Rosaglitazone									
Censored	0	82	134	185	226	273	1200	1959	2034
At Risk	2220	2117	2041	1952	1872	1798	845	75	0
Metformin/SU									
Censored	0	83	134	183	238	314	1234	1950	2036
At Risk	2227	2118	2039	1955	1870	1752	807	86	0

* The Hazard Ratio describes the risk of censoring in the RSG arm relative to the MET/SU arm.
Generated from ct/record/graphs/phase2/q_followup_mace.sas on 22MAR2012 at 10:00

Source: Figure 2.1, pg 128, study report

Figure II.A.2.b:

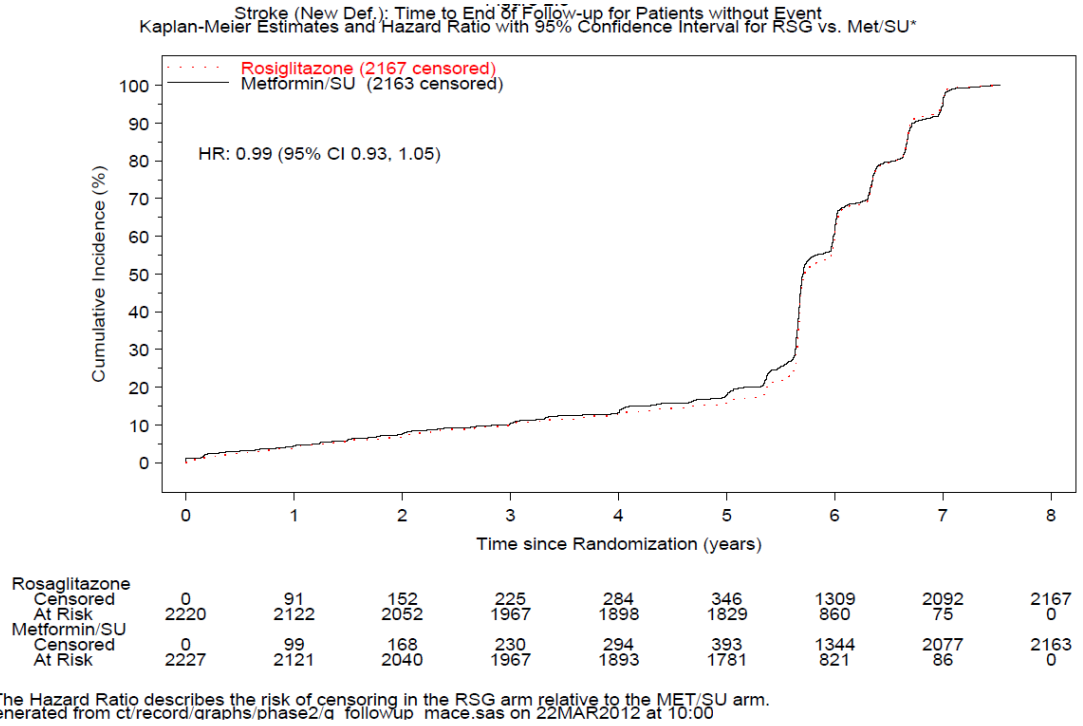


Rosaglitazone									
Censored	0	91	149	220	279	341	1294	2072	2148
At Risk	2220	2119	2049	1963	1888	1817	855	76	0
Metformin/SU									
Censored	0	93	162	225	292	390	1344	2079	2165
At Risk	2227	2117	2041	1968	1891	1781	822	86	0

* The Hazard Ratio describes the risk of censoring in the RSG arm relative to the MET/SU arm.
Generated from ct/record/graphs/phase2/q_followup_mace.sas on 22MAR2012 at 10:00

Source: Figure 2.2, pg 129, study report

Figure II.A.2.c:



Source: Figure 2.3, pg 130, study report

In each of these figures, time to censoring is similar between RSG and comparator. Between 4.25 and 5.75 years, there is slight separation; this may be related to the possibility for RSG patients to add a third oral agent in the event of loss of glycemic control, while MET/SU patients did not have this option. These figures are not suggestive of informative censoring, but cannot completely demonstrate its absence.

MediciGlobal attempted to find additional information on 127 patients previously identified by GSK as having had unknown vital status at end of study. Of these 127 patients, two were determined to have died, 38 were confirmed alive at end of study, and for 87 patients, no additional vital status information was obtained. For those 87 patients for whom MediciGlobal could not obtain vital status information, DCRI determined last date of follow-up. In 38 cases, the DCRI last date of follow-up was the same as the original GSK date; in 46 cases, DCRI dates were prior to GSK dates, and in 3 cases, DCRI dates were after GSK dates.

II.A.3. Analysis of Major Adverse Cardiovascular Events Endpoint (Cardiovascular or Unknown Cause Mortality; Myocardial Infarction; or Stroke)

The DCRI readjudication using the original RECORD event definitions did not demonstrate a difference between RSG and MET/SU for the primary endpoint (cardiovascular or unknown cause mortality; myocardial infarction; or stroke), as displayed in the following table:

Table II.A.3.a: Cardiovascular (or Unknown Cause) Mortality, Myocardial Infarction, or Stroke, DCRI Readjudication Using Original RECORD Event Definitions		
	RSG N=2220 PY=11913	**MET/SU N=2227 PY=11808**
n (%)	181 (8.2%)	188 (8.4%)
Rate per 100 PY (95% CI)	1.52 (1.29, 1.75)	1.59 (1.36, 1.82)
Hazard Ratio (95% CI)	0.95 (0.78, 1.17)	
Absolute Rate Difference per 100 PY	-0.07 (-0.40, 0.25)	
Source: Table 8.1, pg 163, study report		

Results using the "new FDA" definitions were highly similar, with a hazard ratio of 0.97 (95% CI 0.79, 1.18) and an absolute rate difference per 100 PY of -0.05 (-0.38, 0.27) (Source: Table 3.1, pg 131, study report).

Explorations for subgroup interactions were reported. When using either the original RECORD definitions or the "new FDA" definitions, there was an interaction between treatment and use of baseline statins (interaction p = 0.034 using original definitions; source Figure 8.3b, pg 168, study report). For the subgroup using baseline statins, the hazard ratio was 1.59 (95% CI 0.95, 2.67), and for the subgroup not using statins at baseline, the HR was 0.86 (0.69, 1.08). There was evidence of a modest, statistically nonsignificant interaction by duration of diabetes, favoring rosiglitazone among patients who had had diabetes for ≥ 6 years (interaction p = 0.090; source Figure 8.3a, pg 167, study report). Within the subgroup defined by <6 years of diabetes, the hazard ratio was 1.17 (95% CI 0.86, 1.60), while for patients with ≥6 years of diabetes, the hazard ratio was 0.82 (0.62, 1.08). This interaction was seen only when using the original RECORD definitions, but not when using the "new FDA" definitions. There was no evidence of an interaction by the following subgroup characteristics: gender; age < or ≥ age 60 years; BMI; baseline HbA1c categories (<7.4%, 7.4-<7.8%, 7.8-<8.4%, ≥ 8.4%); history of prior heart disease; background stratum (MET or SU); country; or baseline use of ACEI, nitrates or beta blockers.

A sensitivity analysis was conducted to explore the impact of inclusion of deaths due to unknown cause. The following table shows an analysis without deaths due to unknown cause:

Table II.A.3.b: Cardiovascular Mortality (Excluding Deaths Due to Unknown Cause), Myocardial Infarction, or Stroke, DCRI Readjudication Using "New FDA"[1] Event Definitions		
	RSG N=2220 PY=11840	**MET/SU N=2227 PY=11746**
n (%)	143 (6.4%)	142 (6.4%)
Rate per 100 PY (95% CI)	1.21 (1.00, 1.41)	1.21 (1.01, 1.41)
Hazard Ratio (95% CI)	1.00 (0.79, 1.26)	
Absolute Rate Difference per 100 PY	-0.00 (-0.29, 0.28)	
Source: Table 23.1, pg 253, study report **1 DCRI used "new FDA" event definitions for sensitivity analyses**		

Results were similar when either including or excluding deaths due to unknown cause.

During the review process for the original RECORD submission, discussion occurred regarding the noninferiority design of the trial, and whether an "intention-to-treat" (ITT) or "as-treated" approach was more appropriate. Some advocated an "as-treated" approach, using only time on randomized therapy, rather than the ITT approach that had been prespecified for the primary analysis. These types of analyses can also perhaps address, to some extent, the concern regarding somewhat earlier withdrawal rates for rosiglitazone patients due to the inability to add insulin as a concomitant medication in the rosiglitazone arm, while being able to add insulin in the comparator arm (see Figures II.A.2.a, II.A.2.b, and II.A.2.c, and accompanying discussion).

For the DCRI readjudication, analyses were performed using last date of randomized treatment, plus either 30 or 60 days. These analyses are displayed in the following table.

Table II.A.3.c: Cardiovascular (or Unknown Cause) Mortality, Myocardial Infarction, or Stroke, on Randomized Treatment, Plus Either 30 or 60 Days				
	LDRT Plus 30 Days		**LDRT Plus 60 Days**	
	RSG N=2220 PY=10662	**MET/SU N=2227 PY=10080**	**RSG N=2220 PY=10707**	**MET/SU N=2227 PY=10140**
Number of patients with endpoint (%)	128 (5.8%)	129 (5.8%)	135 (6.1%)	133 (6.0%)
Rate per 100 PY (95% CI)	1.20 (0.99, 1.41)	1.28 (1.05, 1.51)	1.26 (1.04, 1.48)	1.31 (1.08, 1.54)
Hazard ratio (95% CI)	0.94 (0.73, 1.20)		0.96 (0.76, 1.22)	
Absolute rate difference per 100 PY (95% CI)	-0.08 (-0.39, 0.23)		-0.05 (-0.36, 0.26)	
Source: Sponsor's Tables 13.1 (pg 195) and 18.1 (pg 224), study report **LDRT = last day of randomized treatment**				

Results were similar by these censoring methods.

For analyses using LDRT + 30 days, and LDRT + 60 days, there was no evidence of a treatment interaction by background therapy, demographics or disease characteristics.

II.A.4. Analysis of Myocardial Infarction Events

The DCRI readjudication using the original RECORD event definitions did not demonstrate a significant difference between RSG and MET/SU for the endpoint of fatal and nonfatal myocardial infarction, although the point estimate for the hazard ratio was >1, as displayed in the following table:

Table II.A.4.a: Fatal and Nonfatal Myocardial Infarction, DCRI Readjudication Using Original RECORD Event Definitions

	RSG N=2220 PY=11965	**MET/SU N=2227 PY=11882**
n (%)	68 (3.1%)	60 (2.7%)
Rate per 100 PY (95% CI)	0.57 (0.43, 0.71)	0.50 (0.37, 0.64)
Hazard Ratio (95% CI)	1.13 (0.80, 1.59)	
Absolute Rate Difference per 100 PY	0.06 (-0.13, 0.25)	
Source: Table 9.1, pg 171, study report		

Results using the "new FDA" definitions were highly similar, with a hazard ratio of 1.15 (95% CI 0.82, 1.62) and an absolute rate difference per 100 PY of 0.08 (-0.12, 0.28) (Source: Table 4.1, pg 139, study report).

There was no evidence of a treatment interaction by any of the tested subgroups.

Nonfatal myocardial infarction was also analyzed, and also showed no significant difference between RSG and MET/SU, although the point estimate for the hazard ratio exceeded 1, as displayed in the following table:

Table II.A.4.b: Nonfatal Myocardial Infarction, DCRI Readjudication Using Original RECORD Event Definitions

	RSG N=2220 PY=11962	**MET/SU N=2227 PY=11880**
n (%)	62 (2.8%)	49 (2.2%)
Rate per 100 PY (95% CI)	0.52 (0.38, 0.65)	0.41 (0.29, 0.53)
Hazard Ratio (95% CI)	1.26 (0.86, 1.83)	
Absolute Rate Difference per 100 PY	0.11 (-0.07, 0.28)	
Source: Table 10.1, pg 179, study report		

Results using the "new FDA" definitions were highly similar, with a hazard ratio of 1.29 (95% CI 0.89, 1.85) and an absolute rate difference per 100 PY of 0.12 (-0.06, 0.31) (Source: Table 5.1, pg 147, study report).

In examining the above two tables, it appears that the numerical difference between RSG and MET/SU regarding myocardial infarction lay in nonfatal events, rather than fatal events, although the number of fatal events was too small to make definitive conclusions. The total number of fatal events contributing to the "fatal + nonfatal" endpoint was 6 events for RSG and 11 events for MET/SU, using the original RECORD definitions. Thus, there was not evidence of an excess of fatal myocardial infarctions contributing to this analysis, which was an analysis to first event of myocardial infarction.

Derivation of the follow-up period for myocardial infarction was done similarly to the derivation of the "parsimonious" approach to survival follow-up, described in the review of the mortality phase. If a patient was determined to have at least one MI, the last follow-up date for this endpoint was the date of the first occurrence of MI, and follow-up was considered uncensored. If a patient did not have an MI, follow-up was censored at the date of the last study visit at which any vital signs measurement (blood pressure, heart rate or weight) were recorded on the VITALS module of the CRF. The rationale for this approach was that after the last study visit with measurements recorded on the VITALS module, patients were not periodically assessed face-to-face, and there may have been a greater chance for a nonfatal event to remain undetected.

When sufficient data were available, the DCRI readjudication assessed whether MIs had ST segment elevation (STEMI vs non-STEMI), and whether Q-waves were present. The following table displays those results:

Table II.A.4.c: Classification of Myocardial Infarctions by ST Segment Elevation and Presence of Q-Waves (All Myocardial Infarctions), "New FDA" Definitions

Classification	Category	RSG N=2220 MIs Orig Def: 76 MIs "New FDA" Def: 84 n/# with specified ECG parameter (%)	MET/SU N=2227 MIs Orig Def: 61 MIs "New FDA" Def: 67 n/# with specified ECG parameter (%)
ST Segment Elevation	**STEMI**	18/83 (21.7%)	17/67 (25.4%)
	Non-STEMI	27/83 (32.5%)	20/67 (29.9%)
	ST Classification Unknown	38/83 (45.8%)	30/67 (44.8%)
Q-Wave	**Q-Wave**	12/83 (14.5%)	9/67 (13.4%)
	Non-Q-Wave	23/83 (27.7%)	11/67 (16.4%)
	Q-Wave Classification Unknown	48/83 (57.8%)	47/67 (70.1%)

Source: Table 1.3a, pg 112, study report
Abbreviations: ECG = electrocardiogram; MET = metformin; Orig = original STEMI = ST segment elevation myocardial infarction; SU = sulfonylurea

Table II.A.4.d: Classification of Myocardial Infarctions by ST Segment Elevation and Presence of Q-Waves (Nonfatal Myocardial Infarctions), "New FDA" Definitions

Classification	Category	RSG N=2220 MIs Orig Def: 71 MIs "New FDA" Def: 75 n/# with specified ECG parameter (%)	MET/SU N=2227 MIs Orig Def: 53 MIs "New FDA" Def: 56 n/# with specified ECG parameter (%)
ST Segment Elevation	**STEMI**	16/75 (21.3%)	16/56 (28.6%)
	Non-STEMI	26/75 (34.7%)	17/56 (30.4%)
	ST Classification Unknown	33/75 (44.0%)	23/56 (41.1%)
Q-Wave	**Q-Wave**	12/75 (16.0%)	8/56 (14.3%)
	Non-Q-Wave	23/75 (30.7%)	10/56 (17.9%)
	Q-Wave Classification Unknown	40/75 (53.3%)	38/56 (67.9%)

Source: Table 1.3b, pg 113, study report
Abbreviations: ECG = electrocardiogram; MET = metformin; Orig = original STEMI = ST segment elevation myocardial infarction; SU = sulfonylurea

In the above tables, for events where Q-wave classification was available, the percentage of MIs that were Q-wave was equal between the RSG and MET/SU groups. The percentage of MIs that were non-Q-wave was numerically higher for the RSG group than for the MET/SU group (all MI 27.7% RSG, 16.4% MET/SU; nonfatal 30.7% RSG, 17.9% MET/SU). The percentage of MIs that were Q-wave was equal between the RSG and MET/SU groups. Extrapolating from the above two tables, there were a total of 8 fatal MIs in the RSG group and 11 fatal MIs in the MET/SU group, using the "New FDA" definitions. It appears that all 8 fatal RSG MIs were among patients for whom Q-wave classification was not available. It appears that for MET/SU, one fatal MI was known to be a Q-wave MI, one fatal MI was known to be a non-Q-wave MI, and for 9 fatal MIs, the Q-wave classification was unknown. Overall, the number of cases for which Q-wave classification was unavailable limits the interpretability of this observation.

There were a total of 14 MIs that were included in the DCRI analysis of MI, and had not been included in the original RECORD analyses. A total of six of these events were in patients who had myocardial infarction listed as cause of death, but who had not been hospitalized. Per the original RECORD protocol, these patients were counted as MI deaths, but were not counted in the MI analyses, because the protocol had specified that only MIs that included a hospitalization were to be included. In the DCRI analyses, these six patients were counted in the MI survival analysis, but were not counted as patients with confirmed MIs, because their only evidence of MI was a listing of MI as cause of death. Inclusion of these events resulted in similar analysis results.

Analyses were performed using the last day of randomized therapy plus either 60 or 90 days, as displayed in the following table:

Table II.A.4.e: Fatal or Nonfatal Myocardial Infarction on Randomized Treatment, Plus Either 30 or 60 Days

	LDRT Plus 30 Days		LDRT Plus 60 Days	
	RSG N=2220 PY=10756	**MET/SU N=2227 PY=10156**	**RSG N=2220 PY=10800**	**MET/SU N=2227 PY=10216**
Number of patients with endpoint (%)	63 (2.8%)	51 (2.3%)	64 (2.9%)	52 (2.3%)
Rate per 100 PY (95% CI)	0.59 (0.44, 0.74)	0.50 (0.36, 0.65)	0.59 (0.44, 0.74)	0.51 (0.37, 0.65)
Hazard ratio (95% CI)	1.17 (0.81, 1.70)		1.17 (0.81, 1.69)	
Absolute rate difference per 100 PY (95% CI)	0.08 (-0.12, 0.29)		0.08 (-0.12, 0.29)	

Source: Sponsor's Tables 14.1 (pg 202) and 19.1 (pg 231), study report
LDRT = last day of randomized treatment

Table II.A.4.f: Nonfatal Myocardial Infarction on Randomized Treatment, Plus Either 30 or 60 Days

	LDRT Plus 30 Days		LDRT Plus 60 Days	
	RSG N=2220 PY=10755	**MET/SU N=2227 PY=10155**	**RSG N=2220 PY=10800**	**MET/SU N=2227 PY=10215**
Number of patients with endpoint (%)	60 (2.7%)	42 (1.9%)	61 (2.7%)	43 (1.9%)
Rate per 100 PY (95% CI)	0.56 (0.41, 0.70)	0.41 (0.28, 0.54)	0.56 (0.42, 0.71)	0.42 (0.29, 0.55)
Hazard ratio (95% CI)	1.35 (0.91, 2.01)		1.35 (0.91, 1.99)	
Absolute rate difference per 100 PY (95% CI)	0.14 (-0.05, 0.34)		0.14 (-0.05, 0.34)	

Source: Sponsor's Tables 15.1 (pg 209) and 20.1 (pg 238), study report
LDRT = last day of randomized treatment

Results were similar by these censoring methods. As with censoring by LDRT, there were fewer fatal myocardial infarctions contributing to the RSG group than to the MET/SU group (3 RSG vs 9 MET/SU at both LDRT + 30 and + 60 days). There was no evidence of a treatment interaction by background therapy, demographics or disease characteristics.

II.A. 5. Analysis of Stroke Events

The DCRI readjudication using the original RECORD event definitions did not demonstrate a difference between RSG and MET/SU for stroke. The point estimate for the hazard ratio was <1, as displayed in the following table:

Table II.A.5.a: Fatal or Nonfatal Stroke, DCRI Readjudication Using Original RECORD Event Definitions

	RSG N=2220 PY=12009	**MET/SU N=2227 PY=11882**
n (%)	50 (2.3%)	63 (2.8%)
Rate per 100 PY (95% CI)	0.42 (0.30, 0.54)	0.53 (0.39, 0.67)
Hazard Ratio (95% CI)	0.79 (0.54, 1.14)	
Absolute Rate Difference per 100 PY	-0.11 (-0.29, 0.07)	
Source: Table 11.1, pg 183, study report		

Results using the "new FDA" definitions were highly similar, with a hazard ratio of 0.82 (95% CI 0.57, 1.18) and an absolute rate difference per 100 PY of -0.10 (-0.28, 0.09) (Source: Table 6.1, pg 151, study report).

There was evidence of a modest interaction by duration of diabetes, favoring rosiglitazone among patients who had had diabetes for ≥ 6 years (interaction p = 0.063). Within the subgroup defined by <6 years of diabetes, the hazard ratio was 1.16 (95% CI 0.67, 2.01), while for patients with ≥6 years of diabetes, the hazard ratio was 0.56 (0.34, 0.95) (Source: Figure 11.3a, pg 187, study report). This interaction was also noted when using the "new FDA" definitions. There was no evidence of an interaction by any other subgroup classification.

Analysis of nonfatal stroke was also performed, and also demonstrated no difference between RSG and MET/SU, with the point estimate for the hazard ratio <1, as displayed in the following table:

Table II.A.5.b: Nonfatal Stroke, DCRI Readjudication Using Original RECORD Event Definitions

	RSG N=2220 PY=12009	**MET/SU N=2227 PY=11879**
n (%)	50 (2.3%)	57 (2.6%)
Rate per 100 PY (95% CI)	0.42 (0.30, 0.54)	0.48 (0.35, 0.61)
Hazard Ratio (95% CI)	0.87 (0.59, 1.27)	
Absolute Rate Difference per 100 PY	-0.06 (-0.24, 0.11)	
Source: Table 12.1, pg 191, study report		

Of note when comparing the two tables above is that none of the strokes which contributed to the RSG group estimates were fatal strokes, while five contributing strokes in the MET/SU group were fatal.

Derivation of the follow-up period for stroke was done similarly to the derivation of the "parsimonious" approach to survival follow-up, described in the review of the mortality phase. If a patient was determined to have at least one stroke, the last follow-up date for this endpoint was the date of the first occurrence of stroke, and follow-up was considered uncensored. If a patient did not have a stroke, follow-up was censored at the date of the last study visit at which any vital signs measurement (blood pressure, heart rate or weight) were recorded on the VITALS module of the CRF. The rationale for this approach was that after the last study visit with measurements recorded on the VITALS module, patients were not periodically assessed face-to-face, and there may have been a greater chance for a nonfatal event to remain undetected.

Table II.A.5.c: Fatal or Nonfatal Stroke on Randomized Treatment, Plus Either 30 or 60 Days

	LDRT Plus 30 Days		LDRT Plus 60 Days	
	RSG N=2220 PY=10772	**MET/SU N=2227 PY=10156**	**RSG N=2220 PY=10818**	**MET/SU N=2227 PY=10217**
Number of patients with endpoint (%)	42 (1.9%)	52 (2.3%)	42 (1.9%)	54 (2.4%)
Rate per 100 PY (95% CI)	0.39 (0.27, 0.51)	0.51 (0.37, 0.66)	0.39 (0.27, 0.51)	0.53 (0.38, 0.67)
Hazard ratio (95% CI)	0.76 (0.51, 1.14)		0.74 (0.49, 1.10)	
Absolute rate difference per 100 PY (95% CI)	-0.12 (-0.31, 0.07)		-0.14 (-0.33, 0.05)	

Source: Sponsor's Tables 16.1 (pg 213) and 21.1 (pg 242), study report
LDRT = last day of randomized treatment

Table II.A.5.d: Nonfatal Stroke on Randomized Treatment, Plus Either 30 or 60 Days

	LDRT Plus 30 Days		LDRT Plus 60 Days	
	RSG N=2220 PY=10772	**MET/SU N=2227 PY=10156**	**RSG N=2220 PY=10818**	**MET/SU N=2227 PY=10216**
Number of patients with endpoint (%)	42 (1.9%)	50 (2.2%)	42 (1.9%)	52 (2.3%)
Rate per 100 PY (95% CI)	0.39 (0.27, 0.51)	0.49 (0.35, 0.63)	0.39 (0.27, 0.51)	0.51 (0.37, 0.65)
Hazard ratio (95% CI)	0.79 (0.53, 1.19)		0.76 (0.51, 1.15)	
Absolute rate difference per 100 PY (95% CI)	-0.10 (-0.29, 0.08)		-0.12 (-0.31, 0.07)	

Source: Sponsor's Tables 17.1 (pg 220) and 22.1 (pg 249), study report
LDRT = last day of randomized treatment

Results were similar by this censoring method.

In subgroup analyses for both LDRT + 30 days and + 60 days, for fatal + nonfatal stroke, there was a treatment-by-subgroup interaction for duration of diabetes, favoring RSG among patients with diabetes for ≥ 6 years (interaction p = 0.020). No other demographic or disease characteristic showed evidence of treatment interaction.

II.B. "Landmark" and Sensitivity Analyses

Several additional analyses were conducted, including "landmark" analyses to explore the effect of a major protocol amendment and an interim publication; additional composites; and explorations regarding unobserved follow-up.

II.B.1. Impact of Amendment 7 of the Original RECORD Protocol

Amendment 7 (dated 27 Feb 2006) of the original RECORD protocol instituted a tracking substudy to collect endpoint data from withdrawn patients who consented to enter the tracking substudy. To assess the impact of this amendment, DCRI conducted landmark analyses prior to and after Amendment 7, as summarized in the following tables.

Table II.B.1.a: Impact of Amendment 7: MACE Before and After 27 Feb 2006 (Date of Amendment 7)

	Before 27 Feb 2006		**After 27 Feb 2006**	
	RSG N=2220 PY=7049	**MET/SU N=2227 PY=7045**	**RSG N=2220 PY=4833**	**MET/SU N=2227 PY=4743**
Number of patients with endpoint (%)	102/2220 (4.6%)	105/2227 (4.7%)	84/1919 (4.4%)	86/1913 (4.5%)
Rate per 100 PY (95% CI)	1.45 (1.16, 1.73)	1.49 (1.20, 1.78)	1.74 (1.36, 2.11)	1.81 (1.42, 2.20)
Hazard ratio (95% CI)	0.97 (0.74, 1.28)		0.96 (0.71, 1.29)	
Absolute rate difference per 100 PY (95% CI)	-0.04 (-0.45, 0.36)		-0.08 (-0.61, 0.46)	

Source: Tables 29.1, pg 271, and 30.1, pg 274, study report

Hazard ratios were similar prior to and after Amendment 7.

Table II.B.1.b: Impact of Amendment 7: Fatal or Nonfatal Myocardial Infarction Before and After 27 Feb 2006 (Date of Amendment 7)				
	Before 27 Feb 2006		**After 27 Feb 2006**	
	RSG N=2220 PY=7079	**MET/SU N=2227 PY=7069**	**RSG N=2220 PY=4879**	**MET/SU N=2227 PY=4808**
Number of patients with endpoint (%)	45/2220 (2.0%)	39/2227 (1.8%)	27/1934 (1.4%)	23/1930 (1.2%)
Rate per 100 PY (95% CI)	0.64 (0.46, 0.83)	0.55 (0.37, 0.73)	0.55 (0.34, 0.77)	0.48 (0.28, 0.68)
Hazard ratio (95% CI)	1.15 (0.75, 1.77)		1.16 (0.67, 2.02)	
Absolute rate difference per 100 PY (95% CI)	0.08 (-0.17, 0.34)		0.07 (-0.22, 0.37)	
Source: Tables 31.1, pg 277 and 32.1, pg 280, study report				

Hazard ratios were similar prior to and after Amendment 7.

Table II.B.1.c: Impact of Amendment 7: Stroke Before and After 27 Feb 2006 (Date of Amendment 7)				
	Before 27 Feb 2006		**After 27 Feb 2006**	
	RSG N=2220 PY=7093	**MET/SU N=2227 PY=7072**	**RSG N=2220 PY=4910**	**MET/SU N=2227 PY=4811**
Number of patients with endpoint (%)	31/2220 (1.4%)	35/2227 (1.6%)	22/1942 (1.1%)	29/1930 (1.5%)
Rate per 100 PY (95% CI)	0.44 (0.28, 0.60)	0.49 (0.33, 0.66)	0.45 (0.26, 0.64)	0.60 (0.38, 0.83)
Hazard ratio (95% CI)	0.89 (0.55, 1.44)		0.74 (0.43, 1.30)	
Absolute rate difference per 100 PY (95% CI)	-0.06 (-0.29, 0.17)		-0.15 (-0.45, 0.14)	
Source: Tables 33.1 (pg 283) and 34.1 (pg 286), study report				

After Amendment 7, the point estimate for the hazard ratio for stroke was somewhat lower, but not significantly so.

II.B.2 Impact of Published Interim Report

On June 5, 2007, an interim report of the RECORD trial was published. For the readjudication, DCRI performed analyses for the time period before and after the interim publication.

Table II.B.2.a: Impact of Interim Analysis Publication: MACE Before and After 5 Jun 2007 (Date of Interim Publication)				
	Before 5 Jun 2007		**After 5 Jun 2007**	
	RSG N=2220 PY=9410	**MET/SU N=2227 PY=9397**	**RSG N=2220 PY= 2466**	**MET/SU N=2227 PY=2391**
Number of patients with endpoint (%)	142/2220 (6.4%)	150/2227 (6.7%)	44/1817 (2.4%)	41/1782 (2.3%)
Rate per 100 PY (95% CI)	1.51 (1.26, 1.76)	1.60 (1.34, 1.86)	1.78 (1.25, 2.32)	1.71 (1.19, 2.24)
Hazard ratio (95% CI)	0.95 (0.75, 1.19)		1.04 (0.68, 1.59)	
Absolute rate difference per 100 PY (95% CI)	-0.09 (-0.45, 0.27)		0.07 (-0.68, 0.82)	
Source: Tables 35.1 (pg 289) and 36.1 (pg 292), study report				

Hazard ratios were similar prior to and after the interim publication.

Table II.B.2.b: Impact of Interim Analysis Publication: Fatal or Nonfatal Myocardial Infarction Before and After 5 Jun 2007 (Date of Interim Publication)				
	Before 5 Jun 2007		**After 5 Jun 2007**	
	RSG N=2220 PY=9465	**MET/SU N=2227 PY=9446**	**RSG N=2220 PY=2493**	**MET/SU N=2227 PY=2432**
Number of patients with endpoint (%)	59/2220 (2.7%)	53/2227 (2.4%)	13/1834 (0.7%)	9/1805 (0.5%)
Rate per 100 PY (95% CI)	0.62 (0.46, 0.79)	0.56 (0.41, 0.72)	0.52 (0.23, 0.81)	0.37 (0.12, 0.62)
Hazard ratio (95% CI)	1.11 (0.77, 1.61)		1.42 (0.60, 3.31)	
Absolute rate difference per 100 PY (95% CI)	0.06 (-0.16, 0.29)		0.15 (-0.23, 0.53)	
Source: Tables 37.1 (pg 295) and 38.1 (pg 298), study report				

The hazard ratio was slightly numerically, but not significantly, higher after the interim publication. It is possible that there was stimulated reporting of events in the RSG arm after the large amount of negative publicity regarding rosiglitazone at the time. It is perhaps noteworthy that this observation does not suggest a fraudulent attempt (as has been alleged by some) to suppress event-reporting for RSG-treated patients after the interim publication.

Table II.B.2.c: Impact of Interim Analysis Publication: Stroke Before and After 5 Jun 2007 (Date of Interim Publication)				
	Before 5 Jun 2007		**After 5 Jun 2007**	
	RSG N=2220 PY=9493	**MET/SU N=2227 PY=9449**	**RSG N=2220 PY=2510**	**MET/SU N=2227 PY=2434**
Number of patients with endpoint (%)	45/2220 (2.0%)	49/2227 (2.2%)	8/1845 (0.4%)	15/1809 (0.8%)
Rate per 100 PY (95% CI)	0.47 (0.33, 0.62)	0.52 (0.37, 0.67)	0.32 (0.09, 0.54)	0.62 (0.30, 0.93)
Hazard ratio (95% CI)	0.92 (0.61, 1.37)		0.52 (0.22, 1.23)	
Absolute rate difference per 100 PY (95% CI)	-0.04 (-0.25, 0.16)		-0.30 (-0.88, 0.09)	
Source: Tables 39.1 (pg 301) and 40.1 (pg 304), study report				

Few stroke events occurred in either group after the interim publication, limiting interpretation of the analysis. The hazard ratio remained <1, with a statistically nonsignificant difference between treatment groups.

As was noted in the original RECORD review, the incidence and rate per 100 PY of events for MACE and its components were somewhat lower in both groups after interim, without a difference between treatment groups, for MACE and its components. The reason for this difference was not entirely clear, but a possible contributing factor was an increased rate of withdrawal (without a primary event) in both treatment groups after the interim publication. Prior to the interim publication, withdrawal without a primary event occurred at a rate of 1.9 withdrawals per 100 PY, while after the interim publication, the rate was 2.5/100 PY.

II.B.3 All-Cause Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke

Table II.B.3: All-Cause Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		
	RSG N=2220 PY=11910	**MET/SU N=2227 PY=11820**
n (%)	235 (10.6%)	252 (11.3%)
Rate per 100 PY (95% CI)	1.97 (1.72, 2.23)	2.13 (1.86, 2.40)
Hazard Ratio (95% CI)	0.93 (0.77, 1.11)	
Absolute Rate Difference per 100 PY	-0.16 (-0.53, 0.21)	
Source: Table 44.1, pg 316, study report		

The point estimate for the hazard ratio for this composite was similar to that for the primary composite, which included cardiovascular (or unknown cause) mortality instead of all-cause mortality.

II.B.4 Cardiovascular (or Unknown Cause) Mortality or Nonfatal Myocardial Infarction

Table II.B.4: Cardiovascular (or Unknown Cause) Mortality or Nonfatal Myocardial Infarction		
	RSG N=2220 PY=12018	**MET/SU N=2227 PY=11940**
n (%)	142 (6.4%)	140 (6.3%)
Rate per 100 PY (95% CI)	1.18 (0.98, 1.38)	1.17 (0.97, 1.37)
Hazard Ratio (95% CI)	1.01 (0.80, 1.27)	
Absolute Rate Difference per 100 PY	0.01 (-0.27, 0.29)	
Source: Table 45.1, pg 319, study report		

Because cardiovascular (or unknown cause) mortality was numerically lower in the RSG group, the composite with myocardial infarction had a lower point estimate for the hazard ratio than that seen for myocardial infarction alone, and the difference between treatment groups remained nonsignificant.

II.B.5 All-Cause Mortality or Nonfatal Myocardial Infarction

Table II.B.5: All-Cause Mortality or Nonfatal Myocardial Infarction		
	RSG N=2220 PY=12037	**MET/SU N=2227 PY=11963**
n (%)	193 (8.7%)	203 (9.1%)
Rate per 100 PY (95% CI)	1.60 (1.37, 1.83)	1.70 (1.46, 1.94)
Hazard Ratio (95% CI)	0.94 (0.77, 1.15)	
Absolute Rate Difference per 100 PY	-0.09 (-0.42, 0.24)	
Source: Table 46.1 (pg 322), study report		

Because all-cause mortality was numerically lower in the RSG group, the composite with myocardial infarction had a lower point estimate (now <1) for the hazard ratio than that seen for myocardial infarction alone, and the difference between treatment groups remained nonsignificant.

II.B.6 Assessment of Impact of Unobserved Follow-up

As mentioned earlier, the following censoring method was used by DCRI in its main analyses: If a patient was determined to have at least one MACE, the last follow-up date for that endpoint was the date of first occurrence of MACE, and follow-up was considered uncensored. If a patient did not have a MACE, follow-up for this endpoint was censored at the date of the last study visit at which any measurements (blood pressure, heart rate, or weight) were recorded on the VITALS module of the CRF. However, some patients continued in the trial after last recorded vital signs measurement, as evidenced by various trial records, such as laboratory results, phone call records, other adverse event reports, et al, up until the end of study (last visit was to have occurred

between 24 Aug 2008 and 24 Dec 2008). When including this time, if full follow-up for MACE had been achieved for all patients in the study, using the original RECORD event definitions, follow-up would have been increased by a maximum of 7.8% (926/11913 PY) for the RSG group and 8.6% (1011/11800 PY) for the MET/SU group. In order to assess the potential impact of potential events that could have occurred during the period from last recorded vital signs to end of trial, DCRI performed simulations to assess what effect various hypothetical event rates in the unobserved period would have had on the hazard ratio. Please see pages 71-74 of the study report for a full description of the simulation methods. The following table displays the results of this simulation.

Table II.B.6: Simulated Analysis of MACE with Imputed Results for Patients with Incomplete Follow-up

	Quantiles of Simulated Final Hazard Ratios										
HR assumed in unobserved follow-up	1%	2.5%	5%	10%	25%	50%	75%	90%	95%	97.5%	99%
New definition*											
Estimated from observed data	0.88	0.89	0.89	0.90	0.92	0.94	0.97	0.99	1.00	1.01	1.02
1.25	0.91	0.92	0.93	0.94	0.95	0.98	1.01	1.03	1.05	1.06	1.08
1.5	0.92	0.93	0.94	0.95	0.98	1.01	1.04	1.07	1.09	1.11	1.13
1.75	0.93	0.94	0.95	0.97	1.00	1.04	1.08	1.11	1.13	1.14	1.16
2	0.94	0.95	0.96	0.97	1.01	1.06	1.10	1.14	1.16	1.18	1.20
Original definition											
Estimated from observed data	0.86	0.87	0.88	0.89	0.91	0.93	0.95	0.97	0.99	1.00	1.01
1.25	0.90	0.91	0.92	0.93	0.95	0.97	1.00	1.03	1.04	1.05	1.07
1.5	0.92	0.93	0.94	0.94	0.97	1.00	1.04	1.06	1.08	1.10	1.12
1.75	0.92	0.93	0.94	0.96	0.99	1.03	1.07	1.10	1.12	1.13	1.15
2	0.93	0.94	0.95	0.96	1.00	1.05	1.10	1.13	1.16	1.17	1.19

* Contemporary definitions under development by FDA through the Standardized Data Collection for Cardiovascular Trials Initiative.
+ Last date observed without event is before 24-Aug-2008

Generated from ct/record/tables/phase2/tbl_unobserved.sas on 17FEB2012 at 16:47

Source: Table S4.1, pg 332, study report

Across a range of assumptions of potential hazard ratios for events in the unobserved time, including an assumption of a hazard ratio of 2 during the unobserved time, the point estimate for the hazard ratio for MACE for the full study would not have changed substantially. For example, using the original RECORD definitions, if the true hazard ratio in the unobserved data was 2.0, then the median final hazard ratio would be 1.05, and in 97.5% of the simulations, the final hazard ratio would be ≤ 1.17. Thus, even if one were to hypothesize that events could have been occurring at a much higher rate during the unobserved time, it would not have changed the final MACE result substantially.

Please also see Dr. Andraca-Carrera's statistical briefing document. Dr. Andraca-Carrera identified all patients who had missing vital status at end of study, and performed an analysis assuming an extreme scenario for the hazard ratio for total mortality in the missing time (simulated hazard ratio of 5.0). Even when exploring under this extreme scenario, the estimated hazard ratio would not have changed substantially (0.86 orig; 0.90 under extreme assumption).

II.C. Results of DCRI Quality Control Process

As described in the mortality phase review, the charter established two Quality Control (QC) processes- one for the readjudication process and one for the manual trigger process.

For the readjudication process Quality Control, a random sample of 5% (n=110) of the total readjudicated MI and stroke events were reviewed by DCRI RECORD CEC physicians who were blinded to the original readjudication result. For 103/110 events, there was no discrepancy between the first DCRI readjudication result and the QC result. In one case, there was an actual discrepancy between the first DCRI readjudication and the QC readjudication regarding event classification. In two cases, there was a minor discrepancy regarding Q-wave classification, and in four cases, there was a minor discrepancy regarding event date/time.

For the manual trigger process Quality Control, 165 subjects were randomly selected, then reviewed by a RECORD CEC physician to determine if additional manual triggers were present. Two additional triggers were noted; both were adjudicated as "no event".

II.D. Use of DCRI Information to Address Concerns from the Original RECORD Review

During the original 2010 review of RECORD, a consultant from the Division of Cardiorenal Products expressed concerns regarding study conduct and other matters, and requested additional information regarding approximately 475 patients. His concerns, particularly his allegations of trial misconduct, contributed in part to the decision to request an independent readjudication of RECORD. Some of his concerns were somewhat speculative and probably cannot be addressed by this readjudication or by other means. Overall, the readjudication process addresses his concerns in a major way, in that it examines whether highly qualified adjudicators, working under a rigorously-defined blinded process, would come up with analysis results similar to those found in the original adjudication. This review also attempts to use the readjudication results to address his concerns in other ways.

For the current review, the endocrine clinical reviewer identified patient ID numbers for those patients mentioned above for whom the 2010 Cardiorenal consultant requested additional information. The following table includes the subset of those patients of concern who had a MACE, and for whom the original RECORD adjudication result differed from the DCRI readjudication result. The table includes the concern expressed (if the concern was documented), the original adjudication result for MACE, and the DCRI readjudication results (original event definitions) for MACE. Many of the concerns expressed by the 2012 Cardiorenal consultant did not relate directly to MACE. However, since these were cases for which the consultant had some type of concern regarding study conduct or other matters, each of the cases was examined to observe how often the MACE result differed between the original study report and the DCRI adjudication. This process was not intended to examine the 2010 Cardiorenal consultant's interpretation of individual cases, but was rather intended to identify a population of cases for which there appeared to be heightened concern for problems, and to examine the outcome of the DCRI readjudication compared to the original RECORD adjudication,

for this population potentially enriched in problem cases. It should be noted that it was not always possible to accurately identify the concerns that led to the Cardiorenal consultant's information requests, but the clinical reviewer has attempted to identify the concern when possible.

As mentioned above, this table includes those identified cases of concern for which there was a difference between the original RECORD adjudication result, and the DCRI readjudication result. In the table, the far right column is used to detail the potential change in outcome for a given case, if one assumes that the original adjudication result was wrong, and the DCRI readjudication result was correct. The column lists the treatment (if any) which would have been "favored" in the MACE analyses by the original adjudication result, if that result was now assumed to be in error.

Table II.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original RECORD Review

Pt ID	Tx	Concern	Orig Adjud Result	DCRI Readjud Result	If Readjud Assumed to be Correct Interpretation, Which Treatment did Orig Adjud Favor?
18122	MET/SU	Death adjud as non-CV	Death, non-CV	Death, unk cause	MET/SU
18195	RSG	Death adjud as non-CV	Death, non-CV	Death, unk cause	RSG
18227	MET/SU	Initial cause of death unk. Info re possible subarachnoid bleed submitted later; death readjud as unk cause. Many annotations on SAE CRF.	No stroke	Stroke	MET/SU
18227	MET/SU	(Same- two events for this patient had discordant readjudication results)	Death, unk cause	Death, acute vascular event	Neither (either counted as cardiovascular death in analysis)
18285	MET/SU	Hosp adjud as "unk, insuff data".	Death, unk cause	Death, non-CV	RSG
18337	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
18388	MET/SU	Hosp for "collapse", during which 3V CAD found, not adjud as CV. Little info on subsequent death. Death captured via SSU after patient withdrawn from CV follow-up. Many annotations on SAE CRF.	No stroke	Stroke	MET/SU
18497	RSG	Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG

Table II.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original RECORD Review

Pt ID	Tx	Concern	Orig Adjud Result	DCRI Readjud Result	If Readjud Assumed to be Correct Interpretation, Which Treatment did Orig Adjud Favor?
18498	MET/SU	Arrhythmia during hosp for cholecystitis; arrhythmia type not specified. Diabetes drug names not redacted from some forms in adjud dossier. CEC record contains 2 reviewer adjud forms, but not full committee adjud form.	No MI	MI	MET/SU
18504	MET/SU	Death adjud as non-CV. Endpoint for which adjud forms were not provided.	Death, non-CV	Death, unk cause	MET/SU
18787	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
19079	RSG	Deletion of SAE and possible MI by investigator. Revised CV adjud form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review. Many annotations on SAE CRF.	No MI	MI	RSG
19450	RSG	Death captured via SSU after patient withdrawn from CV follow-up.	Deaths captured via SSU not adjud; death reported by GSK	DCRI: no data to support death occurred	MET/SU
19735	RSG	Revised CV adjud form submitted by GSK during FDA review. Revised SAS transport dataset for CV adjud forms submitted by GSK during FDA review.	MI	No MI	MET/SU
20025	RSG	Hosp adjud as nonurgent CV procedure or nonspecific symptom.	No stroke	Stroke	RSG
20164	MET/SU	Event detected by endpoint sweep.	Death, heart failure	Death, unk cause	Neither (either counts as CV death)

Table II.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original RECORD Review

Pt ID	Tx	Concern	Orig Adjud Result	DCRI Readjud Result	If Readjud Assumed to be Correct Interpretation, Which Treatment did Orig Adjud Favor?
20187	MET/SU	Hosp adjud as nonurgent CV procedure or nonspecific symptom.	No stroke	Stroke	MET/SU
20230	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
20766	MET/SU	Autopsy report of pulmonary embolism with suspicion of myocardial infarction. MI not referred for adjud.	No MI	MI	MET/SU
20839	RSG	Pt with GI bleed transferred to ICU with chest pain and died. Adjud non-CV death due to inadequate documentation.	Death, unk cause	Death, non-CV	MET/SU
20930	RSG	Event of "collapse" attributed to atrial fibrillation; not sent for adjud.	Death occurred after end of study[1]	Death, unk cause after end of study	Neither
21111	RSG	Death adjud as non-CV.	Death, non-CV	Death, CV	RSG
21153	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
21508	MET/SU	Death adjud as non-CV. Endpoint for which adjud forms were not provided.	Death, non-CV	Death, unk cause	MET/SU
21523	RSG	Hosp adjud as "unk, insuff data". Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG
29440	MET/SU	Death adjud as non-CV. Endpoint for which adjud forms were not provided.	Death, non-CV	Death, unk cause	MET/SU
29583	RSG	Hosp adjud as nonurgent CV procedure or nonspecific symptom. Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG
29696	RSG	Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG
29749	RSG	Revised CV adjud form submitted by GSK during FDA review.	No MI	MI	RSG

Table II.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original RECORD Review

Pt ID	Tx	Concern	Orig Adjud Result	DCRI Readjud Result	If Readjud Assumed to be Correct Interpretation, Which Treatment did Orig Adjud Favor?
29927	RSG	Hosp adjud as "unk, insuff data" (2 endpoints- E18849-701 and E18854-701). Hosp adjud as nonurgent CV procedure or nonspecific symptom (endpoint E18856-701).	No stroke	Stroke	RSG
29971	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
30540	MET/SU	Hosp adjud as "unk, insuff data".	Death, unk cause	Sudden cardiac death	Neither (either counted as CV death)
31183	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
31241	MET/SU	Delay in submission of event to CEC	Death not reported in orig study	Death, unk cause	MET/SU
31316	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
31367	MET/SU	Hosp adjud as nonurgent CV procedure or nonspecific symptom.	No MI	MI	MET/SU
31389	RSG	Hosp adjud as nonurgent CV procedure or nonspecific symptom (2 endpoints- E22848-827 and E22849-827). Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG
31496	RSG	Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG
31553	MET/SU	Death adjud as non-CV.	Death, non-CV	Death, unk cause	MET/SU
31868	MET/SU	Reported lung cancer death with little documentation	Death, unk cause	Death, non-CV	RSG
37804	RSG	Hosp adjud as nonurgent CV procedure or nonspecific symptom.	No MI	MI	RSG
38069	RSG	Had 6 endpoints referred; 3 re-adjud by full CEC as non-CV	Death, heart failure	Death, unk cause	Neither
38180	MET/SU	Hosp adjud as "unk, insuff data".	No MI	MI	MET/SU

Table II.D.1: Original Adjudication and Readjudication Results for Cases for Which Concerns Arose During Original RECORD Review

Pt ID	Tx	Concern	Orig Adjud Result	DCRI Readjud Result	If Readjud Assumed to be Correct Interpretation, Which Treatment did Orig Adjud Favor?
38468	RSG	Death adjud as non-CV.	Death, non-CV	Death, unk cause	RSG
39083	RSG	Hosp adjud as nonurgent CV procedure or nonspecific symptom.	No MI	MI	RSG
43697	RSG	Cerebral hemangioma with left temporal region hematoma and epilepsy not adjud.	No stroke	Stroke	RSG
97954	MET/SU	Question regarding whether autopsy in drowning death followed up appropriately	Death, unk cause	Death, non-CV	RSG

Sources: Inspection report, Dr. Khin U, DARRTS, 11 Jun 2010. NDA 21071 submissions from 25 Aug 2009; 8, 10 and 11 Dec 2009; 2 and 5 Feb 2010; 1, 23 and 24 Mar 2010; 13 Apr 2010; 25 and 26 May 2010; 4, 8, 9 and 15 Jun 2010; and 20 Dec 2011.
Abbreviations: 3V = 3 vessel; Adjud = adjudication; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CEC = Clinical Endpoints Committee; CEVA = Quintiles Clinical Event Validation and Adjudication center; CRF = case report form; CV = cardiovascular; Def = definition; GI = gastrointestinal; hosp = hospitalization; ICU = intensive care unit; ID = identification; info = information; insuff = insufficient; MET = metformin; MI = myocardial infarction; Orig = original; periph = peripheral; Pt = patient; Readjud = readjudication; RSG = rosiglitazone; SAE = serious adverse event; SSU = Survival Status Update; SU = sulfonylurea; subm = submission; Tx = treatment; Undeterm = undetermined; Unk = unknown
1 Death occurred [redacted] study cutoff 31 Dec 2008

Across all identified patients for whom the 2010 Cardiorenal consultant had expressed concerns, there were 47 cases (in 46 patients) for which DCRI readjudication results differed from the original adjudication result with regard to a MACE. Of these 47 cases, if one assumes that the DCRI readjudication is correct and the original adjudication was not correct, the original adjudication would have "biased" (for purposes of the MACE endpoint) in favor of RSG in 19 cases, in favor of MET/SU in 23 cases, and in favor of neither in 5 cases. Therefore, even in this sample which was highly enriched in "problem" cases per the 2010 Cardiorenal consultant's concerns, the DCRI blinded readjudication did not support systematic bias in favor of RSG.

When examining MI and stroke separately from the overall MACE endpoint, if one makes the same assumption that the DCRI readjudication is correct and the original adjudication was not correct, there is again a similar distribution of nonconcordance. For MI, there are 4 cases in which, under this assumption, the original adjudication would have "biased" in favor of RSG, and 5 cases in which it would have "biased" in favor of MET/SU. For stroke, there are 3 cases each for RSG and MET/SU. Therefore, again, in this sample which was highly enriched in "problem" cases, the DCRI blinded readjudication did not support systematic bias in favor of RSG.

In the 2010 Cardiorenal consult, on page 95 (Table 4), the consultant provided eight case examples of "failures to refer events for adjudication". He also cited three (or perhaps four) of these same cases as having had "extreme mishandling of events" (cases begin pg 27 of consult). Because the 2010 Cardiorenal consultant did not use the patient identification numbers for his cases of interest, it was initially difficult to determine precisely to which cases his consult referred. However, the patient identification numbers had been provided to the inspection team for the 2010 inspection, and were extracted from those records. The events about which the 2010 Cardiorenal consultant was concerned are not necessarily MACE. However, examination of these eight cases as examples of extreme mishandling cited by the consultant is another way one may examine concerns identified in the original RECORD review. In six out of eight cases (Patient Identification Numbers 18215, 19338, 20930, 21368, 31427 and 98364), the blinded DCRI readjudication reached the same conclusion as the original adjudication with respect to MACE to be included in analyses. In two patients randomized to RSG, the DCRI readjudication reached a different conclusion (Patients 19079 and 43697 from table below). Therefore, even in the cases cited by the 2010 Cardiorenal consultant as being the most egregious examples of potential trial mishandling of events, DCRI, through actual blinded review, reached the same conclusions, with respect to the effect on the MACE analysis, as the original adjudicators in most (6/8) cases.

Table II.D.2: Outcomes of Adjudication and Readjudication for MACE in Cases Identified in Original Cardiology Consult as Having Had "Failure to Refer Events for Adjudication[1]" or "Extreme Mishandling of Events[2]" (All Patients Randomized to Rosiglitazone)

Patient ID	Original RECORD Adjud Result	DCRI Readjud Result
18215	Non-CV death	Non-CV death
19079	No MI	MI
	Unknown cause of death (insuff data) (counted as CV death in analysis)	Death due to heart failure or cardiogenic shock (counted as CV death in analysis)
19338	Non-CV death	Non-CV death
20930	Death occurred after end of study[3]	Death due to unknown cause, after end of study
21368	Non-CV death	Non-CV death
31427	No MACE	No MACE
43697	Intracerebral hematoma called epilepsy; not referred for adjudication	Stroke
98364	No MACE	No MACE

Source: NDA 21071, submission 26 Jun 2012
1 Source: Cardiorenal consult, DARRTS 15 Jun 2010, pg 95, Table 4
2 Source: Cardiorenal consult, DARRTS 15 Jun 2010, cases begin pg 27
3 Death occurred [redacted] study cutoff 31 Dec 2008

A possible explanation for the difference between the 2010 Cardiorenal consultant's interpretation and that of the original blinded adjudicators and the DCRI blinded adjudicators is that the 2010 Cardiorenal consultant's review was not fully blinded. From the earliest meetings held during the original review cycle for RECORD, the consultant cited cases by case number and treatment assignment, discussing concerns he had about patients assigned to the RSG arm. While he may have later made an attempt at some type

of blinded review, if redaction of treatment assignment was done, it appears he would have done the redaction himself, which causes concern for unblinding from the outset.

In the 2010 Cardiorenal consult, the consultant discussed a concern regarding dates of end of cardiovascular follow-up. He cited several cases where he felt that the actual date of end of cardiovascular follow-up differed from the date that was used in analyses.

As discussed in the mortality review, this concern is addressed in the readjudication by DCRI's use of four different approaches to derive last follow-up dates:

- "Parsimonious" approach: Defined the last known alive date as the last date of a documented face-to-face visit at which one or more vital signs were recorded on the VITALS module of the CRF. Patients with a last known alive date after 24 Aug 2008 were considered to have completed survival follow-up.
- "Primary analysis approach": For patients who, based on the parsimonious approach, had not completed survival follow-up, the primary analysis approach (which was used for the primary analysis) added follow-up information for two additional types of patients. Patients were added who had a vital sign face-to-face in 2008 and a phone visit after 24 Aug 2008. Patients were also added who had an updated last known alive date based on DCRI reviews of case report forms (CRFs) or associated documents.
- "Primary analysis plus test and reported patient events follow-up" approach: This approach added patients using dates for electrocardiograms, lab tests, microvascular endpoints, adverse events and fractures reported in the electronic database.
- "Primary analysis plus test and patient event dates plus survival status and third party survival data collected with RECORD" approach: For patients whose vital status after 24 Aug 2008 could not be determined by the rules described in the first three approaches above, vital status was updated from Survival Status Update and third party search conducted as part of the RECORD study.

In the DCRI report for MACE, derivation of follow-up period for MI and stroke was done similarly to that described in the mortality readjudication review, using the parsimonious approach. If a patient was determined to have at least one MI, the last follow-up date for that endpoint was the date of first occurrence of MI, and follow-up was considered uncensored. If a patient did not have an MI, follow-up for this endpoint was censored at the date of the last study visit at which any measurements (blood pressure, heart rate, or weight) were recorded on the VITALS module of the CRF. A similar approach was used for stroke. The rationale used for this parsimonious approach (rather than allowing follow-up to be documented by the presence of laboratory results, phone call records, reports of adverse events in the database, ECGs, third party survival status information, etc) was that, when there was not evidence that a patient was actually seen face-to-face, there may have been a greater chance for a nonfatal event to remain undetected. Thus, the total person-years were 3-4% lower using this parsimonious approach compared to that used in the original RECORD review, which included time to types of patient contact other than face-to-face visits. In the DCRI readjudication, total person-years of follow-up were similar between the RSG and MET/SU groups (<1% difference).

The following table summarizes the mean follow-up, and the percentage of patients with incomplete follow-up, for each approach.

Table II.D.3: Mean Years of Follow-Up and Percentage of Patients with Incomplete Follow-Up Using Four Methods of Derivation of End of Follow-Up

Approach to Derivation of End of Follow-Up	Yrs of Follow-Up		Patients With Incomplete Follow-Up n (%)	
	RSG Mean (SD)	MET/SU Mean (SD)	RSG n (%) N=2220	MET/SU n (%) N=2227
Parsimonious	5.5 (1.5)	5.4 (1.6)	308 (13.9)	349 (15.7)
Primary	5.8 (1.1)	5.8 (1.2)	74 (3.3)	102 (4.6)
Primary + Test and Event Dates	5.9 (1.1)	5.8 (1.2)	74 (3.3)	101 (4.5)
Primary + Test and Event Dates + Survival Status and Third Party Survival Data	5.9 (1.0)	5.8 (1.2)	44 (2.0)	73 (3.3)

Source: Sponsor's Table 2.1, pg 442, study report

As stated earlier, DCRI used a parsimonious approach to derivation of follow-up for MI and stroke. The following table displays results for MI and stroke for the original RECORD adjudication and for the DCRI readjudication, using both the original definitions and the "new" definitions. Even when using an approach which required recording of vital signs, and thus evidence of a face-to-face visit, for derivation of follow-up, results were highly similar.

Table II.D.4: Results of Analyses for Myocardial Infarction and Stroke Using Original RECORD Approach to Derivation of Follow-up, and DCRI "Parsimonious" Approach

Analysis	Fatal or Nonfatal Myocardial Infarction			Fatal or Nonfatal Stroke		
	RSG N=2220 n (%)	MET/SU N=2227 n (%)	HR (95% CI)	RSG N=2220 n (%)	MET/SU N=2227 n (%)	HR (95% CI)
Original RECORD approach	64 (2.9%)	56 (2.5%)	1.14 (0.80, 1.63)	46 (2.1%)	63 (2.8%)	0.72 (0.49, 1.06)
DCRI "parsimonious" approach, original definitions	68 (3.1%)	60 (2.7%)	1.13 (0.80, 1.59)	50 (2.3%)	63 (2.8%)	0.79 (0.54, 1.14)
DCRI "parsimonious" approach, "new" definitions	72 (3.2%)	62 (2.8%)	1.15 (0.82, 1.62)	53 (2.4%)	64 (2.9%)	0.82 (0.57, 1.18)

Source: Table 12-A, pg 79 and pg 86, study report
Abbreviations: DCRI = Duke Clinical Research Institute; HR = hazard ratio; MET = metformin; RSG = rosiglitazone; SU = sulfonylurea

Using either approach to derivation of end of follow-up, hazard ratios and 95% confidence intervals are similar. Similar results by both methods are not suggestive of informative censoring, but cannot rule it out entirely.

II.E. Summary Display of Original RECORD Adjudication and DCRI Readjudication Results

The following table summarizes the results of the original adjudication and the DCRI readjudication, for MACE as well as for mortality and other endpoints done as sensitivity analyses:

Table II.E: Summary of Original Adjudication and DCRI Readjudication Results

Outcome/Endpoint	Analysis	RSG Total N=2220 n/N (%)	MET/SU Total N=2227 n/N (%)	HR (95% CI)	Rate Diff Per 100 PY (95% CI)
All-cause mortality	Original adjudication	136/2220 (6.1%)	157/2227 (7.0%)	0.86 (0.68, 1.08)	-0.17 (-0.43, 0.09)
	DCRI main readjudication	139/2220 (6.3%)	160/2227 (7.2%)	0.86 (0.68, 1.08)	-0.18 (-0.44, 0.09)
	DCRI, LDRT + 30 days	57/2220 (2.6%)	70/2227 (3.1%)	0.76 (0.54, 1.08)	-0.16 (-0.37, 0.06)
	DCRI, LDRT + 60 days	69/2220 (3.1%)	83/2227 (3.7%)	0.78 (0.57, 1.07)	-0.17 (-0.40, 0.06)
	DCRI, from randomization to date of Amendment 7	66/2220 (3.0%)	73/2227 (3.3%)	0.90 (0.64, 1.25)	-0.10 (-0.42, 0.21)
	DCRI, from date of Amendment 7 to last date observed	73/2104 (3.5%)	87/2091 (4.2%)	0.83 (0.60, 1.13)	-0.28 (-0.74, 0.18)
	DCRI, from randomization to date of interim publication	97/2220 (4.4%)	114/2227 (5.1%)	0.84 (0.64, 1.10)	-0.18 (-0.47, 0.11)
	DCRI, from date of interim publication to last date observed	42/2057 (2.0%)	46/2032 (2.3%)	0.89 (0.59, 1.35)	-0.17 (-0.83, 0.48)
	DCRI, end of follow-up derived by parsimonious approach	139/2220 (6.3%)	160/2227 (7.2%)	0.86 (0.68, 1.08)	-0.18 (-0.47, 0.10)
	DCRI, end of follow-up derived by "primary analysis + test + event dates" approach	139/2220 (6.3%)	160/2227 (7.2%)	0.86 (0.68, 1.08)	-0.18 (-0.44, 0.09)
	DCRI, end of follow-up derived by "primary analysis + test + event dates + survival status + third party survival status information" approach	139/2220 (6.3%)	160/2227 (7.2%)	0.86 (0.68, 1.08)	-0.18 (-0.44, 0.09)
Cardiovascular (or unknown cause) mortality	Original adjudication	60/2220 (2.7%)	71/2227 (3.2%)	0.84 (0.59, 1.18)	-0.09 (-0.27, 0.09)
	DCRI main readjudication, original definition	88/2220 (4.0%)	96/2227 (4.3%)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)
	DCRI main readjudication, "new" definition	88/2220 (4.0%)	96/2227 (4.3%)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)
	DCRI, LDRT + 30 days, "new" definition	34/2220 (1.5%)	43/2227 (1.9%)	0.74 (0.47, 1.16)	-0.11 (-0.27, 0.06)
	DCRI, LDRT + 60 days, "new" definition	41/2220 (1.8%)	44/2227 (2.0%)	0.87 (0.57, 1.34)	-0.05 (-0.23, 0.12)

Table II.E: Summary of Original Adjudication and DCRI Readjudication Results

Outcome/Endpoint	Analysis	RSG Total N=2220 n/N (%)	MET/SU Total N=2227 n/N (%)	HR (95% CI)	Rate Diff Per 100 PY (95% CI)
	DCRI, from randomization to date of Amendment 7, "new" definition	34/2220 (1.5%)	43/2227 (1.9%)	0.79 (0.50, 1.24)	-0.13 (-0.36, 0.11)
	DCRI, from date of Amendment 7 to last date observed, "new" definition	54/2104 (2.6%)	53/2091 (2.5%)	1.00 (0.69, 1.46)	0.00 (-0.37, 0.38)
	DCRI, from randomization to date of interim publication, "new" definition	55/2220 (2.5%)	68/2227 (3.1%)	0.80 (0.56, 1.14)	-0.13 (-0.36, 0.09)
	DCRI, from date of interim publication to last date observed, "new" definition	33/2057 (1.6%)	28/2032 (1.4%)	1.15 (0.70, 1.90)	0.16 (-0.39, 0.70)
	DCRI, end of follow-up derived by parsimonious approach, "new" definition	88/2220 (4.0%)	96/2227 (4.3%)	0.90 (0.68, 1.21)	-0.07 (-0.30, 0.15)
	DCRI, end of follow-up derived by "primary analysis + test + event dates" approach, "new" definition	88/2220 (4.0%)	96/2227 (4.3%)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)
	DCRI, end of follow-up derived by "primary analysis + test + event dates + survival status + third party survival status information" approach, "new" definition	88/2220 (4.0%)	96/2227 (4.3%)	0.90 (0.68, 1.21)	-0.07 (-0.28, 0.14)
Cardiovascular (or unknown cause) mortality, myocardial infarction, or stroke	Original adjudication	154/2220 (6.9%)	165/2227 (7.4%)	0.93 (0.74, 1.15)	-0.10 (-0.39, 0.19)
	DCRI main readjudication, original definition	181/2220 (8.2%)	188/2227 (8.4%)	0.95 (0.78, 1.17)	-0.07 (-0.40, 0.25)
	DCRI main readjudication, "new" definition	186/2220 (8.4%)	191/2227 (8.6%)	0.97 (0.79, 1.18)	-0.05 (-0.38, 0.27)
	DCRI, LDRT + 30 days, "new" definition	128/2220 (5.8%)	129/2227 (5.8%)	0.94 (0.73, 1.20)	-0.08 (-0.39, 0.23)
	DCRI, LDRT + 60 days, "new" definition	135/2220 (6.1%)	133/2227 (6.0%)	0.96 (0.76, 1.22)	-0.05 (-0.36, 0.26)
	DCRI, from randomization to date of Amendment 7, "new" definition	102/2220 (4.6%)	105/2227 (4.7%)	0.97 (0.74, 1.28)	-0.04 (-0.45, 0.36)
	DCRI, from date of Amendment 7 to last date observed, "new" definition	84/1919 (4.4%)	86/1913 (4.5%)	0.96 (0.71, 1.29)	-0.08 (-0.61, 0.46)
	DCRI, from randomization to date of interim publication, "new" definition	142/2220 (6.4%)	150/2227 (6.7%)	0.95 (0.75, 1.19)	-0.09 (-0.45, 0.27)
	DCRI, from date of interim publication to last date observed, "new" definition	44/1817 (2.4%)	41/1782 (2.3%)	1.04 (0.68, 1.59)	0.07 (-0.68, 0.82)
	DCRI, censoring at earliest completion date (rand to earlier of last date observed or 24 Aug 2008), "new" definition	174/2220 (7.8%)	189/2227 (8.5%)	0.91 (0.74, 1.12)	-0.14 (-0.47, 0.19)
Fatal or nonfatal myocardial infarction	Original adjudication	64/2220 (2.9%)	56/2227 (2.5%)	1.14 (0.80, 1.63)	0.06 (-0.11, 0.24)

Table II.E: Summary of Original Adjudication and DCRI Readjudication Results

Outcome/Endpoint	Analysis	RSG Total N=2220 n/N (%)	MET/SU Total N=2227 n/N (%)	HR (95% CI)	Rate Diff Per 100 PY (95% CI)
	DCRI main readjudication, original definition	68/2220 (3.1%)	60/2227 (2.7%)	1.13 (0.80, 1.59)	0.06 (-0.13, 0.25)
	DCRI main readjudication, "new" definition	72/2220 (3.2%)	62/2227 (2.8%)	1.15 (0.82, 1.62)	0.08 (-0.12, 0.28)
	DCRI, LDRT + 30 days, "new" definition	63/2220 (2.8%)	51/2227 (2.3%)	1.17 (0.81, 1.70)	0.08 (-0.12, 0.29)
	DCRI, LDRT + 60 days, "new" definition	64/2220 (2.9%)	52/2227 (2.3%)	1.17 (0.81, 1.69)	0.08 (-0.12, 0.29)
	DCRI, from randomization to date of Amendment 7, "new" definition	45/2220 (2.0%)	39/2227 (1.8%)	1.15 (0.75, 1.77)	0.08 (-0.17, 0.34)
	DCRI, from date of Amendment 7 to last date observed, "new" definition	27/1934 (1.4%)	23/1930 (1.2%)	1.16 (0.67, 2.02)	0.07 (-0.22, 0.37)
	DCRI, from randomization to date of interim publication, "new" definition	59/2220 (2.7%)	53/2227 (2.4%)	1.11 (0.77, 1.61)	0.06 (-0.16, 0.29)
	DCRI, from date of interim publication to last date observed, "new" definition	13/1834 (0.7%)	9/1805 (0.5%)	1.42 (0.60, 3.31)	0.15 (-0.23, 0.53)
	DCRI, censoring at earliest completion date (rand to earlier of last date observed or 24 Aug 2008), "new" definition	70/2220 (3.2%)	61/2227 (2.7%)	1.14 (0.81, 1.61)	0.07 (-0.12, 0.27)
Fatal or nonfatal stroke	Original adjudication	46/2220 (2.1%)	63/2227 (2.8%)	0.72 (0.49, 1.06)	-0.14 (-0.31, 0.02)
	DCRI main readjudication, original definition	50/2220 (2.3%)	63/2227 (2.8%)	0.79 (0.54, 1.14)	-0.11 (-0.29, 0.07)
	DCRI main readjudication, "new" definition	53/2220 (2.4%)	64/2227 (2.9%)	0.82 (0.57, 1.18)	-0.10 (-0.28, 0.09)
	DCRI, LDRT + 30 days, "new" definition	42/2220 (1.9%)	52/2227 (2.3%)	0.76 (0.51, 1.14)	-0.12 (-0.31, 0.07)
	DCRI, LDRT + 60 days, "new" definition	42/2220 (1.9%)	54/2227 (2.4%)	0.74 (0.49, 1.10)	-0.14 (-0.33, 0.05)
	DCRI, from randomization to date of Amendment 7, "new" definition	31/2220 (1.4%)	35/2227 (1.6%)	0.89 (0.55, 1.44)	-0.06 (-0.29, 0.17)
	DCRI, from date of Amendment 7 to last date observed, "new" definition	22/1942 (1.1%)	29/1930 (1.5%)	0.74 (0.43, 1.30)	-0.15 (-0.45, 0.14)
	DCRI, from randomization to date of interim publication, "new" definition	45/2220 (2.0%)	49/2227 (2.2%)	0.92 (0.61, 1.37)	-0.04 (-0.25, 0.16)
	DCRI, from date of interim publication to last date observed, "new" definition	8/1845 (0.4%)	15/1809 (0.8%)	0.52 (0.22, 1.23)	-0.30 (-0.68, 0.09)
	DCRI, censoring at earliest completion date (rand to earlier of last date observed or 24 Aug 2008), "new" definition	51/2220 (2.3%)	64/2227 (2.9%)	0.79 (0.55, 1.14)	-0.12 (-0.30, 0.07)
Total mortality or nonfatal myocardial infarction	DCRI, "new" definition	193/2220 (8.7%)	203/2227 (9.1%)	0.94 (0.77, 1.15)	-0.09 (-0.42, 0.24)

Table II.E: Summary of Original Adjudication and DCRI Readjudication Results

Outcome/Endpoint	Analysis	RSG Total N=2220 n/N (%)	MET/SU Total N=2227 n/N (%)	HR (95% CI)	Rate Diff Per 100 PY (95% CI)
Total mortality, nonfatal myocardial infarction, or nonfatal stroke	DCRI, "new" definition	235/2220 (10.6%)	252/2227 (11.3%)	0.93 (0.77, 1.11)	-0.16 (-0.53, 0.21)
Cardiovascular (or unknown cause) mortality or nonfatal myocardial infarction	DCRI, "new" definition	142/2220 (6.4%)	140/2227 (6.3%)	1.01 (0.80, 1.27)	0.01 (-0.27, 0.29)
Cardiovascular mortality (without unknown cause mortality), nonfatal myocardial infarction, or nonfatal stroke	DCRI, "new" definition	143/2220 (6.4%)	142/2227 (6.4%)	1.00 (0.79, 1.26)	-0.00 (-0.29, 0.28)

Source: Sponsor's submission dated 28 Mar 2012, Tables 44.1 (pg 316), 45.1 (pg 319), and 46.1 (pg 322); and Sponsor's submission dated 4 Oct 2012, pgs 4-5
Abbreviations: Aug = August; diff = difference; DCRI = Duke Clinical Research Institute; HR = hazard ratio; LDRT = last date of randomized therapy; MET = metformin; RSG = rosiglitazone; SU = sulfonylurea
Amendment 7 to the original RECORD protocol instituted a substudy to collect endpoint data from withdrawn subjects who consented

For each composite (and for the individual components) the original RECORD analysis, and the DCRI readjudication analyses by the primary and alternative analysis methods, all showed similar analysis results.

III. Discussion of Limitations and Strengths of the DCRI Readjudication

Please see the mortality phase review (Section IV.A.1) for a more complete discussion of the limitations and strengths of the readjudication.

As discussed in that review, some of the concerns raised in the original review of RECORD probably cannot be addressed by the readjudication. These include trial design issues (open-label, noninferiority design; complexity of adverse event reporting process; expected asymmetry in use of insulin between groups).

There were some concerns that could be addressed, as discussed in Section II.D above, and further discussed below.

III.A. Allegations that There was Widespread Incorrect Interpretation of Adverse Events

During the original RECORD review process, assertions were made that numerous adverse events had been incorrectly interpreted, perhaps with bias in favor of rosiglitazone. This was one of the major factors that contributed to a lack of confidence in the trial's results. The DCRI readjudication analysis results, however, were highly similar to those from the original RECORD trial. There were some cases where a different conclusion was reached regarding whether an event met the definition, or whether there was sufficient information to determine whether an event occurred

according to the precise definition, or to determine exact cause of death. This is expected; indeed, it would be highly suspicious if perfect agreement occurred. Overall, however, the primary analyses and numerous secondary and sensitivity analyses had highly similar results to those from the original RECORD study report.

III.B. Concern that a Large Percentage of Patients Were Not Taking Original Randomized Therapy at End of Study

As with the original study, this concern was addressed by DCRI using analyses utilizing last date of randomized therapy (see Tables II.A.3.c, II.A.4.e, II.A.4.f, II.A.5.c and II.A.5.d and accompanying discussion).

III.C. Concerns Regarding Percentage of Patients Lost to Follow-Up, and Determination of Dates of Last Follow-Up

The DCRI process made a strong and concerted effort to identify the vital status of patients who were deemed to have incomplete follow-up, with DCRI using records that they obtained and the services of MediciGlobal.

As discussed earlier, DCRI addressed concerns regarding last date of follow-up by applying a parsimonious method to derivation of last date of follow-up. Results using this method were similar to those from the original RECORD analyses (see Table II.D.4 above).

III.D. Potential Effect of Publicity and the Published Interim Analysis

This was addressed by DCRI through their landmark analyses of mortality, by treatment group, before and after the interim publication (see Tables II.B.2.a, II.B.2.b, II.B.2.c and accompanying discussion).

III.E. Underascertainment; and Concern the Events Might Not Have Been Referred for Adjudication, or Were Deleted

The DCRI process attempted to address this by an extensive automated and manual triggering process, by record review, by requests for additional information from sites, and by use of MediciGlobal for additional patient follow-up. The triggering process identified many records for examination. Additional record requests and MediciGlobal efforts had limited success. At this point, several years out from the end of an international trial, it is unsurprising that little additional information appears to exist. In the end, few additional events were identified that occurred before the trial cut-off; analyses using these additional events were highly similar to the original RECORD analyses.

No process can address purely speculative remarks regarding the possibility that events were systematically deleted or not referred for adjudication. However, the DCRI process attempted to search for missed events in several additional ways:

- Both electronic and manual triggers were used to identify potential events.
- Manual trigger procedures were extensive.
- Manual trigger procedures included review of all cases that were sent to the original RECORD Clinical Endpoints Committee, including endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator.
- The numbers of triggered cases, and the sources of triggering, were similar between the RSG and MET/SU groups. The triggering process, which was extensive, did not identify evidence of systematic over- or under- identification of potential death events.

III.F. Inclusion of Deaths with Inadequate Data as Cardiovascular Deaths

This was addressed by examining MACE with only cardiovascular death, excluding deaths due to unknown cause (see Table III.A.3.b).

III.G. Strengths of the DCRI Readjudication

As discussed above, the DCRI readjudication process could address some limitations identified in the original RECORD review, and could not address others. There were several strengths to the DCRI readjudication process that are of note:

- Multiple meetings occurred between DCRI and the Agency to refine readjudication procedures. DCRI asked many questions and requested feedback multiple times in order to address as many concerns as possible.
- All procedures for the readjudication process were predefined, and no charter violations were noted.
- DCRI is highly experienced in clinical trial procedures and cardiovascular event adjudication.
- There were no GSK representatives on the CEC committee.
- Careful attention was paid to redaction of treatment assignments from records, and to blinding of adjudicators.
- In addition to being blinded to treatment assignment, adjudication reviewers were blinded to all glucose-lowering agents.
- Both electronic and manual triggers were used to identify potential events.
- Manual trigger procedures were extensive.
- Manual trigger procedures included review of all cases that were sent to the original RECORD Clinical Endpoints Committee, including endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator. There had been concern during the original RECORD review in this area, particularly about cases that were “deleted” by the investigator
- The numbers of triggered cases, and the sources of triggering, were similar between the RSG and MET/SU groups. The triggering process, which was extensive, did not identify evidence of systematic over- or under- identification of potential events.
- A systematic effort was made to identify events that had been deleted by investigators, by reviewing the audit trails of the study’s electronic datasets.
- Repeated efforts were made to obtain missing data.

- A separate contractor, MediciGlobal, was hired to track down patients who were lost to follow-up.
- Quality control checks were prespecified and conducted.

IV. Summary

The Duke Clinical Research Institute has conducted a well-planned and comprehensive readjudication of the RECORD trial major adverse cardiovascular event data. Their analyses showed highly similar results for MACE, and for the components of myocardial infarction and stroke, when compared to the original RECORD adjudication results. No treatment effect was demonstrated.

For the overall MACE composite, for the component of cardiovascular death, and for the component of stroke, point estimates for hazard ratios favored rosiglitazone and confidence intervals included 1, indicating no significant difference between RSG and comparator (MET/SU). None of the strokes which contributed to the RSG group estimates were fatal strokes, while five contributing strokes in the MET/SU group were fatal.

For the component of myocardial infarction, the hazard ratio favored comparator (MET/SU), and the confidence interval again included 1, indicating no significant difference between RSG and comparator. The numerical difference between RSG and MET/SU regarding myocardial infarction lay in nonfatal events, rather than fatal events, although the number of fatal events was too small to make definitive conclusions. The total number of fatal events contributing to the "fatal + nonfatal" myocardial infarction endpoint in the DCRI readjudication, using the original RECORD event definitions, was 6 events for RSG and 11 events for MET/SU.

Numerous subgroup analyses were performed (by gender; age; duration of diabetes; body mass index; prior history of heart disease; baseline HbA1c; background diabetes medication; country; and baseline use of angiotensin converting enzyme inhibitors, statins, nitrates or beta blockers). Among these, the only statistically significant interaction observed was that between treatment and use of baseline statins, favoring MET/SU for the primary composite of cardiovascular (or unknown cause) mortality, nonfatal stroke, or nonfatal myocardial infarction. This interaction was not observed in the component analyses of MI or stroke, and thus apparently derives from the component of cardiovascular (or unknown cause) death. This was discussed in the mortality review; at this point, the clinical reviewer notes no mechanistic or clinical explanation for this observation.

There was some unobserved follow-up time in both treatment groups. Simulations including a variety of assumed event rate scenarios indicated that, even had the hazard ratio been substantially less favorable toward rosiglitazone during the unobserved time, the results of the analyses would not have changed significantly.

This readjudication addressed a major concern raised during the original RECORD review, namely an allegation that there was widespread and potentially biased misinterpretation of adverse events. Overall, readjudication analyses reached highly similar conclusions to the original RECORD adjudication analyses. As expected, readjudication did not reach the exact same conclusion as the original adjudication in every case. However, the differences were equally distributed between treatment groups, without evidence of systematic misclassification. Efforts were made to address several other concerns, including strong efforts at maximum ascertainment and follow-up. The readjudication also addressed a number of other concerns to some extent, including concerns about derivation of end of follow-up, the effect of publicity and the interim results publication, the percentage of patients taking original randomized therapy at end of study, and inclusion of deaths due to unknown cause as potential cardiovascular deaths. Some concerns related to trial design cannot be addressed by a readjudication effort.

Previous clinical trial evidence considered when evaluating the risk of MACE with rosiglitazone has come from meta-analyses of smaller, shorter trials which were not designed to evaluate cardiovascular events. The RECORD trial was a large, longterm, dedicated cardiovascular outcomes trial. The DCRI readjudication of RECORD included 369 MACE in its reanalyses using the original definitions. This represents considerably more MACE than that observed in all trials combined in the largest and most recent updated meta-analysis (included in Dr. McEvoy's briefing document), which included only 107 MACE across all included trials.

Overall, the readjudication of RECORD appears to support the previous observation that in this trial, rosiglitazone was not associated with an increased incidence of major adverse cardiovascular events.

V. References

Home P et al 2009. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized, open-label trial. Lancet 373:2215-35

Preiss D et al 2011. A systematic review of event rates in clinical trials in diabetes mellitus: The importance of quantifying baseline cardiovascular disease history and proteinuria and implications for clinical trial design. Am Heart J 161:210-9

VI. Appendices

VI.A. Patient Identification Numbers for patients identified by the 2010 Cardiorenal consultant as cases of concern, but for whom DCRI reached the same readjudication conclusion as was reached in the original adjudication:

18106, 18107, 18108, 18124, 18143, 18156, 18162, 18169, 18172, 18173, 18187, 18215, 18221, 18253, 18257, 18261, 18267, 18282, 18291, 18296, 18307, 18314, 18317, 18332,

18351, 18356, 18372, 18418, 18419, 18420, 18488, 18491, 18502, 18521, 18522, 18530, 18535, 18536, 18553, 18555, 18566, 18635, 18658, 18660, 18675, 18687, 18702, 18739, 18758, 18769, 18786, 18796, 18799, 18805, 18810, 18832, 18856, 18868, 18874, 18881, 18912, 18931, 18934, 18950, 18971, 18977, 18995, 19042, 19078, 19081, 19110, 19115, 19119, 19123, 19134, 19163, 19189, 19200, 19204, 19216, 19243, 19248, 19269, 19331, 19338, 19350, 19353, 19390, 19437, 19438, 19452, 19481, 19520, 19545, 19628, 19629, 19631, 19642, 19645, 19677, 19680, 19720, 19731, 19734, 19765, 19810, 19825, 19830, 19855, 19870, 19950, 19962, 19973, 19978, 19991, 20011, 20046, 20087, 20100, 20110, 20153, 20154, 20217, 20235, 20270, 20301, 20338, 20353, 20361, 20370, 20493, 20494, 20511, 20512, 20523, 20533, 20554, 20609, 20623, 20662, 20684, 20694, 20699, 20704, 20733, 20773, 20810, 20841, 20844, 20892, 20953, 20965, 21000, 21010, 21027, 21075, 21093, 21102, 21109, 21114, 21134, 21152, 21154, 21178, 21181, 21182, 21209, 21210, 21250, 21261, 21280, 21282, 21292, 21315, 21365, 21368, 21380, 21392, 21395, 21427, 21483, 21486, 21503, 21504, 21505, 21513, 21517, 21527, 21589, 21600, 21612, 21693, 21694, 29057, 29079, 29094, 29098, 29136, 29197, 29200, 29211, 29223, 29227, 29239, 29244, 29267, 29320, 29323, 29331, 29337, 29345, 29351, 29358, 29378, 29397, 29417, 29451, 29458, 29515, 29518, 29519, 29535, 29563, 29570, 29578, 29582, 29588, 29620, 29681, 29691, 29714, 29796, 29895, 29960, 29979, 29985, 30009, 30035, 30063, 30094, 30143, 30165, 30170, 30182, 30187, 30188, 30190, 30308, 30340, 30354, 30355, 30359, 30441, 30444, 30456, 30491, 30494, 30545, 30547, 30579, 30690, 30706, 30730, 30745, 30754, 30757, 30808, 30831, 30842, 30843, 30847, 30866, 30877, 30885, 30914, 30943, 30954, 31000, 31128, 31184, 31195, 31209, 31234, 31237, 31290, 31294, 31302, 31327, 31378, 31379, 31413, 31421, 31427, 31437, 31440, 31507, 31510, 31515, 31546, 31554, 31594, 31598, 31604, 31643, 31679, 31703, 31725, 31729, 31731, 31741, 31756, 31759, 31781, 31785, 31827, 31847, 31851, 31854, 31952, 31985, 31990, 31995, 32005, 32009, 32017, 37303, 37324, 37370, 37371, 37539, 37555, 37556, 37559, 37615, 37622, 37650, 37655, 37660, 37697, 37807, 37814, 37821, 37844, 37879, 37906, 37909, 38013, 38033, 38039, 38040, 38056, 38061, 38067, 38093, 38125, 38161, 38170, 38306, 38333, 38352, 38383, 38451, 38458, 38483, 38489, 38582, 38619, 38628, 38700, 38721, 38743, 38912, 38923, 38938, 38966, 38982, 39103, 39115, 43567, 43587, 43614, 43653, 43686, 43689, 43767, 43883, 43902, 43907, 97520, 97579, 97580, 97593, 97599, 97632, 97660, 97671, 97715, 97742, 97811, 97837, 97858, 97870, 97871, 97917, 97918, 97925, 97958, 97988, 97991, 98033, 98047, 98059, 98159, 98161, 98168, 98172, 98186, 98216, 98256, 98276, 98287, 98343, 98352, 98356, 98364, 98415, 98435, 98463, 98472
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VI.B: Original RECORD Endpoint Definitions

CARDIOVASCULAR DEATH ENDPOINTS

Cardiovascular (CV) death shall be defined as any death for which an unequivocal noncardiovascular cause cannot be established. Cardiovascular death will include death following heart failure, death following acute myocardial infarction (MI), sudden death and death due to acute vascular events. Deaths which are due to unknown causes (and therefore cannot be categorized into the categories listed below), will be classified as

'unknown deaths', but will be counted as CV deaths for the analysis of the 'primary endpoint'.

Death Following Heart Failure

This is defined as death due to the onset and progression of symptoms defining definite heart failure (as listed in the present charter).

Death Following Acute Myocardial Infarction

This is defined as death within 30 days after acute MI.

Sudden Death

This is defined as death due to one of the following reasons:

- within one hour after onset of new symptoms
- witnessed death, without new symptoms occurring within 72 hours preceding death
- cardiac arrest followed by death within 30 days even if temporarily recovered
- unwitnessed death in the absence of new symptoms (the premise for death to be adjudicated in this category is that it is known that the patients did not have any signs or symptoms 24 hours before the death occurred; otherwise it will constitute a death of unknown cause).

Death Due to Acute Vascular Event

This is defined as death due to aortic dissection, aortic aneurysm, pulmonary embolism, stroke or any other vascular cause.

MYOCARDIAL INFARCTION (HOSPITALIZATION FOR ACUTE MYOCARDIAL INFARCTION):

Acute MI will be adjudicated according to the definition in the document: 'Myocardial infarction redefined- a consensus document of the Joint European Society of Cardiology/ American College of Cardiology Committee for the Redefinition of Myocardial Infarction. EHJ 2000 vol 21: 1502-13':
Hospitalization **plus** biochemical markers as defined below:
Elevation of cardiac biomarkers TNI and/or TNT above ULN or CK-MB isoenzyme ≥2x ULN or creatine kinase (CK) >2x ULN
Plus one of the following:
(i) Typical symptoms of cardiac ischemia
(ii) New pathologic ECG findings as defined in the above cited article.

STROKE (HOSPITALIZATION FOR STROKE):

Whenever possible the disease should be confirmed by a neurologist or by CT or MR imaging.

Hospitalization **plus**:

Rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by thrombolysis, surgery or death), with no apparent cause other than a vascular origin: it included patients presenting clinical signs or symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage or cerebral ischemic necrosis.

Secondary stroke events resulting from blood diseases (e.g. leukemia, polycythemia vera), as well as stroke symptoms from brain tumors or brain metastases, should be excluded. Secondary stroke caused by trauma or other disorders (e.g. metabolic disturbance) or peripheral lesion that could cause a localizing neurologic deficit or coma should also be excluded.

Definite focal signs:
Unilateral or bilateral motor impairment (including dyscoordination)
Unilateral or bilateral sensory impairment
Aphasis/dysphasis (nonfluent speech)
Hemianopia (half-sided impairment of visual fields)
Diplopia
Forced gaze (conjugate deviation)
Dysphagia of acute onset
Apraxia of acute onset
Ataxia of acute onset
Perception deficit of acute onset

Not acceptable as sole evidence of focal dysfunction:
Dizziness, vertigo
Localized headache
Blurred vision of both eyes
Dysarthria (slurred speech)
Impaired cognitive function (including confusion)
Impaired consciousness
Seizures
(Although strokes can present in this way, these signs are not specific and cannot therefore be accepted as definite evidence for stroke)

VI.C: DCRI Endpoint Definitions

The following definitions are quoted from pages 408-417 of the DCRI MACE study report.

DEATH

The determination of the specific cause of cardiovascular death is complicated by the fact that we are particularly interested in one underlying cause of death (acute MI) and several

modes of death (arrhythmia and heart failure/ low output). It is noted that heart attack-related deaths are manifested as sudden death or heart failure, so these events need to be carefully defined.

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

Death Due to Acute Myocardial Infarction

Death due to acute myocardial infarction refers to a death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure, inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained or at a time before the appearance of cardiac biomarkers in the blood.

Death resulting from a procedure to treat a myocardial infarction (percutaneous coronary intervention, coronary artery bypass graft surgery, or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.

Sudden Cardiac Death

Sudden cardiac death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

- Death witnessed and instantaneous without new or worsening symptoms
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest AMI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- Death after unsuccessful resuscitation from cardiac arrest
- Death after successful resuscitation from cardiac arrest and without identification of a noncardiac etiology (post-cardiac arrest syndrome)

- Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations:

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death". Typical scenarios include "subject well the previous day but found dead in bed the next day" or "subject found dead at home on the couch with the television on".

- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death". Please see definition of Undetermined Cause of Death for full details.

Death Due to Heart Failure or Cardiogenic Shock

Death due to heart failure or cardiogenic shock refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death and not following an AMI. Note that deaths due to heart failure can have various etiologies, including one or more AMIs (late effect), ischemic or nonischemic cardiomyopathy, or valve disease. Death due to heart failure or cardiogenic shock should include death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implementation of a mechanical assist device. New or worsening signs and/or symptoms of congestive heart failure include any of the following:

- new or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

- heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema

- confinement to bed predominantly due to heart failure symptoms

- pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

- cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

Cardiogenic shock is defined as systolic blood pressure <90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction. Can also be defined if SBP < 90 mm Hg and increases

to ≥ 90 mm Hg in less than one hour with positive inotropic or vasopressor agents alone and/or with mechanical support and associated with at least one of the following signs of hypoperfusion:

- cool, clammy skin
- oliguria (urine output < 30 mL/hr)
- altered sensorium
- cardiac index <2.2 L/min/m^2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than one hour with positive inotropic or vasopressor agents alone and/or with mechanical support (sic).

General Considerations: Heart failure may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g. hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine and dexfenfluramine were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

Death Due to Stroke

Death due to stroke refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

Death Due to Other Cardiovascular Causes

Death due to other cardiovascular causes refers to a cardiovascular death not included in the above categories (e.g. dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention [other than one related to an AMI], aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or nonsurgical revascularization should be classified as cardiovascular deaths.

Definition of Noncardiovascular Death

Noncardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Detailed recommendations on the classification of noncardiovascular causes of death are beyond the scope of this document. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of noncardiovascular deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of noncardiovascular causes of death:

Nonmalignant causes:

- pulmonary
- renal
- gastrointestinal
- hepatobiliary
- pancreatic
- infection (includes sepsis)
- noninfectious (e.g. systemic inflammatory response syndrome)
- hemorrhage, not intracranial
- noncardiovascular system organ failure (e.g. hepatic failure)
- noncardiovascular surgery
- other noncardiovascular, specify: _____
- accidental/trauma
- suicide
- drug overdose

Death due to a gastrointestinal bleed should not be considered a cardiovascular death.

Malignant Causes:

Malignancy should be coded as the cause of death if:

- death results directly from the cancer; or
- death results from a complication of the cancer (e.g. infection, complication of surgery/chemotherapy/radiotherapy); or
- death results from withdrawal of other therapies because of concerns relating the poor prognosis associated with the cancer.

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these two scenarios (i.e. worsening of prior malignancy; new malignancy).

Suggested categorization includes common organ systems, hematologic, or unknown.

Definition of Undetermined Cause of Death

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a noncardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients in well-run clinical trials. A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death, specifically "death due to other cardiovascular causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process. The approach should be prespecified and described in the protocol and other trial documentation such as the endpoint adjudication procedures and/or the statistical analysis plan.

MYOCARDIAL INFARCTION

General Considerations

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

- evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and

- supporting information derived from the clinical presentation, ECG change, or the results of myocardial or coronary artery imaging.

The totality of the clinical, ECG and cardiac biomarker information should be considered to determine whether or not a myocardial infarction has occurred. Specifically, timing and trends in cardiac biomarkers and ECG information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. I (sic) may be adjudicated for an event that has characteristics of a myocardial infarction but which does not meet the strict definition because biomarker or ECG results are not available.

Criteria for Myocardial Infarction

Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic

cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

Biomarker elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the URL and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL. In many studies, particularly those in which patients present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability.

Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, consider evaluating outcomes for these subsets of patients separately.

Electrocardiogram Changes

Electrocardiographic changes can be used to support of confirm a myocardial infarction. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

Criteria for Acute Myocardial Ischemia (in absence of left ventricular hypertrophy and left bundle branch block):

- ST Elevation: New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads

- ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

Criteria for pathological Q-wave:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III and aVF). (The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.)

Criteria for Prior Myocardial Infarction:

- Pathological Q-waves, as defined above
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Myocardial Infarction Subtypes

Several MI subtypes are commonly reported in clinical investigations and each are defined below:

Spontaneous MI:

Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q-waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

If biomarkers are elevated from prior infarction, then a spontaneous MI is defined as:

One of the following:

- Clinical presentation consistent with ischemia

- ECG evidence of acute myocardial ischemia
- New pathological Q-waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

AND

Both of the following:

- evidence that cardiac biomarker values were decreasing (e.g., 2 samples 3-6 hours apart) prior to the suspected MI. (If biomarkers are increasing or a peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.)
- ≥ 20% increase (and >URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

Percutaneous Coronary Intervention-related Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

Biomarker elevations within 48 hours of PCI:

- troponin or CK-MB (preferred) > 3x URL and
- no evidence that cardiac biomarkers were elevated prior to the procedure; or
- both of the following must be true: ≥ 50% increase in the cardiac biomarker result, and evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

New Pathological Q-waves

Autopsy Evidence of Acute MI

Coronary Artery Bypass Grafting-related Myocardial Infarction

Peri-coronary artery bypass graft surgery (CABG) MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

Biomarker elevations within 72 hours of CABG:

- troponin or CK-MB (preferred) >5x URL and
- no evidence that cardiac biomarkers were elevated prior to the procedure; or
- both of the following must be true: ≥ 50% increase in the cardiac biomarker result, and evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

AND

One of the following:

- new pathological Q-waves persistent through 30 days
- new persistent non-rate-related LBBB
- angiographically-documented new graft or native coronary artery occlusion
- other complication in the operating room resulting in loss of myocardium
- imaging evidence of new loss of viable myocardium

OR

Autopsy evidence of acute MI

Silent Myocardial Infarction

Silent MI is defined by the following:

No evidence of acute MI

AND

Any one of the following criteria:

- New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Autopsy evidence of a healed or healing MI

Common Classification Schemes for Myocardial Infarction Categories

For some trials, categorization of MI endpoints may be helpful or necessary using one or more of the classification schemes below:

By the Universal MI Definition:

Clinical classification of different types of myocardial infarction

Type 1

Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection

Type 2

Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension or hypotension

Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a

Myocardial infarction associated with PCI

Type 4b

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5

Myocardial infarction associated with CABG

By ECG features:

- ST-elevation MI (STEMI). (Additional subcategories may include: Q-wave; non-Q-wave; and unknown [no ECG or ECG not interpretable].)
- Non-STEMI (Additional subcategories may include: Q-wave; non-Q-wave; and unknown [no ECG or ECG not interpretable].)
- Unknown (no ECG or ECG not interpretable)

By Biomarker Elevation (per Universal MI Definition)

The magnitude of cardiac biomarker elevation can be calculated as a ratio of the peak biomarker value divided by the 99th percentile URL. The biomarker elevation can be provided for various MI subtypes, as shown in the example below.

Classification of the different types of myocardial infarction according to multiples of the 99th percentile URL of the applied cardiac biomarker

Multiples x 99%	MI Type 1 (spontaneous)	MI Type 2 (secondary)	MI Type 3[1] (sudden death)	MI Type 4[2] (PCI)	MI Type 5[2] (CABG)	Total Number
1-2x						
>2-3x						
>3-5x						
>5-10x						
>10x						
Total number						

1 Biomarkers are not available for this type of MI since the patients expired before biomarker determination could be performed

2 For the sake of completeness, the total distribution of biomarker values should be reported. The hatched areas represent biomarker elevations below the decision limit used for theses types of MI

STROKE

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Stroke Classification

- Ischemic stroke is defined as an acute episode of focal cerebral, spinal or retinal dysfunction caused by an infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

- Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular or subarachnoid hemorrhage.

- Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

Stroke Disability

Stroke disability should be measured by a reliable and valid scale in all cases. For example, the modified Rankin Scale may be used to address this requirement:

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Additional considerations

In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized.

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction, not the transience of the symptoms. In addition to laboratory documentation of infarction, persistence of symptoms is an acceptable indicator of infarction. Thus, symptom transience should be defined for any clinical trial in which it will be used to distinguish between transient ischemia and infarction.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences

Office of Biostatistics

STATISTICAL REVIEW

RECORD Analysis Based on Re-adjudicated Events

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON ROSIGLITAZONE

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting, June 5-6, 2013

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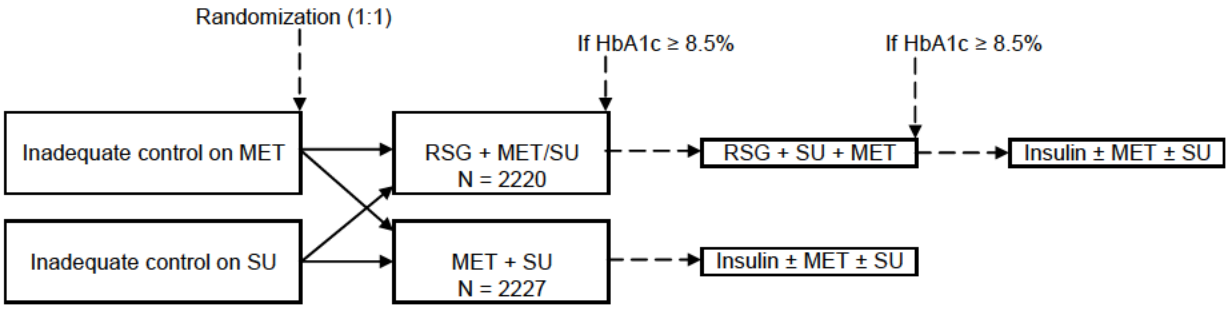
1. Introduction

RECORD was a randomized, open-label clinical trial designed to compare the cardiovascular safety of rosiglitazone (RSG) as an add-on to metformin (MET) or a sulfonylurea (SU) to an active control of metformin plus sulfonylurea. The primary endpoint of RECORD was a composite of cardiovascular death and cardiovascular hospitalization. The treatment randomization scheme of RECORD is summarized in Figure 1. Subjects randomized to RSG who recorded an HbA_1C greater than or equal to 8.5% on two consecutive occasions at least one month apart added the alternate background medication (MET or SU) and received triple therapy (RSG + MET + SU). If subjects on RSG continued to have elevated HbA_1C while on triple therapy, they started insulin and discontinued RSG. Subjects on MET + SU who exceeded the 8.5% HbA1C limit twice in two months also received insulin[1].

Figure 1. RECORD Study Design



Source: Home *et al*. (2004)[1]

According to the final study report of RECORD[2], the estimated hazard ratio and corresponding 95% confidence interval for the pre-specified primary endpoint of cardiovascular hospitalization and cardiovascular death associated with RSG was 0.99 (0.85, 1.16). The corresponding estimated hazard ratio and 95% confidence interval for cardiovascular death was 0.84 (0.59, 1.18), for myocardial infarction 1.14 (0.80, 1.63), and for stroke 0.72 (0.49, 1.06). While the analysis results for RECORD did not suggest an overall increased cardiovascular risk associated with RSG, the trial's design, conduct and adjudication process of cardiovascular adverse events and deaths have been criticized in the scientific literature[3] and in a review by an FDA scientist, Dr. Thomas Marciniak. The adjudication process of RECORD raised questions about the quality of event reporting, ascertainment and capture of follow-up dates. In response to the criticisms of RECORD, the Duke Clinical Research Institute (DCRI) was contracted to review all available information relative to cardiovascular event adjudication collected during the conduct of RECORD, collect additional information if available, and re-adjudicate all deaths, potential myocardial infarctions and strokes. Note that the cardiovascular endpoints of interest re-adjudicated by the DCRI and discussed in this document no longer include cardiovascular hospitalization, which was part of the original primary endpoint of RECORD.

This review does not discuss the DCRI re-adjudication process nor its ability to address the limitations of RECORD. This topic is discussed in detail in the reviews authored by Dr. Preston Dunnmon and Dr. Karen Mahoney. This review maps the re-adjudication of death, myocardial infarctions and strokes, conducted by the DCRI from the original event adjudication. Then using the re-adjudicated endpoints, statistical analyses are updated from the original statistical assessment of the RECORD trial as presented by Dr. David Hoberman at the 2010 Advisory Committee Meeting. Section 2 of this document discusses patients' disposition and follow-up time in RECORD, Sections 3 and 4 assess the level of agreement between the original adjudication and the DCRI re-adjudication of deaths, MIs and strokes. Section 5 presents the updated statistical analyses using data based on the re-adjudication. Lastly, Section 6 presents sensitivity analyses to assess the robustness of the findings.

2. Subject Disposition and Exposure

The status of any given subject enrolled in RECORD is classified into one of three states:

1. completed the trial,
2. died before trial completion or withdrawal from the study, or
3. withdrawn from the study/lost to follow-up/followed for survival only.

This last category includes subjects who declined to be followed for *CV outcomes* at some time during the trial, but agreed to continue to be followed for *survival*. Subjects are considered to have completed the trial if they were followed for CV outcomes and have a recorded visit between August 2008 and December 2008[a]. The DCRI attempted to find the vital status of all subjects in RECORD, including those who withdrew from the trial. For those subjects who withdrew from the trial, were lost to follow-up, or were followed for survival only; the DCRI classified all subjects' vital status as alive, dead, or unknown. Table 1 below shows the number of subjects in each state for both treatment arms. A detailed map of subjects' disposition in RECORD is shown in Figure 7 in the Appendix.

Table 1. Subjects' Disposition in RECORD

	RSG (*N* = 2220)	**MET + SU** (*N* = 2227)
Completed to last visit	1835 (82.7%)	1797 (80.7%)
Died before trial completion or withdrawal from study	111 (5.0%)	138 (6.2%)
Withdrew from study/lost to follow-up/ followed for survival	274 (12.3%)	292 (13.1%)
Alive	210 (9.5%)	216 (9.7%)
Died	30 (1.4%)	23 (1.0%)
Unknown vital status	34 (1.5%)	53 (2.4%)

Source: created by reviewer

[a]Note that 6 subjects randomized to RSG and 6 subjects randomized to MET + SU completed the trial under this criterion, but died afterwards and their deaths were recorded.

During the conduct of RECORD, prior to the trial's completion on 31 December 2008, 139 subjects randomized to RSG and 160 subjects randomized to MET + SU died[b].

Based on the original trial report produced by GSK, 127 subjects had unknown vital status at the end of the trial. The DCRI successfully resolved the vital status of 40 of these subjects; however 87 subjects still had missing vital status at the end of the DCRI search and adjudication process (34 [1.5%] among subjects randomized to RSG and 53 [2.4%] to MET + SU, see Table 1). The potential impact of subjects with unknown vital status on hazard ratio estimates of mortality is discussed in Section 6.

The total numbers of patient years of follow-up in RECORD were similar in both treatment arms: 12996 in the RSG arm and 12856 in the MET/SU arm (Table 2). Follow-up time until censoring or death, and time until censoring or MACE was comparable between treatment arms throughout the duration of RECORD (Figure 2 and Figure 3, respectively). Note that follow-up for mortality is greater than follow-up for CV outcomes in RECORD, because some subjects agreed to be followed for survival only. The DCRI successfully obtained the vital status of all subjects in the trial except for the 87 subjects discussed previously; however, the CV experience (MI or Stroke) of subjects who withdrew from the study or asked to be followed for survival only is unknown.

Table 2. RECORD Exposure Summary

	RSG (*N* = 2220)	**MET + SU** (*N* = 2227)
Total Patient Years of follow-up (mortality)	12996	12856
Median years of follow-up	5.97	5.89
Total patient years spent on dual therapy[1]	9330 (72%)	10227 (80%)
% subjects who stayed on dual therapy[1] until completion, death or withdrawal	67%	76%
% subjects who added triple therapy or insulin	33%	24%

[c]Defined as time until death, censoring, addition of third therapy, or time of last randomized treatment dose + 30 days.
Source: created by reviewer

Even though the total years of follow-up were comparable between subjects randomized to both treatment arms, the rates of discontinuation from the original randomized dual therapy (RSG + MET/SU or MET + SU) were different between both treatment arms (see Appendix Figure 7 for a detailed mapping of subject disposition and exposure). Table 2 shows that subjects randomized to RSG spent fewer total patient years on dual therapy than subjects randomized to MET + SU (72% vs. 80%), were less likely to stay on dual therapy until completion, death or withdrawal (67% vs 76%) and were more likely to switch to triple therapy or to add insulin treatment (33% vs 24%). Figure 4 shows that the

[b] Fifteen additional deaths were found after this date: 8 among subjects randomized to RSG and 7 among subjects randomized to MET + SU. Thus, a total of 147 (6.6%) subjects randomized to RSG died and 167 (7.5%) subjects randomized to MET + SU died

[c] Based on datasets A_outcom (Mortality Outcome Analysis Data) and A_outmac (MACE outcome Analysis Data) created and submitted to the FDA by DCRI.

time to discontinuation of dual therapy occurred earlier on average among subjects randomized to RSG throughout the duration of the trial. The higher rate of discontinuation from randomized dual therapy among subjects randomized to RSG is a limitation of RECORD.

Figure 2. Time to death or discontinuation from survival follow-up

Source: created by reviewer

Figure 3. Time to MACE or discontinuation from CV follow-up

Source: created by reviewer

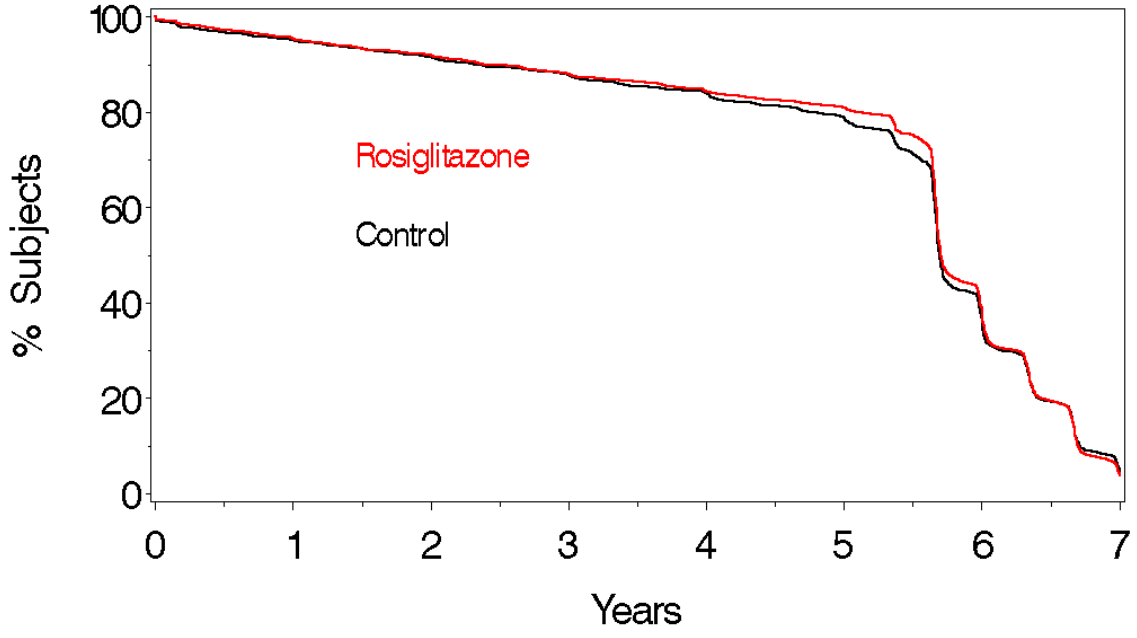
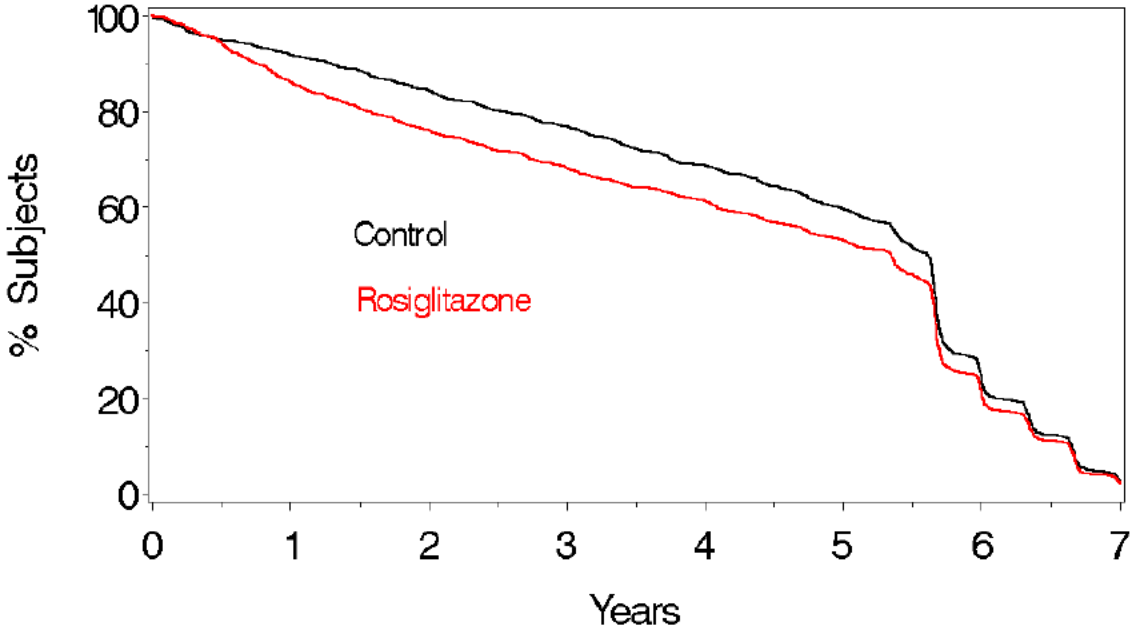


Figure 4. Time to death or discontinuation of dual therapy
Source: created by reviewer



3. Re-adjudication Summaries

3.1 Re-adjudication of Mortality

All suspected deaths in RECORD were reviewed by the DCRI Clinical Endpoint Committee (CEC) according to two definitions: the original RECORD CEC definition and a new definition based on the FDA Standardized Definitions for End Point Events in Cardiovascular Trials[4]. Deaths re-adjudicated by the DCRI were classified as cardiovascular (CV), undetermined, and non-cardiovascular (non-CV). Table 3 shows a summary of the total number of deaths in the original RECORD report (based on the original endpoint definition) and the DCRI re-adjudication based on the new endpoint definition. The DCRI identified 20 additional deaths not found in the original trial's report; 12 of these 20 additional deaths occurred after the end of the trial (31 December 2008).

Table 3. Mortality adjudication summary

	RSG (N=2200)		MET + SU (N=2227)	
	Original	DCRI	Original	DCRI
Total deaths*	135	147	159	167
CV	32	35	38	42
Undetermined	28	61	33	59
CV + Undetermined	60	96	71	101

*Includes 8 deaths on RSG and 7 deaths on MET + SU occurring after 31/12/2008
Source: created by reviewer

Table 4 shows the agreement between the original adjudication of deaths and the DCRI re-adjudication based on the new endpoint definitions by randomized treatment arm. The original adjudication included 3 categories: CV death, non-CV death and death from unknown causes. Two additional categories have been added in Table 4: deaths that were identified but not adjudicated in the original trial's datasets, and deaths that were not identified in the original trial's datasets. All deaths were re-adjudicated by the DCRI as either CV death, non-CV death or death from Undetermined causes.

Few discordant pairs were observed where death was classified as a CV death in the original adjudication and then re-adjudicated as a non-CV death (1 on RSG, 1 on MET+SU). Similarly few non-CV deaths from the original adjudication were classified as CV deaths in the re-adjudication (1 on RSG, 0 on MET+SU).

Twenty four (24) deaths on RSG and 19 on MET + SU were captured in the original submission but were not adjudicated: the DCRI re-adjudicated the majority of these deaths as "Undetermined" (19 of 24 on RSG, and 17 of 19 on MET + SU). As mentioned previously, 20 additional deaths were identified in the DCRI re-adjudication: 12 deaths among subjects randomized to RSG and 8 among subjects randomized to MET + SU. Note that the death counts in Table 4 include 15 total deaths occurring after the completion of the study on 31 December 2008 (these counts are represented in parentheses in Table 4). These late deaths are included in this section for completeness but are excluded from the primary analysis as discussed in Section 5.

The DCRI did not find sufficient information to adjudicate 61 out of 147 deaths on RSG and 59 out of 167 deaths on MET + SU. These deaths were re-adjudicated as "Undetermined". The high proportion of "Undetermined" deaths represents a possible limitation of RECORD. In order to assess the possible impact of these deaths on estimates of hazard ratios, statistical analyses were conducted on deaths re-adjudicated as CV deaths only, as well as deaths re-adjudicated as either CV or Undetermined.

Table 4. Original vs. DCRI adjudication of mortality

Rosiglitazone

Original Adjudication	DCRI Adjudication: CV	Undetermined	Non-CV	Row Total
CV	28	3	1	32
Unknown	4	20	4	28
Non-CV	1	8	42	51
Not Adjudicated	1	18 (+1)	4	23 (+1)
Not Identified	1	4 (+7)	0	5 (+7)
Column Total	35	53 (+8)	51	139 (+8)

MET + SU

Original Adjudication	DCRI Adjudication: CV	Undetermined	Non-CV	Row Total
CV	33	4	1	38
Unknown	8	19	6	33
Non-CV	0	11 (+1)	56 (+1)	67 (+2)
Not Adjudicated	1	17	1	19
Not Identified	0	3 (+4)	0 (+1)	3 (+5)
Column Total	42	54 (+5)	64 (+2)	160 (+7)

Deaths in parentheses are additional deaths that occurred after 31 December 2008.
Source: created by reviewer.

3.2 Re-adjudication of MACE

According to the DCRI report, each potential myocardial infarction was reviewed independently by two physicians. If the two physicians agreed on their adjudication of a potential MI, the endpoint classification was considered complete. If the physicians disagreed, a panel of at least three faculty physicians was called to review the potential event and a decision was reached by consensus. Potential strokes were reviewed by at least two independent neurologists in a similar manner to myocardial infarctions. Sections 3.2.1 and 3.2.2 show the agreement between the original adjudication of MIs and Strokes and the DCRI re-adjudication.

3.2.1 Re-adjudication of Myocardial Infarction

Table 5 shows the agreement between the original adjudication of MI and the re-adjudication conducted by the DCRI. Only 1 event on RSG and 2 events on MET + SU were originally adjudicated as MI but re-adjudicated as Non-MI. The DCRI identified 17 additional MIs not captured in the original study report: 9 on RSG and 8 on MET + SU.

Table 5. Original vs. DCRI adjudication of MI

Rosiglitazone

Original	DCRI Adjudication: MI	Non-MI
MI	63	1
Non-MI / Not reported	9	-

MET + SU

Original	DCRI Adjudication: MI	Non-MI
MI	54	2
Non-MI / Not reported	8	-

Source: created by reviewer

3.2.2 Re-adjudication of Stroke

Table 6 shows the agreement between the original adjudication of Stroke and the re-adjudication conducted by the DCRI. Three events on RSG and 4 events on MET + SU were originally adjudicated as Stroke but re-adjudicated as Non-Stroke. The DCRI found 15 additional strokes not found in the original report: 10 on RSG and 5 on MET + SU.

Table 6. Original vs. DCRI adjudication of Stroke

Rosiglitazone

Original	DCRI Adjudication: MI	DCRI Adjudication: Non-MI
MI	43	3
Non-MI / Not reported	10	-

MET + SU

Original	DCRI Adjudication: MI	DCRI Adjudication: Non-MI
MI	59	4
Non-MI / Not reported	5	-

Source: created by reviewer

4. Statistical Analyses Based on Re-adjudicated Outcomes

The primary outcome of RECORD was a composite of cardiovascular death and cardiovascular hospitalization. According to the final study report of RECORD[2], the estimated hazard ratio and corresponding 95% confidence interval for this outcome associated with RSG was 0.99 (0.85, 1.16). Analyses presented during the 2010 Endocrinologic and Metabolic Drugs Advisory Committee Meeting on this product focused on a different outcome: MACE (CV + Undetermined death, MI and Stroke) and its individual components. The analyses in this document focus on re-adjudicated MACE and its individual components.

The method of analysis used in the original report and the DCRI report is a Cox proportional hazards model with treatment (RSG or comparator) as a covariate. The hazard ratios and corresponding 95% confidence intervals reported in this document were obtained following the same approach.

Given that treatment discontinuation was different between the two treatment arms, as described in Section 2; two analysis populations were used in this document to evaluate the re-adjudicated outcomes:

1. Full follow-up population for each subject and outcome. The full follow-up time for mortality includes all available follow-up time, whereas full follow-up for MACE and its individual components includes only the time during which subjects agreed to be followed for CV outcomes.
2. On dual treatment + 30 days population, censors subjects on the last day of dual treatment + 30 days.

4.1 Mortality Findings

Table 4 shows that among subjects randomized to RSG, fewer total deaths were observed before 31 December 2008 (139 vs 160), fewer CV deaths (35 vs 42), fewer CV + Undetermined deaths (88 vs 96), and fewer Non-CV deaths (51 vs 64) compared to subjects randomized to MET + SU based on the re-adjudicated causes of death.

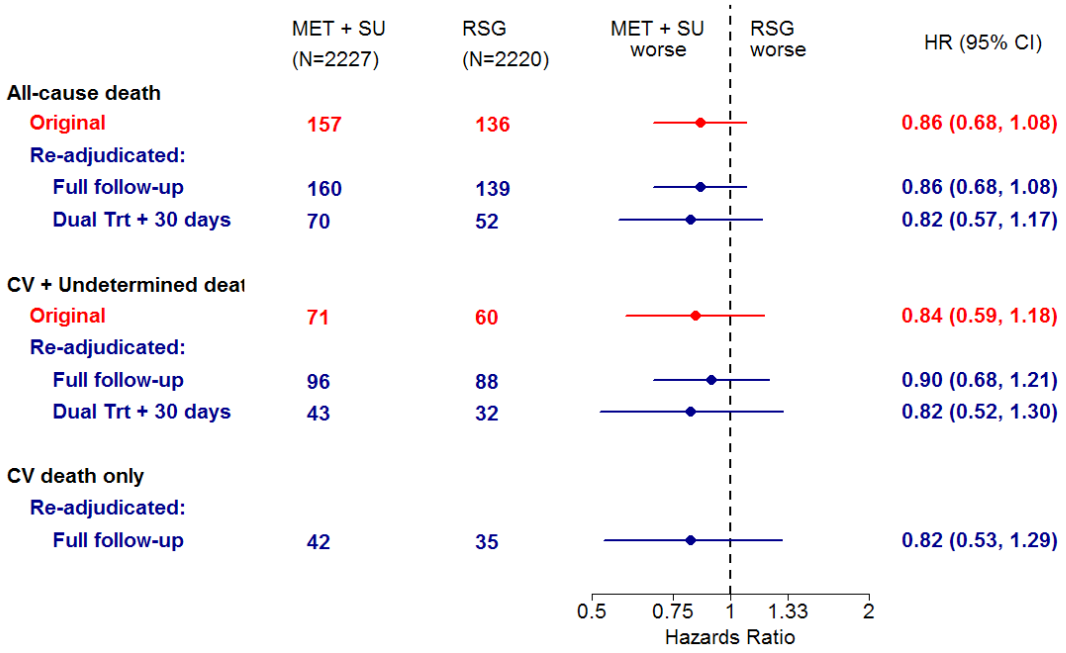
Figure 5 shows the estimated hazard ratios for death associated with RSG relative to MET + SU. The number of events and hazard ratio estimates in the original trial report are shown in red. The re-adjudicated counts of events and hazard ratio estimates are shown in blue based on the full time of follow-up until 31 December 2008 and the time on dual treatment + 30 days.

The original trial report estimated a HR of 0.86 with corresponding 95% CI (0.68, 1.08) for all cause death associated with RSG and 0.84 (0.59, 1.18) for CV death (adjudicated as CV or Unknown). The estimated hazard ratios for all cause death based on the DCRI re-adjudicated endpoints were 0.86 (0.68, 1.08) based on full follow-up and 0.82 (0.57, 1.17) based on time on dual treatment + 30 days. The estimated hazard ratios for CV + Undetermined death (Figure 5) were similar for both the original report and the re-adjudicated outcomes. The estimated hazard ratio for CV death based on the re-adjudicated outcomes and full follow-up (excluding deaths re-adjudicated as "Undetermined") were consistent with the estimated hazard ratios for CV + Undetermined deaths. Note that the original report grouped CV deaths and Undetermined deaths together as "Cardiovascular" and did not conduct analyses on deaths adjudicated as CV only; Figure 5 shows results from this analysis (CV deaths without Undetermined deaths) based on the re-adjudicated events only.

Overall, analyses of all cause death, deaths re-adjudicated as CV or Undetermined, and deaths re-adjudicated as CV only, were consistent with the original report and show no evidence of increased risk of death associated with RSG.

Figure 5. Original vs. re-adjudicated hazard ratio estimates of mortality

Source: created by reviewer



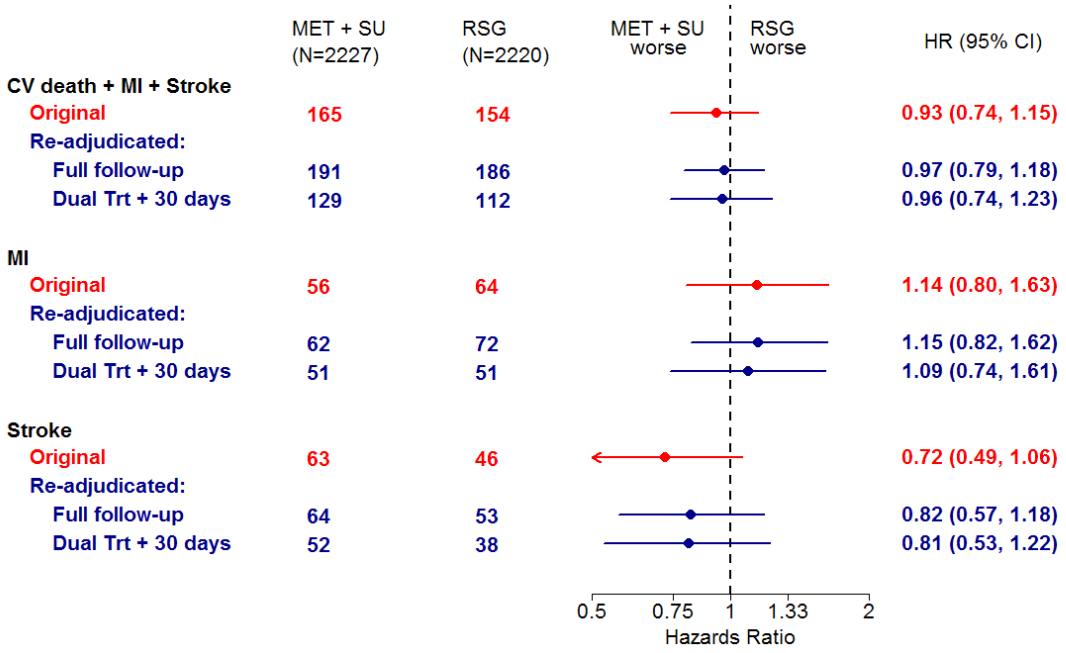
4.2 MACE Findings

Figure 6 shows the estimated hazard ratios for MACE (CV + Undetermined death, MI and Stroke), MI separately and Stroke separately comparing RSG to MET + SU. The estimated hazard ratios based on re-adjudicated events were similar to the originally reported estimates. The estimated hazard ratio of strokes associated with RSG based on re-adjudicated strokes and full follow-up was numerically smaller than 1 with a non-statistically significant 95% CI: 0.82 (0.57, 1.18). The estimated hazard ratio of MIs associated with RSG based on re-adjudicated MIs and full follow-up was numerically larger than 1 with a non-statistically significant 95% CI: 1.15 (0.82, 1.62).

Kaplan-Meier plots of time until death, MACE, MI and Stroke based on the re-adjudicated outcomes and full follow-up are shown in the Appendix (Figures 8-11).

Figure 6. Original vs. re-adjudicated hazard ratio estimates of MACE

Source: created by reviewer



4.3 Sensitivity analyses

4.3.1 Subjects with missing vital status

DCRI was unable to determine the vital status of 87 subjects (approximately 2%): 34 randomized to RSG and 53 to MET + SU (Table 1). In order to assess the potential effect of these subjects on rate ratio estimates of death, had they been followed until the trial's completion, we calculated the expected number of deaths during the unobserved time until completion of RECORD in these 87 subjects under an extreme scenario assuming a five-fold increase in the risk of death associated with RSG relative to MET + SU (i.e. HR = 5.0). For the 53 subjects in the MET + SU arm with unknown vital status we assumed an annual death rate of 1.2%, similar to the rate observed during the full follow-up of RECORD. For the 34 subjects in the RSG arm with unknown vital status, we assumed a rate of events 5 times larger than the MET + SU arm (6% annual death rate). Rate ratios were estimated dividing the number of deaths by the total years of follow-up (observed + imputed).

Table 7 shows the estimated rate ratio of death under the observed full follow-up in RECORD and the estimated rate ratio under the scenario described above adding the observed and the imputed deaths. Even under this extreme scenario (HR = 5 during the unobserved time) the estimated rate ratio of all cause mortality would increase by only approximately 5% (from 0.86 to 0.90). Thus, given the small relative number of subjects with missing vital status (87 out of 4447), it is unlikely that the rate ratio estimates of

death would change substantially had these 87 subjects been observed until completion of the trial and their vital status was known.

Table 7. Rate ratio estimates of death assuming a HR = 5 in subjects with missing vital status comparing RSG to MET + SU

	MET + SU	RSG	Rate Ratio (95% CI)
Known vital status:	**N = 2174**	**N = 2186**	
Unknown vital status:	**N = 53**	**N = 34**	
All Cause Mortality			
Observed	160	139	0.86 (0.69, 1.08)
Expected (Observed + Imputed)	163.2	147.8	0.90 (0.72, 1.13)

* Assuming a death rate of 1.2% per patient year in the MET + SU arm and 6% in the RSG arm during the unobserved time in the 87 subjects with missing vital status.
Source: created by reviewer

4.3.2 Use of statins

The use of statins was balanced at baseline between subjects randomized to RSG and MET + SU; however, throughout the duration of RECORD more subjects on the RSG arm used statins as shown in Table 8. Among subjects randomized to RSG, 55% used statins at some point of the trial, including subjects who started statin use after experiencing MACE. During the time where subjects were being followed for CV endpoints prior to experiencing an event, 46% of the total patient years in the RSG arm included the use of statins, whereas 37% of the total patient years in the MET + SU arm did.

Table 8. Statin use by treatment

	MET + SU	RSG
Baseline Statin use	19%	18%
Subjects with Statin use at any time	47%	55%
Time on Statins during CV follow-up	37%	46%

Source: created by reviewer

The imbalance in the use of statins represents a limitation of RECORD. In order to assess the possible effect of this imbalance on estimated hazard ratios, Table 9 shows hazard ratio estimates obtained using the DCRI re-adjudicated outcomes and full follow-up unadjusted for use of statins, as well as two models adjusted for use of statins. The first model used a binary indicator (yes/no) for the use of statins recorded at any time during the trial and the second model used a Cox model with time-varying statin use as a covariate. Hazard ratio estimates adjusted for time-varying use of statins were similar to the unadjusted estimates. Hazard ratio estimates adjusted for statin use as a binary variable produced hazard ratio estimates 2%-7% higher than the unadjusted estimates. These models are consistent with previous estimates produced by GSK and by FDA reviewer Dr. David Hoberman who estimated that if the proportion of statin users at year 4 had been the same in both treatment groups, the corresponding inflation factor in the

estimated HR of the primary RECORD outcome (composite of CV death and CV hospitalization) would be approximately 1.02.

Table 9. Hazard ratios comparing RSG to MET + SU adjusted for use of statins

Outcome	Hazard Ratio (95% CI)		
	Unadjusted for statins	Adjusted for statins (binary)	Adjusted for statins (time-varying)
All cause death	0.86 (0.68, 1.08)	0.88 (0.70, 1.11)	0.86 (0.69, 1.08)
CV Death, MI and Stroke	0.97 (0.79, 1.18)	1.01 (0.83, 1.24)	0.98 (0.80, 1.20)
MI (fatal + non-fatal)	1.15 (0.82, 1.62)	1.23 (0.87, 1.72)	1.16 (0.83, 1.63)
Stroke (fatal + non-fatal)	0.82 (0.57, 1.18)	0.86 (0.59, 1.23)	0.83 (0.58, 1.19)

Source: created by reviewer

5. Summary

The DCRI re-adjudicated all deaths, potential MI and strokes captured in RECORD. The DCRI found additional events (deaths, MI and strokes) as well as additional follow-up time and updated vital status for subjects in the trial relative to the original trial report as discussed in this document. The results of statistical analyses conducted on the re-adjudicated outcomes were consistent with the original report of RECORD.

- We found no statistically significant difference in the hazard ratio of all-cause death associated with RSG (HR=0.86, 95% CI 0.68-1.08).
- We found no statistically significant difference in the hazard ratio of the composite MACE associated with RSG (HR=0.97, 95% CI 0.79-1.18).
- The estimated hazard ratio of strokes was numerically smaller than 1 with a non-statistically significant 95% CI: 0.82 (0.57, 1.18).
- The estimated hazard ratio of MI associated with RSG based on re-adjudicated MIs was numerically larger than 1 with a non-statistically significant 95% CI: 1.15 (0.82, 1.62).

The DCRI collected the vital status of all subjects in the trial, except for 87 subjects with missing vital status (34 randomized to RSG and 53 to MET + SU). We showed in Section 4.3.1 that the missing vital status of these subjects is not likely to have a major impact on the rate ratio estimates of death.

In this document we have discussed and addressed three limitations of RECORD:

1. The time to discontinuation of dual therapy occurred earlier, on average, among subjects randomized to RSG throughout the duration of the trial. In order to partially address this issue, statistical analyses were conducted on both a full

follow-up population (as randomized) and an "On Dual Treatment + 30 days" population. Both sets of analyses yielded consistent findings.

2. A large percentage of all deaths occurring before 31 December 2008 could not be re-adjudicated as Cardiovascular or Non-CV (38% on RSG, 34% on MET + SU). Hazard ratio estimates of all-cause death, CV + Undetermined death, and CV death alone all showed no evidence of increased risk associated with RSG.

3. Subjects randomized to RSG were more likely to use statins at some time during the trial. Our sensitivity analyses suggest that this differential use of statins did not have a major impact on the findings of RECORD.

Other possible limitations of RECORD, such as its open-label design, are not discussed in this document as these cannot be resolved through statistical analysis.

Overall, the DCRI re-adjudication of death, MI and stroke, and their corresponding statistical analyses were consistent with the original trial's report. These results show no statistically significant evidence to suggest an increased cardiovascular risk associated with RSG.

6. References

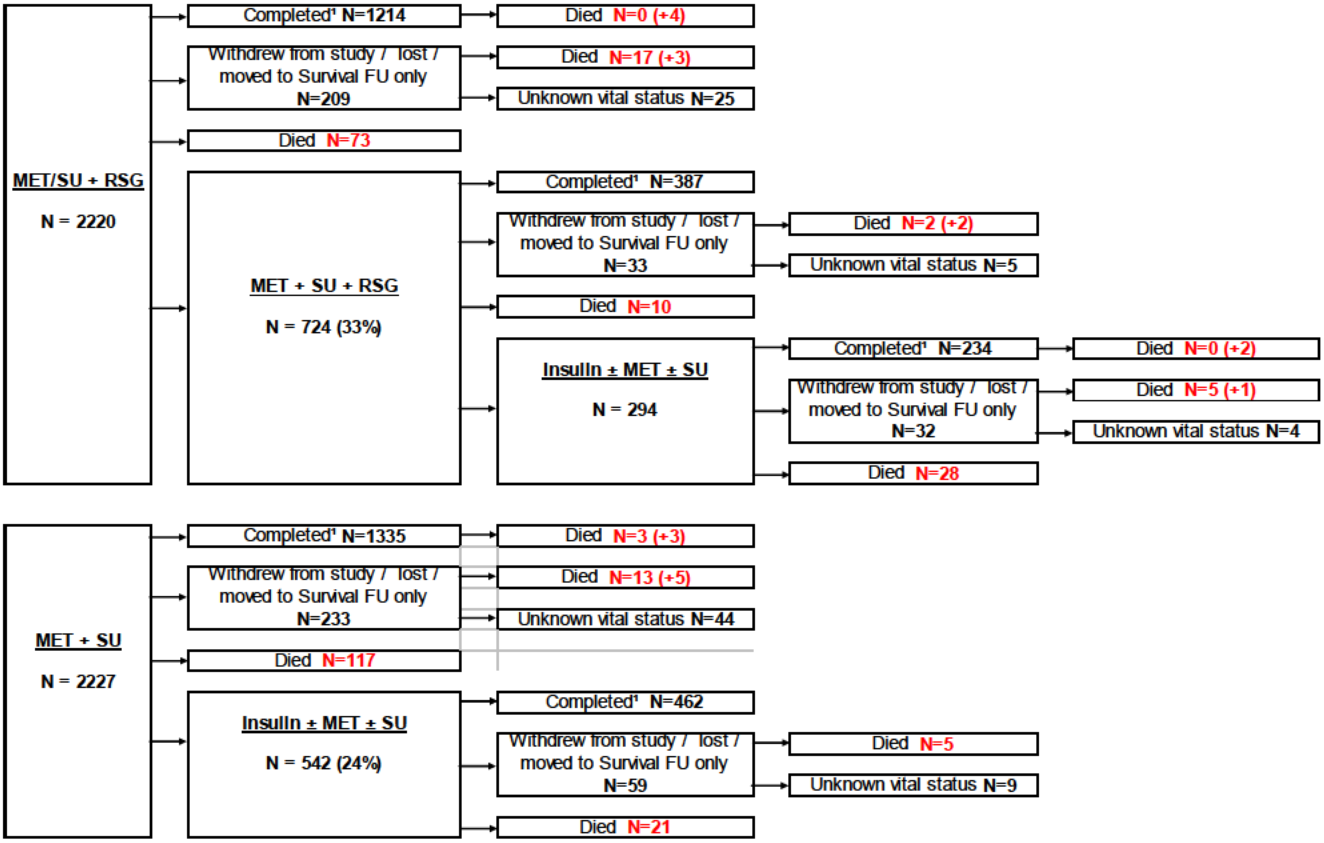
1. Home PD, Pocock SJ, Beck-Nielsen H, *et al*. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. *Diabetologia*. 2005; 48:1726-1735
2. Home PD, Pocock SJ, Beck-Nielsen H, *et al*. (RECORD Study Team). Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD): a multicentre, randomised, open label trial. *Lancet*. 2009; 373: 2125-2135.
3. Nissen SE. Setting the RECORD Straight. *JAMA*. 2010;303(12):1194-1195
4. Hicks KA, Hung JM, Mahaffey KW, *et al*. Standardized Definitions for End Point Events in Cardiovascular Trials. 2010. http://www.cdisc.org/stuff/contentmgr/files/0/2356ae38ac190ab8ca4ae0b222392b37/misc/cdisc_november_16__2010.pdf

7. Appendix

Appendix 1. Disposition of Subjects in RECORD

Figure 7 shows a detailed map of subjects' disposition in RECORD. The map shows the number of subjects who were followed for CV outcomes until at least August 2008 ("Completed"), withdrew from the study or were lost to follow-up or were followed for mortality only and the number of subjects who died throughout the trial. The map also shows the treatment disposition of all subjects and the disposition of the 87 subjects with unknown vital status.

Figure 7. RECORD Full Disposition



¹Completed status means participants were followed for CV outcomes until at least August 2008
(+) Deaths not captured in GSK's datasets but found by the DCRI
*8/147 deaths on RSG and 7/167 deaths on MET/SU occurred after 12/31/2008
Source: created by reviewer from datasets A_outcom, A_enddt, cmanal, death, end, gsk_dth, tteanal

Appendix 2. Survival Plots of Time until Death, MACE, MI and Stroke

Figure 8. All-Cause Mortality based on re-adjudicated outcomes and full follow-up

Source: created by reviewer

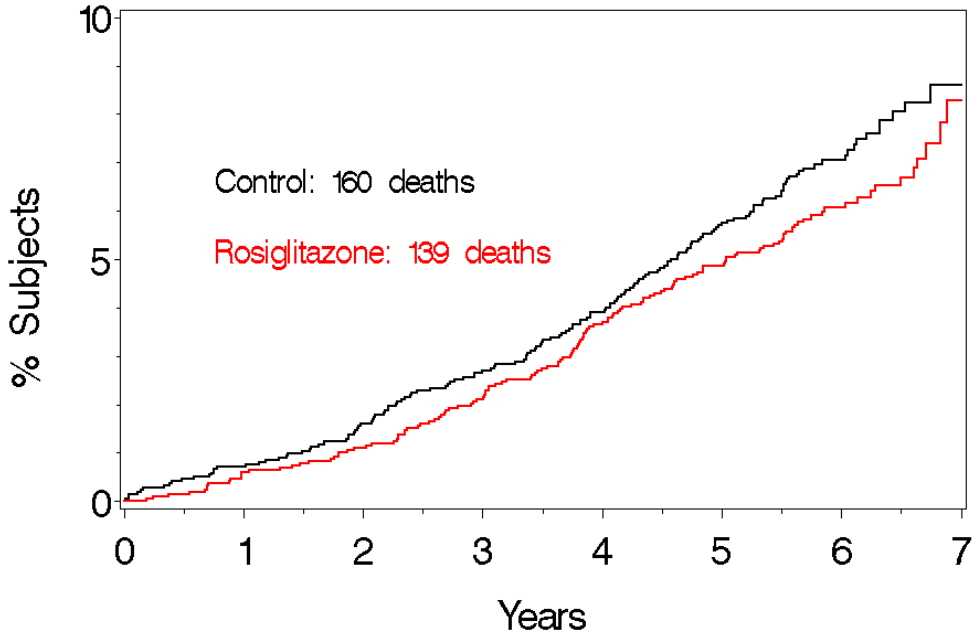


Figure 9. MACE based on re-adjudicated outcomes and full follow-up

Source: created by reviewer

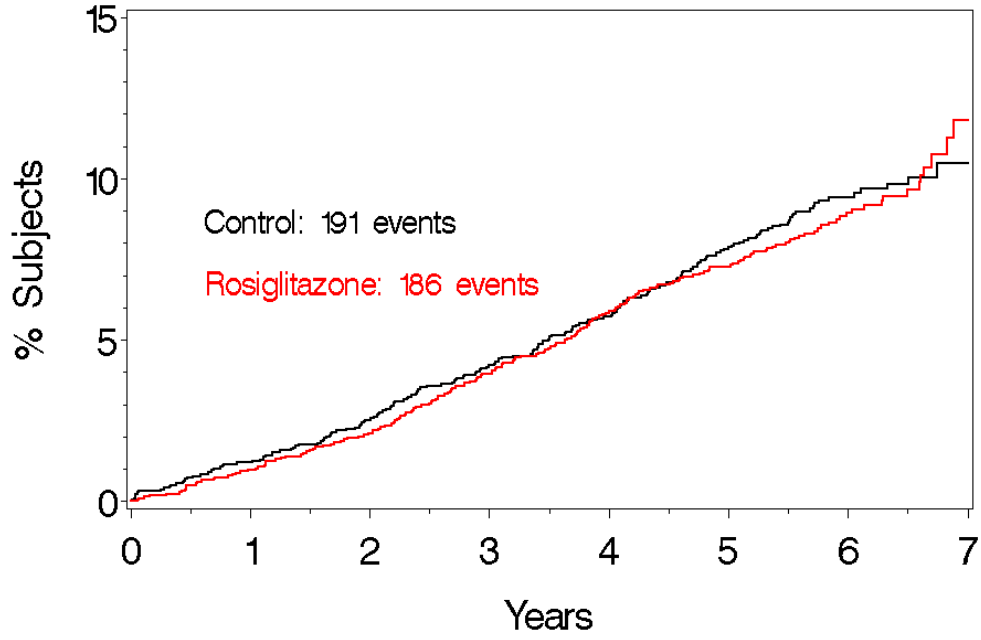


Figure 10. MI based on re-adjudicated outcomes and full follow-up

Source: created by reviewer

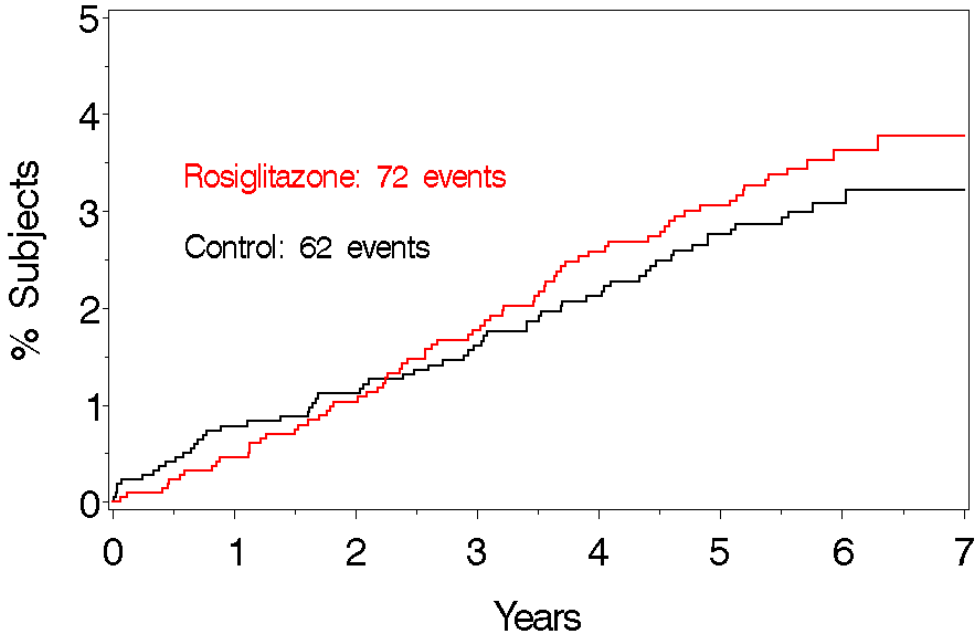
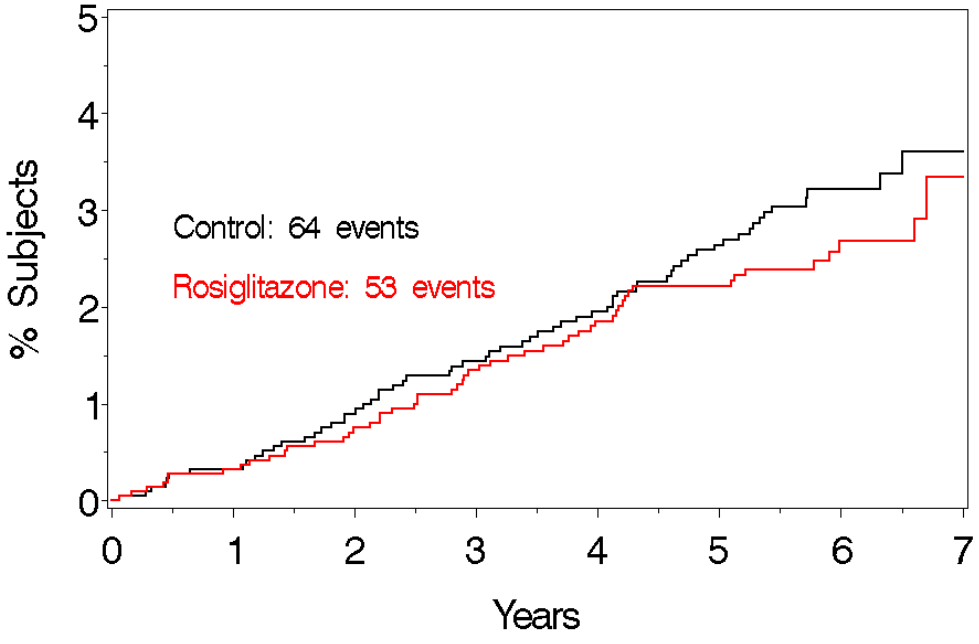


Figure 11. Strokes based on re-adjudicated outcomes and full follow-up

Source: created by reviewer



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW

Meta-Analysis of Rosiglitazone

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON ROSIGLITAZONE

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting, June 5-6, 2013

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1 BACKGROUND

This document describes the methods used and presents the findings from the 2010 FDA rosiglitazone meta-analysis. In addition, results from new analyses are also included to allow for further understanding of the findings from the 2010 meta-analysis and to address statistical concerns raised at the 2010 Advisory Committee (AC) meeting. The new analysis is based on an alternate grouping of trials that reflects specific trial characteristics; such a grouping we refer to as trial-level groups. The alternate trial-level groups are defined by whether the randomized treatment, placebo or active controlled, was administered as a monotherapy or in combination with a background or add-on therapy. These alternate trial-level groups are intended to permit a better understanding of findings from the 2010 meta-analysis. That is, because the trial-level groups explored in the 2010 meta-analysis fixed only one study design element (type of control or type of add-on therapy), it was not possible to evaluate, for example, whether the signal from the placebo-controlled trials was similar in the trials with treatment administered as a monotherapy or in combination with another antidiabetic drug. Also presented in this briefing document, in response to concerns raised by statisticians on the AC panel in 2010, are results from alternative statistical models that incorporate information from trials with no events.

This document does NOT discuss

1) results from the 2010 FDA cardiovascular meta-analysis of Actos (pioglitazone, marketed by Takeda); pioglitazone is a antidiabetic drug in the same class as rosiglitazone; nor
2) how the results from the 2007 FDA rosiglitazone meta-analysis compare with the 2010 meta-analysis.

Refer to the 2010 FDA briefing document for additional details on these two points.

2 METHODS

2.1 Trial Inclusion/Exclusion Criteria

Trials conducted by GlaxoSmithKline (GSK) were included in the FDA meta-analyses if they were randomized, double-blind trials between 2 months and 2 years in duration completed by December 2009 with targeted total daily dose of 4 or 8 mg with available subject-level data. Trials with investigative drugs that were not FDA approved were excluded. Non-randomized or open-label trial extension phases were excluded.

Trials with duration exceeding 2 years were excluded from the meta-analysis since they enrolled a large number of subjects and would therefore dominate the findings, and are viewed as providing independent sources of information.

2.2 Endpoints

Safety endpoints were identified by GSK using a FDA specified list of preferred terms (PT) from the Medical Dictionary for Regulatory Activity (MedDRA) coding system (see appendix in 2010 briefing document for list of terms). For trials that prospectively collected and adjudicated events, the adjudicated event was used. Events that occurred from randomization up to and including 30 days after last dose on study drug were included. The last dose on study drug was truncated to the protocol defined nominal treatment duration plus 30 days.

The primary endpoint was major adverse cardiovascular event (MACE), defined as cardiovascular death, stroke, or myocardial infarction. Secondary safety outcomes were cardiovascular death, stroke, myocardial infarction (MIF), all-cause death, serious myocardial ischemia, total myocardial ischemia, and

congestive heart failure (CHF). Myocardial ischemia (MIS) was a broad category of events, including angina, myocardial infarction, ventricular fibrillation and other events based on adverse events. Serious myocardial ischemia events were myocardial ischemia events based on serious adverse events.

2.3 Statistical Methods

The primary analysis method was the exact method for a stratified odds ratio and associated 95% confidence interval[1]. The stratification factor was the trial.

Due to the concern raised at the 2010 AC meeting regarding how the primary analysis method handles information from trials without any events, results from the following two alternative statistical models are presented: Bayesian fixed effect logistic regression model and stratified Mantel-Haenszel method for the risk difference, stratified by trial. The alternative statistical models, which incorporate information from trials without any events, are applied to the primary and secondary cardiovascular endpoints for the primary analysis set, and the MACE endpoint in the alternate trial-level groups described in Section 2.4.

The Bayesian fixed effect logistic regression model assumes a common log-odds ratio across trials. The average event probability (on the log-odds scale) in a trial is assumed to follow a hierarchical distribution with unknown parameters to be estimated from the data. Parameters for the prior distribution were chosen to be reasonably diffuse to minimize the prior distribution's influence on the posterior evaluation. Estimates of the odds ratio are presented along with the 95% credible interval (CrI). Additional details of this model are given in Section 5.2.

Estimates of the risk difference and associated 95% CI's are calculated using Mantel-Haenszel methods stratified by trial[2]. Note that estimates from this model were presented at the 2010 AC meeting but were not included in the 2010 FDA briefing document.

The primary analysis group consisted of all subjects in trials that met the trial inclusion and exclusion criteria above. Subjects assigned to treatment that includes rosiglitazone were compared to subjects assigned to treatment that did not include rosiglitazone. Group definition was based on randomization, intent-to-treat.

2.4 Alternate Trial-Level Groups

To allow for further understanding of the findings from the 2010 meta-analysis, analyses were performed in refined subgroups of trials. These alternate trial-level groups are based on whether the randomized treatment, placebo- or active-control, was administered as a monotherapy or in combination with a background or add-on therapy. In addition, because the signal from insulin add-on trials (which were all placebo-controlled) was notable in the 2010 meta-analysis, the placebo-controlled combination therapy trials are analyzed including and excluding the insulin add-on trials. For reference, results from the following trial groups examined in the 2010 meta-analysis are presented: placebo-controlled trial group, active-controlled trial group, and insulin add-on trialgroup.

Note that trials may contribute to more than one type of randomized comparator and/or types of add-on therapy. For example, in a trial that randomized subjects to placebo, an active-control, or rosiglitazone, the rosiglitazone arm and placebo arm would contribute to the placebo-controlled trial group, while the (same) rosiglitazone arm and the active-control arm would contribute to the active-controlled trial group. For a given analysis events were not double counted.

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[1] Agresti, A. Categorical Data Analysis. John Wiley & Sons. 1990.

[2] Greenland, S., and Robins, J. M. (1985), Estimation of a Common Effect Parameter from Sparse Follow-Up Data. *Biometrics* 41: 55-68.

3 RESULTS

3.1 Primary Analysis Set

3.1.1 Reclassification of Select Studies

Based on the reexamination of study synopsis for trials included in the 2010 meta-analysis, several trials in the various trial-level groups were reclassified. Results presented in this briefing document are based on the reclassification of these studies. The following studies were reclassified:

- *Study 284*: This study is reclassified as a metformin controlled study instead of a placebo controlled study since subjects were randomized to either rosiglitazone or metformin. All subjects received open-label metformin, making it also a metformin add-on study.
- *Study 311*: Select study arms are no longer classified as metformin controlled since subjects were randomized to either rosiglitazone (4mg QD or 4mg BID) or placebo. This study is still classified as being a monotherapy and metformin add-on study; the classification depends whether subjects were treated for ≥ 2 months with a stable dose metformin prior to randomization, which the protocol specified they were to maintain throughout the study.
- *Study 374*: This study is reclassified as a placebo controlled background add-on study instead of a placebo controlled monotherapy study since all subjects received an alpha-glucosidase as a background concomitant medication through the study period. It should also be noted that trials that included unapproved drugs for the treatment of type 2 diabetes – either as background or add-on therapies – were not included in the meta-analysis. An exception was made for this study since this trial included patients taking arcabose (approved) or voglibose (not approved).
- *Study 712753/002*: This study is reclassified from a placebo controlled metformin add-on study to a metformin controlled metformin add-on study. The reason for the reclassification is that subjects were randomized at baseline to a fixed dose combination therapy of rosiglitazone and metformin (4mg RSG/2g MET) or high dose metformin (MET 2.5g). Thus, considering the 2g MET the subjects received as a metformin add-on therapy, the comparison is between 4mg RSG and 0.5g metformin.

3.1.2 Primary Analysis Trials and Patient Populations

A summary of the populations for each of the alternate trial-level groups is displayed in Table 1. Note that some trial groupings were not exclusive since trials may have been used in more than one group.

In total, the 52 trials enrolled 16,995 subjects, 10,039 (59%) randomized to rosiglitazone and 6,956 (41%) to the comparator. The majority of trials had a placebo-control arm with most of them having treatment administered as a combination therapy. Among the 14 trials that had an active-control arm, the majority of trials utilized sulfonylurea as the control arm followed by metformin. While there were more trials with the active-control administered as a monotherapy compared to combination therapy (9 trials compared to 5 trials), the number of subjects in the monotherapy trial group (2886) was similar to the number in the combination therapy trial group (2464).

There were more subjects enrolled in trials between 2 and 6 months in duration (69%), followed by 6 months to 1 year (25%) and 1 and 2 years (5%).

Table 1. Summary of alternate trial-level groups

Trial Group	Trials	Comparator N	Rosiglitazone N	Total N
Primary analysis set	52	6956	10039	16995
Placebo controlled	44	4972	7453	12425
Monotherapy	10	781	1830	2611
Combination therapy (incl. insulin)	35	4191	5623	9814
Combination therapy (excl. insulin)	29	3376	4605	7981
Insulin add-on only	7	815	1018	1833
Active controlled	14	2575	2775	5350
Monotherapy	9	1350	1536	2886
Combination therapy	5	1225	1239	2464

Source: created by reviewer.

Overall, the subject-level characteristics were balanced between rosiglitazone and control arms (Tables 2 and 3). The majority of subjects were under 65 years of age (71%), male (59%), had a body mass index of under 30 (52%) and participated in trials outside the US (56%). With regard to baseline cardiovascular (CV) risk factors, at baseline, the majority of patients had been diagnosed as diabetic for less than 10 years (75%), had prior ug treatment (78%), had no history of coronary heart disease (CHD, 83%), had no history of CHD and nitrate use (95%), had no history of CHF (97%), and were not taking nitrates (95%), ACE inhibitors (65%), loop diuretics (95%) or beta-blockers (84%).

Table 2: Subject characteristics

Characteristic		Comparator N=6956 n (%)	RSG N=10039 n (%)	Total N=16995 n (%)
Age	< 65	4912 (71)	7157 (71)	12069 (71)
	≥ 65	2044 (29)	2882 (29)	4926 (29)
	Mean (Std.)	58 (10)	58 (10)	58 (10)
	Range (min-max)	(27-88)	(26-79)	(26-88)
Body mass index	< 30	3638 (52)	5184 (52)	8822 (52)
	≥ 30	3318 (48)	4855 (48)	8173 (48)
	Mean (Std.)	30 (6)	31 (6)	30 (6)
	Range (min-max)	(16-52)	(16-75)	(16-75)
Gender	Male	4155 (60)	5904 (59)	10059 (59)
	Female	2801 (40)	4135 (41)	6936 (41)
Location	United States	2771 (40)	4679 (47)	7450 (44)
	Other	4185 (60)	5360 (53)	9545 (56)
Treatment duration (days)	Mean (Std.)	191 (122)	186 (112)	188 (116)
	Range (min-max)	(1-758)	(1-758)	(1-758)

Source: created by reviewer.

Table 3: Subject baseline cardiovascular risk factors

Characteristic		Comparator N=6956 n (%)	RSG N=10039 n (%)	Total N=16995 n (%)
Duration diabetes (yrs)	≥ 10 yrs	1757 (25)	2484 (25)	4241 (25)
	< 10 yrs	5199 (75)	7555 (75)	12754 (75)
	Missing	2 (0)	2 (0)	4 (0)
	Mean (Std.)	7 (6)	7 (6)	7 (6)
	Range (min-max)	(0-36)	(0-45)	(0-45)
Previously treated for diabetes	Yes	5538 (80)	7710 (77)	13248 (78)
	No	1412 (20)	2325 (23)	3737 (22)
	Missing	6 (0)	4 (0)	10 (0)
History of CHD	Yes	1209 (17)	1597 (16)	2806 (17)
	No	5747 (83)	8442 (84)	14189 (83)
History of CHD & baseline nitrate use	Yes	366 (5)	458 (5)	824 (5)
	No	6590 (95)	9581 (95)	16171 (95)
History of CHF	Yes	238 (3)	285 (3)	523 (3)
	No	6718 (97)	9754 (97)	16472 (97)
Nitrate	Yes	396 (6)	505 (5)	901 (5)
	No	6560 (94)	9534 (95)	16094 (95)
Ace inhibitors	Yes	2506 (36)	3406 (34)	5912 (35)
	No	4450 (64)	6633 (66)	11083 (65)
Loop diuretic	Yes	358 (5)	473 (5)	831 (5)
	No	6598 (95)	9566 (95)	16164 (95)
Beta-blockers	Yes	1190 (17)	1502 (15)	2692 (16)
	No	5766 (83)	8537 (85)	14303 (84)

Source: created by reviewer.

3.1.3 Results from Primary Analysis Set

Table 4 displays counts and estimates of odds ratios for the primary and secondary safety endpoints utilizing the full set of 52 trials. A total of 109 subjects reported a primary MACE of which 39 (0.6%) were reported in subjects randomized to comparator and 70 (0.7%) were reported in subjects randomized to rosiglitazone.

Overall, the relative risk estimates were greater than one across the safety endpoints except for stroke.

For the primary endpoint, MACE, the relative risk estimate was greater than one (OR=1.44) with a 95% CI of (0.95, 2.20). Among the individual MACE components, the relative risk estimate for myocardial infarction was greater than one and statistically significant at the nominal α=0.05 level (OR=1.80; 95% CI = 1.03, 3.25).

For the other secondary endpoints, the relative risk estimates were greater than one and statistically significant at the nominal α=0.05 level for serious myocardial ischemia (OR=1.46; 95% CI =1.06, 2.03), total myocardial ischemia (OR=1.34; 95% CI =1.07, 1.70) and congestive heart failure (OR=1.93; 95% CI = 1.30, 2.93).

Table 4. Analysis of safety endpoints (All trials)

	Comparator N=6956 n (%)	Rosiglitazone N=10039 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	39 (0.6)	70 (0.7)	1.44 (0.95, 2.20)
Secondary Outcomes			
CV death	9 (0.1)	17 (0.2)	1.46 (0.60, 3.77)
MIF	20 (0.3)	45 (0.4)	1.80 (1.03, 3.25)
Stroke	16 (0.2)	18 (0.2)	0.86 (0.40, 1.83)
All-cause death	17 (0.2)	29 (0.3)	1.38 (0.72, 2.72)
Serious MIS	66 (0.9)	118 (1.2)	1.46 (1.06, 2.03)
Total MIS	132 (1.9)	221 (2.2)	1.34 (1.07, 1.70)
CHF	40 (0.6)	88 (0.9)	1.93 (1.30, 2.93)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2 Alternate Trial-Level Groups

3.2.1 Placebo-Controlled Trial Group

Table 5 displays event counts and relative risk estimates for the placebo–controlled trial group; findings presented in the 2010 briefing document are included to show the impact of the reclassification of select studies. Overall, this reclassification did not alter the findings for this trial-level group.

Similar to the finding in the previous section for all 52 studies, the relative risk estimates were greater than one across the safety endpoints except for stroke; the magnitude of the risk estimate were similar for this group compared to the overall analysis. Rosiglitazone had a statistically significant greater risk than placebo for myocardial infarction, total and serious myocardial ischemia, and congestive heart failure at the nominal α=0.05 level.

Table 5. Analysis of safety endpoints (Placebo-controlled trial group)

	2010 Meta-Analysis			2013 Regrouping		
	Comparator N=5636 n (%)	RSG N=8124 n (%)	Stratified OR† (95% CI)	Comparator N=4972 n (%)	RSG N=7453 n (%)	Stratified OR† (95% CI)
Primary Endpoint						
MACE	28 (0.50)	54 (0.66)	1.53 (0.94, 2.54)	28 (0.6)	51 (0.7)	1.42 (0.87, 2.38)
Secondary Outcomes						
CV death	5 (0.09)	15 (0.18)	2.32 (0.78, 8.32)	5 (0.1)	15 (0.2)	2.32 (0.78, 8.32)
MIF	13 (0.23)	35 (0.43)	2.23 (1.14, 4.64)	13 (0.3)	32 (0.4)	2.01 (1.01, 4.21)
Stroke	14 (0.25)	13 (0.16)	0.65 (0.27, 1.52)	14 (0.3)	13 (0.2)	0.65 (0.27, 1.52)
All-cause death	9 (0.16)	22 (0.27)	1.89 (0.82, 4.73)	9 (0.2)	20 (0.3)	1.68 (0.71, 4.25)
Serious MIS	32 (0.57)	82 (1.01)	2.05 (1.33, 3.22)	32 (0.6)	76 (1.0)	1.87 (1.21, 2.95)
Total MIS	70 (1.24)	154 (1.90)	1.73 (1.28, 2.35)	69 (1.4)	145 (1.9)	1.62 (1.20, 2.22)
CHF	31 (0.55)	76 (0.94)	2.20 (1.40, 3.51)	28 (0.6)	73 (1.0)	2.33 (1.46, 3.82)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.2 Placebo-Controlled Monotherapy Trial Group

The placebo-controlled monotherapy trial group included a total of 2611 subjects from 10 trials. Event counts and relative risk estimates for this group of trials are displayed in Table 6. For MACE, a total of 13 events were reported with an estimated odds ratio of 0.96 with a 95% CI (0.26, 4.40). Findings from this trial-level group should be interpreted with caution due to the limited number of cardiovascular events.

Table 6. Analysis of safety endpoints (Placebo-controlled monotherapy trial group)

	Comparator N=781 n (%)	Rosiglitazone N=1830 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	4 (0.5)	9 (0.5)	0.96 (0.26, 4.40)
Secondary Outcomes			
CV death	1 (0.1)	2 (0.1)	1.01 (0.05, 65.39)
MIF	2 (0.3)	6 (0.3)	1.40 (0.24, 14.59)
Stroke	2 (0.3)	3 (0.2)	0.56 (0.06, 6.96)
All-cause death	1 (0.1)	4 (0.2)	1.82 (0.17, 94.75)
Serious MIS	4 (0.5)	16 (0.9)	1.68 (0.53, 7.07)
Total MIS	11 (1.4)	28 (1.5)	1.07 (0.50, 2.45)
CHF	1 (0.1)	2 (0.1)	0.79 (0.04, 48.27)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.3 Placebo-Controlled Combination (incl. insulin) Trial Group

The placebo-controlled combination therapy trial group including trials with insulin add-on is composed of 9814 subjects from 35 trials. Table 7 displays event counts and relative risk estimates for this trial group. Similar to the findings in the placebo-controlled trials, the relative risk estimates were greater than one across the safety endpoints except for stroke and statistically significant for myocardial infarction, total and serious myocardial ischemia, and congestive heart failure at the nominal α=0.05 level. The magnitude of the risk estimates were slightly larger for this group compared to the placebo-controlled trials.

Table 7. Analysis of safety endpoints (Placebo-controlled combination trials including insulin add-on)

	Comparator N=4191 n (%)	Rosiglitazone N=5623 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	24 (0.6)	42 (0.7)	1.52 (0.89, 2.65)
Secondary Outcomes			
CV death	4 (0.1)	13 (0.2)	2.68 (0.81, 11.46)
MIF	11 (0.3)	26 (0.5)	2.13 (1.01, 4.83)
Stroke	12 (0.3)	10 (0.2)	0.66 (0.25, 1.70)
All-cause death	8 (0.2)	16 (0.3)	1.65 (0.66, 4.53)
Serious MIS	28 (0.7)	60 (1.1)	1.90 (1.18, 3.12)
Total MIS	58 (1.4)	117 (2.1)	1.75 (1.26, 2.47)
CHF	27 (0.6)	71 (1.3)	2.40 (1.49, 3.97)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.4 Placebo-Controlled Combination (excl. insulin) Trial Group

A total of 29 trials had a placebo-control combination therapy component where trials with insulin add-on were *excluded*. Table 8 displays event counts and relative risk estimates for this group of trials that includes data from 7981 subjects. The exclusion of insulin add-on trials did not alter the trends in risk described in the previous section.

Table 8. Analysis of safety endpoints (Placebo-controlled combination trials excluding insulin add-on)

	Comparator N=3376 n (%)	Rosiglitazone N=4605 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	19 (0.6)	29 (0.6)	1.34 (0.72, 2.58)
Secondary Outcomes			
CV death	4 (0.1)	9 (0.2)	1.91 (0.52, 8.63)
MIF	10 (0.3)	20 (0.4)	1.78 (0.79, 4.32)
Stroke	8 (0.2)	5 (0.1)	0.51 (0.13, 1.84)
All-cause death	6 (0.2)	10 (0.2)	1.46 (0.47, 4.98)
Serious MIS	25 (0.7)	45 (1.0)	1.62 (0.96, 2.79)
Total MIS	48 (1.4)	89 (1.9)	1.66 (1.14, 2.44)
CHF	19 (0.6)	48 (1.0)	2.51 (1.40, 4.65)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.5 Placebo-Controlled Insulin-add-on Trial Group

Event counts and relative risk estimates from the 7 trials included in the placebo-controlled insulin add-on trial group are displayed in Table 9. While the risk estimates were greater than two for all endpoints except stroke, the interpretation of results should be done cautiously due to the large uncertainty around the risk estimate as seen in the bounds of the 95% confidence intervals.

Table 9. Analysis of safety endpoints (Placebo-controlled insulin add-on trial group)

	Comparator N=815 n (%)	Rosiglitazone N=1018 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	5 (0.6)	13 (1.3)	2.14 (0.70, 7.83)
Secondary Outcomes			
CV death	0 (0.0)	4 (0.4)	3.90 (0.47, ∞)
MIF	1 (0.1)	6 (0.6)	5.64 (0.67, 262.72)
Stroke	4 (0.5)	5 (0.5)	0.92 (0.19, 4.78)
All-cause death	2 (0.2)	6 (0.6)	2.19 (0.38, 22.60)
Serious MIS	3 (0.4)	15 (1.5)	4.16 (1.15, 22.67)
Total MIS	10 (1.2)	28 (2.8)	2.18 (1.01, 5.10)
CHF	8 (1.0)	23 (2.3)	2.19 (0.92, 5.77)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.6 Active-Controlled Trial Group

Table 10 displays event counts and relative risk estimates for the 5350 subjects in 14 trials included in the active-controlled trial group; findings presented in the 2010 briefing document are included to show the impact of the reclassification of select trials. For MACE, the reclassification resulted in an additional 3 events counted in the rosiglitazone groups and 1 less in the comparator groups. As a consequence, the magnitude of the odds ratio risk estimate for MACE increased from 1.05, near the null value, to 1.39, a value near that observed in the meta-analysis of the placebo-controlled trial group. However, due to the few observed events, the confidence bound for such a comparison is wide.

Table 10. Analysis of safety endpoints (Active-controlled trial group)

	2010 Meta-Analysis			**2013 Regrouping**		
	Comparator N=1918 n (%)	RSG N=2119 n (%)	Stratified OR† (95% CI)	Comparator N=2575 n (%)	RSG N=2775 n (%)	Stratified OR† (95% CI)
Primary Endpoint						
MACE	14 (0.73)	16 (0.76)	1.05 (0.48, 2.34)	13 (0.5)	19 (0.7)	1.39 (0.64, 3.08)
Secondary Outcomes						
CV death	5 (0.26)	2 (0.09)	0.40 (0.04, 2.45)	5 (0.2)	2 (0.1)	0.40 (0.04, 2.45)
MIF	9 (0.47)	10 (0.47)	1.00 (0.36, 2.82)	9 (0.3)	13 (0.5)	1.33 (0.52, 3.54)
Stroke	3 (0.16)	5 (0.24)	1.54 (0.29, 10.02)	2 (0.1)	5 (0.2)	2.52 (0.41, 26.51)
All-cause death	9 (0.47)	7 (0.33)	0.79 (0.25, 2.38)	9 (0.3)	9 (0.3)	1.01 (0.35, 2.88)
Serious MIS	37 (1.93)	36 (1.70)	0.90 (0.54, 1.48)	37 (1.4)	42 (1.5)	1.06 (0.66, 1.72)
Total MIS	68 (3.55)	67 (3.16)	0.88 (0.61, 1.28)	69 (2.7)	76 (2.7)	1.01 (0.70, 1.44)
CHF	9 (0.47)	12 (0.57)	1.23 (0.47, 3.32)	12 (0.5)	15 (0.5)	1.17 (0.51, 2.75)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.7 Active-Controlled Monotherapy Trial Group

Event counts and relative risk estimates for the 2886 subjects in 9 trials included in the active-controlled monotherapy trial group are displayed in Table 11. For MACE, a total of 21 events were reported with an estimated odds ratio of 1.58 with 95% CI (0.58, 4.29) that includes the null value of 1. Few events are reported for the individual components of the composite MACE endpoint, all cause death, and CHF to make inferences on the risk.

Table 11. Analysis of safety endpoints (Active-controlled monotherapy trial group)

	Comparator N=1350 n (%)	Rosiglitazone N=1536 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	8 (0.6)	13 (0.8)	1.52 (0.58, 4.29)
Secondary Outcomes			
CV death	3 (0.2)	1 (0.1)	0.34 (0.01, 4.23)
MIF	6 (0.4)	9 (0.6)	1.35 (0.42, 4.67)
Stroke	1 (0.1)	4 (0.3)	4.10 (0.40, 203.00)
All-cause death	6 (0.4)	5 (0.3)	0.85 (0.20, 3.36)
Serious MIS	28 (2.1)	33 (2.1)	1.10 (0.63, 1.92)
Total MIS	58 (4.3)	63 (4.1)	0.98 (0.66, 1.46)
CHF	6 (0.4)	9 (0.6)	1.35 (0.42, 4.68)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.2.8 Active-Controlled Combination Trial Group

Table 12 displays event counts and relative risk estimates for the 2464 subjects in 5 trials included in the active-controlled combination therapy trial group. For MACE, a total of 11 events were reported with an estimated odds ratio of 1.17 with 95% CI (0.30, 4.85) that includes the null value of 1. Few events are reported for the secondary safety outcomes to make inferences on the risk.

Table 12. Analysis of safety endpoints (Active-controlled combination trial group)

	Comparator N=1225 n (%)	Rosiglitazone N=1239 n (%)	Stratified OR† (95% CI)
Primary Endpoint			
MACE	5 (0.4)	6 (0.5)	1.17 (0.30, 4.85)
Secondary Outcomes			
CV death	2 (0.2)	1 (0.1)	0.49 (0.01, 9.46)
MIF	3 (0.2)	4 (0.3)	1.28 (0.22, 8.76)
Stroke	1 (0.1)	1 (0.1)	0.96 (0.01, 75.77)
All-cause death	3 (0.2)	4 (0.3)	1.33 (0.22, 9.10)
Serious MIS	9 (0.7)	9 (0.7)	0.95 (0.33, 2.72)
Total MIS	11 (0.9)	13 (1.0)	1.13 (0.47, 2.81)
CHF	6 (0.5)	6 (0.5)	0.98 (0.26, 3.68)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

3.3 Alternative Statistical Models

3.3.1 Primary Analysis Set

For the primary analysis set of 52 trials, the number of trials with at least 1 cardiovascular endpoint and the sample size among these trials is shown in Table 13. These numbers summarize the number of trials and subjects that effectively contributed to the risk estimate for the primary analysis method using the exact method for a stratified odds ratio.

Table 13. The number of trials and sample size among trials with at least one event by safety endpoint

	Trials with at least one event	Effective sample size
Primary Endpoint		
MACE	36	13,573
Secondary Outcomes		
CV death	19	8,158
MIF	31	12,382
Stroke	18	6,670
All-cause death	23	10,043
Serious MIS	41	15,669
Total MIS	45	15,996
CHF	31	12,225

Source: created by reviewer.

Table 14 displays the results from the primary analysis method (as shown in Table 4) and the Bayesian model, which accounts for information from trials without any events. Note that the two estimates of the odds ratio from the Bayesian analysis correspond to 1) the posterior mean, and 2) the posterior median. Both quantities are provided since the different summaries of central tendency are not the same, which is a consequence of the posterior distribution of the odds ratio not being symmetric for some outcomes; Figure 1 in Section 5.1 illustrates this asymmetry for the cardiovascular death endpoint.

Across the separate endpoints, the estimates from the primary analysis were of a similar magnitude as the estimate from the Bayesian analysis. The credible interval from the Bayesian analysis was slightly narrower than the confidence interval from the primary method. The similarity in findings suggests that the conclusions based on the primary analysis method are not sensitive to the handling of trials without any events.

Table 14. Analysis of safety endpoints – comparison of methods (All trials)

	Comparator N=6956 n (%)	Rosiglitazone N=10039 n (%)	Stratified OR† (95% CI)	Bayesian OR Post. mean, Post. median (95% CrI)
Primary Endpoint				
MACE	39 (0.6)	70 (0.7)	1.44 (0.95, 2.20)	1.45, 1.41 (0.95, 2.14)
Secondary Outcomes				
CV death	9 (0.1)	17 (0.2)	1.46 (0.60, 3.77)	1.51, 1.36 (0.61, 3.25)
MIF	20 (0.3)	45 (0.4)	1.80 (1.03, 3.25)	1.81, 1.74 (1.03, 3.04)
Stroke	16 (0.2)	18 (0.2)	0.86 (0.40, 1.83)	0.91, 0.85 (0.43, 1.71)
All-cause death	17 (0.2)	29 (0.3)	1.38 (0.72, 2.72)	1.41, 1.34 (0.73, 2.52)
Serious MIS	66 (0.9)	118 (1.2)	1.46 (1.06, 2.03)	1.46, 1.43 (1.06, 1.98)
Total MIS	132 (1.9)	221 (2.2)	1.34 (1.07, 1.70)	1.34, 1.33 (1.06, 1.67)
CHF	40 (0.6)	88 (0.9)	1.93 (1.30, 2.93)	1.96, 1.91 (1.31, 2.85)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

Table 15 displays the results based upon the stratified Mantel-Haenszel method for the risk difference, stratified by trial. For MACE, rosiglitazone had an estimated increase of 2.31 events per 1,000 patients compared to control with 95% CI (-0.25, 4.87) that included the null value 0. Overall, endpoints with odds ratio estimates larger than 1 also had risk difference estimates larger than 0, and endpoints that had statistically significant risk increases based on the odds ratio were also significant using the risk difference. Thus, findings based upon risk differences that incorporate trials with no events were similar to the primary analysis method that excluded trials with no events.

Table 15. Analysis of safety endpoints using risk difference (All trials)

	Comparator N=6956 n (%)	Rosiglitazone N=10039 n (%)	Risk difference per 1000 patients (95% CI)
Primary Endpoint			
MACE	39 (0.6)	70 (0.7)	2.31 (-0.25, 4.87)
Secondary Outcomes			
CV death	9 (0.1)	17 (0.2)	0.57 (-0.66, 1.81)
MIF	20 (0.3)	45 (0.4)	2.20 (0.21, 4.19)
Stroke	16 (0.2)	18 (0.2)	-0.32 (-1.77, 1.13)
All-cause death	17 (0.2)	29 (0.3)	0.90 (-0.72, 2.52)
Serious MIS	66 (0.9)	118 (1.2)	4.02 (0.80, 7.24)
Total MIS	132 (1.9)	221 (2.2)	5.84 (1.44, 10.25)
CHF	40 (0.6)	88 (0.9)	4.73 (2.10, 7.37)

Source: created by reviewer.

3.3.2 MACE across the Alternative Trial-Level Groups

In this section, we examine findings on the primary endpoint MACE utilizing the alternate statistical methods applied to the various trial-level groups. The number of trials with at least 1 MACE and the number of subjects that effectively contributed to the risk estimate (effective sample size) for the primary analysis method for MACE across trial-groups is shown in Table 16 below.

Table 16. The number of trials and sample size among trials with at least one MACE event across trial-level groups

Trial Groups	Trials (N)	Effective size: Trials (N)
Primary analysis set	52 (16995)	36 (13573)
Placebo controlled	44 (12425)	29 (9309)
Monotherapy	10 (2611)	5 (2146)
Combination therapy (incl. ins.)	35 (9814)	24 (7141)
Combination therapy (excl. ins.)	29 (7981)	21 (6032)
Insulin add-on only	7 (1833)	4 (1109)
Active controlled	14 (5350)	9 (4324)
Monotherapy	9 (2886)	5 (2005)
Combination therapy	5 (2464)	4 (2319)

Source: created by reviewer.

Table 17 displays the results from the primary analysis method and the Bayesian model. Overall, across the separate trial-level groups the MACE estimates from the primary analysis method were of a similar magnitude as the median value from the Bayesian analysis, and similar for most trial-groups using the mean posterior value. Among trial-groups with few events there were differences between the odds ratio estimate from the primary method and the posterior mean from Bayesian analysis.

Table 17. Analysis of MACE endpoint – comparison of methods (Alternate trial-level groups)

Trial Groups	Comparator n/N	Rosiglitazone n/N	Stratified OR† (95% CI)	Bayesian OR Post. mean, Post. median (95% CrI)
Primary analysis set	39/6956	70/10039	1.44 (0.95,2.20)	1.45, 1.41 (0.95, 2.14)
Placebo controlled	28/4972	51/7453	1.42 (0.87, 2.38)	1.45, 1.40 (0.88, 2.28)
Monotherapy	4/781	9/1830	0.96 (0.26, 4.40)	1.32, 1.03 (0.33, 4.07)
Combination therapy (incl. ins.)	24/4191	42/5623	1.52 (0.89, 2.65)	1.55, 1.49 (0.91, 2.52)
Combination therapy (excl. ins.)	19/3376	29/4605	1.34 (0.72, 2.58)	1.38, 1.31 (0.73, 2.43)
Insulin add-on only	5/815	13/1018	2.14 (0.70, 7.83)	2.73, 2.25 (0.82, 7.54)
Active controlled	13/2575	19/2775	1.39 (0.64, 3.08)	1.51, 1.41 (0.69, 2.92)
Monotherapy	8/1350	13/1536	1.52 (0.58, 4.29)	1.77, 1.56 (0.64, 4.08)
Combination therapy	5/1225	6/1239	1.17 (0.30, 4.85)	1.48, 1.20 (0.35, 4.25)

† Exact method for a stratified odds ratio, strata is trial; Source: created by reviewer.

Table 18 displays the results from risk difference approach for MACE across trial-groups. Across trial-level groups, the trend in MACE estimates using odds ratio were consistent with the risk difference.

Table 18. Analysis of MACE using risk difference (Alternate trial-level groups)

Trial Groups	Comparator n/N	Rosiglitazone n/N	Risk difference per 1000 patients (95% CI)
Primary analysis set	39/6956	70/10039	2.31 (-0.25, 4.87)
Placebo controlled	28/4972	51/7453	2.23 (-0.76, 5.22)
Monotherapy	4/781	9/1830	-0.18 (-6.57, 6.20)
Combination therapy (incl. ins.)	24/4191	42/5623	2.75 (-0.62, 6.12)
Combination therapy (excl. ins.)	19/3376	29/4605	1.79 (-1.83, 5.40)
Insulin add-on only	5/815	13/1018	6.78 (-1.98, 15.53)
Active controlled	13/2575	19/2775	1.91 (-2.24, 6.06)
Monotherapy	8/1350	13/1536	2.98 (-3.27, 9.23)
Combination therapy	5/1225	6/1239	0.68 (-4.62, 5.98)

Source: created by reviewer.

4 SUMMARY OF FINDINGS

This document includes

1) additional analyses within alternate trial-level groups defined by whether the randomized treatment, placebo or active controlled, was administered as a monotherapy or in combination with a background or add-on therapy, and
2) results from alternative statistical models that incorporate information from trials without any event.

Note that results from the 2010 meta-analysis were also included or referenced in various sections above to document any changes based upon the current presentation of the results as findings are based upon the same data utilized in the 2010 meta-analysis.

Upon review of study synopses for trials included in the 2010 meta-analysis, the grouping of four trials into the various trial-level groups was reclassified. The trials that were reclassified were

- Trial 284 (2010: placebo controlled; 2013: metformin controlled),
- Trial 311 (2010: placebo/metformin controlled; 2013: placebo controlled),
- Trial 374 (2010: monotherapy add-on; 2013: background add-on), and
- Trial 712753/002 (2010: placebo controlled; 2013: metformin controlled).

In total, the 52 trials enrolled 16,995 subjects, 10,039 (59%) randomized to rosiglitazone and 6,956 (41%) to the comparator. The majority of trials had a placebo control (44) and were of a duration of 6 months or less (40).

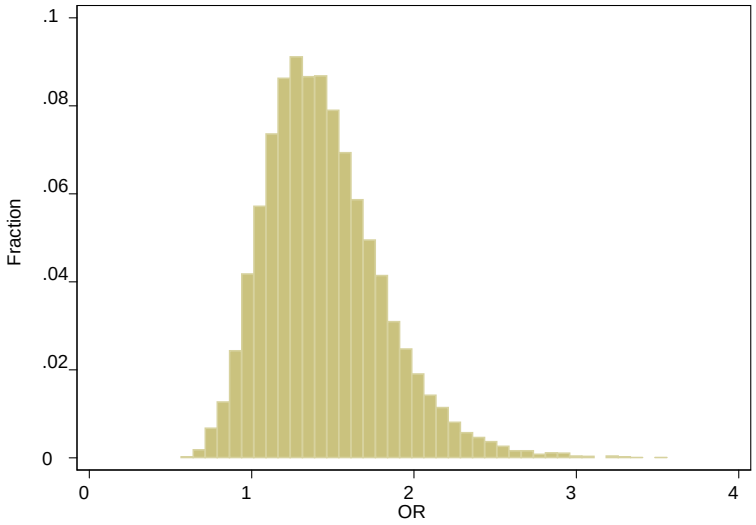
Overall, a total of 109 subjects reported a primary MACE, 39 (0.6%) reported in subjects randomized to comparator and 70 (0.7%) were reported in subjects randomized to rosiglitazone, leading to an odds ratio estimate greater than one and nearly statistically significant (OR=1.44; 95% CI=0.95, 2.20). In placebo-controlled trials, the odds ratio estimate for MACE was 1.42 with 95% CI (0.87, 2.38); this estimate is slightly smaller than the estimate presented in the 2010 briefing document (OR = 1.53; 95% CI = 0.94, 2.54) due to the reclassification of select trials. In active-control trials, the odds ratio estimate for MACE was 1.39 with 95% CI (0.64, 3.08); this estimate was larger than the estimate presented in the 2010 briefing document (OR=1.05; 95% CI =0.48, 2.34) due to the reclassification of select trials.

Results from alternative statistical models that include information from trials without any events were found to be similar to results from the primary analysis method, which does not include information from these trials. Thus, the conclusions based on the primary analysis method are not considered to be sensitive to the handling of trials without any events.

5 APPENDIX

5.1 Miscellaneous Figures

Figure 1. Posterior distribution of odds ratio for cardiovascular death.



Source: created by reviewer.

5.2 Overview of Bayesian Approach

This section formally describes the Bayesian model used to investigate the impact of trials without any events. The formulation of the model and WinBUGS program code is adapted from Smith et al. (1995)[3]. To define the model we introduce the following notation. For the N_l^t subjects randomized to treatment $t=\{T,C\}$ in trial l, $l=1,\ldots,L$, let y_l^t denote the number subjects that experienced the endpoint. Let $t=T$ denote the treatment arm containing rosiglitazone and $t=C$ denote the treatment arm without rosiglitazone. Assume the probability of an event depends on the trial and treatment arm, so that $y_k^t \mid N_l^t, \pi_k^t \sim Binomial(N_l^t, \pi_k^t)$. The difference in probabilities between the two groups is model on the log-odds scale, so that $\lambda = \text{logit}(\pi_l^T) - \text{logit}(\pi_l^C)$, which is assumed the same across studies. Let the average risk (on the log-odds scale) within trial l be $\nu_1 = (\text{logit}(\pi_l^T) + \text{logit}(\pi_l^C))/2$, and assume the individual trial effects are drawn from a Normal distribution with unknown mean a_ν and variance b_ν^2.

The Bayesian model is specified as follows:

$$y_l^t \mid N_l^t, \pi_l^t \sim Binomial(N_l^t, \pi_l^t)$$
$$\text{logit}(\pi_l^T) = \nu_l + \lambda/2$$
$$\text{logit}(\pi_l^C) = \nu_l - \lambda/2$$
$$\nu_l \sim Normal(a_\nu, b_\nu^2)$$
$$\lambda \sim Normal(0, 10^2)$$
$$a_\nu \sim Normal(-7, 5^2) \text{ and } b_\nu \sim Uniform(0, 5).$$

The values used for the hyperparmeters are uninformative, meaning the influence of the prior distribution on the posterior inferences will be negligible. For example, the hyperparameters associated with the intercept term, a_ν, centers our belief of a cardiovascular event at around 1 in 1100, which may not be too unreasonable. However, the standard deviation of 5 reflects a large amount of uncertainty in this belief which minimizes the impact of such a belief on the inferences.

Markov chain Monte Carlo methods are used to sample from the posterior distribution. Two independent chains of length 100,000 were run with samples analyzed after having a burn-in of 10,000 samples and taking every 10th draw to minimize autocorrelation in the samples.

[3] Smith, T. C., Spiegelhalter, D. J., and Thomas, A. (1995), Bayesian Approaches to Random-Effects Meta-Analysis: A Comparative Study. *Statistics in Medicine* 14: 2685-2699.

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Consultation for NDA 021071 SDN1652

DATE: Consult requested: 12/20/2011
Date of reassignment: 01/24/2012
Desired completion date: 04/30/2012
Date of review: 04/28/2012
Date of revision 05/07/2012

FROM: Preston M. Dunnmon, M.D., Clinical Reviewer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Jena M. Weber
Regulatory Project Manager
Director, Division of Metabolism and Endocrinology Products

SUBJECT: DCRP consult to review and to comment on both all-cause and CV deaths from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia and Diabetes trial (RECORD, BRL-049653/231), according to the Phase-I re-adjudication of the trial's mortality outcomes by the Duke Clinical Research Institute (DCRI)

This memo responds to your consult to us requesting review of DCRI's re-adjudication of the mortality results from RECORD (NDA 021071 SDN1652), which compared cardiovascular (CV) outcomes between rosiglitazone (RSG) therapy in combination with metformin (MET) or a sulfonylurea (SU) to CV outcomes with the MET/SU combination. DCRP reviewed the following material:

- Prior DCRP consult (June 14, 2010)
- FDA Briefing Document Advisory Committee Meeting for NDA 21071 (July 13 and 14, 2010)
- RECORD final study report (FSR)
- Original RECORD CEC charter
- DCRI Re-adjudication Protocol AVD115170 for RECORD, Report of the First Phase: Blinded Re-adjudication of All-cause Mortality and Cardiovascular Mortality
- DCRI re-adjudication mortality dataset

Regulatory Background

The cardiovascular safety of AVANDIA® (rosiglitazone) has been the subject of two recent public proceedings:

- July 30, 2007 - joint public advisory committee concluded that AVANDIA® increases cardiac ischemic risk in type 2 diabetes mellitus based on then available data but that the overall risk-benefit profile of AVANDIA® supported its continued marketing in the US

- July 13-14, 2010 – advisory committee meeting for AVANDIA® (NDA 021071, rosiglitazone maleate) considered data from three newly available long-term outcome studies (RECORD, ADOPT, and DREAM) in a discussion regarding whether rosiglitazone should continue to be marketed in the United States.

As part of the 2010 advisory committee briefing document, the weaknesses of RECORD's open label non-inferiority design, as well as the consequent opportunities for ascertainment biases, were very thoroughly vetted. At the completion of the July 2010 adviory committee, FDA decided that rosiglitazone could remain on the market in the US if:

1. GSK undertook a restricted access program under a REMS with ETASU

2. GSK commissioned an independent re-adjudication of the RECORD study outcomes. If the mortality finding were found to be valid on the first phase of re-adjudication, then a second phase re-adjudication of other MACE elements would be performed (nonfatal MI, nonfatal CVA, and CV Death).

3. The TIDE trial was placed on full clinical hold.

GSK agreed to the above conditions for continued marketing of rosiglitazone in the US, and commissioned the DCRI to perform a full and independent re-adjudication of the RECORD study's cardiovascular outcomes as delineated by FDA. Accordingly, the phase-I mortality re-adjudication has now been completed. The purpose of this document is to review the findings of the phase-I (mortality) re-adjudication.

During this re-evaluation period, the labeled indication for rosiglitazone has read as follows:

> *After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA®, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are already taking AVANDIA®, or not already taking AVANDIA® and are unable to achieve adequate glycemic control on other*

diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) for medical reasons.

Background – RECORD Study design

RECORD was a post-marketing commitment to the European Medicines Agency. Its design was reviewed and approved by the Committee for Proprietary Medicinal Products (now known as the Committee for Medicinal Products for Human Use). RECORD was not conducted under a U.S. IND.

RECORD was a randomized, multicenter, open-label, parallel group trial of 4447 subjects with type 2 diabetes, comparing cardiovascular outcomes in subjects randomized to rosiglitazone in combination with metformin or a sulfonylurea to the combination of metformin plus a sulfonylurea. A four-week run-in period was followed by a proposed median of 6 years of treatment with study medication, in addition to continuation of background glucose-lowering therapy. Patients on background metformin (MET) were randomized to receive, in addition to continued metformin, either rosiglitazone or a sulfonylurea (glibenclamide, gliclazide or glimepiride), in a ratio of 1:1. Patients inadequately controlled on background SU were randomized to receive, in addition to continued sulfonylurea (SU), either RSG or MET, in a ratio of 1:1. Equal numbers of patients on background MET and SU were to be randomized.

Throughout study, target hemoglobin A1c (HbA1c) was to be ≤7%. After 8 weeks of treatment, if a patient's HbA1c was >7%, the investigator was to increase the dose of study medication. If tolerated, RSG was to be titrated to a dose of 8 mg/day, administered as 4 mg BID, in order to achieve an HbA1c of 7%. Doses of MET and SU were to be titrated to the maximum allowable dose approved by the regulatory authority of the country in which the study site was located, also to achieve an HbA1c of 7%.

If a patient's HbA1c remained ≥8.5% after at least 8 weeks on the maximum permitted or tolerated dose of add-on study medication, a confirmatory HbA1c was to be performed at least 1 month later. If the HbA1c was still ≥8.5%, another agent was added. For patients in the RSG + MET group, SU was added. For patients in the RSG + SU group, MET was added. For patients in the MET + SU group, insulin was added; with or without continuation of MET and/or SU, "according to local clinical practice".

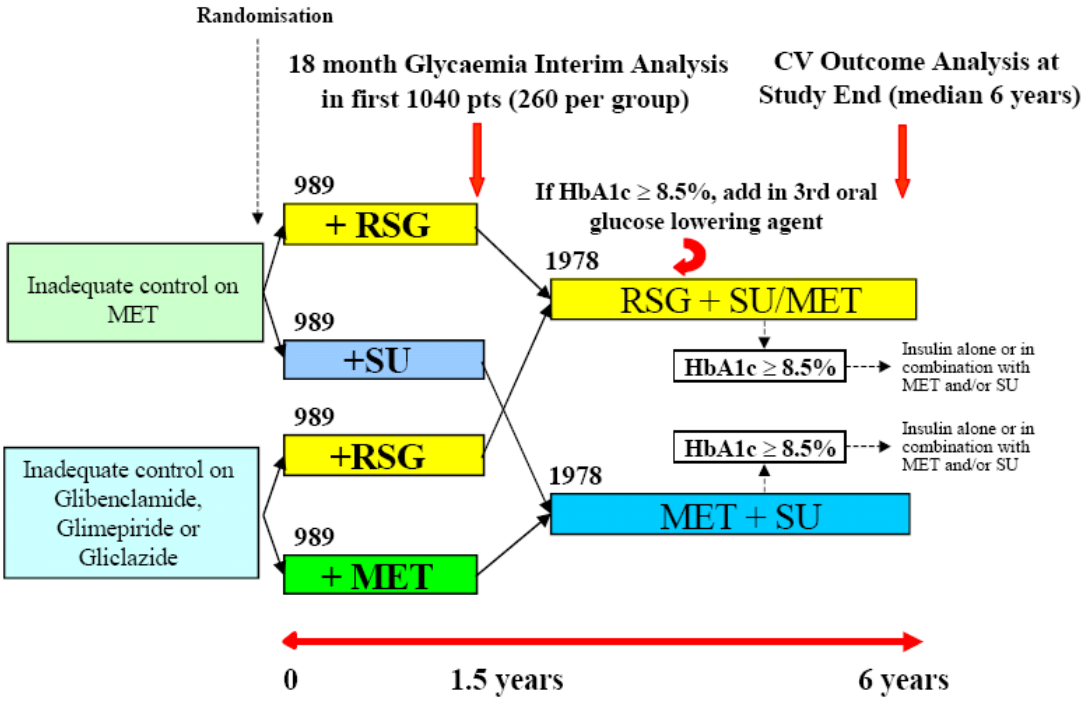
For patients in the RSG groups who had progressed to triple oral therapy, had remained on the maximum permitted or tolerated dose of the triple therapy for at least 8 weeks, and still had a HbA1c ≥8.5%, insulin was added and rosiglitazone was discontinued. The combination of RSG and insulin was not approved in Europe at the time the study was initiated. For these patients, MET and/or SU might or might not be continued, again according to local clinical practice.

The primary endpoint/analysis of RECORD was an ITT analysis of the time to first adjudicated CV hospitalization or CV death (any death for which an unequivocal non-CV cause count not be established (acute MI, heart failure, sudden death, acute vascular

events, other CV mortality, unknown causes), over the full duration of the study. To reiterate, deaths of unknown cause were counted as CV deaths.

The objective of the study was to rule out a 20% increase in the relative hazard of RSG combination compared to the combined control groups (MET/SU). Formal non-inferiority was to be achieved, according to protocol definition, if the upper limit of the 95% confidence interval for the hazard ratio of RSG versus MET/SU at study end was less than 1.2.

The following figure illustrates the study phases from randomization through initiation of insulin in both treatment groups:



DCRI Methodology

Overview

Re-adjudication and analysis of mortality for the RECORD study was performed in accordance with the following documents:

- Re-adjudication Protocol for RECORD, Version 1, 28 January 2011
- Re-adjudication Protocol for RECORD, Amendment Version 2, 24 June 2011
- Statistical Analysis Plan: First Phase (Mortality), 13 July 2011

DCRI-CEC processes for the re-adjudication of RECORD mortality were described in the DCRI CDC Charter for Re-adjudication of RECORD (Effective Date: 02 May 2011). Subsequently, DCRI developed a comprehensive trigger process of automated and manual procedures to systematically identify all suspected endpoint events from all potential data sources in which deaths may have been reported by the site investigators (RECORD Re-Adjudication Trigger Specifications, August 4, 2011). Data sources for re-adjudication included:

- The original RECORD dataset
- Original RECORD paper case report forms
- Original RECORD SAE reports
- Event packets used in the original adjudication (and the source documents they contained)
- Site queries for additional information and query responses
- All information collected by GSK between November 2010 and March 2011 regarding patients whose last contact was made during the survival status follow-up phase as recorded in the CRF
- Third party search for end-of-study documentation – MediciGlobal, an independent third party vendor (King of Prussia, Pennsylvania), was employed to search for additional vital status information on patients that DCRI identified as missing vital status information at the end of the study
- GSK retrieved available source documents from the Investigators' Archive so that these would be available to DCRI during the re-adjudication of RECORD
- Quintiles sent a letter to each site explaining the request for source data; a copy of the letter was to be submitted to each site's ethics committee for notification. A remote call was placed to each site to further explain the requirements and to understand the site's ability to provide the requested source data.

Triggers for Identification of Suspected Events and DCRI CEC Review

DCRI employed a comprehensive combination of both automated program triggers and manual trigger procedures to identified suspected mortality events for review by their CEC, described as follows:

- Automated trigger program – computer trigger program that included:
  - Screening of all Adverse Experience (AE) and Serious Adverse Experience (SAE) forms from the CRF data fields in the GSK RECORD datasets
  - Pre-specified MedDRA coded terms. The coded preferred terms were reviewed by Clinical, CEC and Safety experts to identify terms that would potentially be indicative of an endpoint with a low threshold. A similar approach has been used in previous re-adjudication efforts
  - Death Form (Form D) when present in the database.

- Manual trigger procedures – RECORD CEC Coordinators performed manual review of paper documents as well as reviewing the output from the automated trigger program. All were experienced in cardiology event

reporting and CEC methodologies. Paper sources that the CEC Coordinators reviewed to identify potential endpoints included:

- The unscheduled visit form
- Source documents used as part of the original RECORD CEC adjudication process and any additional source documents collected as part of the re-adjudication activities (discharge summaries, progress notes, pertinent lab values, and physician narratives)
- Investigator verbatim
- All SAE and AE forms - SAEs and AEs that were deleted by RECORD investigators were identified from the audit trail of the study's electronic datasets, which GSK provided to DCRI. The electronic data sets were sent to the DCRI prior to the event packet files which included data from the CRF and source documents.
- All cases that were sent to the original RECORD CEC; this would include endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator
- All Death Endpoint Forms
- All Myocardial Infarction/Unstable Angina Endpoint Forms
- All Stroke/TIA Endpoint Forms
- All Hospitalizations
- All Survival Status Forms
- All Documentation of Third Party Survival Data Forms
- All Tracking Forms for Completely Withdraw Patients
- All Study Completion Forms

Patient Dispositions – Incomplete Follow-up

One objective of the re-adjudication of mortality in RECORD was to define independently the study follow-up phases and derive dates last observed without an event (i.e., date last known surviving) for patients who were not reported to have died, because precise determination of end-of-study dates could not be done for all patients based on the SAS datasets alone. For each patient who did not have a last face-to-face visit well-documented in the SAS datasets, additional efforts were made to determine the patient's vital status at the study end.

Patients were considered to have completed follow-up if the patient died, had a face-to-face visit with vital signs recorded on or after 24 August 2008, or had a face-to-face visit in 2008 and a phone visit (no vital signs recorded) after 24 August 2008. On this basis:

- 3,843 patients were designated as having completed follow-up
- 604 patients were deemed incomplete (included the 127 patients who were reported in the original RECORD trial to have unknown vital status at study end).

For the 604 patients deemed incomplete due to unknown vital status at the end of the study, the following was done:

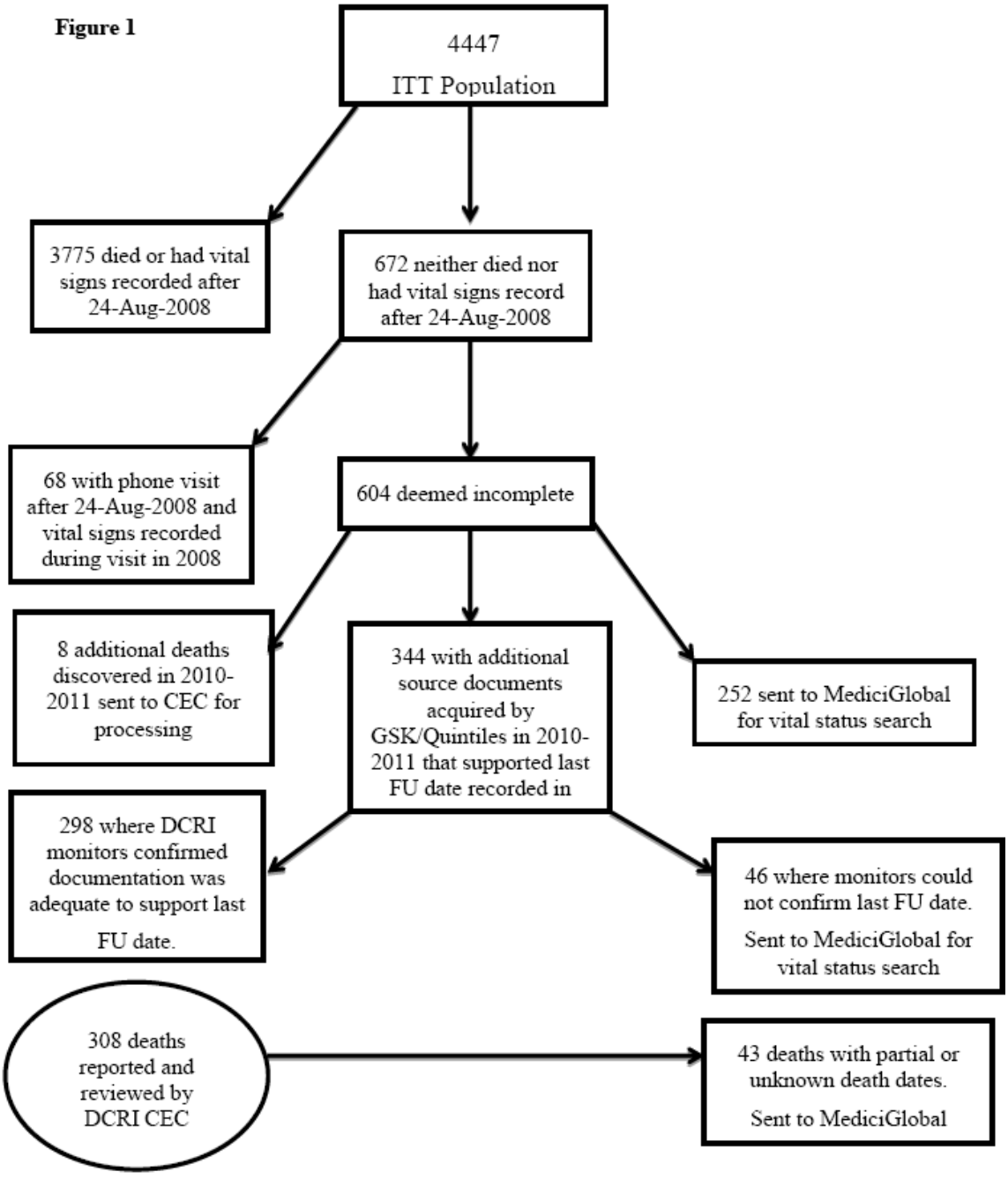
- For 298 patients, additional source documentation was obtained by GSK/Quintiles in the 2010-2011 post-study time frame that confirmed a last follow-up date
- For another 298 patients, additional source documents were either not available, or additional source documents could not confirm a last follow-up date, and so these cases were sent to MediciGlobal for vital status search
- 8 additional deaths were discovered in the 2010-2011 time frame that were sent to the DCRI CEC for processing.

In addition, 308 known deaths were reported to and reviewed by the DCRI CEC, of which 43 had partial or unknown death dates and were referred to MediciGlobal for vital status search.

See the figure below for a diagrammatic representation of the disposition of patients with incomplete follow-up (from DCRI phase I report, Figure 1; "ITT" population excludes 11 randomized patients who never took study drug):

12.1.1 Patients with Incomplete Follow-up

Figure 1



DCRI CEC Query of Suspected Events

The DCRI CEC issued 127 queries for additional information to follow up on death events classified as “unknown” and “insufficient information”. Response to these queries approximately two to three years after the study was completed was predictably poor:

- 43 queries were closed with no response from the site
- 61 queries were closed with a response from the site that no additional data is available
- 23 queries were closed with additional data received from the site. Of these 23 queries,
    - 16 events were re-reviewed with no change to the adjudication result
    - 7 events were re-reviewed with a change to the adjudication result from "unknown" to a known cause of death.

Disposition of Events Triggered for Re-adjudication: All-Cause Mortality

A total of 419 triggers for all-cause mortality were identified representing 9.4% of the 4447 patients included in the ITT Population in the original RECORD report. Of the 419 patients who triggered, 396 (94.5%) were identified from the automatic trigger program and 23 (5.5%) were identified manually. Adverse event forms, death forms, and study continuation/withdraw forms accounted for the large majority of triggers identified programmatically. All triggers identified manually were found in source documents.

Of the 419 potential deaths triggered, 102 death triggers were set to a status of "No action needed" and not adjudicated because the source documentation present indicated that the subject was still alive. The remaining 316 death triggers were adjudicated.

Between all patients treated with RSG (N=2220) and all treated with MET/SU (N=2227), DCRI reported that the proportional distribution of patients by triggering method and by sources of triggers appeared to be similar with no evidence of clinically important differences between the treatment groups.

All of the 316 death triggers referred for re-adjudication were reviewed by DCRI's CEC Phase 1 re-adjudication committee. Because of disagreement between CEC Phase-1 reviewers regarding death classification and/or death sub-classification, 86 death triggers were also reviewed by the CEC Phase-2 committee; that is, a full Adjudication Committee comprising at least 3 faculty physicians.

> *Reviewer Comment: I would inquire of DCRI the breakdown of new deaths and deaths with incomplete vital status by study arm. There were 604 DCRI-identified patients with incomplete vital status information/dates versus 127 for GSK/Quintiles – a substantial difference. How many ended up having vital status/censoring dates changed that were part of the original 127 versus the remaining 477? There were 127 DCRI CEC generated queries for vital status. Were these the same 127 patients identified by GSK as having unknown vital status at the end of the study?*

New Death Events Found on RE-adjudication

In accord with DCRI's prospective statistical analysis plan (SAP) for the re-adjudication, all deaths occurring on or before 31 December 2008 were included in the primary re-analyses of all-cause mortality, CV mortality, and non-CV mortality. In the original RECORD trial, the date of last follow up was the latest date the subject was known alive on or before 31 December 2008.

Twenty-three (23) death events, in addition to those identified in the original RECORD data set, were discovered after DCRI re-adjudication efforts began, as follows:

- Eight (8) newly discovered events occurred before 31 December 2008: 3 deaths were found by the GSK/Quintiles search effort, 3 deaths were found from the AVANDIA® IND annual reporting of the ongoing RECORD observational follow-up substudy, and 2 deaths were found by the MediciGlobal effort.
- Eleven (11) newly discovered deaths occurred after 31 December 2008: 5 deaths were found by the GSK/Quintiles search effort, 1 death was found from the IND annual reporting, and 5 deaths were found from the MediciGlobal effort.
- The remaining 4 deaths occurred on an unknown date, 2 identified from the Quintiles tracking database and 2 from the MediciGlobal effort.

  Reviewer's comment: I would inquire of DCRI how the 4 deaths of unknown date were handled in the data re-adjudication.

Alternative Derivations of End of Follow-up

Final follow-up dates were derived by four different sets of rules, outlined in the DCRI stat plan, as follows:

1. Parsimonious approach: defined the last known alive date as the last date of a documented face-to-face visit at which one or more vital signs were recorded on the VITALS module of the CRF. Patients with a last known alive date after 24 August 2008 were considered to have completed survival follow-up.
2. Primary analysis: for patients who, based on the parsimonious approach, had not completed survival follow-up, the primary approach (used for the primary analysis) added follow-up information for 1) patients with a vital sign face-to-face visit in 2008 and phone visit after 24 August 2008; 2) patients with an updated last known alive date based on independent third party search; and 3) patients with an updated last known alive date based on DCRI review of CRFs or associated documents.
3. Primary analysis + tests and events: using dates for electrocardiogram assessments, laboratory tests, microvascular (diabetes-related) endpoints, adverse events, and fractures reported in the electronic data base, survival follow-up was updated for patients whose vital status was unknown after 24 August 2008 with the primary approach.
4. Primary analysis + tests and events + survival status: for patients whose vital status after 24 August 2008 could not be determined by the rules described in the first 3

approaches, vital status was updated from Survival Status follow-up and third party search conducted as part of the RECORD study.

To assess the possible impact of censoring / follow-up end-date derivation methodology, analyses for overall mortality and CV mortality were repeated using the three approaches other than the primary analysis survival follow-up for deriving study phase end dates. For analyses of mortality by these alternative rules, follow-up for patients was started at randomization and censored on date last know alive on or before 31 December 2008.

Quality Control

Twenty-five adjudicated death events were randomly selected for QC review by the lead (blinded) statistician and "QC re-adjudicated" by the DCRI RECORD CEC Committee. Of the 25 QC events, the following was determined:

- For 14 QC events, the QC result matched the original DCRI RECORD CEC re-adjudication result on all variables
- For 11 QC events, the QC result did not match the original DCRI RECORD CEC re-adjudication result on all variables.

OF the 11 QC events that did not match the original re-adjudication on all variables, six (6) events had a minor discrepancy between the QC re-adjudication and the original DCRI re-adjudication result regarding event date/time. No further action was taken for these events. The original adjudication result remained unchanged in the database. Three (3) events had a minor discrepancy between the QC re-adjudication and the original DCRI re-adjudication result regarding death sub-classification. These 3 events were re-reviewed and reconciled by the DCRI RECORD. The adjudication result was updated in the database as necessary. Two (2) events had a major discrepancy between the QC re-adjudication and the original DCRI re-adjudication result regarding the death classification. These 2 events were re-reviewed and reconciled by the DCRI RECORD CEC Committee. The re-adjudication result was updated in the database as necessary.

Re-adjudication Results – All cause Mortality

A total of 313 deaths were identified by the re-adjudication process, 299 before and 14 after the 31 December 2008 last RECORD follow-up date. Of these 313 deaths, there was insufficient evidence to determine cause of death (cardiovascular vs. non-cardiovascular) in 120 cases (38% of all deaths). The distribution of cause of death (cardiovascular, non-cardiovascular or unknown) was identical by the original RECORD and new FDA definitions. Follow-up for patients who did not die was censored on the date they were last known to be alive on or before 31 December 2008.

Based on the survival primary analysis (DCRI Table 3.1 below), all-cause mortality occurred in 139 of 2220 patients (6.3%) in the RSG group at a rate of 1.07 events per 100 patient years (95% CI: 0.89, 1.26). All-cause mortality occurred in 160 of 2227 patients (7.2%) in the MET/SU group at a rate of 1.25 events per 100 patient years (95% CI: 1.05,

1.45). The hazard ratio (95% CI) for RSG vs. MET/SU was 0.86 (0.68, 1.08); there was no evidence of a treatment effect (DCRI Table 3.1 and Figure 3.1 below), no interaction observed between treatment and background therapy, and no treatment-by-subgroup interaction for characteristics tested.

RECORD Trial: DCRI Independent Review

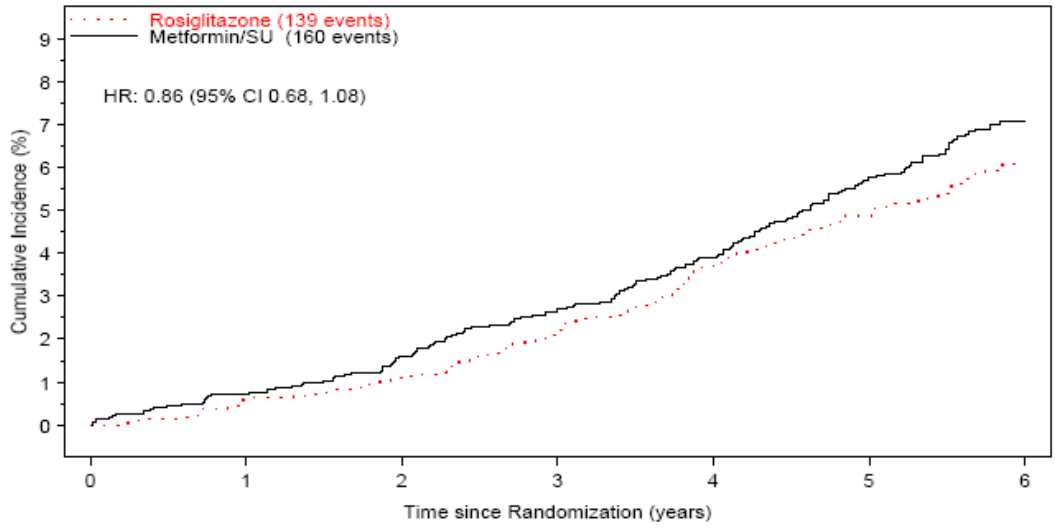
Table 3.1 (page 1 of 1)
All-Cause Mortality: Summary by Treatment Arm
Based on Survival Follow-up for Primary Analysis*

		Treatment	
	Total (N=4447 PY=25768.6)	Combined RSG (N=2220 PY=12953.6)	Combined MET/SU (N=2227 PY=12815.0)
Number of patients with an event	299 / 4447 (6.7%)	139 / 2220 (6.3%)	160 / 2227 (7.2%)
Rate per 100 patient years (95% CI)	1.16 (1.02, 1.30)	1.07 (0.89, 1.26)	1.25 (1.05, 1.45)
Hazard Ratio** (95% CI)		0.86 (0.68, 1.08)	
Absolute rate difference per 100 patient years (95% CI)		-0.18 (-0.44, 0.09)	

* Follow-up for patients who did not die is censored on date last known alive on or before 31-Dec-2008.
** Hazard ratio from a Cox proportional hazards model stratified by background therapy. A hazard ratio < 1 favors RSG.
Generated from ct/record/tables/tbl_allcause_outcome.sas on 30NOV2011 at 17:26

RECORD Trial: DCRI Independent Review

Figure 3.1
All-Cause Mortality - Time to Death
Kaplan-Meier Estimates and Hazard Ratio with 95% Confidence Interval for RSG vs. Met/SU
Based on Survival Follow-up for Primary Analysis



Rosaglitazone							
Events	0	13	24	46	81	106	129
At Risk	2220	2190	2165	2130	2087	2048	988
Metformin/SU							
Events	0	16	35	59	85	125	150
At Risk	2227	2181	2140	2110	2079	2019	953

Generated from ct/record/graphs/a_allcause_outcome.sas on 30NOV2011 at 17:31

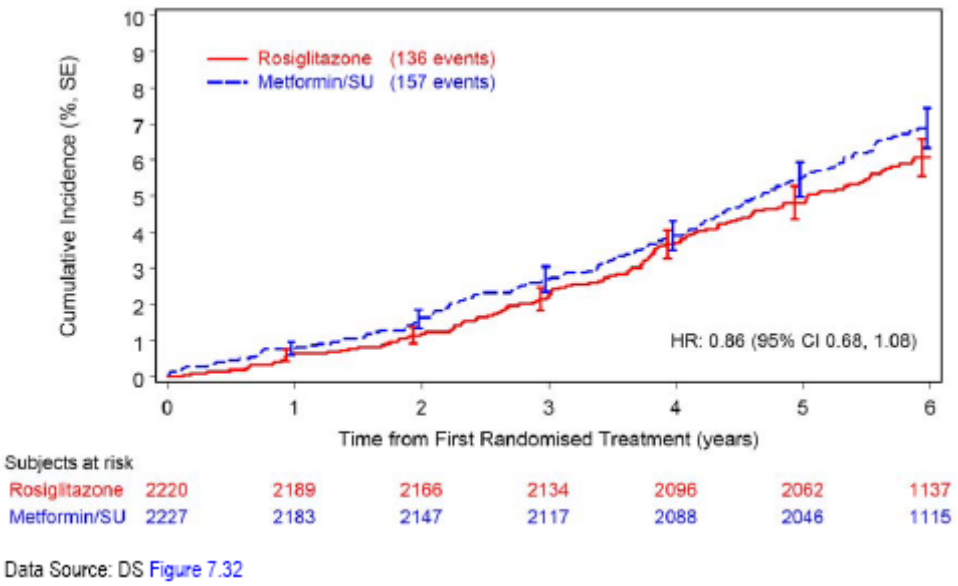
From the original RECORD study analysis, the "death from any cause, ITT population, vital status follow-up" is the counterpart to the DCRI all-cause mortality analysis above. Overall, there were six fewer all-cause deaths in the RECORD analysis, but the deficiency was evenly split, with 3 fewer deaths in both the RSG and the SU/MET arms (table 81 below, from the original RECORD FSR), and the Kaplan Meir appearance virtually identical to the DCRI re-analysis of all-cause mortality (Figure 22 below, from the original RECORD FSR):

Table 81 Death from Any Cause Including Survival Status Updates (ITT population)

All-Cause Death (including survival status update)	Treatment Group: Combined RSG (N=2220)	Treatment Group: MET/SU (N=2227)
No. subjects (%) who died (all-cause) during the study including survival status updates	136 (6.1)	157 (7.0)
Incidence: rate/100 PY[1] (95% CI)	1.05 (0.88, 1.24)	1.22 (1.04, 1.43)
Hazard ratio[2], (95% CI); p-value	0.86 (0.68, 1.08); p=0.1934	
Absolute rate difference/100PY[1]	-0.17 (-0.43, 0.09)	

Data Source: DS Table 7.114 and DS Table 7.115

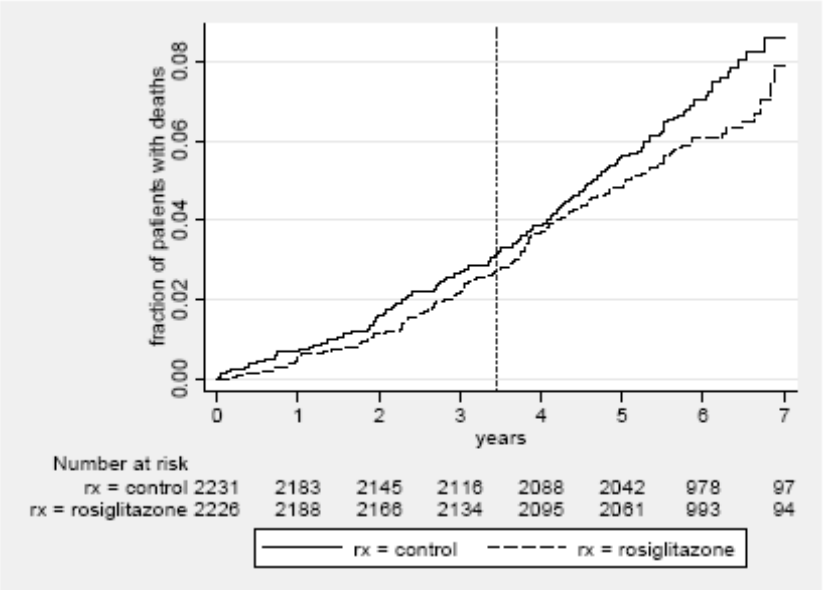
1. Person-years up to first event/censoring.
2. Based on Stratified (by background stratum) Cox's Proportional Hazards Model: Time = Treatment. HR is relative to MET/SU.



Data Source: DS Figure 7.32

The FDA plot of time to all-cause death, produced for the July 2010 Advisory committee, demonstrates essentially the same K-M morphology as well (Figure 11 below, Marciniak, June 2010):

Figure 11: K-M Plot for Time to All-Cause Deaths



Re-adjudication Results – CV and Unknown Mortality

Reviewer Comment: The RECORD trial included deaths of unknown cause in its definition of CV death. Therefore, CV death in RECORD is equivalent to CV+unknown cause death in the DCRI re-adjudication.

Based on the survival primary analysis, CV and unknown cause mortality as per the new FDA definitions occurred in 88 of 2220 patients (4.0%) in the RSG group at a rate of 0.68 events per 100 patient years (95% CI: 0.53, 0.83). Cardiovascular and unknown cause mortality occurred in 96 of 2227 patients (4.3%) in the MET/SU group at a rate of 0.75 events per 100 patient years (95% CI: 0.59, 0.90). The hazard ratio (95% CI) for RSG vs. MET/SU treatment was 0.90 (0.68, 1.21).

For CV and unknown cause deaths, primary survival analysis based on the original RECORD CEC definitions and the new FDA definitions produced identical results, including number of patients with an event, event rates, hazard ratios (RSG vs. MET/SU) by treatment and background therapy, and subgroup interaction results. There was no evidence of a treatment effect (DCRI Table 5.1 and Figure 5.1 below):

RECORD Trial: DCRI Independent Review

Table 5.1 (page 1 of 1)
CV and Unk. Cause Mortality (Original Def.): Summary by Treatment Arm
Based on Survival Follow-up for Primary Analysis*

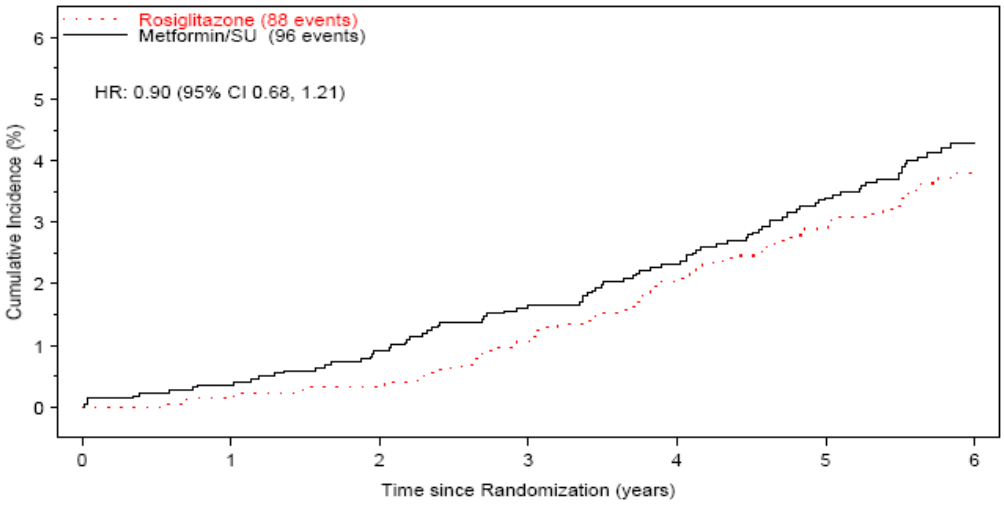
		Treatment	
	Total (N=4447 PY=25768.6)	Combined RSG (N=2220 PY=12953.6)	Combined MET/SU (N=2227 PY=12815.0)
Number of patients with an event	184 / 4447 (4.1%)	88 / 2220 (4.0%)	96 / 2227 (4.3%)
Rate per 100 patient years (95% CI)	0.71 (0.61, 0.82)	0.68 (0.53, 0.83)	0.75 (0.59, 0.90)
Hazard Ratio** (95% CI)		0.90 (0.68, 1.21)	
Absolute rate difference per 100 patient years (95% CI)		-0.07 (-0.28, 0.14)	

* Follow-up for patients not reaching endpoint is censored on date last known alive on or before 31-Dec-2008.
** Hazard ratio from a Cox proportional hazards model stratified by background therapy. A hazard ratio < 1 favors RSG.
Generated from ct/record/tables/tbl_allcause_outcome.sas on 30NOV2011 at 17:26

RECORD Trial: DCRI Independent Review

Figure 5.1

CV and Unk. Cause Mortality (Original Def.) - Time to Endpoint
Kaplan-Meier Estimates and Hazard Ratio with 95% Confidence Interval for RSG vs. Met/SU
Based on Survival Follow-up for Primary Analysis



Rosaglitazone							
Events	0	4	7	23	45	62	79
At Risk	2220	2190	2165	2130	2087	2048	988
Metformin/SU							
Events	0	8	20	36	50	73	89
At Risk	2227	2181	2140	2110	2079	2019	953

Generated from ct/record/graphs/d_allcause_outcome.sas on 30NOV2011 at 17:31

There was some evidence of treatment-by-subgroup interaction for duration of diabetes < 6 years or ≥ 6 years (p=0.069). The hazard ratio (95% CI) was 1.24 (0.80, 1.94) for the subgroup with diabetes < 6 years and 0.72 (0.49, 1.06) for the subgroup with diabetes ≥ 6 years. No other demographic or disease characteristic showed evidence of treatment interaction.

There was some evidence of treatment-by-baseline therapy (MET or SU) interaction (p=0.093). There was also evidence of interaction by baseline use of statins or not (p=0.003). Among patients using statins at baseline, the hazard ratio (95% CI) was 2.29 (1.16, 4.54) favoring MET/SU. Among patients *not* using statins at baseline, the hazard ratio (95%) was 0.72 (0.52, 1.00) favoring RSG.

From the original RECORD analysis, the definition of CV death included deaths of unknown cause. As opposed to a total of 184 CV + Unknown-cause deaths in the DCRI re-adjudication, there were only 131 total CV + Unknown-cause deaths in the original RECORD report (53 additional deaths of this classification in the DCRI re-adjudication). From the original RECORD analysis, there was no evidence of treatment effect on CV + Unknown-cause mortality (RECORD Table 76 and Figure 20 below):

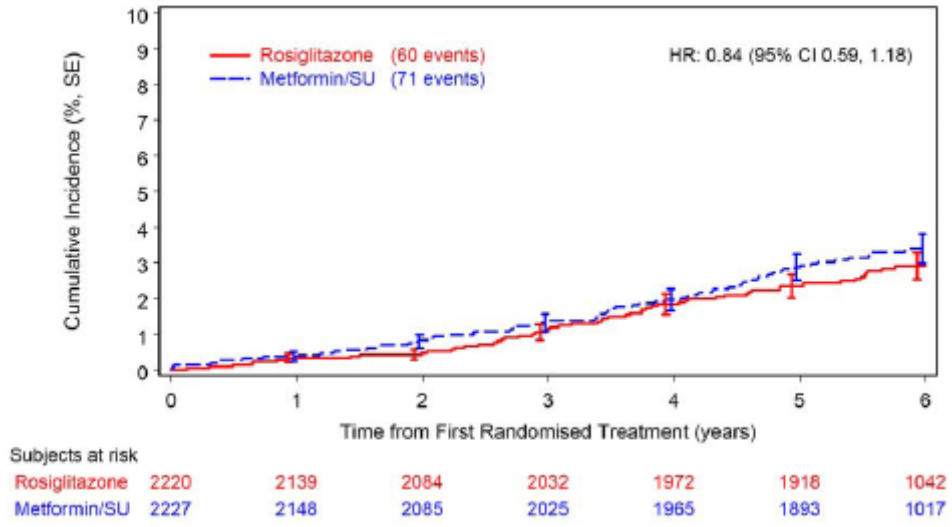
Table 76 Occurrence of Death from CV Causes (ITT population)

Time to CV Death	Treatment Group: Combined RSG (N=2220)	Treatment Group: MET/SU (N=2227)
No. (%) subjects who died from CV causes	60 (2.7)	71 (3.2)
Incidence: rate/100 PY[1] (95% CI)	0.49 (0.37, 0.63)	0.58 (0.45, 0.73)
Hazard ratio[2], (95% CI); p-value	0.84 (0.59, 1.18); p=0.3158	
Absolute rate difference/100PY[1]	-0.09 (-0.27, 0.09)	

Data Source: DS Table 7.102 and DS Table 7.103

1. Person-years up to first event/censoring.
2. Based on Stratified (by background stratum) Cox's Proportional Hazards Model: Time = Treatment. HR is relative to MET/SU.

Figure 20 Cumulative Incidence of Time to Death from CV Causes (ITT population)



Data Source: DS Figure 7.28

As shown in the table below, of the 53 additional deaths included in the DCRI analysis of CV + Unknown deaths, 46 were additional "unknown cause" deaths – only seven were additional CV deaths. Both the RECORD original analysis and the DCRI re-analysis demonstrate numerically higher CV deaths from the MET/SU arm than from the combined RSG arm:

Adjudicated Death Events				
	RSG (N=2200)		MET/SU (N=2227)	
	RECORD	DCRI	RECORD	DCRI
CV+Unk	60	88	71	96
Unk	28	53	33	54
CV	32	35	38	42

To further characterize re-adjudicated "unknown-cause" deaths from the DCRI CEC as compared to the original RECORD CEC, an assessment was made of how these two patient groups overlapped, and what their outcomes were (Mahoney, 2012). 61 deaths were adjudicated to be of unknown-cause in the original RECORD FSR. These were not a perfect subset of the 120 deaths re-adjudicated to be of unknown-cause by the DCRI:

- Of the 120 deaths due to unknown-cause in the DCRI re-adjudication, 82 had not been adjudicated as due to unknown cause in the original RECORD adjudication. These 82 deaths were evenly distributed between the RSG group and the MET/SU comparator group (41 deaths each).

- Of the 61 deaths originally adjudicated as due to an unknown-cause, 23 of these were not re-adjudicated by the DCRI as being due to an unknown cause. Among these 23 cases, 9 were in the RSG group, and 14 were in the comparator group. OF the 9 deaths in the RSG group, DCRI re-adjudicated 4 as CV deaths, and 5 as non-CV deaths. OF the 14 deaths in the MET/SU comparator group, DCRI adjudicated 8 as CV and 6 as non-CV deaths.

Re-adjudication Results – CV Mortality

An analysis of CV mortality without "unknown-cause" death was not performed in the original RECORD analysis, though a breakdown of the total numbers of the CV versus unknown-cause events are shown in the CV + Unknown-cause mortality section above.

DCRI analyzed CV deaths (without deaths of unknown-cause), using both the original RECORD definitions for CV death, as well as the new draft FDA definitions for CV death. In this analysis, 76 CV deaths were confirmed by re-adjudication representing 1.7% of the total ITT population (N=4447) (See DCRI Table 1.5 below). All confirmed CV deaths occurred on or before 31 December 2008; no CV deaths occurring after the RECORD end of follow-up date were identified. Cardiovascular death events occurred in 34 of 2220 patients (1.5%) in the combined RSG treatment group and 42 of 2227 (1.9%) in the combined MET/SU treatment group.

Of note, deaths due to CHF were strikingly more frequent in the RSG group as opposed to the MET/SU comparator group, both by the original definition (9/34 (26.5%) vs. 1/42 (2.4%), respectively) and by the new definition (8/34 (23.5%) vs. 1/42 (2.4%), respectively). On the other hand, acute vascular events were more common in the MET/SU group by the original definition (and stroke + other CV deaths more common in the MET/SU group by the new definition).

RECORD Trial: DCRI Independent Review

Table 1.5 (page 1 of 1)
Cardiovascular Mortality by Time Period

	Deaths Occurring On or Before 31-Dec-2008			Deaths Occurring After 31-Dec-2008		
		Treatment			Treatment	
	Total (N=4447)	Combined RSG (N=2220)	Combined MET/SU (N=2227)	Total (N=4447)	Combined RSG (N=2220)	Combined MET/SU (N=2227)
Original Definition						
Total Cardiovascular Deaths	76 / 4447 (1.7%)	34 / 2220 (1.5%)	42 / 2227 (1.9%)	0 / 4447	0 / 2220	0 / 2227
Cause of Death						
Heart Failure or Cardiogenic Shock	10 / 76 (13.2%)	9 / 34 (26.5%)	1 / 42 (2.4%)	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction	20 / 76 (26.3%)	8 / 34 (23.5%)	12 / 42 (28.6%)	0 / 0	0 / 0	0 / 0
Sudden Cardiac	29 / 76 (38.2%)	14 / 34 (41.2%)	15 / 42 (35.7%)	0 / 0	0 / 0	0 / 0
Acute Vascular Event	13 / 76 (17.1%)	1 / 34 (2.9%)	12 / 42 (28.6%)	0 / 0	0 / 0	0 / 0
Other Cardiovascular Cause	4 / 76 (5.3%)	2 / 34 (5.9%)	2 / 42 (4.8%)	0 / 0	0 / 0	0 / 0
New Definition*						
Total Cardiovascular Deaths	76 / 4447 (1.7%)	34 / 2220 (1.5%)	42 / 2227 (1.9%)	0 / 4447	0 / 2220	0 / 2227
Cause of Death						
Heart Failure or Cardiogenic Shock	9 / 76 (11.8%)	8 / 34 (23.5%)	1 / 42 (2.4%)	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction	21 / 76 (27.6%)	8 / 34 (23.5%)	13 / 42 (31.0%)	0 / 0	0 / 0	0 / 0
Sudden Cardiac	29 / 76 (38.2%)	14 / 34 (41.2%)	15 / 42 (35.7%)	0 / 0	0 / 0	0 / 0
Stroke	6 / 76 (7.9%)	0 / 34	6 / 42 (14.3%)	0 / 0	0 / 0	0 / 0
Other Cardiovascular Cause	11 / 76 (14.5%)	4 / 34 (11.8%)	7 / 42 (16.7%)	0 / 0	0 / 0	0 / 0

* Contemporary definitions under development by FDA through the Standardized Data Collection for Cardiovascular Trials Initiative.
Generated from ct/record/tables/tbl_cv_dth_time.sas on 30NOV2011 at 17:25

Re-adjudication Results – All-cause Mortality on Treatment LDRT + 30 days

No treatment effect or background therapy effect was demonstrated.

Re-adjudication Results – CV + Unknown-cause Mortality on Treatment LDRT + 30 days

No treatment effect or background therapy effect was demonstrated. Primary survival analysis based on the original RECORD CEC definitions and the new FDA definitions produced identical results, including number of patients with an event, event rates, hazard ratios (RSG vs. MET/SU) by treatment and background therapy, and subgroup interaction results.

Re-adjudication Results – All-cause Mortality on Treatment LDRT + 60 days

No treatment effect or background therapy effect was demonstrated.

Re-adjudication Results – CV + Unknown-cause Mortality on Treatment LDRT + 60 days

No treatment effect or background therapy effect was demonstrated. Primary survival analysis based on the original RECORD CEC definitions and the new FDA definitions

produced similar results, including number of patients with an event, event rates, hazard ratios (RSG vs. MET/SU) by treatment and background therapy, and subgroup interaction results.

Re-adjudication Results – Sensitivity Analyses

- CV mortality using original and new FDA definitions – no evidence of treatment effect
- Impact of Amendment 7 (tracking study to collect endpoint data from withdrawn patients) on all-cause mortality – no evidence of treatment effect and no interaction with background therapy
- Landmark analysis, Amendment 7 to 31 December 2008, all-cause mortality – no evidence of treatment effect and no interaction with background therapy
- CV + Unknown-cause mortality prior to Amendment 7 – no evidence of treatment effect and no interaction with background therapy
- Landmark analysis, Amendment 7 to 31 December 2008, CV + Unknown-cause mortality – no evidence of treatment effect and no interaction with background therapy
- All-cause mortality prior to published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- All-cause mortality following published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- CV + Unknown cause mortality (new definition) prior to published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- CV + Unknown cause mortality (new definition) following published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- All-cause mortality by alternative rules for derivation of end of follow-up – the three alternative approaches (parsimonious, primary analysis + tests and events, primary analysis + tests and events + survival status) demonstrated no evidence of treatment effect and no interaction with background therapy
- CV + Unknown-cause mortality by alternative rules for derivation of end of follow-up – the three alternative approaches (parsimonious, primary analysis + tests and events, primary analysis + tests and events + survival status) demonstrated no evidence of treatment effect and no interaction with background therapy
- Impact of censoring at earliest study completion date (24 August 2008 instead of 31 December 2008) on all-cause mortality – no evidence of treatment effect (no test for background therapy interaction)
- Impact of censoring at earliest study completion date (24 August 2008 instead of 31 December 2008) on CV + Unknown-cause mortality (new definition) – no evidence of treatment effect (no test for background therapy interaction)

Assessment

This well-conceived and comprehensive re-adjudication of the RECORD trial mortality experience demonstrated no evidence of a difference in all-cause mortality, cardiovascular plus unknown-cause mortality or non-cardiovascular mortality between the RSG and MET/SU treatment arms of RECORD. This was true regardless of whether the original RECORD definitions or new/draft FDA definitions of mortality endpoints was utilized. Hazard ratios for RSG vs MET/SU for all-cause mortality, CV+Unknown-cause mortality, and non-CV mortality were all less than 1.0 in the DCRI re-adjudication of the mITT results of RECORD. None of the many sensitivity analyses demonstrated a treatment effect. Accordingly, the findings of this phase-I mortality re-analysis corroborate the mortality findings of the original RECORD analysis.

The degree to which no stone was left unturned in this re-analysis is highlighted by the number of patients who ultimately required imputed end-dates for study events. Recall, 604 patients were deemed by DCRI to have incomplete follow-up. By the end of the investigations and record reviews by DCRI and MediciGlobal, only 21 patients required imputation of death dates. Of these 21 patients, a year of death was documented for all. For 11 of the 21 patients, documentation for a month and year were found, requiring imputation only for the day of the month of death.

To be sure, the critic would point out that of the 127 queries for information that went out to sites, only 23 of the 127 generated additional data (response rate 18%), and only 7 of these resulted in a change to the adjudication (action rate 6%). Yet we would point out that these queries went out to sites after the study had been closed for approximately 2-3 years. Furthermore, considering staffing limitations (and sometimes closure of practices), this response rate should have surprised no one, as most investigators simply do not have the capacity to open up large paper data files to look for details on a study that has long since been shut down.

Mortality Re-adjudication Limitations

- Of the 313 deaths that DCRI identified and re-adjudicated, there was insufficient evidence to determine cause of death (cardiovascular vs. non-cardiovascular) in 120 cases (38% of all deaths).

- After all avenues for determining final disposition of patients had been explored and exhausted, vital status remained unknown for 87 patients.

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Follow-up Consultation for NDA 021071 SDN1652

DATE: Consult requested: 4/30/2012
Desired completion date: 9/3/12
Date of review: 9/3/2012

FROM: Preston M. Dunnmon, M.D., Clinical Reviewer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Jena M. Weber, Regulatory Project Manager
Director, Division of Metabolism and Endocrinology Products

SUBJECT:

The Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia and Diabetes trial (RECORD, BRL-049653/231) compared cardiovascular (CV) outcomes between rosiglitazone (RSG) therapy in combination with metformin (MET) or a sulfonylurea (SU) to CV outcomes with the MET/SU combination (NDA 021071 SDN1652). In response to your prior consult, DCRP reviewed all-cause and CV mortality from RECORD according to the Phase-I re-adjudication of the trial's mortality outcomes by the Duke Clinical Research Institute (DCRI) (final consult dated 5/7/2012). This memo responds to your follow-up consult requesting that DCRP review the phase II DCRI re-adjudication of the MACE results (cardiovascular or unknown cause mortality, non-fatal myocardial infarction, or non-fatal stroke) from RECORD. DCRP has the following material:

- Prior DCRP consult (June 14, 2010)
- Prior DCRP consult (May 7, 2012)
- FDA Briefing Document Advisory Committee Meeting for NDA 21071 (July 13 and 14, 2010)
- RECORD final study report (FSR)
- Original RECORD CEC charter
- DCRI Re-adjudication Protocol AVD115170 for RECORD, Report of the First Phase: Blinded Re-adjudication of All-cause Mortality and Cardiovascular Mortality
- DCRI Re-adjudication Protocol AVD115170 for RECORD, Report of the Second Phase: Blinded Re-adjudication of Major Cardiovascular Endpoints

Regulatory Background

The cardiovascular safety of AVANDIA® (rosiglitazone) has been the subject of two recent public proceedings:

- July 30, 2007 - joint public advisory committee concluded that AVANDIA® increases cardiac ischemic risk in type 2 diabetes mellitus based on then available data but that the overall risk-benefit profile of AVANDIA® supported its continued marketing in the US

- July 13-14, 2010 – advisory committee meeting for AVANDIA® (NDA 021071, rosiglitazone maleate) considered data from three newly available long-term outcome studies (RECORD, ADOPT, and DREAM) in a discussion regarding whether rosiglitazone should continue to be marketed in the United States.

As part of the 2010 advisory committee briefing document, the weaknesses of RECORD's open label non-inferiority design, as well as the consequent opportunities for ascertainment biases, were very thoroughly vetted. At the completion of the July 2010 adviory committee, FDA decided that rosiglitazone could remain on the market in the US if:

1. GSK undertook a restricted access program under a REMS with ETASU

2. GSK commissioned an independent re-adjudication of the RECORD study outcomes. If the mortality finding were found to be valid on the first phase of re-adjudication, then a second phase re-adjudication of other MACE elements would be performed (nonfatal MI, nonfatal CVA, and CV death).

3. The TIDE trial was placed on full clinical hold.

GSK agreed to the above conditions for continued marketing of rosiglitazone in the US and commissioned the DCRI to perform a full and independent re-adjudication of the RECORD study's cardiovascular outcomes as delineated by FDA. Accordingly, the phase-II MACE re-adjudication has now been completed. The purpose of this document is to review the findings of the phase-II (MACE) re-adjudication.

During this re-evaluation period, the labeled indication for rosiglitazone has read as follows:

> *After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA®, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are already taking AVANDIA®, or not already taking AVANDIA® and are unable to achieve adequate glycemic control on other*

diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) for medical reasons.

Background – RECORD Study design

RECORD was a post-marketing commitment to the European Medicines Agency. Its design was reviewed and approved by the Committee for Proprietary Medicinal Products (now known as the Committee for Medicinal Products for Human Use). RECORD was not conducted under a U.S. IND.

RECORD was a randomized, multicenter, open-label, parallel group trial of 4447 subjects with type 2 diabetes, comparing cardiovascular outcomes in subjects randomized to rosiglitazone in combination with metformin or a sulfonylurea to the combination of metformin plus a sulfonylurea. A four-week run-in period was followed by a proposed median of 6 years of treatment with study medication, in addition to continuation of background glucose-lowering therapy. Patients on background metformin (MET) were randomized to receive, in addition to continued metformin, either rosiglitazone or a sulfonylurea (glibenclamide, gliclazide or glimepiride), in a ratio of 1:1. Patients inadequately controlled on background SU were randomized to receive, in addition to continued sulfonylurea (SU), either RSG or MET, in a ratio of 1:1. Equal numbers of patients on background MET and SU were to be randomized.

Throughout study, target hemoglobin A1c (HbA1c) was to be ≤7%. After 8 weeks of treatment, if a patient's HbA1c was >7%, the investigator was to increase the dose of study medication. If tolerated, RSG was to be titrated to a dose of 8 mg/day, administered as 4 mg BID, in order to achieve an HbA1c of 7%. Doses of MET and SU were to be titrated to the maximum allowable dose approved by the regulatory authority of the country in which the study site was located, also to achieve an HbA1c of 7%.

If a patient's HbA1c remained ≥8.5% after at least 8 weeks on the maximum permitted or tolerated dose of add-on study medication, a confirmatory HbA1c was to be performed at least 1 month later. If the HbA1c was still ≥8.5%, another agent was added. For patients in the RSG + MET group, SU was added. For patients in the RSG + SU group, MET was added. For patients in the MET + SU group, insulin was added, with or without continuation of MET and/or SU, "according to local clinical practice".

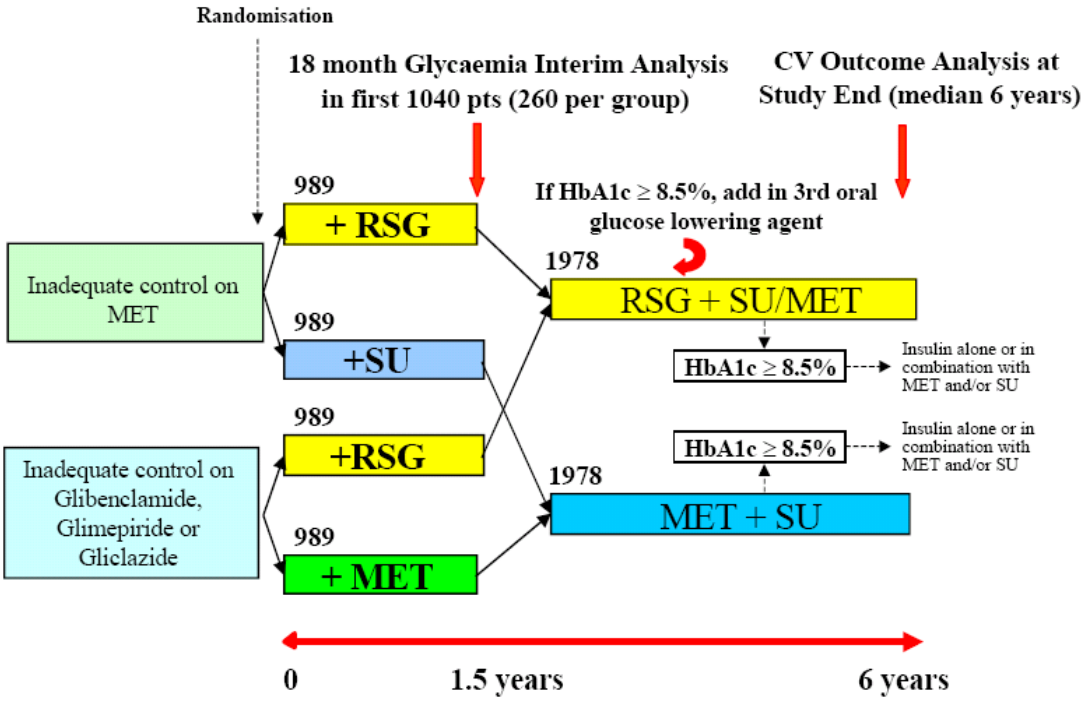
For patients in the RSG groups who had progressed to triple oral therapy, had remained on the maximum permitted or tolerated dose of the triple therapy for at least 8 weeks, and still had a HbA1c ≥8.5%, insulin was added and rosiglitazone was discontinued. The combination of RSG and insulin was not approved in Europe at the time the study was initiated. For these patients, MET and/or SU might or might not be continued, again according to local clinical practice.

The primary endpoint/analysis of RECORD was an ITT analysis of the time to first adjudicated CV hospitalization or CV death (any death for which an unequivocal non-CV

cause could not be established (acute MI, heart failure, sudden death, acute vascular events, other CV mortality, unknown causes), over the full duration of the study. To reiterate, deaths of unknown cause were counted as CV deaths.

The objective of the study was to rule out a 20% increase in the relative hazard of RSG combination compared to the combined control groups (MET/SU). Formal non-inferiority was to be achieved, according to protocol definition, if the upper limit of the 95% confidence interval for the hazard ratio of RSG versus MET/SU at study end was less than 1.2.

The following figure illustrates the study phases from randomization through initiation of insulin in both treatment groups:



DCRI Methodology

Re-adjudication and analysis of MACE for the RECORD study was performed in accordance with the following documents:

- Re-adjudication Protocol for RECORD, Version 1, 28 January 2011
- Re-adjudication Protocol for RECORD, Amendment Version 2, 24 June 2011
- Statistical Analysis Plan: Second Phase (Major Cardiovascular Events), 24 January 2012

DCRI-CEC processes for the re-adjudication of RECORD MACE events were described in the DCRI Clinical Events Classification (CEC) Charter for Re-adjudication of RECORD (Version 3.0, Effective Date: 07 December 2011).

There were five key objectives to the MACE re-adjudication as follows:

1. Systematic identification of all deaths, all suspected myocardial infarction (MI), and all suspected stroke events using all possible data sources while blinded to patient level treatment assignment.
2. Standard preparation of all events for adjudication without filtering of suspected events by site or central personnel with knowledge or potential knowledge of patient level treatment assignment.
3. Adjudication of all events using the original RECORD endpoint definitions and contemporary definitions under development by FDA (Standardized Data Collection for Cardiovascular Trials Initiative).
4. Independent definition of study follow-up phases and derivation of dates last observed without event for patients who were not reported to die or experience MI or stroke.
5. Statistical analysis of the mortality and non-fatal MI and non-fatal stroke outcomes by treatment assignment as well as a series of complementary analyses to evaluate potential confounders and data limitations in the original analyses.

Ascertainment

Ascertainment and analysis of mortality was the subject of the DCRP consult dated 5/7/2012, so that component of the MACE analysis will not be re-reviewed here (though analyses of total MACE will include mortality).

With respect to the MACE ascertainment in RECORD, DCRI developed a comprehensive trigger process of automated and manual procedures to identify systematically all suspected endpoint events from all potential data sources in which cardiovascular (or unknown cause) deaths, MI, or stroke events may have been reported by the site investigators. Trigger specifications were detailed in a document titled RECORD Re-Adjudication Trigger Specifications (August 4, 2011). Data sources for re-adjudication included but were not limited to:

- The original RECORD dataset
- Original RECORD paper case report forms
- Original RECORD SAE reports
- Event packets used in the original adjudication (and the source documents they contained)
- Original site queries for additional information and query responses
- DCRI CEC query responses
- Additional source documents from the sites as a result of DCRI CEC queries
- Available ECGs from the site files and ECG sub-study files
- Correspondence from GSK

- All information collected by GSK between November 2010 and March 2011 regarding patients whose last contact was made during the survival status follow-up phase as recorded in the CRF
- Third party (MediciGlobal) search for end-of-study documentation of vital status.

In addition, GSK retrieved available source documents from the Investigators' Archive so that these would be available to DCRI during the re-adjudication of RECORD, and Quintiles sent a letter to each site explaining the request for source data; a copy of the letter was to be submitted to each site's ethics committee for notification. A remote call was placed to each site to explain further the requirements and to understand the site's ability to provide the requested source data.

Specific documents that were requested by DCRI from GSK with respect to relevant Mace endpoint components that had been referred to the original RECORD event committee were as follows:

- Death in hospital
    - Death summary or investigator narrative
    - Autopsy report if available
- Death Out-of-Hospital:
    - Narrative of investigator
    - Autopsy Report if available
    - Police report/family records/whatever documents could be provided to clarify the circumstances
- All hospitalizations
    - hospital discharge letter, or a narrative about the hospital stay from the investigator
- Hospitalizations for MI
    - Hospital discharge summary including the results of the patient's electrocardiogram(s) taken during the hospital admission and results of cardiac biomarker laboratory tests
    - If the hospital discharge summary was lacking ECG and enzyme details, a hardcopy of the ECG plus a hardcopy of the cardiac biomarker results was required. If a hard copy of the cardiac biomarker results was not available, the investigator had to complete the Myocardial Infarction/Unstable Angina endpoint form (section Cardiac Biomarkers)
- Hospitalizations for Stroke
    - Hospital discharge summary with results of a neurologists investigations provided in the discharge summary. If the discharge summary did not provide sufficient detail, the translated neurological report was requested. If the neurological report was not obtainable, the investigator summarized a verbal account from the neurologist in the endpoint CRF pages for stroke and transient ischemic attack (TIA).

For new events that were identified by DCRI, the following documents were requested:

- Death events:
  - Death summary
  - Investigator narrative
  - Autopsy report if available
- Myocardial Infarction events:
  - Hospital discharge summary
  - Hardcopies of baseline and at least 2 event electrocardiograms
  - Cardiac biomarker laboratory tests, including units and reference ranges
- Stroke events
  - Investigator narrative
  - Hospital discharge summary
  - Imaging study reports (MRI/MRA, CT/CTA)
  - Neurology consult notes.

Triggers for Identification of Suspected Events and DCRI CEC Review

DCRI employed a combination of both automated program triggers and manual trigger procedures to identify suspected MACE events from source materials reviewed by their CEC, described as follows:

- Automated trigger program – computer trigger program that included:
  - Screening of all Adverse Experience (AE) and Serious Adverse Experience (SAE) forms from the CRF data fields in the GSK RECORD datasets
  - Pre-specified MedDRA coded terms. The coded preferred terms were reviewed by Clinical, CEC and Safety experts to identify terms that would potentially be indicative of an endpoint with a low threshold. A similar approach has been used in previous re-adjudication efforts
  - Death Form (Form D) when present in the database.

- Manual trigger procedures – RECORD CEC Coordinators performed manual review of paper documents as well as reviewing the output from the automated trigger program. All were experienced in cardiology event reporting and CEC methodologies. Paper sources that the CEC Coordinators reviewed to identify potential endpoints included:
  - The unscheduled visit form (all visits)
  - Source documents used as part of the original RECORD CEC adjudication process and any additional source documents collected as part of the re-adjudication activities (discharge summaries, progress notes, pertinent lab values, and physician narratives)
  - Investigator verbatim
  - All SAE and AE forms - SAEs and AEs that were deleted by RECORD investigators were identified from the audit trail of the study's electronic datasets, which GSK provided to DCRI. The electronic data sets were sent

to the DCRI prior to the event packet files which included data from the CRF and source documents.

- All cases that were sent to the original RECORD CEC; this would include endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator
- All Death Endpoint Forms
- All Myocardial Infarction/Unstable Angina Endpoint Forms
- All Stroke/TIA Endpoint Forms
- All Hospitalizations
- All Survival Status Forms
- All Documentation of Third Party Survival Data Forms
- All Tracking Forms for Completely Withdraw Patients
- All Study Completion Forms
- All available12 lead ECG tracings for subjects that were not included in the RECORD ECG sub-study
- All available 12 lead ECG tracings for subjects that were included in the RECORD ECG sub-study, and triggered for a potential MI event per automated trigger program
- All available 12 lead ECG tracings for subjects that were included in the RECORD ECG sub-study, and were determined to have a new q wave MI per sub-study analysis.

CEC Query of Suspected MI and Stroke Events

A total of 2597 MI/Stroke triggers were identified: 2101 myocardial infarctions (MIs) and 496 strokes. Of the 2597 triggers identified, 4 were set to a status of "No action needed" and not adjudicated because there was no evidence in the medical records that a potential event occurred. 697 triggers were set to a "linked" status and not adjudicated because they were duplicate triggers directly linked to another trigger that was sent for adjudication. The remaining 1896 MI and stroke triggers (1474 MIs, 422 strokes) were adjudicated.

70 CEC queries requesting additional information from the site investigators or coordinators were issued for MI and stroke events:

- 31 queries were closed with no response from the site investigator;
- 20 queries were closed with a response from the site investigator that no additional data were available;
- 19 queries were closed with additional data received from the site investigator.

Of the 19 MI and stroke queries that resulted in additional information, only 2 resulted in changed adjudication results: one from MI "yes" to "no", and one from MI "no" to "yes". For 9 of the 19 queries, the adjudication did not change with additional information received, and for 8 other queries, there had been no adjudication result prior to receiving the additional data.

An effort was made to obtain additional information from the sites for some suspected events. However, only 27% of queries resulted in additional information being received from the site investigator and the remaining queries were unanswered or the response from the site indicated no additional information could be obtained.

Data Collection

All data sent to the DCRI RECORD CEC group was to have subject personal identifiers, treatment assignment, and glucose lowering agents redacted (electronic datasets as well as source documents and paper CRFs). GSK was responsible for the redacting prior to delivery of data or documents to the DCRI. The RECORD CEC Coordinators, Clinical Data Assistant, and Clinical Trial Assistants ensured that information had been blinded or redacted prior to sending event packets to the CEC physicians. If during the course of DCRI activities it is noted that information that should have been redacted was not, then DCRI RECORD CEC Coordinators, Clinical Data Assistant, and/or Clinical Trial Assistants redacted the information, documented the event and notified GSK.

When additional information was needed to aid in the CEC adjudication, sites were contacted directly by the DCRI CEC for supporting documentation or data clarification in order to help render an adjudicated result. DCRI CEC generated requests for source documents for endpoints that were previously adjudicated as well as for all new endpoints. DCRI CEC requested any documents from sites that were missing from the previous adjudication process. All requests were tracked. Sites were to submit additional information directly to the DCRI CEC RECORD email inbox. Additional documentation that is added to event packet was noted as "new information" at the top of the page of the source document and tracked in the CEC tracker so that comparisons between the re-adjudication results and the original adjudication results allowed analysis of whether additional source documents were used during the re-adjudication process.

When additional source documentation was needed to support the adjudication for a suspected event, DCRI CEC made 2 attempts to gain resolution of the request for information from the sites. If additional information was not available for an endpoint, the site was to note that on the request form and that information was provided in the event packet. If additional information was received after the adjudication had been completed that might affect the adjudication result, the event was re-reviewed. The CEC adjudication form and database were subsequently updated to reflect any changes to the initial adjudication.

The DCRI accepted documents that were not in English, and then contracted with an independent vendor for translation services.

Database transfers

Electronic data files containing raw data from CRFs were transferred from GSK to DCRI as SAS datasets in three phases as follows:

- Phase 1 - raw CRF datasets needed to provide electronic identification of events for referral to the DCRI CEC. Treatment information was redacted from this data, and confirmation of the redaction was done by a DCRI statistical programmer before the datasets were made available to the blinded statistical team. The phase 1 data transfer was completed on 26 January 2011.

- Phase 2 - AE and CV procedure endpoint numbers, dummy randomization data, treatment start and stop dates, subgroups reported in the original RECORD study, and a dataset containing the ID numbers of patients whose deaths had been reported in the original study. The phase 2 data transfer was completed on completed on 12 August 2011.

- Phase 3 - treatment information and re-delivery of all previously delivered datasets with redacted information un-redacted (completed 01 November 2011). These data were placed in a secure folder on the DCRI server and access was granted to the DCRI statistician and other persons intentionally unblinded for development of the phase 1 (mortality) report. Access by the statistical team members responsible for producing the report of re-adjudicated MACE was granted only after the database lock for the second re-adjudication phase, on 09 February 2012.

Adjudication process

The DCRI RECORD CEC physicians adjudicated each suspected event using the pre-specified endpoint criteria based on the preponderance of the evidence and clinical knowledge and experience. All events were reviewed using the original RECORD Clinical Endpoint Committee definitions and the new definitions based on the FDA definitions (FDA Standardized Definitions for End Point Events in Cardiovascular Trials).

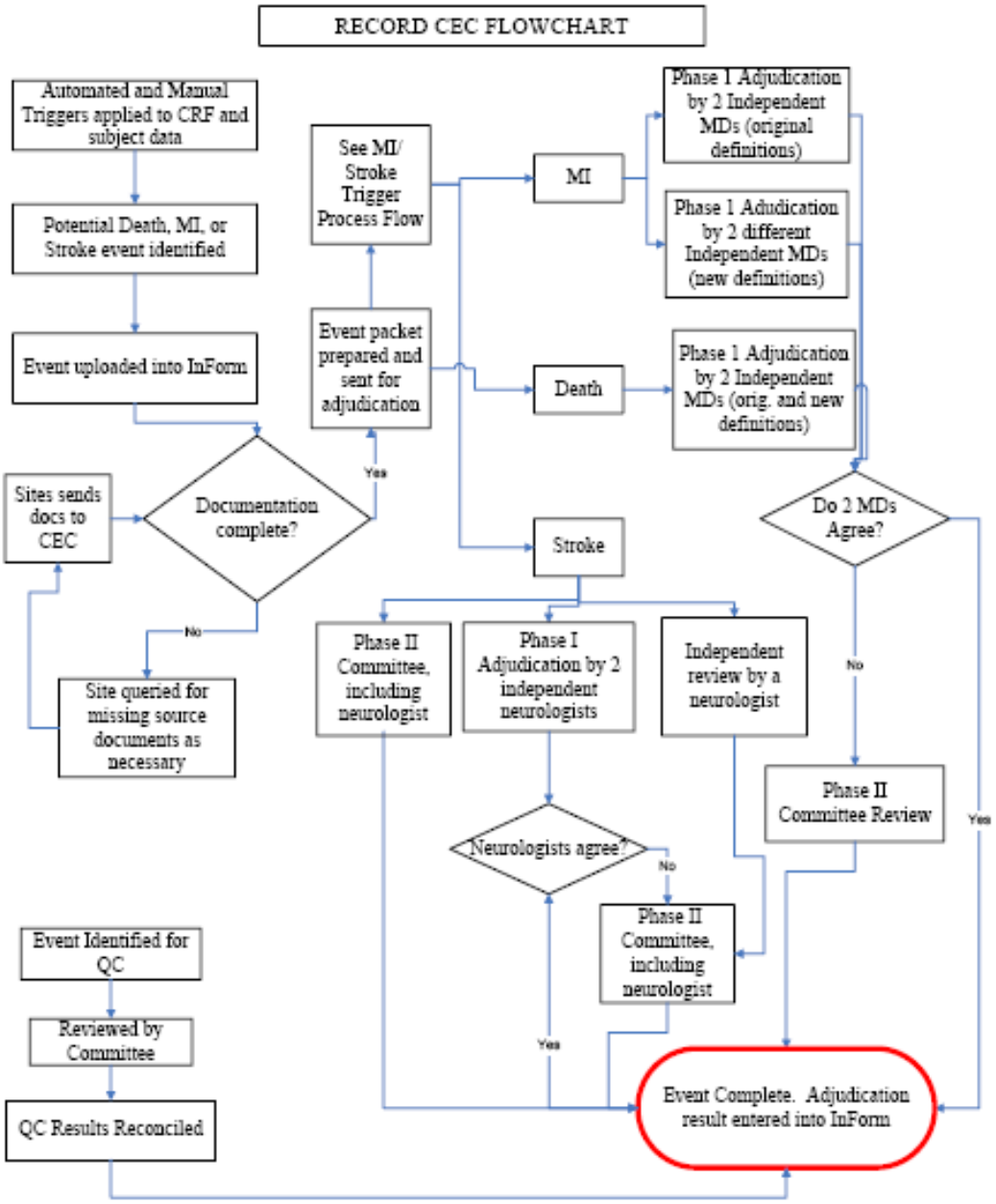
Potential events triggered from an adverse event term with no hospitalization or source documentation present were reviewed by a single clinician (RECORD CEC Coordinator or physician). That clinician reviewed the data present to determine whether or not a potential event occurred. If there were no data to support that an event occurred, a RECORD CEC Adjudication Form was completed indicating no event. If there were data present to indicate that an event may have occurred, the event packet and data were forwarded to Phase I review for potential MI events and Phase I or Neurologist/Phase II review for potential stroke events.

Phase I review was defined as a process whereby two physicians independently adjudicated each suspected event using specific event criteria:

- Cause-specific deaths using both the original RECORD Clinical Endpoint Committee definitions and new proposed standardized definitions
- Myocardial Infarction (MI) events using the original definitions, and a different set of two physicians reviewed the same MI event with the new proposed standard definitions
- Stoke events using original RECORD Clinical Endpoint Committee definitions and proposed new standard definitions, by two independent neurologists.

If the Phase I reviewers agreed in their adjudication of the suspected event, the endpoint classification was complete. If the Phase I reviewers did not agree regarding the classification of the suspected event, the event is adjudicated by Phase II review.

Phase II review was a process whereby an Adjudication Committee meeting was organized comprising at least three faculty physicians. All disagreements from the Phase I review process were presented at the Adjudication Committee meeting of faculty members, each event was reviewed, and a decision was made by consensus of the Phase II reviewers. For stroke, the Phase II committee was comprised of at least three RECORD CEC physicians, including a neurologist. The overall CEC adjudication work flow is as diagramed below:



Derivation of Follow-up Dates (per DCRI phase 2 report)

Derivation of the follow-up period for MI and stroke ascertainment was done similarly to the derivation of the Parsimonious approach to survival follow-up (described in the DCRP consult on the phase I mortality review, dated 5/7/2012). If a patient was determined to have at least one MI, the last follow-up date for this endpoint was the date of the first occurrence of MI, and follow-up was considered uncensored. If a patient did not have an MI, follow-up for this endpoint was censored at the date of the last study visit at which any measurements (blood pressure, heart rate, or weight) were recorded on the

VITALS module of the CRF. A similar approach was used to derive follow-up dates for stroke. The rationale for this approach is that after the last study visit with measurements recorded on the VITALS module, patients were not periodically assessed face-to-face, and there may have been a greater chance for a non-fatal event to remain undetected.

Follow-up dates for MI and stroke were derived independently. For example, if a patient experienced an MI and did not have a stroke, the last follow-up date for the analysis of stroke would be the last study visit with measurements recorded on the VITALS module. That is, it would not be assumed that the patient remained stroke free from the last study visit to the date of the MI. Similarly the occurrence of a stroke in a patient who did not have an MI would not increase the follow-up for MI beyond the date of the last study visit with measurements recorded on the VITALS module.

Last follow-up date for patients experiencing a MACE event (cardiovascular or unknown cause death, non-fatal MI, or non-fatal stroke) was the date of earliest occurrence among these events. Last follow-up date for patients who did not experience any of these events was the date of the last study visit with measurements recorded on the VITALS module.

Quality Control: Re-adjudication Process and Manual Triggers

In accordance with the CEC charter, an internal QC analysis was conducted through blinded CEC review of a random sample of stroke and MI events that had already undergone re-adjudication by the DCRI CEC. Data for 110 re-adjudicated stroke and MI events (to represent at least a 5% sample of the total re-adjudicated events) were randomly selected by the DCRI statistician and reviewed by DCRI RECORD CEC physicians who were blinded to the original re-adjudication result. The events in the QC sample were reviewed by RECORD CEC physicians during DCRI RECORD CEC Committee Meetings. The QC result was then compared to the first DCRI CEC re-adjudication result, and revealed the following:

- 103 events: No discrepancy between QC results and original adjudication result
- 1 event: Major discrepancy involving event classification
- 2 events: Minor discrepancy involving q wave classification
- 4 events: Minor discrepancy involving event date/time.

The QC effort showed that the re-adjudication process met DCRI CEC standards. The QC effort resulted in no findings that necessitated changes to the DCRI RECORD re-adjudication process or amendment of the RECORD CEC Charter.

Also per the CEC charter, an internal QC analysis was conducted on the manual trigger procedures performed on RECORD subject data. This QC analysis involved two stages:

- 5% random sample of subjects who did not trigger for a potential event (automated or manual) were reassessed by the CEC coordinator, and 5% by a RECORD CEC physician.

- 5% random sample of subjects who triggered for a potential event through the manual procedures were reassessed by the CEC coordinator, and 5% by a RECORD CEC physician.

Of note, additional triggers identified during this QC analysis were adjudicated as "no event", and the QC process resulted in no findings that necessitated changes to the manual trigger review procedures.

Redaction

There were no deviations from the planned re-adjudication processes, including no instances of data transferred from GSK to DCRI with un-redacted treatment assignment.

Re-adjudication Results – MI

Imputed dates of fatal events: An MI was classified as fatal only if it was included as a cause of death on the adjudication form. The date of the fatal MI was the date of the most recent occurrence of an adjudicated MI within 30 days of the date of death. If there was no adjudicated MI within 30 days of the date of death, the date of the fatal MI was the date of death. Classification of fatal stroke was done similarly.

RECORD Triggers for MI Events

- Original RECORD adjudication
    - 1126 triggers for potential MIs in 2220 combined RSG-treated patients
    - 926 triggers for potential MIs in 2227 MET/SU-treated patients

- DCRI re-adjudication
    - 813 triggers for unique MIs in 2220 combined RSG-treated patients
    - 664 triggers for unique MIs in 2227 MET/SU-treated patients

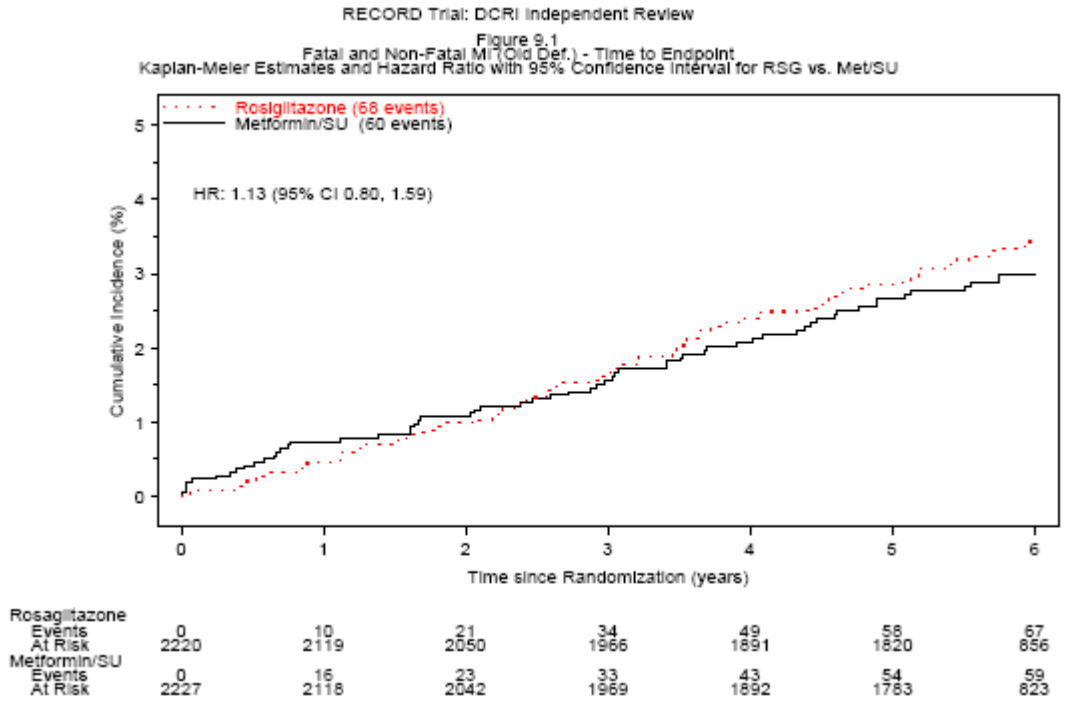
In the original RECORD study, fatal or non-fatal endpoint MI events were reported for 120 patients. (Home, *Lancet*, 2009). In the DCRI re-adjudication, 137 fatal or non-fatal MI events in 122 patients using the original RECORD definitions and 151 events in 134 patients using the new FDA definitions were reported by the DCRI CEC group. Thus, an additional 2 (original definition) and 14 (new definition) patients with a fatal or non-fatal MI event were included in the DCRI re-analyses compared with the original RECORD report. A summary table of confirmed MIs by treatment group and background therapy is reproduced below (Table 7-A, DCRI report, page 31):

Summary of Confirmed MIs by Treatment and Background Therapy

All MIs (Fatal and non-fatal)	Combined RSG (N=2220)		Combined MET/SU (N=2227)	
	Original Definitions	New Definitions*	Original Definitions	New Definitions*
Patients with confirmed MI[1]	65 / 2220 (2.9%)	72 / 2220 (3.2%)	57 / 2227 (2.6%)	62 / 2227 (2.8%)
Total confirmed MIs [1]	76	84	61	67
Sufficient information	65 / 76 (85.5%)	65 / 84 (77.4%)	53 / 61 (86.9%)	53 / 67 (79.1%)
Insufficient information	11 / 76 (14.5%)	19 / 84 (22.6%)	8 / 61 (13.1%)	14 / 67 (20.9%)
No. of MIs in patients with background therapy SU[2]	32	37	36	37
Sufficient information	25 / 32 (78.1%)	27 / 37 (73.0%)	30 / 36 (83.3%)	27 / 37 (73.0%)
Insufficient information	7 / 32 (21.9%)	10 / 37 (27.0%)	6 / 36 (16.7%)	10 / 37 (27.0%)
No. of MIs in patients with background therapy MET[3]	44	47	25	30
Sufficient information	40 / 44 (90.9%)	38 / 47 (80.9%)	23 / 25 (92.0%)	26 / 30 (86.7%)
Insufficient information	4 / 44 (9.1%)	9 / 47 (19.1%)	2 / 25 (8.0%)	4 / 30 (13.3%)
Non-fatal MIs	Original Definitions	New Definitions*	Original Definitions	New Definitions*
Patients with confirmed non-fatal MI(s)[1]	62 / 2220 (2.8%)	66 / 2220 (3.0%)	49 / 2227 (2.2%)	51 / 2227 (2.3%)
No. of MIs in all patients[1]	71	75	53	56
Sufficient information	61 / 71 (85.9%)	58 / 75 (77.3%)	46 / 53 (86.8%)	44 / 56 (78.6%)
Insufficient information	10 / 71 (14.1%)	17 / 75 (22.7%)	7 / 53 (13.2%)	12 / 56 (21.4%)
No. of non-fatal MIs in patients with background therapy SU[2]	30	33	30	30
Sufficient information	23 / 30 (76.7%)	24 / 33 (72.7%)	24 / 30 (80.0%)	21 / 30 (70.0%)
Insufficient information	7 / 30 (23.3%)	9 / 33 (27.3%)	6 / 30 (20.0%)	9 / 30 (30.0%)
No. of non-fatal MIs in patients with background therapy MET[3]	41	42	23	26
Sufficient information	38 / 41 (92.7%)	34 / 42 (81.0%)	22 / 23 (95.7%)	23 / 26 (88.5%)
Insufficient information	3 / 41 (7.3%)	8 / 42 (19.0%)	1 / 23 (4.3%)	3 / 26 (11.5%)

RSG=rosiglitazone; MET=metformin; SU=sulphonylurea; MIs=myocardial infarctions.
Source: [1] Table 1.2; [2] Table 1.2a; [3] Table 1.2b.

There were numerically more confirmed MIs and more patients with MIs in the combined RSG arm as opposed to the combined MET/SU arm, but the difference was not significant, as shown in the K-M plot of time to first MI (fatal or nonfatal, old definitions) below (DCRI report, Page 173):



Time to fatal + nonfatal MI event with new definitions was similar (HR: 1.15 (95% CI 0.82, 1.62).

Re-adjudication Results - Stroke

- Original RECORD adjudication
  - 208 triggers for potential strokes in 2220 combined RSG-treated patients
  - 259 triggers for potential strokes in 2227 MET/SU-treated patients

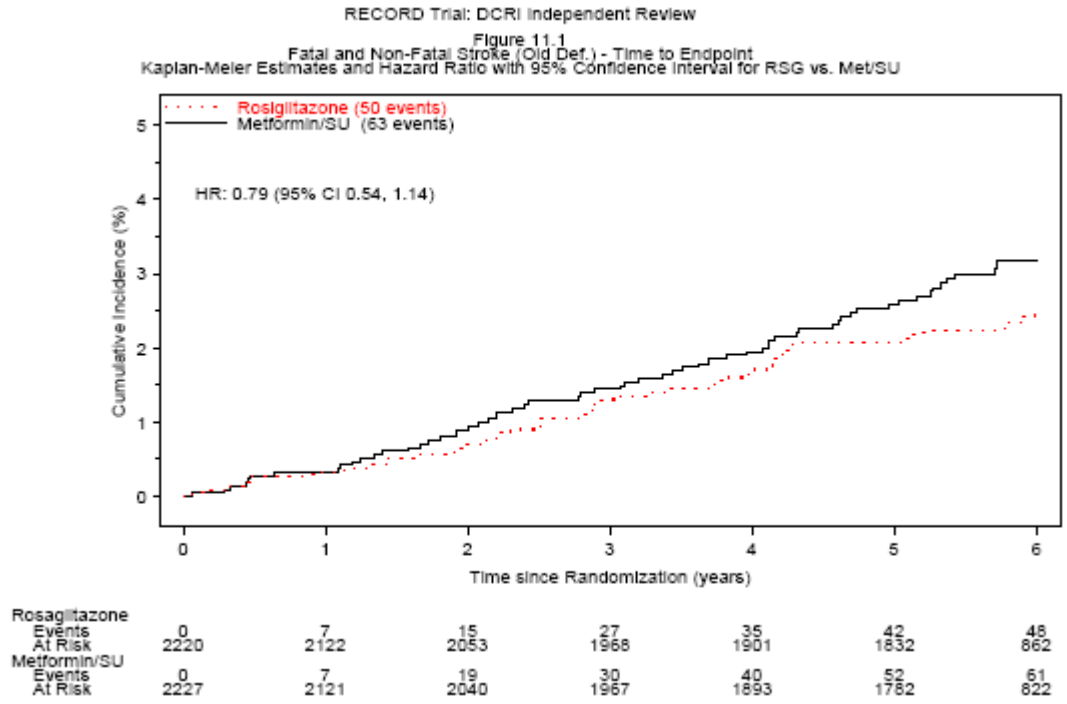
- DCRI re-adjudication
  - 193 triggers for unique strokes in 2220 combined RSG-treated patients
  - 230 triggers for unique strokes in 2227 MET/SU-treated patients

In the original RECORD study, 109 patients were reported to have a stroke. The DCRI CEC group identified 119 fatal or non-fatal stroke events in 113 patients using the original RECORD definitions and 123 events in 117 patients using the new FDA definitions. Thus, an additional 4 (original definition) and 8 (new definition) patients with fatal or non-fatal stroke events were included in the DCRI re-analyses compared with the original RECORD report. A summary table of confirmed strokes by treatment group and background therapy is reproduced below (Table 7-C, DCRI report, page 34):

Summary of Confirmed CVA by Treatment and Background Rx

	Treatment			
	Combined RSG (N=2220)		Combined MET/SU (N=2227)	
	Original Definitions	New Definitions*	Original Definitions	New Definitions*
All Strokes (Fatal and non-fatal)				
Patients with confirmed stroke[1]	50 / 2220 (2.3%)	53 / 2220 (2.4%)	63 / 2227 (2.8%)	64 / 2227 (2.9%)
Total confirmed strokes in all patients[1]	53	56	66	67
Sufficient information	52 / 53 (98.1%)	55 / 56 (98.2%)	60 / 66 (90.9%)	61 / 67 (91.0%)
Insufficient information	1 / 53 (1.9%)	1 / 56 (1.8%)	6 / 66 (9.1%)	6 / 67 (9.0%)
No. of strokes in patients with background therapy SU[2]	30	31	33	33
Sufficient information	30 / 30 (100%)	31 / 31 (100%)	30 / 33 (90.9%)	30 / 33 (90.9%)
Insufficient information	0 / 30	0 / 31	3 / 33 (9.1%)	3 / 33 (9.1%)
No. of strokes in patients with background therapy MET[3]	23	25	33	34
Sufficient information	22 / 23 (95.7%)	24 / 25 (96.0%)	30 / 33 (90.9%)	31 / 34 (91.2%)
Insufficient information	1 / 23 (4.3%)	1 / 25 (4.0%)	3 / 33 (9.1%)	3 / 34 (8.8%)
Non-fatal Strokes				
Patients with confirmed non-fatal stroke[1]	50 / 2220 (2.3%)	53 / 2220 (2.4%)	57 / 2227 (2.6%)	58 / 2227 (2.6%)
Confirmed non-fatal strokes in all patients [1]	53	56	59	60
Sufficient information	52 / 53 (98.1%)	55 / 56 (98.2%)	55 / 59 (93.2%)	56 / 60 (93.3%)
Insufficient information	1 / 53 (1.9%)	1 / 56 (1.8%)	4 / 59 (6.8%)	4 / 60 (6.7%)

There were numerically fewer confirmed strokes and fewer patients with strokes in the combined RSG arm as opposed to the combined MET/SU arm, but the difference was not significant, as shown in the K-M plot of time to first stroke (fatal or nonfatal, old definitions) below (DCRI report, Page 185):



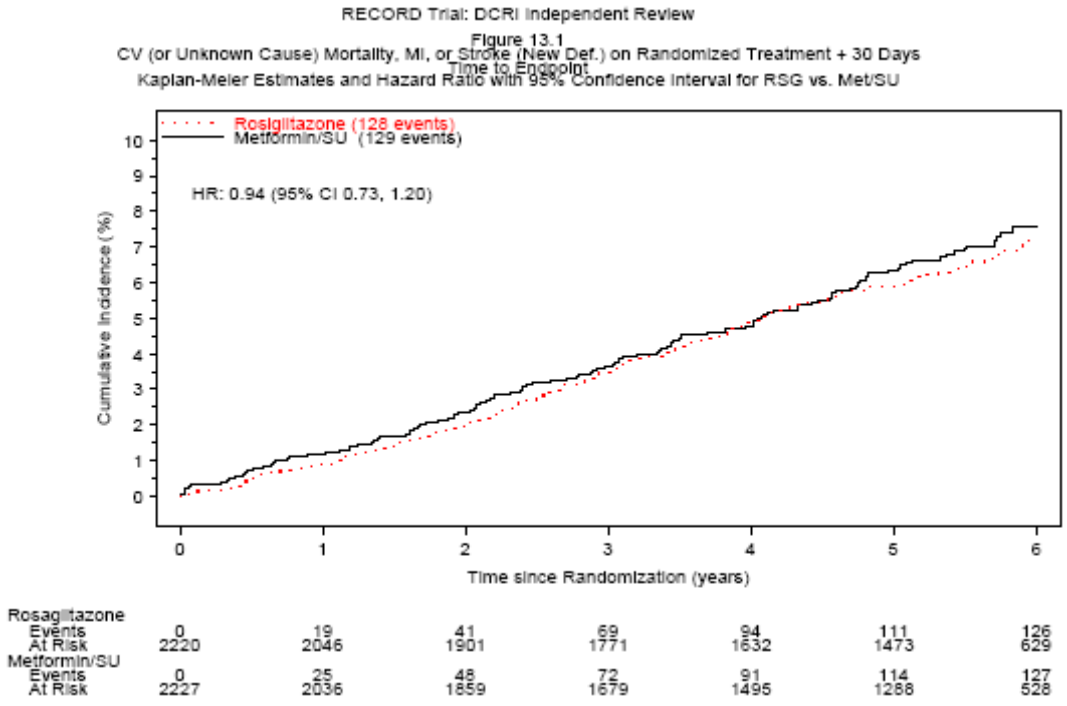
Time to fatal + nonfatal stroke event with new definitions was similar, HR: 0.82 (95% CI 0.57, 1.18).

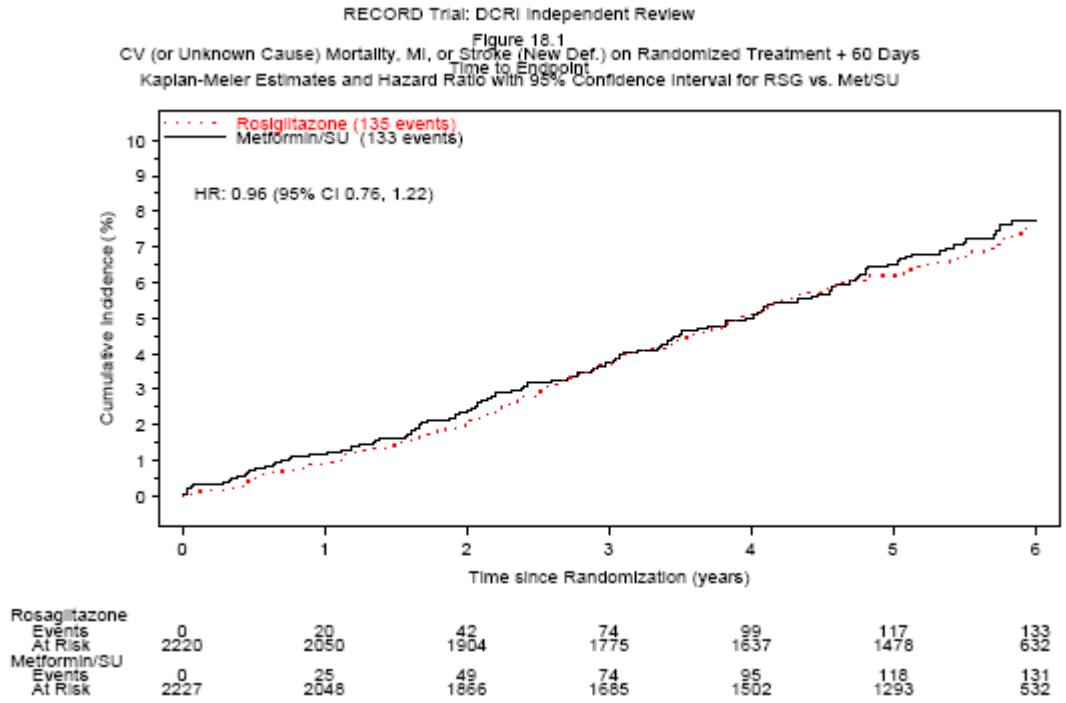
Re-adjudication Results – All MACE

Combining CV mortality (reviewed in DCRP consult dated 5/7/2012) with stroke and MI reviewed above, there was no difference between the treatment arms of RECORD in the rate of MACE events, per table 7-D below. Likewise sensitivity analyses of the time to first MACE event (LD+30 days) and first MACE event (LD+60 days) showed no differences between the treatment arms (figure 13.1 and 18.1 below, from the DCRI report).

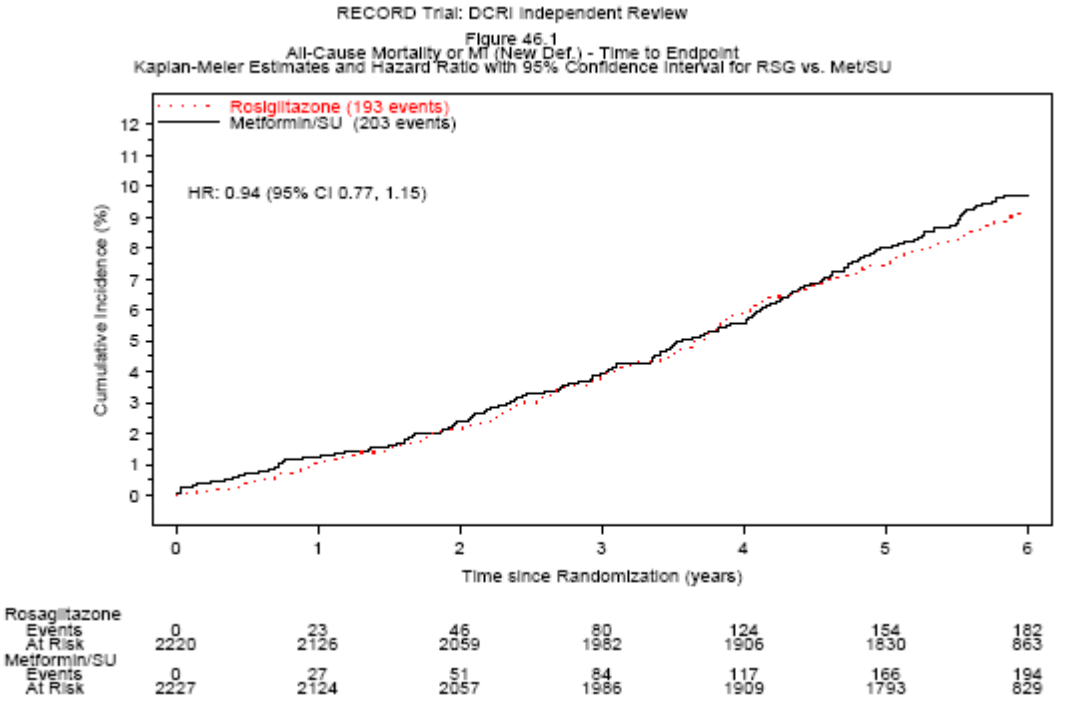
Table 7-D All MACE per Re-adjudication: New FDA Definitions vs Original RECORD Definitions (Page 37)

Re-adjudication results: all MACE events	New FDA definitions[1]		Original RECORD definitions[2]	
	Randomized to RSG	Randomized to MET or SU	Randomized to RSG	Randomized to MET or SU
All patients [3]	(N=2220)	(N=2227)	(N=2220)	(N=2227)
Total follow-up[4] (PY)	11892	11800	PY=11913	PY=11808
No. of patients with event	186/2220 (8.4%)	191/2227 (8.6%)	181/2220 (8.2%)	188/2227 (8.4%)
Rate per 100 PY (95% CI)	1.56 (1.33, 1.79)	1.62 (1.38, 1.85)	1.52 (1.29, 1.75)	1.59 (1.36, 1.82)
Hazard ratio (95% CI)	0.97 (0.79, 1.18)		0.95 (0.78, 1.17)	
Background therapy: MET[5]	(N=1117)	(N=1105)	N=1117	N=1105
Rate per 100 PY (95% CI)	1.53 (1.21, 1.84)	1.42 (1.11, 1.73)	1.49 (1.18, 1.80)	1.37 (1.07, 1.67)
Hazard ratio (95% CI)	1.07 (0.80, 1.44)		1.09 (0.81, 1.47	
Background therapy: SU[5]	(N=1103)	(N=1122)	(N=1103)	(N=1122)
Rate per 100 PY (95% CI)	1.60 (1.27, 1.93)	1.82 (1.47, 2.16)	1.55 (1.22, 1.87)	1.82 (1.47, 2.16)
Hazard ratio (95% CI)	0.88 (0.67, 1.16)		0.85 (0.64, 1.13)	





Sensitivity analysis was also performed for the additional composite of all-cause mortality or MI, showing no difference between the treatment arms, as seen in figure 46.1 below:



Missing Follow-up Data

In the RECORD trial, some of the patients were not followed for MI and stroke to the end of the study (final visits to be conducted between 24 August 2008 and 24 December 2008). The person-years of missed exposure, as compared to the total follow-up, is seen in table 10-B below:

Table 10-B Summary of Incomplete follow-up for MACE (time to first occurrence of CV (or unknown cause) death, MI, or stroke) – Original RECORD Definitions

	Background Therapy	Total	RSG	MET/SU
Total Follow-up (person years)	Combined	23721	11913	11808
	Sulphonylurea	11773	5880	5894
	Metformin	11948	6033	5915
Person-years unobserved	Combined	1937	926	1011
	Sulphonylurea	1124	537	587
	Metformin	813	389	424
Number (%) of patients with incomplete follow-up	Combined	744 / 4447 (16.7%)	346 / 2220 (15.6%)	398 / 2227 (17.9%)
	Sulphonylurea	397 / 2225 (17.8%)	186 / 1103 (16.9%)	211 / 1122 (18.8%)
	Metformin	347 / 2222 (15.6%)	160 / 1117 (14.3%)	187 / 1105 (16.9%)

Source: Table S2.1, Table S2.1a, Table S2.1b.

Simulations by DCRI suggest that an increased risk of MACE events with RSG on the order of 50% or more in the unobserved data might have been required to result in an estimated final hazard ratio > 1 for the MACE outcome.

Assessment

As with the mortality re-analysis that was the subject of our consult dated May 7, 2012, this was a well-conceived, well-executed, and comprehensive re-adjudication of the RECORD MACE events by the DCRI. While a small number of additional events were identified by the re-adjudication process, these did not substantially change the results that were originally reported for RECORD.

As was the case for site queries for information about mortality, the response to DCRPs queries to sites for information regarding CV events was low, and for the same reasons (2-3 years time lag between end of study and queries, closure of sites, closure of practices, staffing limitations, laws preventing additional information gathering, etc).

Given the size and design complexity of the RECORD trial, the high degree of concordance of the original results with the DCRI re-analysis is impressive, undoubtedly due at least in part to the "hard" endpoints that were measured – MI, stroke, and death. Simulations performed by DCRI are reassuring in suggesting that an increased risk of MACE events with RSG on the order of 50% or more in the unobserved data might have been required to result in an estimated final hazard ratio > 1 for the MACE outcome.

This review is focused on the information that DCRI received and the analyses that it performed. The DCRI ascertainment procedure with its extensive manual review and automated triggers were applied to the entire original dataset, and there were no indications communicated by DCRI that any potential endpoint events that the sponsor had become aware of had not been either relayed to the original CEC or subsequently to DCRI. As with any trial, it is possible that there will be variability in what may get missed because of things like patients going to outside hospitals for care and not informing their study sites of events. There is no reason to expect bias in reporting for such things. On the other hand, there is some concern about reporting bias because of the trial being unblinded. However, the thorough review of the source data performed by DCRI uncovered no evidence for such bias.

MACE Re-adjudication Limitations

- At least some data was missing for:
  - 744 / 4447 (16.7%) of subjects
  - Approximately 8% of total pt-year exposure.

- While missingness was similar between the treatment arms with respect to pt-year exposure and percentage of subjects missing data, the true occurrence rates of CV events within these missing data groups remains unknown.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Literature Review

Date:	April 26, 2013
Reviewer(s):	Kate Gelperin, MD, MPH Esther Zhou, MD, PhD Division of Epidemiology-1 (DEPI-1)
Deputy Division Director	Tarek A. Hammad, MD, PhD, MSc, MS Deputy Director, DEPI-1
Division Director	Solomon Iyasu, MD, MPH Director, DEPI-1
Subject:	Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone: Update (July 2010 through November 2012)
Drug Name(s):	Avandia® (rosiglitazone); NDA 021071; GlaxoSmithKline Actos® (pioglitazone); NDA 021073: Takeda
OSE RCM #:	2012-2660

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EXECUTIVE SUMMARY

This review follows a request from the FDA/CDER/OND Division of Metabolism and Endocrinology Products (DMEP) to OSE Division of Epidemiology-1 (DEPI-1) to provide an updated literature review describing any new epidemiologic data evaluating the cardiovascular safety of rosiglitazone published after July 15, 2010.

A systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone was conducted in preparation for the July 13-14, 2010 joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Committee (DSaRM) Advisory Committees at which cardiovascular safety of rosiglitazone was discussed. This current review provides an update to the systematic review of observational studies previously conducted in 2010, with a focus on direct comparisons of rosiglitazone versus pioglitazone. Published articles were evaluated for inclusion in the current analysis using the same protocol that was used in the previous systematic review. Studies were eligible for inclusion if they are controlled (case-control or cohort design), and report on cardiovascular risks associated with the use in population settings of rosiglitazone or pioglitazone. The summary of the systematic review is qualitative. No quantitative meta-analysis was planned. Summary results of cardiovascular endpoints for the individual studies are displayed using tables and forest plots.

Titles and abstracts identified by the initial library searches were independently evaluated by an epidemiology reviewer. After the second round of reviews by a different epidemiology reviewer and a statistician, seven publications were considered to meet the inclusion criteria. Six of the seven studies published after July 2010 report results of direct comparisons between rosiglitazone and pioglitazone. In the previous systematic review, there were nine observational studies (published prior to July 2010) which reported results of direct comparisons of rosiglitazone and pioglitazone. Three studies published after July 2010 describe results of direct comparisons between rosiglitazone and pioglitazone for outcomes of interest in older patients (≥65 years of age). In the previous systematic review, there were two studies which reported results of direct comparisons of rosiglitazone and pioglitazone in older patients.

A published meta-analysis of observational studies of cardiovascular risk with rosiglitazone compared to pioglitazone was identified during this review. The pooled analysis found that rosiglitazone was associated with a statistically significant increased risk of myocardial infarction (OR 1.16, 95% CI 1.07-1.24; $p<0.001$), heart failure (OR 1.22, 95% CI 1.14-1.31; $p<0.001$), and all-cause mortality (OR 1.14, 95% CI 1.09-1.20; $p<0.001$), compared to pioglitazone. Three studies included in this current review were not included in the pooled analysis because they were published later.

Overall, comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, heart failure and all-cause mortality tended to favor pioglitazone. These results suggest that the cardiovascular safety profile of pioglitazone is favorable compared to that of rosiglitazone, especially in older patients ≥65 years of age. A signal for increased all-cause mortality with rosiglitazone in older patients (>65 years of age), which was demonstrated in four observational studies, may be a reflection of increased cardiovascular risk with rosiglitazone compared to pioglitazone.

1 INTRODUCTION

This review follows a request from the FDA/CDER/OND Division of Metabolism and Endocrinology Products (DMEP) to OSE Division of Epidemiology-1 (DEPI-1) to provide an updated literature review describing any new epidemiologic data evaluating the cardiovascular safety of rosiglitazone published after July 15, 2010.

1.1 BACKGROUND

A systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone was conducted in preparation for the July 13-14, 2010 joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Committee (DSaRM) Advisory Committees at which cardiovascular safety of rosiglitazone was discussed.[1]

Results of the previous systematic review found that comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, heart failure, and all-cause mortality tended to favor pioglitazone. No studies were identified with results suggesting a protective cardiovascular effect of rosiglitazone compared to pioglitazone.

Regarding comparisons of rosiglitazone with other antidiabetic agents, we considered the results of the systematic review of observational studies to be consistent with those of the meta-analyses of randomized clinical trials conducted by FDA staff and presented at the 2010 AC meeting, which suggested increased cardiovascular risk with rosiglitazone, but were not definitive. [2]

This current review provides an update to the systematic review of observational studies previously conducted in 2010, with a focus on direct comparisons of rosiglitazone versus pioglitazone.

1.2 REGULATORY HISTORY

Questions of cardiovascular safety with rosiglitazone have been discussed previously at two public Advisory Committee meetings with the EMDAC and DSaRM, held on July 30, 2007 and July 13-14, 2010. Subsequently, availability of rosiglitazone was restricted in the US under a REMS due to these concerns.

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[1] FDA/CDER/OSE/DEPI Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. RCM #2010-277; dated June 15, 2010. Joint Meeting of the EMDAC and the DSaRM Advisory Committee Meeting. July 13 - 14, 2010; page 373; Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf.

[2] FDA/CDER/OB/DB7 Statistics Review. FDA Rosiglitazone and Pioglitazone Meta-Analyses; Review dated June 15, 2010. Joint Meeting of the EMDAC and DSaRM Advisory Committee Meeting. July 13 - 14, 2010. page 549. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf.

1.3 ABBREVIATIONS

Abbreviations used in this review include the following:

- ACS acute coronary syndrome
- ACM all-cause mortality
- AHF acute heart failure
- AMI acute myocardial infarction
- CI confidence interval
- combo combination therapy
- CMS Centers for Medicare and Medicaid Services
- CRV coronary revascularization
- CV cardiovascular
- CVA cerebrovascular accident (or stroke)
- DM diabetes mellitus
- GPRD General Practice Research Database
- HF or CHF heart failure (or congestive heart failure)
- HR Hazard Ratio
- mono monotherapy
- NDI National Death Index
- NMI nonfatal myocardial infarction
- PERR Prior Event Rate Ratio
- Pio (or P) pioglitazone
- PS propensity score
- REMS Risk Evaluation and Mitigation Strategies
- Rosi (or R) rosiglitazone
- SSMBR Social Security Master Beneficiary Record
- TZD thiazolidinedione
- UK United Kingdom

2 METHODS AND MATERIALS

Searches for published literature that may be pertinent to this research question were conducted by FDA staff.[3] Details of the library searches are presented in Appendix 7.1. Published articles were evaluated for inclusion in the current analysis using the same protocol that was used in the previous systematic review (Appendix 7.2).[4]

2.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

This review includes published controlled epidemiologic studies with a cohort or case-control design for which a full manuscript is available. Studies available as an abstract

[3] FDA/CDER/OSE/DEPI Bright PL. Literature search for new epidemiologic data evaluating the cardiovascular safety of rosiglitazone since the July 2010 Advisory Committee meeting. RCM #2012-2660; review dated November 27, 2012.

[4] FDA/CDER/OSE/DEPI Gelperin K, Zhou E. Protocol for Cochrane-type systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. RCM #2010-277; dated May 24, 2010.

only are not included. Cross-sectional studies, case-series, and studies based on a single institution's experience are excluded. Randomized clinical trials and nonclinical studies are excluded.

This review includes observational studies of cardiovascular endpoints in patients treated with rosiglitazone or pioglitazone. Individual patient-level data were not available for this review.

2.2 TYPES OF OUTCOME MEASURES

This review describes the magnitude and direction of estimates of effect (e.g. relative risk, odds ratios, hazard ratios) from results of observational studies with cardiovascular endpoints including: myocardial infarction, acute coronary syndrome, coronary revascularization, cardiovascular mortality, total mortality, heart failure, or stroke. If applicable, the review includes composite endpoints comprising some or all of these individual cardiovascular outcomes.

2.3 DATA COLLECTION AND ANALYSIS

Assessment of identified abstracts and published articles was performed independently by reviewers from DEPI-1 and from the FDA/Office of Biostatistics/Division of Biometrics-7 (DB-7), with resolution of any discrepancies by senior reviewers from DEPI-1 and DB-7. While desirable to conduct the study selection process in a blinded fashion, it was not feasible; however, study selection was conducted in a transparent fashion, with documentation of reasons for study exclusion.

Studies were eligible for inclusion if they are controlled (case-control or cohort design), and report on cardiovascular risks associated with the use in population settings of rosiglitazone or pioglitazone.

Potential reasons for exclusion include:

- duplicate studies
- not relevant to study questions
- no targeted drugs (rosiglitazone and/or pioglitazone)
- not a targeted study design (i.e. cohort or case-control)
- review
- meta-analysis of randomized clinical trials
- case report or case series
- randomized or uncontrolled clinical trial
- no prespecified cardiovascular endpoint
- full article not available
- targeted drugs combined into single TZD treatment group (separate analysis of rosiglitazone and/or pioglitazone not available)
- no comparison group
- not a population-based epidemiological study

Individual studies may meet multiple criteria for exclusion.

2.4 DATA EXTRACTION AND MANAGEMENT

Data extraction was performed by a statistical reviewer independently. Results were checked for accuracy by DEPI-1 reviewers. Discrepancies were resolved by consensus. Study characteristics and results were tabulated.

2.5 ASSESSMENT OF STUDY QUALITY

The Newcastle Ottawa scale was used as a measure of study quality for this review.[5] Two epidemiology reviewers assessed each published study independently. Questions were resolved by consensus.

2.6 DATA SYNTHESIS

The summary of the systematic review is qualitative. No quantitative meta-analysis was planned. Summary results of cardiovascular endpoints for the individual studies are displayed using tables and forest plots.

The primary summary measures for the individual studies are odds ratio (OR), relative risk (RR), or hazard ratio (HR), and associated 95% confidence interval (CI), when available. For studies of rosiglitazone versus other treatments, the ratio is expressed as the comparison of rosiglitazone versus the comparator treatment. For studies of pioglitazone versus other treatments (not including rosiglitazone), the ratio is expressed as the comparison of pioglitazone versus the other treatment.

The final selected studies were reviewed by a statistician to summarize and assess the statistical methodology.[6] No re-analysis of the individual study data was performed.

For outcomes of interest for which two or more relevant results were identified, forest plots were prepared which visually present the association of safety endpoints and treatment comparing rosiglitazone exposure versus pioglitazone exposure.

Studies were grouped for visual inspection of results of interest, as follows:

- If there were more than two studies with the same outcome (for a comparison of interest), they were combined and displayed on a single forest plot labeled with the outcome of interest.
- Results of pertinent studies published after July 2010 identified in this current review were combined with results from the previous systematic review for display in appropriate forest plots. A different color was used to help identify new studies on the plots.
- The outcomes of interest for which forest plots were prepared include:
    - Acute myocardial infarction (AMI)
    - Heart failure (CHF)

[5] Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK). John Wiley & Sons, 2008

[6] FDA/CDER/OTS/OB/DB7 Yap JS. Statistical Review and Evaluation. Avandia and Actos. Review dated April 23, 2013.

- All-cause death
- Stroke (CVA)

- Both crude and adjusted estimates for comparisons of interest were included in the forest plots whenever available.
- If a study included results for various drug exposure duration periods (e.g., current/recent/remote), the most current exposure period result was chosen.
- In addition, forest plots were prepared for the subset of studies which reported outcomes of interest in older patients (≥65 yrs. of age).
- A decision was made for the current review not to give a weight to each study by the box size to avoid emphasizing any quantitative measure among the studies.

3 RESULTS

3.1 DESCRIPTION OF STUDIES

3.1.1 Results of the search

Titles and abstracts identified by the initial library searches were independently evaluated by an epidemiology reviewer. The initial review identified 13 references for which full published articles were obtained (see Appendix 8.1 for details). After the second round of reviews by a different epidemiology reviewer and a statistician, seven publications were considered to meet the inclusion criteria.

3.1.2 Included studies (published after July 2010)

Included studies are listed below by year of publication (starting with most recent), and alphabetically by author last name.

1. Tannen R, Xie D, Wang X, Menggang Y, Weiner MG. A new "Comparative Effectiveness" assessment strategy using the THIN database: Comparison of the cardiac complications of pioglitazone and rosiglitazone. Pharmacoepi Drug Saf 2012 Oct 16.
2. Chou CC, Chen WL, Kao TW, Chang YW, Loh CH, Wang CC. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. Clin Ther 2011; 33(12):1904-13.
3. Gallagher AM, Smeeth L, Seabroke S, Leufkens H, van Staa TP. Risk of death and cardiovascular outcomes with thiazolidinediones: A study with the general practice research database and secondary care data. PLoS ONE 2011; 6(12):e28157 [pages1-9].
4. Loebstein R, Dushinat M, Vesterman-Landes J, Silverman B, Friedman N, Katzir, I, Kurnik D, Lomnicky Y, Kokia E, Halkin H. Database evaluation of long-term rosiglitazone treatment on cardiovascular outcomes in patients with Type 2 diabetes. J Clin Pharmacol 2011; 51:173-180.
5. Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, HsiaoVC, Tseng CW, Mangione CM, Lasser NL, Crosson JC, Herman WH. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). Pharmacoepidemiol Drug Saf 2010; 19:715-21.

6. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304(4):411-418.
7. Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circ Cardiovasc Qual Outcomes 2010; 3:538-45.

Included studies are referenced for discussion in this review by the first author's last name and publication year. Two of the seven studies (Graham 2010, and Wertz 2010) were discussed at the Advisory Committee meeting on July 13-14, 2010, but were not included in the previous systematic review because they were not published until after the AC meeting.

3.2 CHARACTERISTICS OF INCLUDED STUDIES

A tabular summary of the characteristics of the seven studies published after July 2010 is presented in Section 5.1, and includes information about study methods, population details, data source, comparisons and outcome measures.

3.2.1 Design

All seven studies are retrospective cohort studies.

3.2.2 Setting

Data sources reflect considerable geographic diversity, representing Israel (Loebstein 2011), UK (Tannen 2012, Gallagher 2011), USA (Bilik 2010, Graham 2010, Wertz 2010) and Taiwan (Chou 2011).

Databases include: Maccabi Healthcare Services, Israel (Loebstein 2011); GPRD / THIN, UK ((Tannen 2012, Gallagher 2011); TRIAD (Translating Research into Action for Diabetes), USA (Bilik 2010); Medicare, USA (Graham 2010); HealthCore Integrated Research Database (HIRD) - WellPoint, USA (Wertz 2010); and Taiwanese National Health Insurance (NHI) database, Taiwan (Chou 2011).

3.2.3 Methods

All of the studies except one (Gallagher 2011) performed time-to-event analyses using the Cox Proportional Hazards (PH) model. Two studies (Tannen 2012, and Wertz 2010) used propensity scores (PS) to balance covariates between treatment groups. One study (Gallagher 2011) used Poisson regression. Other statistical methods utilized include Kaplan-Meier (Gallagher 2011, and Graham 2010); and the Prior Event Rate Ratio (PERR) adjustment method, which is intended to reduce bias from unmeasured confounders (Tannen 2012).

All of the studies adjusted for various patient-level covariates; however, these differed markedly among the studies, as follows:

- Tannen 2012: (1) Cox model adjusted for age, sex, systolic blood pressure, BMI, smoking, myocardial infarction, stroke; angina and/or ischemic cardiovascular disease (CVD) and/or nitrate therapy; transient ischemic attack and/or ischemic cerebrovascular

disease; prior coronary revascularization; and baseline insulin or other diabetic medications. (2) Propensity score method adjusted for all baseline variables, preexisting diagnoses, and medications at baseline; and adjusted the five-quintile propensity score. (3) "PERR" adjustment technique further adjusted the event rate for outcome during the exposure interval.

- Chou 2011: Covariates controlled for multiple variables in Cox model but were not clearly specified. May have included: time span between treatment of DM and TZD use, age, specialist, use of HT medication, statins, and fibrates.
- Gallagher 2011: Poisson regression was used to estimate relative rates (RRs). These models included age, sex, calendar year, socioeconomic status, smoking status, use of alcohol, body mass index, medical history ever before of coronary heart disease, coronary revascularization, hyperlipidemia, hypertension, peripheral vascular disease, renal impairment and stable angina, and prescribing in the 6 months before of angiotensin II receptor blockers, antiplatelets, beta blockers, calcium channel blockers, diuretics, nitrates, NSAIDs or aspirin and statins. In addition, the models included use of current use of the various classes of diabetes medication. Missing values for alcohol use, smoking status and body mass index were included as separate categories in the regression analyses.
- Loebstein 2011: Cox model controlled for: age, gender, insulin, sulfonylurea, clopidogrel, ACE/ARB, history of hypertension, CHF, IHD, other cardiac diseases, creatinine, HbA1c, HDL, LDL, triglycerides, duration of therapy.
- Bilik 2010: Cox proportional hazard models adjusted for age, sex, race/ethnicity, income, history of diabetic nephropathy, history of CVD, insulin use, and health plan.
- Graham 2010: Controlled for multiple variables in Cox model: age, gender, race/ethnicity, low-income subsidy, extended care, Charlson score, and medication classes. Core CV medical conditions and medications used during the 12- or 6-months preceding initiation of TZD: AMI, Coronary revascularization, HF, other ischemic heart disease, stroke; diabetes-related disorders included: microvascular disease, peripheral vascular disease; CV medications included: ACE inhibitors and ARBs, antiarrhythmics, anticoagulants, antiplatelet drugs, B-Blockers, calcium channel blockers, digoxin, diuretics, nitrates, diabetes-related medications included: insulin, metformin, sulfonylureas, other, lipid-lowering medications included: fibrates, statins; alcohol abuse, chronic liver disease, COPD, dementia, gout, hypercholesterolemia, hypertension, hypertriglyceridemia, hypothyroidism, inflammatory arthritis, kidney failure, malignancy, obesity, organ transplantation, peptic ulcer disease, smoking, medications, antidepressants, bisphosphonates, estrogen, H2 antagonists, NSAIDs, PPI, thyroid hormone replacement.
- Wertz 2010: Included Cox model analysis of PS-matched sets of patients, with included list of variables similar to Graham 2010 (as referenced).

3.2.4 Outcomes

The outcomes studied include: acute myocardial infarction (AMI), stroke, coronary revascularization (CRV), congestive heart failure (CHF), angina, cerebral vascular accident (CVA), acute coronary syndrome ACS), heart failure (HF), death or all-cause mortality (ACM), as well as composites of these outcomes.

Outcomes differed among the studies, as follows:

- Tannen 2012: Stroke, AMI, CRV, CHF, Death
- Chou 2011: MI, CHF, Angina, CVA

- Gallagher 2011: ACS, stroke, HF, ACM (including cause of death)
- Loebstein 2011: AMI, ACS, CRV, CHF, ACM
- Bilik 2010: Nonfatal MI, CRV, Nonfatal Stroke, CV Mortality, ACM
- Graham 2010: AMI, Stroke, HF, ACM
- Wertz 2010: AMI, AHF, Death

3.2.5 Assessment of study quality

The Newcastle-Ottawa scale was utilized for this review. Two epidemiology reviewers completed the assessment independently. All of the seven studies included in this review received a final consensus score of either 8 or 9 points, with nine being the maximum high score for this instrument.

3.3 EFFECTS OF INTERVENTIONS ON CARDIOVASCULAR OUTCOMES

Formal data synthesis was not conducted for this review due to the methodologic diversity among the studies, as well as the many challenges involved in making objective determinations of observational study quality based solely on the published manuscript. However, as recommended in the Cochrane Handbook chapter which deals with synthesis of data from non-randomized studies, summary results for selected comparisons of rosiglitazone and pioglitazone were displayed for visual inspection in forest plots.[7]

3.3.1 Direct comparisons between rosiglitazone and pioglitazone

Six of the studies published after July 2010 (Tannen 2012, Chou 2011, Gallagher 2011, Bilik 2010, Graham 2010, and Wertz 2010) describe results of direct comparisons between rosiglitazone and pioglitazone. In the previous systematic review, there were nine observational studies identified (published prior to July 2010) which reported results of direct comparisons of rosiglitazone and pioglitazone. [8] [9] [10] [11] [12] [13] [14] [15] [16]

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[7] Reeves BC, Deeks JJ, Higgins JPT, et al. 2008. *op.cit.* Page 423.

[8] Brownstein, J.S.; Murphy, S.N.; Goldfine, A.B.; Grant, R.W.; Sordo, M.; Gainer, V.; Colecchi, J.A.; Dubey, A.; Nathan, D.M.; Glaser, J.P.; Kohane, I.S. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care, vol 33, no. 3; 2010.

[9] Dormuth, C.R.; Maclure, M.; Carney, G.; Schneeweiss, S.; Bassett, K.; Wright, J. M. Rosiglitazone and myocardial infarction in patients previously prescribed metformin. PLoS One, vol 4(6), e6080; 2009.

[10] Hsiao, F.Y.; Huang, W.F.; Wen, Y.W.; Chen, P.F.; Kuo, K.N.; Tsai, Y.W. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: A retrospective cohort study of over 473,000 patients using the national health insurance database in Taiwan. Drug Safety, 32(8):675-690, 2009.

[11] Juurlink, D.N.; Gomes, T.; Lipscombe, L.L.; Austin, P.C.; Hux, J.E.; Mamdani, M. M. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: Population based cohort study. BMJ 339:b2942; 2009.

[12] Stockl, K.M.; Le, L.; Zhang, S.; Harada, A.S. Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiol and Drug Safety, 18:166-174, 2009.

[13] Ziyadeh, N.; McAfee, A.T.; Koro, C.; Landon, J.; Chan, K.A. The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: A retrospective cohort study using a US health insurance database. Clinical Therapeutics, vol 31, 2665-2677; 2009.

Section 4.1 presents forest plots which show study results for direct comparisons of rosiglitazone and pioglitazone for the following outcomes: acute myocardial infarction, heart failure, all-cause mortality, and stroke. When available, both the crude and the adjusted estimates are provided in the graphic. All available study results (from studies published both before and after July 2010) are included in each of the four forest plots. Some studies were identified in the previous review which reported separate comparisons of rosiglitazone or pioglitazone to other antidiabetic agents and for which estimated unadjusted odds ratios were calculated from data available in the published report.[17] [18] [19] A tabular summary of the characteristics of the nine studies published prior to July 2010 is presented in Section 5.2, and includes information about study methods, population details, data source, comparisons and outcome measures.

3.3.2 Comparisons versus other antidiabetic agents

Two of the included studies published after July 2010 (Tannen 2012, and Loebstein 2011) describe results of comparisons of rosiglitazone or pioglitazone and other non-TZD antidiabetic agents. In addition, one study (Gallagher 2011) compared diabetic patients treated with thiazolidinediones (rosiglitazone or pioglitazone) with a control group. The authors conducted a bias analysis, and concluded that "comparisons of different classes of diabetes medications are likely to be prone to substantial confounding, while the within class comparison of rosiglitazone versus pioglitazone is less prone to selection bias and confounding." The clinical basis for this distinction is likely a reflection of diabetes treatment algorithms which typically recommend lifestyle intervention, followed by monotherapy, dual therapy, triple therapy, and/or the addition of insulin in sequential fashion depending on an individual patient's glycemic control and disease progression.[20] For this reason, there can be substantial diversity among patients initiating therapy with various antidiabetic agents which are not in the same therapeutic class. A results table describing numerical study results from all comparisons is included in Appendix 8.3.

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[14] Walker, A.M.; Koro, C.E.; Landon, J. Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database 2000-2007. Pharmacoepidemiol and Drug Safety, 17:760-768; 2008.

[15] Winkelmayer, W.C.; Setoguchi, S.; Levin, R.; Solomon, D.H. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. Arch Intern Med, 168(21): 2368-2375; 2008.

[16] Gerrits, C.M.; Bhattacharya, M.; Manthena, S.; Baran, R.; Perez, A.; Kupfer, S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol and Drug Safety, 16:1065-1071; 2007.

[17] Lipscombe, L.L.; Gomes, T.; Levesque, L.E.; Hux, J.E.; Juurlink, D.N.; Alter, D.A. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA, vol 298, no 22; 2007.

[18] Koro, C.E.; Fu, Q.; Stender, M. An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiol and Drug Safety, 17:989-996; 2008.

[19] Azoulay, L.; Schneider-Lindner, V.; Dell'aniello, S.; Filion, K. B.; Suissa, S. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol and Drug Safety, 2009.

[20] American Association of Clinical Endocrinologists. AACE Comprehensive Diabetes Management Algorithm. Endocr Pract. 2013;19(No. 2).

Forest plots are not included in this review for comparisons of rosiglitazone or pioglitazone with other antidiabetic agents.

3.3.3 Studies in older populations

Three of the included studies published after July 2010 (Gallagher 2011, Graham 2010, and Wertz 2010) describe results of direct comparisons between rosiglitazone and pioglitazone for outcomes of interest in older patients (≥65 years of age). In the previous systematic review, there were two studies identified (published prior to July 2010) which reported results of direct comparisons of rosiglitazone and pioglitazone in older patients (≥65 years of age). [21] [22] Section 4.2 presents forest plots which show study results for direct comparisons of rosiglitazone and pioglitazone in older patients (≥65 years of age) for the following outcomes: acute myocardial infarction, heart failure, all-cause mortality, and stroke. When available, both the crude and the adjusted estimates are provided in the graphic. All available study results (from studies published both before and after July 2010) are included in each of the four forest plots.

3.4 PUBLISHED META-ANALYSIS OF OBSERVATIONAL STUDIES

A published meta-analysis[23] of observational studies of cardiovascular risk with rosiglitazone compared to pioglitazone was identified during this review. A brief description is included here for reference. A random effects meta-analysis (inverse variance method) was used to calculate the odds ratios for cardiovascular outcomes in studies with direct comparisons of rosiglitazone and pioglitazone in patients with type 2 diabetes mellitus. A systematic review identified 16 observational studies (4 case-control and 12 cohort studies) comprising 810,000 exposed patients. Statistical heterogeneity was assessed using the I^2 statistic. Based on results of the pooled analysis, rosiglitazone was associated with a statistically significant increased risk of myocardial infarction (OR 1.16, 95% CI 1.07-1.24; p<0.001), heart failure (OR 1.22, 95% CI 1.14-1.31; p<0.001), and all-cause mortality (OR 1.14, 95% CI 1.09-1.20; p<0.001), compared to pioglitazone. The authors reported a moderate level of heterogeneity (I^2=46%) for the pooled results for myocardial infarction due to combining the unadjusted and adjusted study results together for the overall estimate, as well as for heart failure (I^2=37%). The authors found no evidence of statistical heterogeneity for the outcome all-cause mortality (I^2=0%). Results from three of the studies included in this current review (Chou 2011, Gallagher 2011, and Tannen 2012) were not included in the published meta-analysis because they were published later.

[21] Juurlink 2009, *op.cit.*

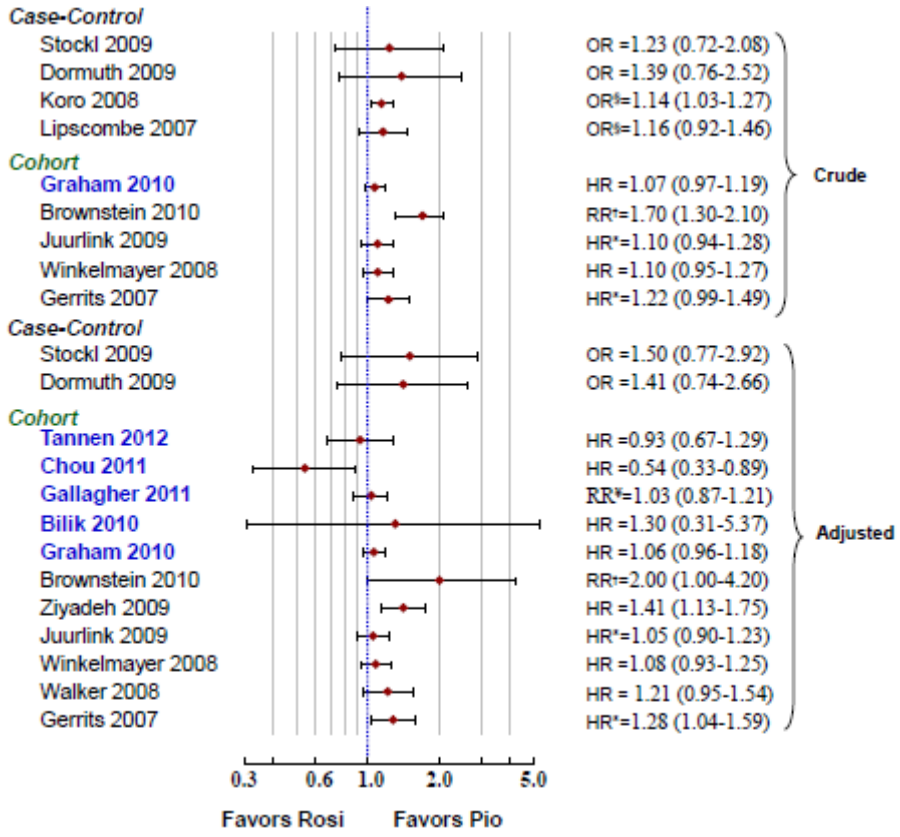
[22] Winkelmayer 2008, *op.cit.*

[23] Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 2011;342:d1309 [pages 1-9].

4 DATA AND ANALYSES

4.1 FOREST PLOTS - COMPARISONS OF ROSIGLITAZONE VS PIOGLITAZONE

4.1.1 Acute myocardial infarction

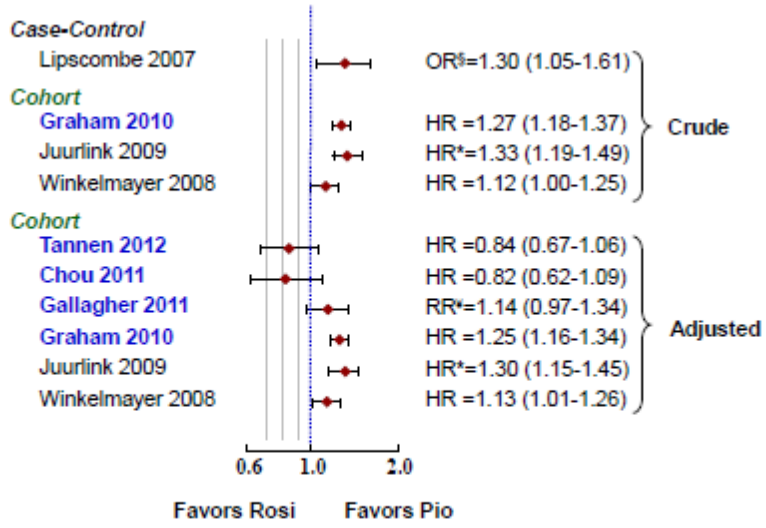


Outcome acute myocardial infarction (AMI): R versus P

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article
† Rate Ratio
¥ Relative Risk
* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)
Note: outcome in Gallagher 2011 is ACS
Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=1.03 (95% CI 0.91-1.15).
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Five studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of AMI, and are indicated in blue font on the forest plot above. In addition, ten studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. The outcome in one study using the GPRD database (Gallagher 2011) was described as "acute coronary syndrome" but was included in this forest plot because the authors did not conduct a separate analysis of AMI. Overall, point estimates were >1 in all but two studies; however, confidence intervals included one in most comparisons. One additional study (Wertz 2010) evaluated a composite outcome which included AMI and found no difference in risk between the two drugs.

4.1.2 Heart failure

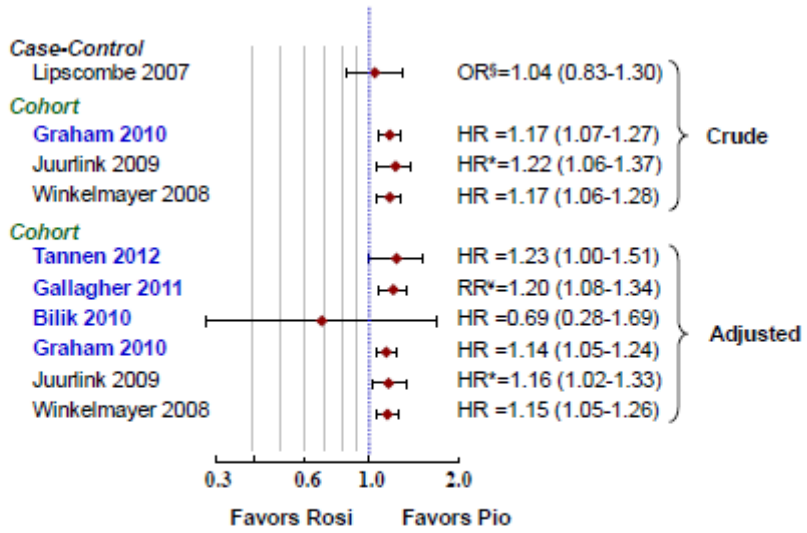


Outcome heart failure (CHF): R versus P

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article
¥ Relative Risk
* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)
Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=1.03 (95% CI 0.91-1.15).
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Five studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of heart failure, and are indicated in blue font on the forest plot above. In addition, three studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. Overall, point estimates were >1 in all but two studies. Statistically significant increased risk with rosiglitazone was reported in three studies. One additional study (Wertz 2010) evaluated a composite outcome which included heart failure and found no difference in risk between the two drugs.

4.1.3 All-cause mortality

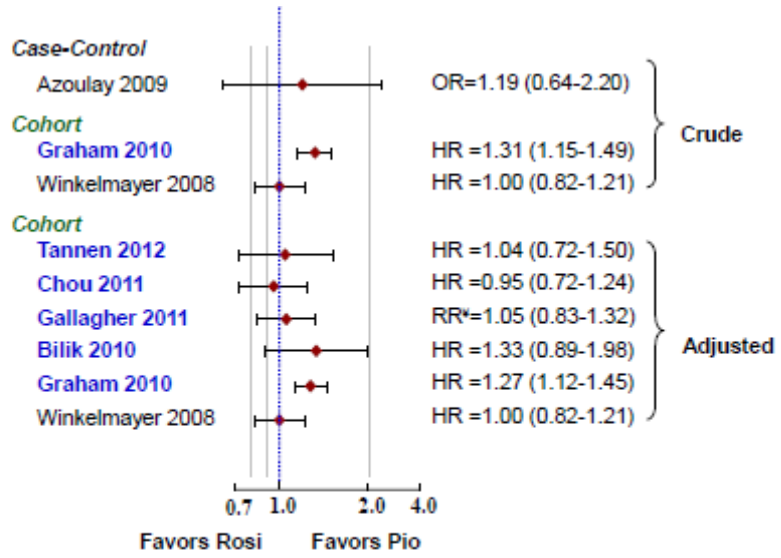


Outcome all-cause mortality: R versus P

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article
¥ Relative Risk
* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)
Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=1.03 (95% CI 0.91-1.15).
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Five studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of all-cause mortality, and are indicated in blue font on the forest plot above. In addition, three studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. Overall, point estimates were >1 in all but one study (Bilik 2010) with very broad confidence intervals (HR 0.69, 95% CI, 0.28-1.69). Sample size in the Bilik 2010 study was very small (773 rosiglitazone vs 711 pioglitazone), with formulary restrictions in three of the ten health plans, contributing to lack of power and potential bias.
Statistically significant increased risk for all-cause mortality was reported with rosiglitazone in four studies. One additional study (Wertz 2010) evaluated a composite outcome which included all-cause mortality and found no difference in risk between the two drugs.

4.1.4 Stroke



Outcome stroke: R versus P

¥ Relative Risk

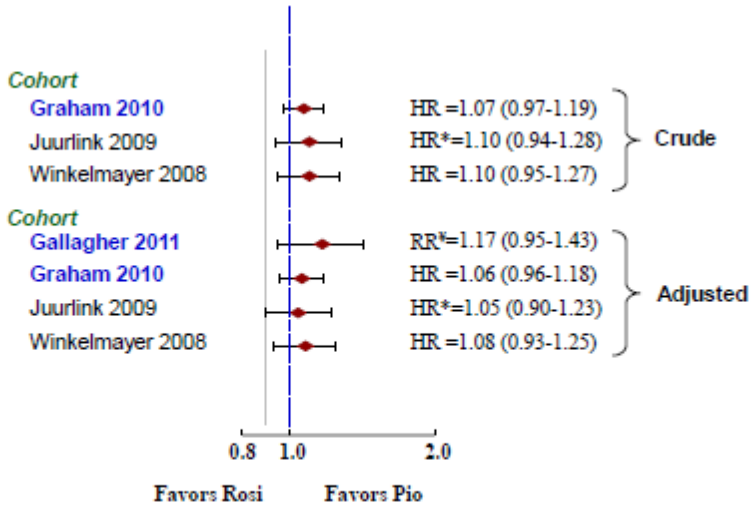
Note: definition of stroke in Winkelmayer 2008 study includes TIA

Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Five studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk stroke, and are indicated in blue font on the forest plot above. In addition, two studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. Overall, point estimates were >1 five studies, with one study (Graham 2010) reporting statistically significant increased risk with rosiglitazone. Two studies (Azoulay 2009 and Gallagher 2011) utilized GPRD as a data source. There is a possibility that some data from overlapping time periods may be represented in both studies.

4.2 FOREST PLOTS - COMPARISONS OF ROSIGLITAZONE VS PIOGLITAZONE - OLDER PATIENTS

4.2.1 Acute myocardial infarction - older patients

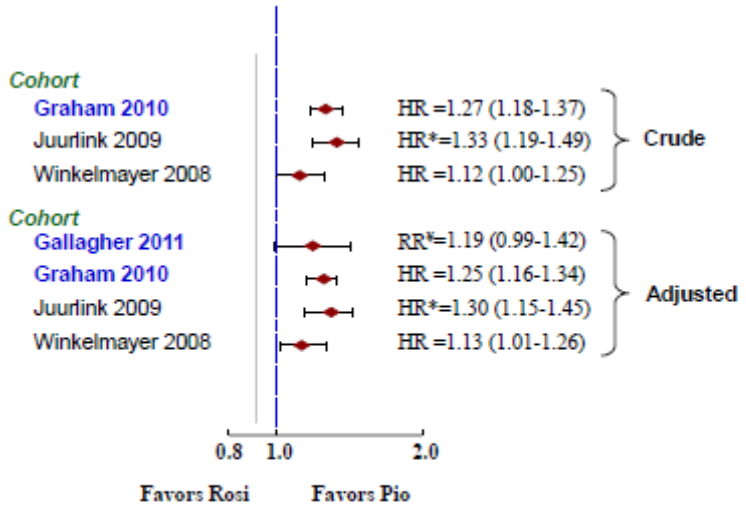


Outcome AMI: R vs. P (studies restricted to older patients ≥65 years)

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)
¥ Relative Risk
Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=0.97 (95% CI 0.83-1.12).
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Several studies identified in the current review, as well as in the previous review, focused exclusively on older patient populations, or included analyses of older patients (≥65 years). Two studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of AMI in older patients, and are indicated in blue font on the forest plot above. In addition, two studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. The outcome in one study using the GPRD database (Gallagher 2011) was described as "acute coronary syndrome" but is included in this forest plot because the authors did not conduct a separate analysis of AMI. Overall, point estimates were >1 in all of the studies; however, confidence intervals included one in all comparisons. One additional study (Wertz 2010) evaluated a composite outcome which included AMI and found no difference in risk between the two drugs in a subset of patients ≥65 years.

4.2.2 Heart failure - older patients

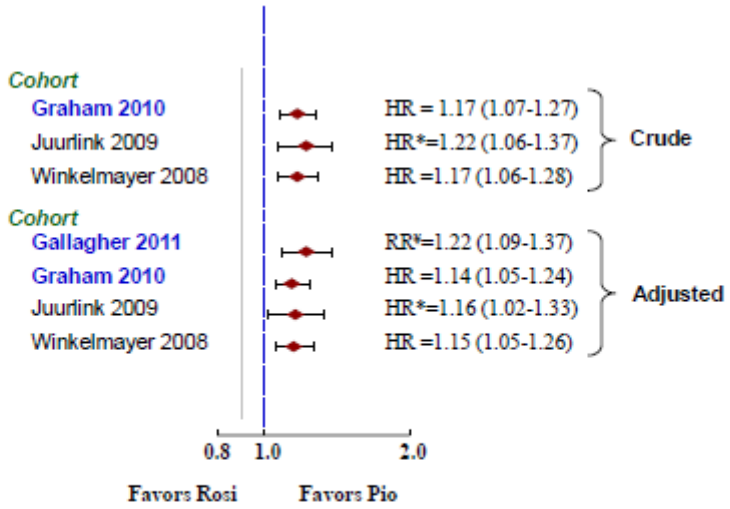


Outcome CHF: R vs. P (studies restricted to older patients ≥65 years)

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)
¥ Relative Risk
Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=0.97 (95% CI 0.83-1.12).
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Several studies identified in the current review, as well as in the previous review, focused exclusively on older patient populations, or included analyses of older patients (≥65 years). Two studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of heart failure in older patients, and are indicated in blue font on the forest plot above. In addition, two studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. Risk estimates were statistically significant favoring pioglitazone in three of the four studies. One additional study (Wertz 2010) evaluated a composite outcome which included heart failure and found no difference in risk between the two drugs in a subset of patients ≥65 years.

4.2.3 All-cause mortality - older patients

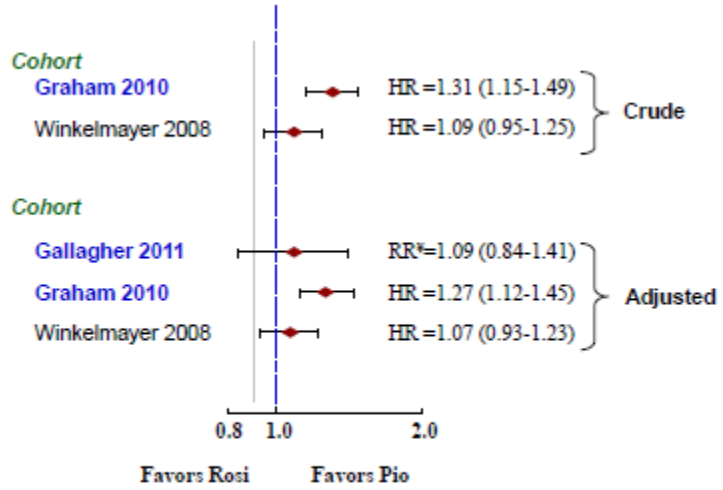


Outcome all-cause mortality: R vs. P (studies restricted to patients ≥65 years)

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)
¥ Relative Risk
Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=0.97 (95% CI 0.83-1.12).
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Several studies identified in the current review, as well as in the previous review, focused exclusively on older patient populations, or included analyses of older patients (≥65 years). Two studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of all-cause mortality in older patients, and are indicated in blue font on the forest plot above. In addition, two studies published prior to July 2010 were identified in the previous systematic review, and are displayed in black font on the forest plot. Risk estimates were statistically significant favoring pioglitazone in all four studies. One additional study (Wertz 2010) evaluated a composite outcome which included all-cause mortality and found no difference in risk between the two drugs in a subset of patients ≥65 years.

4.2.4 Stroke - older patients



Outcome stroke: R vs. P (studies restricted to older patients ≥65 years)

** Definition of stroke in Winkelmayer 2008 study includes TIA*
¥ Relative Risk
Note: blue font color denotes studies published after July 2010 AC

Reviewer comments: Several studies identified in the current review, as well as in the previous review, focused exclusively on older patient populations, or included analyses of older patients (≥65 years). Two studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of all-cause mortality in older patients, and are indicated in blue font on the forest plot above. In addition, one study published prior to July 2010 was identified in the previous systematic review, and is displayed in black font on the forest plot. Overall, risk estimates were >1,and results were statistically significant favoring pioglitazone in one study (Graham 2010).

5 CHARACTERISTICS OF INCLUDED STUDIES

5.1 CHARACTERISTICS OF STUDIES PUBLISHED AFTER JULY 2010 (N=7)

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Confounding Adjustment	Comparison Groups
[1] Tannen et al., 2012	Stroke, AMI, CRV, CHF; Death	Rosi, Pio	The Health Improvement Network Database (THIN) (UK)	12/1/2000-6/1/2008	709 (Pio) and 2,001 (Rosi) in replication studies; 3,844 (Pio), and 10,862 (Rosi) in expanded studies	Type 2 DM patients (by prescription) ages 35-75 years; with and without pre-existing ischemic CV diseases.	• Cox PH model • PS (stratification) • PERR adjustment	Cox model used in each PS quintile and combined into overall estimate; also used PERR adj.	Combo
[2] Chou et al., 2011	MI, CHF, Angina, CVA (ICD-9 codes)	Rosi, Pio	Longitudinal Health Insurance Database 2005 (Taiwan)	1/1/1998-12/31/2006	6,048 (Rosi); 1,677 (Pio)	Type 2 DM Taiwanese patients (by prescription and ICD-9 diagnosis codes).	Cox PH model	Controlled for multiple variables in Cox model.	Combo
[3] Gallagher et al., 2011	ACS, stroke, heart failure; ACM (including cause of death)	Rosi, Pio, Insulin, Metformin, Sulphonylurea	General Practice Research Database (GPRD) (UK)	Not stated (but covers the year 2007)	22,636 (Rosi); 18,953 (Pio); 121,637 (Metformin); 76,863 (Sulphonylurea); 26,458 (Insulin)	Type 2 DM patients age 40 years and over (from the UK GPRD).	• Poisson regression • Kaplan-Meier	Controlled for multiple variables in regression model.	Unclear (possibly combo)
[4] Loebstein et al., 2011	AMI, ACS, CRV, CHF (ICD-9 codes); ACM	Rosi, Metformin	Maccabi Healthcare Services (MHS) (Israel)	1/1/2000-6/30/2007	745 (Rosi); 2,753 (Rosi-Metformin); 11,938 (Metformin)	Patients with American Diabetes Association defined criteria for diabetes (from Israel MHS); purchased Rosi, Metformin	Cox PH model	Controlled for multiple variables in Cox model.	Combo
[5] Bilik et al., 2010	NMI, CRV, Nonfatal Stroke (ICD-9 codes); CV Mortality, ACM (NDI)	Rosi, Pio	TRIAD (10 managed care health plans, 68 provider groups) (US)	1999-2003	773 (Rosi); 711 (Pio)	Type 2 diabetes patients (by prescription); exclude age at diagnosis <30 yrs and treatment with insulin only	Cox PH model	Controlled for multiple variables in Cox model.	Combo (some patients used insulin)
[6] Graham et al., 2010	AMI, Stroke, Heart failure (ICD-9 codes); ACM (SSMBR database)	Rosi, Pio	Medicare (US)	7/2006-6/2009	67,593 (Rosi); 159,978 (Pio)	TZD-exposed patients 65 yrs and older.	• Cox PH model • Kaplan-Meier	Controlled for multiple variables in Cox model.	Combo
[7] Wertz et al., 2010	AMI, AHF (ICD-9 codes); Death (NDI)	Rosi, Pio	HealthCore Integrated Research Database (HIRD) (WellPoint) (US)	1/1/2001-12/31/2005	14,469 PS-matched Rosi and Pio patients	Patients ≥18 years of age, newly initiated on Rosi or Pio	• Cox PH model • PS (matching)	Included Cox model analysis of PS-matched sets of patients.	Unclear (possibly combo)

AMI=acute myocardial infarction; CHF=congestive heart failure; MI=myocardial infarction; CVA=cerebral vascular accident; ACM=all-cause mortality; ACS= acute coronary syndrome; CRV=coronary revascularization; NMI=nonfatal MI; CV=cardiovascular; AHF=acute heart failure; NDI=National Death Index; PS=propensity score; SSMBR= Social Security Master Beneficiary Record

5.2 CHARACTERISTICS OF STUDIES PUBLISHED BEFORE JULY 2010

Note: Tables in Section 7.3 are excerpted from FDA/CDER/OSE/DEPI Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. RCM #2010-277; dated June 15, 2010; pages 18-20.

5.2.1 Case-control studies comparing rosiglitazone and pioglitazone (n=2)

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Cases/ Controls	Population Details	Statistical Method	Model Estimate
Dormuth 2009	AMI; ICD-9 code 410	Rosi, Pio, Sulfonylurea, Glyburide	PharmaNet database in British Columbia	5/1/03-3/31/07	2,244/ 8,903	DM2 patients in British Columbia.	CLR	Odds Ratio
Stockl 2009	AMI (ICD-9 code 410.xx)	Rosi, Pio, Insulin, Others (unspecified)	Prescription Solutions	1/02-6/06	1,681/6,653 (primary analysis); 271/242 (secondary analysis)	Diabetes patients 18-84 yrs old; CA, TX, OK, OR, WA	CLR	Odds Ratio
CHF=congestive heart failure; DM2=diabetes mellitus 2; AMI=acute myocardial infarction; CVD=cardiovascular disease; PS=propensity score; CLR=conditional logistic regression; DM2=diabetes mellitus 2 UK=United Kingdom ; Pio=pioglitazone; Rosi=rosiglitazone								

5.2.2 Cohort studies comparing rosiglitazone and pioglitazone (n=7)

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Model Estimate
Brownstein 2009	Acute MI; ICD-9 code 410	Rosi, Pio, Metformin, Sulfonylurea	Partners Healthcare System	1/1/00-12/31/06	1,879 (Rosi), 806 (Pio), 12,490 (Met), 11,200 (Sul)	DM patients >18 yrs; ICD9 code DM 250.XX or an AIC>6% and ≥1 record of prescription	Poisson GLM	Rate Ratio
Hsiao 2009	MI (ICD-9-CM codes 410.xx and 411.xx), CHF (428.xx, 402.01, 402.11, 402.91, 404.01, 404.11 and 404.xx), AP (413.xx and 414.xx), stroke (433.xx and 414.xx), TIA (435.xx and 437.1), and composite of any of these outcomes	Rosi, Pio, Metformin, Sulfonylurea	National Health Insurance database (Taiwan)	3/1/01-12/31/05	2,093 (Rosi), 495 (Pio), 104,023 (Sul+), 49,626 (Met+)	DM2 patients in Taiwan.	• Survival via KM method • Cox PH model	Hazard Ratio
Juurlink 2009	Composite of death or hospital admission for acute MI (ICD-10 I20-I22) or HF (I50)	Rosi, Pio	Ontario Public Drug Benefit Program	4/2/2002-3//31/08	22,785 (Rosi)/ 16,951 (Pio)	Ontario, CA residents; DM2 patients ≥66 yrs; no insulin use	• Survival via KM method • Cox PH model	Hazard Ratio
Ziyadeh 2009	MI (ICD-9 codes 410.xx), CR (ICD-9 code 36.xx; current procedural terminology codes 33500-33572, 92980-92984, or 92995-92996), death (ICD-9 798.x)	Rosi, Pio	From i3 Drug Safety	7/1/00-3/31/07	47,501 (Rosi), 47,501 (Pio)	Diabetes patients ≥18 yrs; ≥6 months of health plan membership; 25 states.	• PS matching • Cox PH model • Survival via KM method • Log-rank test	Hazard Ratio
Walker 2008	MI, CR	Rosi, Pio, Metformin, Sulfonylurea	PharMetrics	7/00-3/07	57K (Rosi), 51K (Pio), 275K (Met), 160K (Sul)	Diabetes patients ≥18 yrs from over 80 US health plans with ≥6 month plan membership	PS-stratified Cox PH model	Hazard Ratio
Winkelmayer 2008	All-cause mortality (primary), MI, stroke, CHF	Rosi, Pio	NJPAAD and PPACE	1/1/00-12/31/05 [1/1/99-12/31/04 (NJPAAD), 1/1/99-12/31/05 (PPACE)]	14,101 (Rosi), 14,260 (Pio)	NJ and PA patients ≥65 yrs old.	Cox PH model	Hazard Ratio
Gerrits 2007	Acute MI (ICD-9 code 410.xx), CR (ICD-9 code 36.xx)	Rosi, Pio	Ingenix Research Database	03-06	14,807 (Pio)/15,104 (Rosi)	Diabetes (ICD-9 code 250.xx) patients	Cox PH model	Hazard Ratio

CAD=coronary artery disease; CHF=congestive heart failure; MI=myocardial infarction; HF=heart failure; AP=angina pectoris, TIA=transient ischaemic attack; CVA=cerebrovascular accidents; CHD= coronary heart disease; CR=coronary revascularization; CARP=coronary artery reperfusion procedures; EHR=electronic health record; DM2=diabetes mellitus 2; KM=Kaplan-Meier; PH=proportional hazards; +=combination therapy; PS=propensity score; GLM=generalized linear model; NJPAAD=New Jersey Pharmaceutical Assistance for the Aged and Disabled; PPACE=Pennsylvania Pharmaceutical Assistance Contract for the Elderly; K=000; UK=United Kingdom ; Pio=pioglitazone; Rosi=rosiglitazone

6 DISCUSSION

6.1 SUMMARY OF MAIN RESULTS

Results of this review are presented in a series of eight forest plots in Section 4. Overall, comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, congestive heart failure and all-cause mortality tended to favor pioglitazone.

Five studies published after the July 2010 Advisory Committee meeting were identified which included a direct comparison of rosiglitazone and pioglitazone regarding risk of acute myocardial infarction. In addition, there were ten studies published prior to July 2010 identified in the previous systematic review. Although risk estimates generally favored pioglitazone, confidence intervals included one in most comparisons. Results are displayed in a forest plot (Section 4.1.1). One additional study (Wertz 2010) evaluated a composite outcome which included AMI and found no difference in risk between the two drugs.

Five studies published after July 2010 were identified with a direct comparison of rosiglitazone and pioglitazone regarding risk of all-cause mortality in addition to three studies published prior to July 2010 identified previously. A statistically significant increased risk of all-cause mortality was reported with rosiglitazone in four studies. Point estimates were >1 favoring pioglitazone in all but one study (Bilik 2010) which reported a decreased risk with rosiglitazone (HR 0.69, 95% CI, 0.28-1.69). Sample size in the Bilik 2010 study was very small (773 rosiglitazone vs 711 pioglitazone), with formulary restrictions in three of the ten health plans. These limitations suggest lack of power to detect an effect, and potential bias in the results. One other study (Wertz 2010) which evaluated a composite outcome (AMI, acute heart failure, and all-cause mortality) as the primary analysis, reported no difference in risk between rosiglitazone and pioglitazone for the composite (HR 1.03; 95% CI, 0.91-1.15). Results are displayed in a forest plot (Section 4.1.3).

Four studies were identified which analyzed all-cause mortality with rosiglitazone versus pioglitazone in older patients (≥65 years). Statistically significant increased risk with rosiglitazone was described in all 4 studies with point estimates ranging from 1.14 to 1.22. Results are displayed in a forest plot (Section 4.2.3).

One other study (Wertz 2010) which evaluated a composite outcome as the primary analysis, reported no difference in risk between rosiglitazone and pioglitazone for the composite in a subset of older patients (HR 0.97; 95% CI, 0.83-1.12). The authors (Wertz 2010) point out that a limitation of the study is that patients enrolled in commercial health plans "could reflect a healthier population" and that "even elderly patients in the current study have full health coverage and may still be employed, thus they may be healthier than other older study populations."[24]

[24] Wertz 2010, op.cit. page 543.

In diabetic patients, all-cause death may be a reasonable indicator of cardiovascular death trends, since cardiovascular causes of death predominate in diabetic patients.[25]

7 CONCLUSION

Results of this review suggest that the cardiovascular safety profile of pioglitazone is favorable compared to that of rosiglitazone, especially in older patients ≥65 years of age.

A signal for increased all-cause mortality with rosiglitazone in older patients (>65 years of age), which was demonstrated in four observational studies, may be a reflection of the increased cardiovascular risk with rosiglitazone compared to pioglitazone.

[25] Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino RB Sr, Savage PJ, Levy D, Fox CS. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. 2009 Apr 7; 119(13):1728-35.

8 APPENDICES

8.1 LITERATURE SEARCH

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Literature Search

Date:	November 27, 2012
Reviewer:	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., Epidemiology Team Leader, DEPI 1, OPE, OSE
Division Director:	Solomon Iyasu, M.D., M.P.H., Director, DEPI 1, OPE, OSE
Subject:	Literature search for new epidemiologic data evaluating the cardiovascular safety of rosiglitazone since the July 2010 Advisory Committee meeting
Drug Name:	Rosiglitazone
OSE RCM #:	2012-2660

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1 INTRODUCTION

The Division of Metabolism and Endocrinologic Products (DMEP) asked the staff of the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology 1 (OSE/OPE/DEPI1) to search the medical literature for published epidemiology studies evaluating the cardiovascular safety of rosiglitazone since the July 2010 Advisory Committee meeting. DMEP requested the sources and publications.

2 REVIEW METHODS AND MATERIALS

DEPI staff initiated this literature search using four approaches:

- DEPI consulted the FDA librarians requesting a literature search to answer the following question: "Are there any new epidemiologic data available evaluating the cardiovascular safety of rosiglitazone since July 15, 2010?"

  The general search statement was: (rosiglitazone OR avandia) AND (epidemiologic OR epidemiology) AND (Cardiovascular Diseases OR myocardial infarction OR "heart attack*" OR" Heart Diseases" OR "Heart Failure" OR "heart infarction" OR "cerebrovascular accident" OR "Stroke"). The search was carried out in Embase, PubMed, and the Web of Science.

- Using the Web of Science, DEPI generated a list of articles that cited the following publication (from time of publication until November 8, 2012): Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304(4):411-418.

- Using the Web of Science, DEPI generated a list of articles that cited the following meta-analysis (from time of publication until November 8, 2012): Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ* 2011;342;d1309 [pages 1-9].

- DEPI also checked the reference lists for all the 2012 publications included in this review to identify other potential sources of new epidemiologic data.

We found the following epidemiologic studies that were published after July 2010 or were not included in the review presented at the Advisory Committee meeting.

3 REVIEW RESULTS

The following publications appear to contain new epidemiologic data evaluating the cardiovascular safety of rosiglitazone since July 2010. The abstracts are listed chronologically by year and are presented without interpretation. The full references are attached.

a) Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ* 2011;342:d1309 [pages 1-9].

DEPI Reviewer Comment: 13/16 studies included in this review were discussed at the July 2010 advisory committee meeting. The three studies not discussed are as follows: Bilik 2010, Pantalone 2009, and Wertz 2010. These three abstracts are attached in the Appendix.

OBJECTIVE: To determine the comparative effects of the thiazolidinediones (rosiglitazone and pioglitazone) on myocardial infarction, congestive heart failure, and mortality in patients with type 2 diabetes.
DESIGN: Systematic review and meta-analysis of observational studies.
DATA SOURCES: Searches of Medline and Embase in September 2010.
STUDY SELECTION: Observational studies that directly compared the risk of cardiovascular outcomes for rosiglitazone and pioglitazone among patients with type 2 diabetes mellitus were included.
DATA EXTRACTION: Random effects meta-analysis (inverse variance method) was used to calculate the odds ratios for cardiovascular outcomes with thiazolidinedione use. The I(2)statistic was used to assess statistical heterogeneity.
RESULTS: Cardiovascular outcomes from 16 observational studies (4 case-control studies and 12 retrospective cohort studies), including 810,000 thiazolidinedione users, were evaluated after a detailed review of 189 citations. Compared with pioglitazone, use of rosiglitazone was associated with a statistically significant increase in the odds of myocardial infarction (n = 15 studies; odds ratio 1.16, 95% confidence interval 1.07 to 1.24; $P < 0.001$; I(2) = 46%), congestive heart failure (n = 8; 1.22, 1.14 to 1.31; $P < 0.001$; I(2) = 37%), and death (n = 8; 1.14, 1.09 to 1.20; $P < 0.001$; I(2) = 0%). Numbers needed to treat to harm (NNH), depending on the population at risk, suggest 170 excess myocardial infarctions, 649 excess cases of heart failure, and 431 excess deaths for every 100,000 patients who receive rosiglitazone rather than pioglitazone.
CONCLUSION: Among patients with type 2 diabetes, use of rosiglitazone is associated with significantly higher odds of congestive heart failure, myocardial infarction, and death relative to pioglitazone in real world settings.

b) Loebstein R, Dushinat M, Vesterman-Landes J, Silverman B, Friedman N, Katzir, I, Kurnik D, Lomnicky Y, Kokia E, Halkin H. Database evaluation of long-term rosiglitazone treatment on cardiovascular outcomes in patients with Type 2 diabetes. *J Clin Pharmacol* 2011;51:173-180.

DEPI Reviewer Comment: The upper limit of the 95% CI in the text for the CHF hazard ratio was reported as 3.53 instead of 1.95 which appears in the Abstract. Since the hazard ratio was reported as 2.23, the 95% upper limit 1.95 in the Abstract appears to be an error.

BACKGROUND: Recent meta-analyses suggest an increased risk of acute myocardial infarction (AMI) in patients with type 2 diabetes mellitus (T2DM) treated with rosiglitazone. These meta-analyses have drawn considerable criticisms. Retrospective observational studies do not consistently support this association.
OBJECTIVE: The objective of this study was to compare rates of adverse cardiovascular outcomes in T2DM patients treated with rosiglitazone alone or combined with metformin or metformin alone.
METHODS: This retrospective study, using the health maintenance organization database, included patients who were dispensed rosiglitazone (alone or with metformin) for at least 6 months as follows: rosiglitazone alone (n = 745), rosiglitazone and metformin (n = 2753), and metformin alone (n = 11 938). Adverse cardiovascular outcomes were new diagnosis of AMI, acute coronary syndrome (ACS), coronary revascularization (CRV), congestive heart failure (CHF), and all-cause mortality.
RESULTS: Mean on-treatment follow-up was 30 months. After adjustment for covariates found to be significant in univariate analyses, rosiglitazone was associated only with CHF (hazard ratio [HR] = 2.23; 95% confidence interval [CI]: 1.41-1.95) with no increase of risk for AMI (HR = 1.13; 95%CI: 0.60-2.12), ACS (HR = 0.85; 95% CI: 0.57-1.26), coronary revascularization (HR = 1.22; 95% CI:0.82-1.54), or all-cause mortality (HR = 1.15; 95% CI: 0.85-1.56).
CONCLUSION: In this community-based cohort, 30 months of therapy with rosiglitazone treatment was associated with increased risk of CHF but was not associated with increased risk of AMI, ACS, coronary revascularization, or all-cause mortality.

c) Berthet S, Pascale O, Montastruc JL, Lapeyre-Mestre M. Drug safety of rosiglitazone and pioglitazone in France: A study using the French PharmacoVigilance database. *BMC Clinical Pharmacology*, 2011;11:5 [pages 1-6].

BACKGROUND: Thiazolidinediones (TZDs), rosiglitazone (RGZ) and pioglitazone (PGZ) are widely used as hypoglycemic drugs in patients with type 2 diabetes mellitus. The aim of our study was to investigate the profile of adverse drug reactions (ADRs) related to TZDs and to investigate potential risk factors of these ADRs.
METHODS: Type 2 diabetic patients were identified from the French Database of PharmacoVigilance (FPVD) between 2002 and 2006. We investigated ADR related to TZD, focusing on 4 ADR: edema, heart failure, myocardial infarction and hepatitis corresponding to specific WHO-ART terms.
RESULTS: Among a total of 99,284 adult patients in the FPVD, 2295 reports concerned type 2 diabetic patients (2.3% of the whole database), with 161 (7%) exposed to TZDs. The frequency of edema and cardiac failure was significantly higher with TZDs than in other patients (18% and 7.4% versus 0.8% and 0.1% respectively, $p < 0.001$) whereas the frequency of hepatitis was similar (5.9% versus 4%, NS). A multiple logistic regression model taking into account potential confounding factors (age, gender, drug exposure and co-morbidities)

found that TZD exposure remained associated with heart failure and edema, but not with hepatitis or myocardial infarction.
CONCLUSION: Thiazolidinediones exposure is associated with an increased risk of edema and heart failure in patients with type 2 diabetes even when recommendations for use are respected. In contrast, the risk of hepatic reactions and myocardial infarction with this class of drugs seems to be similar to other hypoglycemic agents.

d) Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. *Am J Cardiovasc Drugs* 2011;11(2):115-28.

DEPI Reviewer Comment: This is a 2011 meta-analysis of randomized controlled trials conducted before 2009 so is unlikely to contain new data since 2010.

BACKGROUND: Recent meta-analyses of randomized clinical trials (RCTs) demonstrated a higher risk of heart failure (HF) with the use of thiazolidinediones (TZDs). However, this effect may have been diluted by including active controls. Also, it is uncertain whether the risk of HF is similar with rosiglitazone and pioglitazone.
OBJECTIVES: This study quantified the risks of HF with the use of TZDs in patients with or at high risk of developing type 2 diabetes mellitus (DM), and evaluated differential effects by type of TZD. Secondarily, we evaluated risks of peripheral edema.
METHODS: We performed a systematic review and meta-analysis of placebo-controlled RCTs evaluating the effect of rosiglitazone or pioglitazone on investigator-reported HF and edema. Articles published before 31 December 2009 were searched in MEDLINE, The Web of Science, and Scopus, and the data were extracted by three investigators. RCTs with >/=100 patients and >/=3 months of follow-up were included. We quantified the effect of TZDs as odds ratios (ORs) by using the Mantel-Haenzel and alternative models. We further evaluated the risk of serious/severe HF, and the effect of several trial characteristics on HF risk by subgroup analysis and meta-regression analysis.
RESULTS: 29 trials (n = 20 254) were evaluated. TZDs were significantly associated with HF (TZD 360/6807 [5.3%] vs placebo 234/6328 [3.7%], OR 1.59; 95% CI 1.34, 1.89; p < 0.00001). The risk of HF was higher with rosiglitazone than with pioglitazone (2.73 [95% CI 1.46, 5.10] vs 1.51 [1.26, 1.81]; p = 0.06). TZDs were associated with a similar risk of serious/severe HF (OR 1.47; 95% CI 1.16, 1.87; p = 0.002). Use of TZDs was also associated with edema (OR 2.04; 95% CI 1.85, 2.26; p < 0.00001). HF and edema risks were consistent using Peto and random effects models. Risks of HF were significantly high for the subgroups of trials including patients with or at high risk for type 2 DM, and for the subgroup of trials with >/=12 months of follow-up. Meta-regression analysis showed that trials with lower overall baseline risk had higher HF risks.
CONCLUSION: In placebo-controlled trials of adult patients with or at high risk for type 2 DM, TZD therapy is significantly and consistently associated with a

higher risk of HF. The risk of serious/severe HF is also increased with the use of TZDs. HF risks are similar to those of meta-analyses combining active- and placebo-controlled trials. The benefit/risk profile of TZDs should be considered when treating diabetic patients with or without prior HF.

e) Chou CC, Chen WL, Kao TW, Chang YW, Loh CH, Wang CC. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. *Clin Ther* 2011; 33(12):1904-13.

BACKGROUND: Thiazolidinediones (TZDs) are oral antihyperglycemic drugs that are used to treat insulin resistance. Rosiglitazone is a TZD that has been found to increase the risk of cardiovascular events, especially of myocardial ischemic events.
OBJECTIVE: The aim of this study was to conduct a direct comparison of TZDs (pioglitazone and rosiglitazone) and their relationship to cardiovascular events (myocardial infarction [MI], angina, congestive heart failure [CHF], and cerebral vascular accident [CVA]) in Taiwanese patients with type 2 diabetes mellitus (DM).
METHODS: A retrospective study with second data analysis was performed from January 1, 1998, to December 31, 2006. We selected those who were prescribed only 1 kind of TZD for at least 120 days in the 180-day period; those who switched to another TZD during the above-mentioned periods and had cardiovascular events before the use of TZD were excluded. Stringent definitions for MI, angina, CHF, and CVA were set, and survival analysis was performed.
RESULTS: A total of 7725 type 2 DM cases were included in the final analysis. In our model, the hazard ratio (HR) for development of MI in rosiglitazone-treated patients was 0.539 (95% CI, 0.327-0.889; P = 0.015) compared with pioglitazone-treated patients for whom age, gender, medical specialist, duration of DM, and histories of antihypertensive, statin, and fibrate medications were controlled. There were no significant differences in HRs among angina (HR = 0.543; 95% CI, 0.293-1.006; P = 0.052), CHF (HR = 0.820; 95% CI, 0.619-1.086; P = 0.166), and CVA (HR = 0.949; 95% CI, 0.724-1.244; P = 0.705) groups. Antihypertensive and statin therapy led to significantly different HRs for cardiovascular events depending on when they were first prescribed. If statins were prescribed after TZD, the HR relative to patients who never used statins was 3.896 for MI (95% CI, 2.071-7.328; P < 0.001), 3.194 for angina (95% CI, 1.514-6.737; P = 0.002), and 1.303 for CHF (95% CI, 1.011-1.678; P = 0.041). If antihypertensives were prescribed after TZD, the HR relative to patients never treated with antihypertensives was 7.654 for angina (95% CI, 1.922-32.921; P = 0.004), 3.900 for CHF (95% CI, 2.437-6.242; P < 0.001), 2.242 for CVA (95% CI, 1.613-3.116; P < 0.001), and 2.325 for MI (95% CI, 1.109-4.873; P = 0.026).
CONCLUSION: Our data suggested that, as an add-on treatment for diabetic patients, rosiglitazone had significantly lower HRs for MI compared with those for pioglitazone. Diabetic hypertensive patients treated with TZD were at a high risk for angina, CHF, CVA, and MI, whereas statin use increased the risk for MI, angina, and CHF. There are some potential limitations to this study owing to the

analysis methodology and retrospective design. In addition, all enrolled type 2 DM patients were treated with TZD medications, but diabetes patients treated with nonpharmacologic therapy, including lifestyle modifications, were not included.

f) Gallagher AM, Smeeth L, Seabroke S, Leufkens H, van Staa TP. Risk of death and cardiovascular outcomes with thiazolidinediones: A study with the general practice research database and secondary care data. *PLoS ONE* 2011;6(12):e28157 [pages1-9].

OBJECTIVE: To describe the likely extent of confounding in evaluating the risks of cardiovascular (CV) events and mortality in patients using diabetes medication.
METHODS: The General Practice Research Database was used to identify inception cohorts of insulin and different oral antidiabetics. An analysis of bias and incidence of mortality, acute coronary syndrome, stroke and heart failure were analysed in GPRD, Hospital Episode Statistics and death certificates.
RESULTS: 206,940 patients were identified. The bias analysis showed that past thiazolidinedione users had a lower mortality risk compared to past metformin users. There were no differences between past users of rosiglitazone and pioglitazone (adjusted RR of 1.04; 95% CI 0.93-1.18). Current rosiglitazone users had an increased risk of death (adjusted RR 1.20; 95% CI 1.08-1.34) and of hospitalisation for heart failure (adjusted RR of 1.73; 95% CI 1.19-2.51) compared to current pioglitazone users. Risk of mortality was increased two-fold shortly after starting rosiglitazone. Excess risk of death over 3 years with rosiglitazone was 0.3 per 100 in those aged 50-64 years, 2.0 aged 65-74, 3.0 aged 75-84, and 7.0 aged 85+. The cause of death with rosiglitazone was more likely to be due to a disease of the circulatory system.
CONCLUSION: Higher risks for death (overall and due to cardiovascular disease) and heart failure were found for rosiglitazone compared to pioglitazone. These excess risks were largest in patients aged 65 years or older. The European regulatory decision to suspend rosiglitazone is supported by this study.

g) Motola D, Piccinni C, Biagi C, Raschi E, Marra A, Marchesini G, Pluzzi E. Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones: A disproportionality analysis of the US FDA adverse event reporting database. 2012;35(4):315-323.

BACKGROUND: The risk of myocardial infarction, macular oedema and bone fractures associated with thiazolidinediones (TZDs) has been extensively investigated.
OBJECTIVE: The aim of the study was to verify if the analysis of a large spontaneous reporting database could generate early signals on these adverse drug reactions (ADRs) associated with TZDs.
METHODS: A case/non-case study, restricted to antidiabetic drugs, was performed on spontaneous reports of ADRs (2005-2008) in the US FDA Adverse Event Reporting System (AERS). The method was applied to TZDs, both as a drug class and as single agents. The reporting odds ratio (ROR) with 95% CI was

calculated as a measure of disproportionality in the whole dataset and in a quarter-by-quarter analysis.
RESULTS: TZD use was registered in 49,589 out of 301,950 drug-reaction pairs (16%), with significant disproportionality for myocardial infarction (ROR 4.71; 95% CI 4.40, 5.05), macular oedema, (3.88; 2.79, 5.39) and bone fractures (1.73; 1.53,1.96). Separate analysis of the two TZDs showed that only rosiglitazone was associated with myocardial infarction (7.86; 7.34, 8.34) and macular oedema (5.55; 3.94, 7.79), whereas pioglitazone was associated with multiple site fractures (2.00; 1.70, 2.35), in particular upper and lower limb and pelvic fractures. The quarter-by-quarter analysis identified disproportionality for myocardial infarction (3.13; 2.38, 4.10) and bone fractures since January-March 2005 (2.70; 1.04, 2.78).
CONCLUSION: The frequency of reporting of myocardial infarction, macular oedema and fractures was significantly higher for TZDs in comparison with other antidiabetic drugs, with large intraclass differences. Both myocardial infarction and bone fracture signals appeared before major publications on these safety issues.

h) Choy-Shan A, Zinn A, Shah B, Danoff A, Donnino R, Schwartzbard AZ, Lorin JD, Grossi E, Sedlis SP. Effect of rosiglitazone on survival in patients with diabetes mellitus treated for coronary artery disease. *Coron Artery Dis* 2012;23(5):354-8.

OBJECTIVES: The purpose of this study was to assess the impact of rosiglitazone on survival in patients with diabetes mellitus (DM) and coronary artery disease (CAD).
METHODS: We carried out a drug-exposure analysis in 801 patients with DM and CAD in a cardiac catheterization laboratory registry (490 patients treated with a percutaneous coronary intervention, 224 patients treated with coronary artery bypass grafting, and 87 patients treated with medication alone).
RESULTS: A total of 193 patients (24.1%) were exposed to rosiglitazone. The median survival from the date of cardiac catheterization in the rosiglitazone group was 146.7 months versus 109.1 months in the unexposed group (P<0.001). At 5 years, the unadjusted survival was 82% in the rosiglitazone-exposed group versus 69% in the unexposed group (P<0.001). There was no difference in survival between rosiglitazone-exposed and rosiglitazone-unexposed patients in the groups treated with coronary artery bypass grafting or medical therapy (P=0.37 and 0.11, respectively). In a multivariable model, rosiglitazone exposure had no effect on mortality (hazard ratio=0.737; 95% confidence interval: 0.521-1.044, P=0.86).
CONCLUSION: We conclude that exposure to rosiglitazone is not associated with increased mortality in diabetics who are treated for CAD. These findings support the notion that insulin sensitization with a thiazolidinedione is safe in carefully selected and treated patients with DM and CAD.

i) Halimi S, Aubert JP, Fontbonne A, Guillausseau PJ, Nachit F, Bouée S, Detournay B. A real-life study of the use, effectiveness and tolerability of

rosiglitazone in France: The AVANCE study. *Diabetes and Metabolism* 2012;38(4):343-351.

AIM: The study aimed to determine the effectiveness and tolerability of rosiglitazone, and its profile in terms of treatment adherence, treated patients and prescribing recommendations under everyday conditions of care.
METHODS: This was a " real-life" observational longitudinal study including patients with type 2 diabetes mellitus (T2DM) starting treatment with rosiglitazone and followed for up to 2 years. A questionnaire was completed at the time of inclusion and during routine consultations at around 6, 12, 18 and 24 months following inclusion. Information was collected on sociodemographics, clinical history, treatments, co-morbidities, laboratory data and compliance with treatment. There were three primary outcome measures: treatment response (defined as an HbA1c (less-than or equal to) 8.0% or a decrease in HbA1c (greater-than or equal to) 0.7%); switch to insulin (as considered necessary by the physician); and occurrence of adverse events requiring a change or discontinuation of treatment.
RESULTS: The evaluation included 670 patients (61.1%) treated with rosiglitazone/metformin as fixed-dose combination tablets and 427 (38.9%) with standard rosiglitazone tablets. Rates of HbA1c response, defined as an HbA1c less than or equal to 8.0% or a decrease in HbA1c greater than or equal to 0.7%, ranged from 80.6% to 92.1% depending on the follow-up time. The percentage of patients with an HbA1c less than 7% was 18.4% before rosiglitazone was prescribed, and ranged from 48.2% to 57.8% depending on the follow-up period. Sixty-two patients (6.1%, 95% CI: 4.6-7.6%) switched to insulin therapy during the follow-up period. Spontaneously reported adverse events leading to a change or discontinuation of treatment were seen in 45 patients (4.4%, 95% CI: 3.2-5.6%).
CONCLUSION: Rosiglitazone showed sustained efficacy, with around 90% of patients defined as responders to the treatment in terms of reduction in HbA1c, and was relatively well tolerated. The adverse-event profile was consistent with the known effects of rosiglitazone, and no signs of increased cardiovascular ischaemic risk were observed. These results are in agreement with previous studies on rosiglitazone.

j) Tannen R, Xie D, Wang X, Menggang Y, Weiner MG. A new "Comparative Effectiveness" assessment strategy using the THIN database: Comparison of the cardiac complications of pioglitazone and rosiglitazone. *Pharmacoepidemio Drug Saf* 2012 Oct 16. doi: 10.1002/pds.3360. [Epub ahead of print]

PURPOSE: Examine feasibility of a new strategy to perform Electronic Medical Record database valid Comparative Effectiveness Research (CER), using determination of whether rosiglitazone (ROS) treatment increases Acute myocardial infarction (MI) in comparison to pioglitazone (PIO) as a model question.
METHODS: Using the UK The Health Improvement Network Database, a retrospective cohort design replicated the proactive RCT of diabetics with

ischemic cardiovascular disease (CVD). Replication studies using PIO or ROS, as well as expanded studies of subjects not requiring CVD, were performed. MI assessment used multiple analytics comparing ROS and PIO exposed patients including: unexposed subjects, the proactive RCT, and directly between ROS to PIO exposed cohorts.
RESULTS: PIO replication studies did not affect MI [HR 0.88 (0.49 to 1.42)], but ROS increased MI, with prior event rate ratio (PERR) adjusted HR (which overcomes unmeasured confounding) results of: [HR 1.31 (0.94 to 1.74)] versus proactive RCT [HR 0.83 (0.65 to 1.06)] (p=0.02). Direct ROS to PIO exposed cohort comparisons yielded PERR adj HR of 1.55 (0.98 to 2.65). By contrast, expanded studies showed no differences between ROS and PIO exposure.
CONCLUSION: These results provide new insight regarding the effects of ROS and PIO on MI. In a population with established ischemic CVD, ROS increased MI in contrast to PIO; whereas in an unselected population, ROS and PIO have reasonably comparable effects. Most importantly, this study demonstrates the feasibility and advantages of a new strategy to perform reliable "CER" using an EMR database.

k) The TIDE Trial Investigators. Design, history, and results of the thiazolidinediones intervention with vitamin D evaluation (TIDE) randomized controlled trial. *Diabetologia* 2012;55:36-45.

AIMS/OBJECTIVE: Conflicting data regarding cardiovascular effects of thiazolidinediones (TZDs) and extra-skeletal effects of vitamin D supported the need for a definitive trial. The Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) trial aimed to assess the effects of TZDs (rosiglitazone and pioglitazone) on cardiovascular outcomes and the effects of vitamin D (cholecalciferol) on cancers and mortality.
METHODS: A large multicentre 3 × 2 factorial double-blind placebo-controlled randomised trial recruited from outpatient primary care and specialty clinics in 33 countries. From June 2009 to July 2010, 1,332 people with type 2 diabetes and other cardiovascular risk factors aged ≥ 50 years whose HbA(1c) was 6.5-9.5% (48-80 mmol/mol) when using two or fewer glucose-lowering drugs were randomised by a central computer system to placebo (n = 541), rosiglitazone 4-8 mg/day (n = 399) or pioglitazone 30-45 mg/day (n = 392); 1,221 participants were randomised to placebo (n = 614) or vitamin D 1,000 IU/day (n = 607). Participants and all study personnel were blind to treatment allocation. The primary outcome for the TZD arm was the composite of myocardial infarction, stroke or cardiovascular death, and for the vitamin D arm it was cancer or all-cause death. All randomised participants were included in the primary analysis.
RESULTS: From the study design, 16,000 people were to be followed for approximately 5.5 years. However, the trial was stopped prematurely because of regulatory concerns after a mean of 162 days without consideration of the accrued data. In the TZD arm, the cardiovascular outcome occurred in five participants (0.9%) in the placebo groups and three participants (0.4%) in the TZD groups (two allocated to pioglitazone, one to rosiglitazone). In the vitamin D arm, the

primary outcome occurred in three participants (0.5%) in the placebo group and in two participants (0.3%) receiving vitamin D. Adverse events were comparable in all groups.
CONCLUSION: Uncertainty persists regarding the clinically relevant risks and benefits of TZDs and vitamin D because of the early cancellation of this comprehensive trial.

cc: EganA/WeberJ/MahoneyKM/GuettierJM/YanoffL/ParksM/DMEP
TossaM/OSE
BrightP/WysowskiD/HammadT/IyasuS/DEPI 1

4 APPENDIX

This Appendix includes abstracts from three publications included in the review article (a) by Loke et al. that were not discussed in the July 2010 advisory committee meeting.

i. Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, HsiaoVC, Tseng CW, Mangione CM, Lasser NL, Crosson JC, Herman WH. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). *Pharmacoepidemiol Drug Saf* 2010;19:715-21.

BACKGROUND: Studies have associated thiazolidinedione (TZD) treatment with cardiovascular disease (CVD) and questioned whether the two available TZDs, rosiglitazone and pioglitazone, have different CVD risks. We compared CVD incidence, cardiovascular (CV), and all-cause mortality in type 2 diabetic patients treated with rosiglitazone or pioglitazone as their only TZD.
METHODS: We analyzed survey, medical record, administrative, and National Death Index (NDI) data from 1999 through 2003 from Translating Research Into Action for Diabetes (TRIAD), a prospective observational study of diabetes care in managed care. Medications, CV procedures, and CVD were determined from health plan (HP) administrative data, and mortality was from NDI. Adjusted hazard rates (AHR) were derived from Cox proportional hazard models adjusted for age, sex, race/ethnicity, income, history of diabetic nephropathy, history of CVD, insulin use, and HP.
RESULTS: Across TRIAD's 10 HPs, 1,815 patients (24%) filled prescriptions for a TZD, 773 (10%) for only rosiglitazone, 711 (10%) for only pioglitazone, and 331 (4%) for multiple TZDs. In the seven HPs using both TZDs, 1,159 patients (33%) filled a prescription for a TZD, 564 (16%) for only rosiglitazone, 334 (10%) for only pioglitazone, and 261 (7%) for multiple TZDs. For all CV events, CV, and all-cause mortality, we found no significant difference between rosiglitazone and pioglitazone.
CONCLUSION: In this relatively small, prospective, observational study, we found no statistically significant differences in CV outcomes for rosiglitazone- compared to pioglitazone-treated patients. There does not appear to be a pattern of clinically meaningful differences in CV outcomes for rosiglitazone- versus pioglitazone-treated patients.

ii. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, Atreja A, Zimmerman RS. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. *Acta Diabetol* 2009;46:145-54.

Oral anti-diabetic agents have been associated with adverse cardiovascular events in type 2 diabetes (DM2). We investigated the risk of coronary artery disease (CAD), congestive heart failure (CHF), and mortality using multivariable Cox models in a retrospective cohort of 20,450 DM2 patients from our electronic health record (EHR). We observed no differences in CAD risk among the agents. Metformin was associated with a reduced risk of CHF (HR 0.76, 95% CI 0.64-0.91) and mortality (HR 0.54, 95% CI 0.46-0.64) when compared to sulfonylurea. Pioglitazone was also associated with a lower risk of mortality when compared to sulfonylurea (HR 0.59, 95% CI 0.43-0.81). No other significant differences were found between the oral agents. In conclusions, our results did not identify an increased CAD risk with rosiglitazone in clinical practice. However, the results do reinforce a possible increased risk of adverse events in DM2 patients prescribed sulfonylureas.

iii. Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. *Circ Cardiovasc Qual Outcomes* 2010;3:538-45.

BACKGROUND: This study directly compares risk of acute myocardial infarction (AMI), acute heart failure (AHF), or all-cause death among pioglitazone- and rosiglitazone-treated patients in a managed-care population.
METHODS AND RESULTS: Patients ≥18 years of age, newly initiated on rosiglitazone or pioglitazone between January 1, 2001, and December 12, 2005, were included. The date of the first pharmacy claim for rosiglitazone or pioglitazone was defined as index date. Patients were excluded if they had <1 year continuous eligibility preindex or a preindex insulin claim. Primary outcome measure was time to composite event of AMI, AHF or death among pioglitazone- and rosiglitazone-treated patients. The National Death Index database was accessed to obtain date of death for patients who died during the study period. Propensity score matching was used to control for potential confounders. The Cox proportional hazards model was used to evaluate effects of exposure to rosiglitazone and pioglitazone on time to event. A total of 36 628 patients (58% male; mean age, 54 years) were identified. Of the rosiglitazone-treated patients, 602 (4.16%) had an AMI, AHF, or death compared with 599 (4.14%) propensity score-matched pioglitazone-treated patients. No significant difference was observed between matched groups for risk of composite event (hazard ratio, 1.03; 95% confidence interval, 0.91 to 1.15; P=0.666) when patients were followed from index date until end of study period, termination of enrollment status, or diagnosis of AMI/AHF/death.
CONCLUSION: In this retrospective cohort study directly comparing rosiglitazone and pioglitazone with a propensity score-matched population that includes mortality data, no significant differences were found in the risk of AMI, AHF or death.

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/s/

PATRICIA L BRIGHT
11/27/2012

DIANE K WYSOWSKI
11/27/2012

SOLOMON IYASU
11/27/2012

8.2 PROTOCOL FOR SYSTEMATIC REVIEW

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 24, 2010
To:	File
Through:	Gerald Dal Pan, M.D., M.H.S., Director Office of Surveillance and Epidemiology (OSE) Solomon Iyasu, M.D., M.P.H., Director Division of Epidemiology (DEPI) / OSE
From:	Kate Gelperin, M.D., M.P.H. Esther Zhou, M.D., Ph.D. Scientific Leads OSE Thiazolidinedione Cardiovascular Safety Review Team
Subject:	Protocol for Cochrane-type systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone
Drug Name(s):	AVANDIA® (rosiglitazone); NDA # 21-071 ACTOS® (pioglitazone), NDA # 21-073
Applicant/sponsor:	GlaxoSmithKline; Takeda
OSE RCM #:	2010-277

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1 BACKGROUND

1.1 DESCRIPTION OF THE ISSUE

A signal for increased cardiovascular risk in patients treated with rosiglitazone has been identified in several pooled analyses and meta-analyses of rosiglitazone randomized controlled trials. [1] [2] [3] [4]

Avandia (rosiglitazone maleate; GlaxoSmithKline) and Actos (pioglitazone hydrochloride; Takeda) are oral antidiabetic agents that act primarily by decreasing insulin resistance. Both rosiglitazone and pioglitazone were approved by FDA in 1999, and are the only currently approved thiazolidinedione (TZD) drugs. Troglitazone had been approved by FDA in 1997, but was removed from the market in 2000 due to serious hepatotoxicity. TZDs are selective ligands of the nuclear transcription factor peroxisome proliferator-activated receptors (PPARs) which regulate gene expression in response to ligand binding.[5]

Previously published Cochrane reviews of rosiglitazone[6] and pioglitazone[7] included randomized controlled trials only. A systematic review of observational studies of cardiovascular risk with the TZDs has not previously been conducted.

1.2 WHY IT IS IMPORTANT TO DO THIS REVIEW

A recently published consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes[8] advised against using rosiglitazone based on several meta-analyses which have suggested a 30 –40% relative increase in risk for myocardial infarction with rosiglitazone, and no indications of similar risk with pioglitazone.

If the observed signal from rosiglitazone clinical trials is real, the public health significance of a 40% increased risk of myocardial ischemia in diabetic patients is unacceptably high. Though a

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[1] GlaxoSmithKline. NDA 21-071/Supplement 022. Avandia® (rosiglitazone maleate). "Cardiovascular Event Modeling Project" final study report. Date of Submission: August 4, 2006.

[2] Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). In US Food and Drug Administration Advisory Committee background package, June 4, 2007. Available at: http://www fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf, pp 13-105.

[3] Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med 2007; 356:2457.

[4] Cobitz A, Zambanini A, Sowell M, Heise M, Louridas B, McMorn S, Semigran M,Koch G. A retrospective evaluation of congestive heart failure and myocardial ischemia events in 14,237 patients with type 2 diabetes mellitus enrolled in 42 short-term, double-blind, randomized clinical studies with rosiglitazone. Pharmacoepidemiol Drug Saf. 2008 Aug;17(8):769-81.

[5] Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med*. 351:1106-1118, 2004.

[6] Richter B, Bandiera-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes. Cochrane Database System Rev 2007 Jul 18; (3):CD006063.

[7] Richter B, Bandiera-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes. Cochrane Database Syst Rev 2007 Oct 18; (4):CD006060

[8] Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32(1):193–203.

relative risk of 40% may seem like a modest signal from an epidemiological point of view, the public health burden of this level of risk elevation is substantial, given the high background rate (about 2- 4% per year) of myocardial infarction in diabetics. Given this range of background rate of myocardial infarction and observed relative risk, the absolute risk would be in the range of 0.8-1.6% - i.e., 0.8-1.6% of rosiglitazone-treated patients would experience a myocardial infarction due to rosiglitazone treatment. In other words, as many as one in 60 patients treated with rosiglitazone would experience a myocardial infarction as a result of rosiglitazone treatment.[9]

To date, there have been no completed large randomized trials which directly compare cardiovascular endpoints with rosiglitazone versus pioglitazone; however, there are several recently published observational studies which directly compare these two drugs with regard to cardiovascular risk. This review seeks to identify all published observational studies of adequate quality that may be relevant to this research question.

2 OBJECTIVES

The goal of this review is to evaluate published controlled epidemiologic studies designed to quantify cardiovascular risk(s) with rosiglitazone and/or pioglitazone, especially studies which directly compare cardiovascular endpoints for rosiglitazone versus pioglitazone.

3 METHODS

3.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

3.1.1 Types of studies

The review will include published controlled epidemiologic studies with a cohort or case-control design for which a full manuscript is available. Studies available as an abstract only will not be included.

Cross-sectional studies, case-series, and studies based on a single institution's experience will be excluded. Experimental and nonclinical studies will be excluded.

3.1.2 Types of data

The review will include observational studies of cardiovascular endpoints in patients treated with rosiglitazone or pioglitazone. Individual patient-level data will not be requested or used for this review.

3.1.3 Types of outcome measures

This review will describe the magnitude and direction of estimates of effect (e.g. relative risk, odds ratios, hazard ratios, risk differences) from results of observational studies with cardiovascular endpoints including (but not limited to): myocardial infarction, acute coronary syndrome, coronary revascularization, cardiovascular mortality, total mortality, heart failure, or stroke.

If applicable, the review may also include composite endpoints comprising some or all of these individual cardiovascular outcomes.

[9] Dal Pan, G. NDA 21-071/S-022; a) Office Director Memorandum b) Response to Request for Consultation from Office of Regulatory Policy Regarding Citizen Petition (Docket FDA 2008-P-0580). Review date October 23, 2009.

3.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

3.2.1 Time period

Searches of electronic databases will be conducted to cover the time period up to March 30, 2010.

3.2.2 Electronic database searches

We will use the following sources for the identification of studies:

- PubMed
- EMBASE
- Web of Science
- The Cochrane Library

The search strategy and syntax used for PubMed is described in Appendix 1. The same search strategy with slight adaptations appropriate to each database will be used for EMBASE, Web of Science, and the Cochrane Library.

The search terms will be compiled from the names of individual drugs, the therapeutic class, cardiovascular endpoint terms, and study design terms.

Two independent electronic database searches will be conducted by two individuals, one epidemiologist and one FDA Bioscience librarian. Search results from the two separate searches will be combined for the review.

Searches will be repeated using additional search terms identified from articles considered relevant to the review, if necessary. Searches will be limited to publications in English language only.

Reviewers will conduct additional hand searches from reference lists, review articles, peer-reviewed journals, and conference proceedings as necessary.

3.3 DATA COLLECTION AND ANALYSIS

3.3.1 Selection of studies

Assessment of identified abstracts will be performed independently by two reviewers from the Division of Epidemiology, with resolution of any discrepancies by a third reviewer (a senior medical epidemiologist).

While desirable to conduct the study selection process in a blinded fashion, it is not feasible for this current project; however, the selection of studies will be conducted in a fully transparent fashion, with complete documentation of reasons for study exclusion.

Studies will be eligible for inclusion if they are controlled (case-control or cohort design), and report on cardiovascular risks associated with the use in population settings of rosiglitazone or pioglitazone.

Reasons for exclusion of abstracts will be identified by the reviewers and tabulated, based on the following categories:

- Duplicate studies
- Not relevant to study questions
- No targeted drugs (rosiglitazone and/or pioglitazone)

- Not a targeted study design (i.e. cohort or case-control)
- Review
- Meta-analysis of RCTs only
- Case report/case series
- Randomized or uncontrolled clinical trial
- No prespecified cardiovascular endpoint
- Full article not available
- Targeted drugs combined into single TZD treatment group (separate analysis of rosiglitazone and/or pioglitazone not available)
- No comparison group
- Not a population-based epidemiological study

Individual studies may meet multiple criteria for exclusion.

3.3.2 Data extraction and management

Data extraction will be performed by an epidemiologist (co-author) independently. Results will be checked for accuracy by another epidemiologist (co-author). Discrepancies and questions will be resolved by a consensus process with a third reviewer (a senior medical epidemiologist).

Study characteristics and results will be tabulated including the following:

- Study Design
- Source/ Funding
- Setting
- Population Details
- Duration
- Exposure/ Comparison
- Drug Prescription Restriction (e.g. formulary restrictions)
- Covariates (e.g. baseline renal dysfunction, Charlson co-morbidity index, etc)
- Statistical Analysis
- Cardiovascular Endpoints
- Results
- Limitations

3.3.3 Assessment of risk of bias in included studies

Two authors will assess each trial independently. Possible disagreement will be resolved by consensus, or with consultation of a third reviewer in case of disagreement. The Newcastle Ottawa scale[10] (see Appendices 2 and 3) will be used for this review as a measure of study quality.

[10] Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester (UK). John Wiley & Sons, 2008.

3.3.4 Data synthesis

The summary of the systematic review will be qualitative. The totality of evidence will be summarized using scientific judgment. No quantitative meta-analysis to produce a consensus value is planned. Summary results of cardiovascular endpoints for the individual studies will be displayed using tables and forest plots.

The primary summary measure for the individual studies will be the odds ratio (OR) or relative risk (RR) and associated 95% confidence interval (CI), when available. For studies of rosiglitazone versus other treatments, the OR or RR will be expressed as the OR or RR of rosiglitazone versus the comparator treatment. For studies of pioglitazone versus other treatments (not including rosiglitazone), the OR or RR will be expressed as the OR or RR of pioglitazone versus the comparator treatment. When the study provides the reciprocal of these, the OR or RR and 95% CI will be converted by taking the reciprocals.

The final selected studies will be reviewed by a statistician to summarize and assess the statistical methodology. No re-analysis of the individual study data will be performed.

4 APPENDICES

4.1 APPENDIX 1: SEARCH TERMS AND STRATEGIES

Search terms:

1. Drug terms:

    Rosiglitazone OR Avandia OR pioglitazone OR Actos OR Thiazolidinedione OR Thiazolidinediones OR TZD OR TZDs

2. Study design terms:

    Cohort OR case control OR case-control OR observational OR epidemiologic OR retrospective OR meta analysis OR meta-analysis OR meta analyses OR meta-analyses

3. Cardiovascular endpoint terms:

    Cardiovascular OR cardiac OR coronary OR ischemic OR ischemia OR myocardial OR revascularization OR heart OR CVD OR CAD OR IHD OR HF OR CHF OR hospital OR mortality OR death OR stroke OR cerebrovascular accident OR CVA OR cerebral hemorrhage OR subarachnoid hemorrhage OR cerebral thrombosis OR cerebral infarction OR brain infarction OR cerebral infarct

4. 1 AND 2 AND 3

5. Limit 4 to English language

4.2 APPENDIX 2: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (CASE CONTROL STUDIES)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

a) yes, with independent validation [11] ✵

b) yes, e.g., record linkage or based on self reports

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases ✵

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls[12] ✵

b) hospital controls

c) no description

4) Definition of Controls

a) no history of disease (endpoint) [13] ✵

b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for _____[14]_____ (Select the most important factor.) ✵

[11] Either validation of outcome codes in the current study, or previous validation of the same codes in the same type of data source, will qualify for a star.

[12] If both cases and controls are drawn from a population of insured persons who may or may not have been admitted to hospital a star can be given.

[13] If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. (per NOS coding manual)

[14] Age and gender

b) study controls for any additional factor [15] ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure

a) secure record (e.g., surgical records)[16] ✵

b) structured interview where blind to case/control status ✵

c) interview not blinded to case/control status

d) written self report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes ✵

b) no

3) Non-Response rate

a) same rate for both groups [17] ✵

b) non respondents described

c) rate different and no designation

[15] Other cardiovascular risk factors

[16] Administrative or computer pharmacy records will qualify for a star

[17] If study design precludes the possibility of differential non-response, a star will be given

4.3 APPENDIX 3: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (COHORT STUDIES)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____[18]_____ (describe) in the community ✵

b) somewhat representative of the average _____ in the community ✵

c) selected group of users (e.g., nurses, volunteers)

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ✵

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (e.g., surgical records)[19] ✵

b) structured interview ✵

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes [20] ✵

b) no

[18] Refers to users of rosiglitazone or pioglitazone; studies limited to elderly or sicker patients will also qualify for a star as "somewhat representative." Community in this context refers to the study population.

[19] Administrative claims or electronic medical records will qualify for a star

[20] If new (not necessarily first) occurrence of outcome of interest is being studied in exposed patients, then unexposed patients with previous occurrences of outcome of interest should not be excluded to qualify for a star.

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for __[21]____ (select the most important factor) ✸

b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.) [22]

Outcome

1) Assessment of outcome

a) independent blind assessment ✸

b) record linkage [23] ✸

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest)[24] ✸

b) no

3) Adequacy of follow up of cohorts [25]

a) complete follow up - all subjects accounted for [26] ✸

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

[21] Age and gender

[22] Other cardiovascular risk factors

[23] Validation of outcome codes in the current study, or previous validation of the same codes in the same type of data source (in a previously published study), will qualify for a star.

[24] Three (3) months or longer follow up period will qualify for a star

[25] It is anticipated that observational epidemiologic studies using claims data or electronic medical records will generally not have differential follow-up for outcome ascertainment between exposed and unexposed groups, and will qualify for a star.

[26] If censoring criteria are specified and all patients are accounted for a star can be given

8.3 STATISTICAL REVIEW

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

POSTMARKET REVIEW

NDA Number:	21071 (Avandia), 21073 (Actos)
Drug Name:	Avandia (rosiglitazone maleate) and Actos (pioglitazone)
Indication(s):	Treatment of Type 2 Diabetes Mellitus
Sponsor:	GlaxoSmithKline (Avandia) and Takeda (Actos)
Date(s):	April 23, 2013 (review date)
Biometrics Division:	Division of Biometrics 7
Statistical Reviewer:	John Stephen Yap, PhD (DB7)
Concurring Reviewers:	Mark Levenson, PhD (Deputy Director, DB7)
Study Division:	Division of Epidemiology I, Office of Surveillance and Epidemiology
Study Team:	Kate Gelperin, MD, MPH; Esther Zhou, MD, PhD; Tarek Hammad, MD, PhD, MSc, MS
Project Manager:	Margarita Tossa

Keywords: Thiazolidinedione, TZD, Avandia, Actos, Rosiglitazone, Pioglitazone, Diabetes, Observational Study, Systematic Review

I. Introduction

A. Background

Avandia (rosiglitazone maleate) was originally approved in 1999 for the treatment of patients with type 2 diabetes mellitus (DM). Joint meetings of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Committees were held in 2007 and 2010 to assess the cardiovascular (CV) safety of Avandia. After the 2010 AC meeting, the FDA restricted the distribution of Avandia.

In April 2010, the Office of Surveillance and Epidemiology (OSE) requested the Division of Biometrics 7 (DB7) in the Office of Biostatistics (OB) to conduct an independent statistical review of the methodology described in each of 21 published observational studies that evaluated cardiovascular risks associated with thiazolidinediones (TZDs) (the class of drugs that includes Avandia and Actos) in patients with DM. The 21 studies were identified by OSE following a systematic review study protocol. The findings in the statistical review were referenced in a final OSE systematic review that was presented at the 2010 AC meeting.

Another AC meeting for Avandia is scheduled on June 5-6, 2013. The focus of the meeting will be the readjudication of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial. However, evidences presented at the 2010 AC will be reviewed and new evidences available after the 2010 AC will be evaluated. Among the new evidences are from published observational studies that were not available at the time of the 2010 OSE systematic review.

B. Scope of Statistics Review

This review will cover 7 published observational studies that evaluated CV risks associated with TZDs that were not available for the 2010 statistical review. Six of the 7 publications were identified in a literature search by Dr. Patricia Bright of the Division of Epidemiology I in OSE. Dr. Bright's literature search initially identified 13 publications. This number was reduced to 6 after the publications were subjected to the same inclusion/exclusion criteria that were used in the 2010 OSE systematic review. In summary, the reasons for inclusion/exclusion were: no appropriate comparator (1), meta-analysis of observational studies (1), spontaneous reports (2), randomized clinical trials (2), and study sample size was too small (1). See the 2013 OSE systematic review for more details regarding the study selection. The 7th publication is by Graham et al. (2010). Graham et al. (2010) was not included in 2010 OSE systematic review but was presented at the 2010 AC meeting.

This review will summarize and comment on the statistical methodology described in each of the 7 selected observational studies. An assessment or interpretation of individual study results and conclusions will not be included. However, this review will include a tabulation of the primary numerical results in each of the 7 studies, which will be used to create tabular and graphical summaries for the background package for the June 2013 AC.

Only published manuscripts were provided and no subject-level data were available for this review. From hereon, Avandia will be referred to as rosi and Actos will be referred to as pio.

II. Summary of Studies

A. Overview of Studies

Table 1 summarizes the studies included in this review.

Outcomes Evaluated

All 7 studies evaluated a subset of the following outcomes:

- acute myocardial infarction (AMI)
- stroke
- coronary revascularization (CRV)
- congestive heart failure (CHF)
- angina
- cerebral vascular accident (CVA)
- acute coronary syndrome (ACS)
- heart failure
- death or all-cause mortality (ACM)

All studies except one ([2]) studied ACM. Studies that evaluated cardiovascular (CV) outcomes used International Classification of Diseases version 9 (ICD-9) codes ([2, 4-7]) or the United Kingdom (UK) General Practice Research Database (GPRD) coding system ([3]). Studies that evaluated death used the National Death Index (NDI) ([5, 7]), GPRD coding system ([3]), Macabi Healthcare Services (Israel) coding system ([4]), or the Social Security Master Beneficiary Record Database ([6]). One study ([1]) did not describe how CV or death outcomes were assessed.

Antidiabetic Drugs Evaluated

All studies except one ([4]) evaluated both rosi and pio. Study [4] evaluated rosi and metformin. Study [3] evaluated insulin, metformin, and sulfonylurea in addition to rosi and pio.

Data Source

Table 2 shows a summary of the databases used in the 7 publications. Three of the 7 studies ([5-7]) used national databases in the United States. Other studies used databases in Israel ([4]), Taiwan ([2]), and United Kingdom ([1, 3]).

Table 1: Summary of Observational Studies

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Confounding Adjustment	Comparison Groups
[1] Tannen et al., 2012	Stroke, AMI, CRV, CHF; Death	Rosi, Pio	The Health Improvement Network Database (THIN) (UK)	12/1/2000-6/1/2008	709 (Pio) and 2,001 (Rosi) in replication studies; 3,844 (Pio), and 10,862 (Rosi) in expanded studies	Type 2 DM patients (by prescription) ages 35-75 years; with and without pre-existing ischemic CV diseases.	• Cox PH model • PS (stratification) • PERR adjustment	Cox model used in each PS quintile and combined into overall estimate; also used PERR adj.	Combo
[2] Chou et al., 2011	MI, CHF, Angina, CVA (ICD-9 codes)	Rosi, Pio	Longitudinal Health Insurance Database 2005 (Taiwan)	1/1/1998-12/31/2006	6,048 (Rosi); 1,677 (Pio)	Type 2 DM Taiwanese patients (by prescription and ICD-9 diagnosis codes).	Cox PH model	Controlled for multiple variables in Cox model.	Combo
[3] Gallagher et al., 2011	ACS, stroke, heart failure; ACM (including cause of death)	Rosi, Pio, Insulin, Metformin, Sulphonylurea	General Practice Research Database (GPRD) (UK)	Not stated (but covers the year 2007)	22,636 (Rosi); 18,953 (Pio); 121,637 (Metformin); 76,863 (Sulphonylurea); 26,458 (Insulin)	Type 2 DM patients age 40 years and over (from the UK GPRD).	• Poisson regression • Kaplan-Meier	Controlled for multiple variables in regression model.	Unclear (possibly combo)
[4] Loebstein et al., 2011	AMI, ACS, CRV, CHF (ICD-9 codes); ACM	Rosi, Metformin	Macabi Healthcare Services (MHS) (Israel)	1/1/2000-6/30/2007	745 (Rosi); 2,753 (Rosi-Metformin); 11,938 (Metformin)	Patients with American Diabetes Association defined criteria for diabetes (from Israel MHS); purchased Rosi, Metformin	Cox PH model	Controlled for multiple variables in Cox model.	Combo
[5] Bilik et al., 2010	NMI, CRV, Nonfatal Stroke (ICD-9 codes); CV Mortality, ACM (NDI)	Rosi, Pio	TRIAD (10 managed care health plans, 68 provider groups) (US)	1999-2003	773 (Rosi); 711 (Pio)	Type 2 diabetes patients (by prescription); exclude age at diagnosis <30 yrs and treatment with insulin only	Cox PH model	Controlled for multiple variables in Cox model.	Combo (some patients used insulin)
[6] Graham et al., 2010	AMI, Stroke, Heart failure (ICD-9 codes); ACM (SSMBR database)	Rosi, Pio	Medicare (US)	7/2006-6/2009	67,593 (Rosi); 159,978 (Pio)	TZD-exposed patients 65 yrs and older.	• Cox PH model • Kaplan-Meier	Controlled for multiple variables in Cox model.	Combo
[7] Wertz et al., 2010	AMI, AHF (ICD-9 codes); Death (NDI)	Rosi, Pio	Healthcore Integrated Research Database (HIRD) (Wellpoint) (US)	1/1/2001-12/31/2005	14,469 PS-matched Rosi and Pio patients	Patients ≥18 years of age, newly initiated on Rosi or Pio	• Cox PH model • PS (matching)	Included Cox model analysis of PS-matched sets of patients.	Unclear (possibly combo)

AMI=acute myocardial infarction; CHF=congestive heart failure; MI=myocardial infarction; CVA=cerebral vascular accident; ACM=all-cause mortality; ACS= acute coronary syndrome; CRV=coronary revascularization; NMI=nonfatal MI; CV=cardiovascular; AHF=acute heart failure; NDI=National Death Index; PS=propensity score; SSMBR= Social Security Master Beneficiary Record

Table 2: Summary of Study Databases

Country of Study	Database (Publication Number)
1. United States (National Databases)	Translating Research Into Action for Diabetes (TRIAD) ([5]); Medicare ([6]); Healthcore Integrated Research Database – Wellpoint ([7])
2. Israel	Macabi Healthcare Services ([4])
3. Taiwan	Longitudinal Health Insurance Database 2005 ([2])
4. United Kingdom	General Practitioner Research Database ([3]); The Health Information Network in United Kingdom ([1])

Reviewer's Comments: In the 2010 OSE systematic review, one study used the The Health Improvement Network Database (THIN) database and two studies used the General Practice Research Database (GPRD). These databases are from the United Kingdom. In this review, study [1] used the THIN database while study [3] used the GPRD. One study in the 2010 review also used the National Health Insurance (NHI) database in Taiwan. The same database was used in study [2] in this review. The studies in the 2010 OSE systematic review and the studies in the current review that use the same database overlap in the years exposure data were obtained as shown in Table 3.

Table 3: Overlap in Study Databases from 2010 and 2013 Systematic Reviews

	Overlap in Exposure Period (Calendar Years)	
Database	**2010 Review**	**2013 Review**
UK GPRD	Azoulay et al., 2009: 1988-2008	[3] Gallagher et al., 2011: not stated but covers the year 2007
	Tzoulaki et al., 2009: 1990-2005	
UK THIN	Margolis et al., 2008: 2002-2006	[1] Tannen et al., 2012: 2000-2008
Taiwan NHI	Hsiao et al., 2009: 2001-2005	[2] Chou et al., 2001: 1998-2006

Exposure Period

The study exposure periods ranged from 4-8 years:

- 4 years: [6]
- 5 years: [5], [7]
- 8 years: [1], [2], [4]
- Unknown: [3]

The earliest study start date was 1/1/1998 ([2]) which was a few months earlier than the marketing approval dates of rosi (5/25/1999) and pio (7/15/1999) in the United States. The latest study start date was 7/2006 ([6]).

The study end dates were mostly prior to the 2007 AC meeting except for [1] (12/1/2000-6/1/2008) and [6] (7/2006-6/2009). Study [3] did not specify an exposure period although it indicated that the year 2007 was within the study's exposure period.

Reviewer's Comment: The exposure periods for studies [1] and [6] include the date of the 2007 AC meeting that discussed the CV risks of rosi exposure. The outcome of the 2007 AC meeting may have led to a decrease in the number of rosi patients and/or an increase

in the number of pio patients in these two studies. Additionally, the characteristics of the patients taking these drugs may have changed after the 2007 AC meeting.

Number of Exposed/Unexposed

The numbers of exposed/unexposed patients ranged from small ([5]), moderate ([1-2, 4]), to large ([3, 6-7]) (see Table 1).

Reviewer's Comment: Study [5] may be underpowered to detect a clinically meaningful risk.

Population Details

The study populations were patients with type 2 DM. Generally, the patients were identified by their record of antidiabetes prescriptions in the databases. One study used ICD-9 diagnosis codes in addition to an antidiabetic prescription to identify diabetes patients ([2]). There were no age restrictions in two studies ([2, 4]) while other studies had the following age restrictions: 35-75 ([1]), ≥18 years ([7]), ≥30 years ([5]), ≥40 years ([3]), and ≥65 years ([6]). One study ([1]) performed analyses on patients with and without pre-existing ischemic CV diseases. Study populations varied by locations: US ([5-7]), Israel ([4]), Taiwan ([2]), and UK ([1, 3]).

Statistical Methods

All 7 studies, except [3], performed time-to-event analyses using the Cox proportional hazards (PH) model. Two of the studies that used the Cox PH model also used propensity scores (PS) to balance covariates between treatment groups: study [1] used PS stratification while [7] used PS matching. Study [3] used Poisson regression. The Cox PH model and Poisson regression estimate risk in the form of hazard ratio (HR) and relative rate, respectively. The statistical models in all studies included adjustments for multiple variables or covariates.

Other statistical methods that studies used include the Kaplan-Meier ([3, 6]) and prior event rate ratio ("PERR") adjustment for reducing bias from unmeasured confounders ([1]).

Confounding Adjustment

All studies included methods to address confounding. The typical approach was to include multiple variables that were potentially confounders into the Cox PH or Poisson regression models ([2-6]). Other studies ([1, 7]) used PS. Study [1] stratified patients into PS quintiles and used the Cox model in each quintile; an overall estimate of the hazard ratio was obtained by combining estimates from each quintile. Study [7] used PS matching and the Cox model was applied to the PS-matched sets of patients. Study [1] also performed analyses using the PERR adjustment to address unmeasured confounding.

Table 4: Summary of Study Drug Comparisons

Studies	Comparisons	Comments
[1] Tannen et al., 2012	(1) Rosi/Pio vs Control; (2) Rosi vs Pio	Some patients received other antidiabetes medication.
[2] Chou et al., 2011	(1) Rosi vs Pio	Rosi and pio were add-on antidiabetes medications.
[3] Gallagher et al., 2011	(1) Insulin, Sulphonylurea, TZD, Metformin (past exposures) vs Controls; (2) Insulin, Sulphonylurea, TZD (past exposures) vs past exposure to Metformin; (3) Rosi vs Pio (current exposures); (4) Rosi vs Pio (current exposures, stratified by age, co-prescribing of insulin, and calendar time); (5) Rosi vs Pio (mortality)	Study patients may have received other antidiabetes medications but it is not clear in the publication.
[4] Loebstein et al., 2011	(1) Rosi mono vs Rosi-Metformin combo (2) Rosi mono vs Metformin mono (3) Rosi-Metformin combo vs Metformin mono	Rosi mono was not strictly monotherapy but an overlap of <10% between the exposure period of the rosi and metformin. Some patients received insulin or sulphonylurea.
[5] Bilik et al., 2010	(1) Rosi vs Pio	Some patients used insulin.
[6] Graham et al., 2010	(1) Rosi vs Pio	Some patients received other antidiabetes medication.
[7] Wertz et al., 2010	(1) Rosi vs Pio	Study patients may have received other antidiabetes medications but it is not clear in the publication.

mono=monotherapy; combo=combination therapy

Comparison Groups

The comparisons differed among the studies. Table 4 summarizes the comparisons that were performed in each study. Studies [2, 5-7] compared rosi versus pio patients only. Other studies compared rosi versus pio in addition to comparing rosi/pio versus controls ([1, 3]) or rosi/pio versus past exposure to metformin ([3]). One study ([4]) compared rosi versus metformin only as either mono- or combination therapy. The study comparison groups were also classified in this review as to whether the antidiabetic drugs were administered alone (monotherapy) or in combination with (or add-on to) other antidiabetic drugs (combo). The 7 studies were classified as follows:

- Combo: [1, 2, 4, 5, 6]
- Unclear (possibly combo): [3, 7]

B. Review of Studies

The following is a detailed summary of the statistical review of each of the 7 observational studies. The studies are arranged according to the year of publication (starting with the most recent) and by last name of the first author (a-z). Each publication review includes a brief summary of the study followed by comments by the statistical reviewer.

1. **Tannen R, Xie D, Wang X, Menggang Y, Weiner MG. A new "Comparative Effectiveness" assessment strategy using the THIN database: Comparison of the cardiac complications of pioglitazone and rosiglitazone. *Pharmacoepidemio Drug Saf* 2012 Oct 16. doi: 10.1002/pds.3360. [Epub ahead of print]**

This was a retrospective observational study with a cohort design of type 2 DM patients using the The Health Improvement Network (THIN) database in the United Kingdom. THIN is a large database in the United Kingdom with approximately 7.5 million patient records. The study included replication and expanded studies (Figure 1). The replication studies used the same study design attributes of the Proactive trial (pio vs placebo) including study and enrollment duration, patient age (35 - 75 years), and inclusion/exclusion criteria. Like the Proactive trial, patients in the replication studies had ischemic CV disease. The expanded studies were similar to the replication studies except that patients were not required to have pre-existing ischemic CV diseases.

The replication and expanded studies included rosi- and pio- exposed groups of patients. These patients were initially selected based on their record of rosi and pio prescriptions during the recruitment period. Patients in each group were matched to unexposed patients (1 rosi/pio patient: 3 control patients) in the THIN database based on age, sex, and study start date. Within the replication and expanded studies, the rosi and pio exposure groups were each compared to their matched controls, and also with each other.

The study included simulated “intention-to-treat” and “as-treated” time-to-event analyses. In the “intention-to-treat” analyses, patients in the exposed and unexposed groups continued until death, loss to follow-up, or the study end date; a stop point occurred if one TZD treatment was switched to another. In the “as-treated” analyses,

patients in the exposed groups "…reached a stop point 90 days after the end of the last TZD prescription duration, and the unexposed group if TZD treatment was initiated." Time-to-event analyses were performed using the Cox PH model. The study also used PS quintiles as strata in the Cox model and the "PERR" adjustment technique, an adjustment method used to reduce bias from unmeasured confounders.

The study adjusted for various baseline confounders in the Cox PH model including histories of pre-existing ischemic CV diseases. Imputation for missing confounders was not performed because the percentage of missing data (systolic blood pressure, smoking, and/or body mass index) was less than 5%.

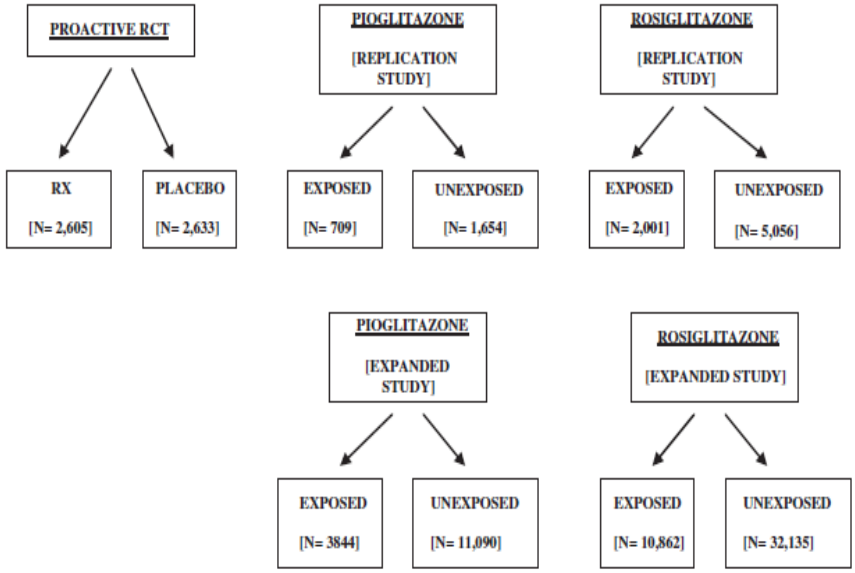

Figure 1. Overall study design. The overall study design, along with the number of subjects in each cohort, and in the Proactive RCT is shown
Figure 1 copied from page 2 of publication.

Reviewer's Comments:

- ***The study states that validation studies have been published about the THIN database.***
- ***Patients in the rosi and pio groups were exposed to other antidiabetic drugs.***
- ***The authors did not describe the study outcomes and how these outcomes were assessed e.g. via ICD-9 codes. However, the THIN database use Read codes.***
- ***The publication states that, in the "intention-to-treat" analysis, a stop point occurred if TZD treatment was switched from rosi to pio or vice versa. However, under the clinical trial meaning of "intention-to-treat", a switch from rosi to pio or vice versa is not considered a stop point. This definition appears to be consistent with an "as-treated" analysis instead.***
- ***The publication is unclear in its definition for "as-treated" analysis. In the reviewer's understanding of this definition, a stop point occurred 90 days after the last TZD prescription for patients in the exposed (to TZD) group or 90 days after the last non-TZD prescription for patients in the unexposed (to TZD) group who switched to TZDs. Under the strict meaning of "as-treated", the stop point should***

occur after zero (0) instead of 90 days; otherwise, this analysis more closely resembles an "intention-to-treat" analysis.

- ***The study did not state whether the PH assumption of the Cox model was satisfied or not.***
- ***The study period was from 12/1/2000 to 6/1/2008. This study period covers the 2007 AC meeting for Rosi.***

2. Chou CC, Chen WL, Kao TW, Chang YW, Loh CH, Wang CC. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. *Clin Ther* 2011; 33(12):1904-13.

This was a retrospective observational study of Taiwanese patients who were prescribed antihyperglycemic agents and diagnosed with diabetes (ICD-9 CM code 250.XX) from January 1, 1998 through December 31, 2006. Patients were required to have had diabetes medication for > 120 days within 180 days after the indexed date of inclusion and treated with only one kind of TZD (rosi or pio). Patients who switched medications were excluded. Medical data, including prescription medications were obtained from the Longitudinal Health Insurance Database 2005 of Taiwan which contains original claims data of 1 million beneficiaries which were sampled from the year 2005 Registry for Beneficiaries of the National Health Insurance Database.

The study focused on four CV events: MI, angina, CHF, and CVA. MI was defined by ICD-9 CM diagnosis codes (410, 411, and 413) during hospitalization or emergency contact. CHF was defined by ICD-9 CM diagnosis code (428) on outpatient or emergency contact and prescription of diuretics. Angina pectoris was defined by ICD-9 CM diagnosis code (413) and at least 3 emergency managements. CVA was defined by ICD-9 CM diagnosis codes (430-432, 434-437) and computer tomography or magnetic resonance image in the same record.

Comparisons were made between groups of patients exposed to rosi and pio. The study performed survival analyses including Cox regression. The study adjusted for multiple variables in the Cox model.

Reviewer's Comments:

- ***In the time-to-event analyses, the study did not define the event(s) and censoring.***
- ***The rosi and pio patients received other antidiabetic medications (e.g. metformin or sulfonylurea).***
- ***Univariate analyses showed that gender and stratified age were not statistically significantly different between the rosi and pio groups. It appears that in adjusted analyses, gender was excluded; stratified age was included but the subcategory of patients <40 years old was excluded. The authors did not provide any reason for these exclusions. The subcategory of patients <40 years old comprises 3.5% and 4.5% of the rosi and pio groups, respectively.***
- ***The study did not state whether the PH assumption of the Cox model was satisfied or not.***
- ***The study did not describe how missing data were handled.***

3. **Gallagher AM, Smeeth L, Seabroke S, Leufkens H, van Staa TP. Risk of death and cardiovascular outcomes with thiazolidinediones: A study with the general practice research database and secondary care data. *PLoS ONE* 2011; 6(12):e28157 [pages1-9].**

This was a retrospective observational study of the risk of death and CV outcomes from TZD exposure using the General Practice Research Database (GPRD) in the United Kingdom. The primary study objective was to describe the likely extent of confounding in evaluating the risks of CV events and mortality in patients using diabetes medication.

The study included an exposed cohort consisting of adults 40 years and older with a prescription for insulin or oral antidiabetic drugs (OAD) at least one year after start of data collection. Patients with type I diabetes were excluded. The index date was the first prescription for insulin or OAD one year after the start of GPRD data collection. The follow-up period was from the index date until censor date defined as transfer out of practice, last collection from the practice, or death.

Exposed patients were matched to control patients by age (within 5 years), sex, practice, and index date. The medications of interest in this study include TZD (rosiglitazone and pioglitazone), insulins, metformin, and sulphonylurea. Inception cohorts were identified for each class of diabetes medication. Two separate inception cohorts were also created for rosi and pio. The publication stated that, "Patients prescribed multi-constituent preparations were included in multiple classes of diabetes medication." Patients could belong to multiple inception cohorts and in comparisons between different diabetes medications, patients were censored at the start of treatment with medication of the reference group. The period of follow-up was divided into (a) current (from date of first prescription up to 3 months), (b) recent (the period from 3 to 12 months after the most recent prescription), and (c) past (the period after 12 months after the most recent prescription) exposure. Patients could move between exposure categories over time.

The outcomes of interest were death due to any cause, cause of death, acute coronary syndrome (ACS), stroke, and heart failure. Data for these outcomes were taken from the GPRD, death certificates, or Hospital Episode Statistics (HES).

There were four sets of analyses performed: (1) Comparison of various outcome incidences between past exposure for exposed versus matched control patients (using Poisson regression), (2) Comparison of outcome rates during current use of different diabetes medications (restricted to the types of diabetes medications that did not have major differences in risk during past use; stratified by age, co-prescribing of insulin and calendar time [before and after 2007]), (3) Description of the pattern of risks over duration of treatment for current exposure to diabetes medication, and (4) Estimation of the cumulative incidence over time with current use of various diabetes medications.

The main study comparisons were (1) insulin, sulphonylurea, TZD, metformin past exposures vs controls, (2) insulin, sulphonylurea, TZD past exposures vs metformin past exposure, (3) rosi vs pio current exposures (also stratified by age, co-prescribing of insulin, and calendar time, and (4) rosi vs pio mortality.

Time-to-event analyses were also performed via Kaplan-Meier. Regression models were adjusted for various covariates. Missing values for alcohol use, smoking status, and body mass index were included as separate categories in the statistical models.

Reviewer's Comments:

- ***Control patients were not clearly defined in the study.***
- ***The comparisons between different inception cohorts could be biased because, as stated in the study, patients could belong to multiple inception cohorts.***
- ***The study performed a comparison between exposed diabetic patients versus unexposed control patients without diabetes (analysis (1) above). A comparison between exposed diabetes patients versus unexposed diabetes patients would be a more appropriate comparison.***
- ***The comparison for current exposure may be inadequate to assess the effects of diabetes medications because, as defined above, current exposure is only a three month period. Additionally, patients may have been previously exposed to multiple antidiabetic medications or had concomitant antidiabetic exposures.***
- ***A potential issue when using Poisson regression is overdispersion where the variance of the data is much larger than the mean. The study did not state whether the Poisson model was assessed for overdispersion.***
- ***The study stated that missing data (for alcohol use, smoking status, and body mass index) were classified into a subcategory for the respective covariates in the statistical model. It is unclear how much missing data there was.***

4. **Loebstein R, Dushinat M, Vesterman-Landes J, Silverman B, Friedman N, Katzir, I, Kurnik D, Lomnicky Y, Kokia E, Halkin H. Database evaluation of long-term rosiglitazone treatment on cardiovascular outcomes in patients with Type 2 diabetes.** ***J Clin Pharmacol*** **2011; 51:173-180.**

This was a retrospective observational study of adverse CV outcomes in type 2 diabetes patients who were exposed to rosi and metformin. Patient data were obtained from the Maccabi Healthcare Services (MHS), one of the four public health insurers in Israel. MHS offers comprehensive health coverage to approximately 1,800,000 people nationwide.

Study patients were selected from the Maccabi diabetes mellitus registry and satisfied criteria defined by the American Diabetes Association (fasting plasma glucose > 126 mg/dL or a casual plasma glucose concentration of at least 200 mg/dL). These patients also had a record of purchase of rosi and/or metformin for a period of at least 6 months (between January 1, 2000 and June 30, 2007) with a medication possession ratio (no. of daily doses dispensed over x days divided by x days) of at least 0.7 and no gaps in treatment longer than 3 months. There were three study comparison groups: (1) rosi alone (<10% overlap in rosi exposure with metformin), (2) rosi and metformin combined (>50% overlap in rosi exposure with metformin), and (3) metformin alone.

The study outcomes were AMI, ACS, need for coronary revascularization (either by coronary artery bypass graft or coronary angioplasty with or without stent implantation), CHF, and ACM. Patients with these outcomes were determined from new entries in the Maccabi Heart Registry or from hospital ICD-9 discharge diagnosis codes. Only outcomes that occurred at least 1 month after the first drug purchase until 1 month after drug discontinuation were considered in the analyses.

Time-to-event analyses were performed using the Cox PH model comparing the three study groups (with the metformin group as the reference).

Reviewer's Comments:

- ***Patients with >10% and <50% overlap in rosi exposure with metformin were excluded in the analyses.***
- ***The comparison groups were rosi, metformin, or a combination of both drugs. However, some of the patients in either group were also exposed to insulin or sulfonylurea.***
- ***The study abstract suggests that covariates were included in the statistical models for adjustment only when univariate analyses found them to be significantly different between comparison groups. A variable selection procedure that accounts for correlations among multiple variables may be more appropriate.***
- ***The results tables for each study outcome are labeled "logistic regression" although the study stated that the Cox PH model was used in the analyses.***
- ***The study did not state whether the PH assumption of the Cox model was satisfied or not.***
- ***The study did not describe how missing data were handled.***

5. **Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, Hsiao VC, Tseng CW, Mangione CM, Lasser NL, Crosson JC, Herman WH. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD).** ***Pharmacoepidemiol Drug Saf*** **2010; 19:715-21.**

This was a study that analyzed survey, medical record, administrative, and National Death Index (NDI) data from 1999 through 2003 from the Translating Research Into Action for Diabetes (TRIAD) study, a prospective observational study of diabetes care in managed care. TRIAD involved six research centers collaborating with 10 managed care health plans (HP) and 68 provider groups. Patients were enrolled from July 2000 until August 2001 and included patients who were at least 18 years old, not pregnant, community-dwelling, English or Spanish speaking, and continuously enrolled in the HP for at least 18 months prior to a baseline patient survey. The study involved medical record review at baseline, collection of HP data from 1999 through 2003, and death searches in the National Death Index (NDI) occurring through 2003. This study analyzed type 2 diabetes patients from TRIAD who had complete data, excluding those with age at diagnosis under 30 years and with treatment with insulin only.

HP administrative data was used to determine TZD exposure. Among the 10 HPs, 7 HPs had both TZD's (rosiglitazone and pioglitazone) on formulary.

Insulin treatment at baseline was assessed using patient surveys and medical record reviews. Subsequent insulin treatment was determined using administrative data.

The study ascertained non-fatal AMI, stroke, or percutaneous or surgical CV intervention from HP administrative data. These outcomes were ICD-9 diagnosis codes. Deaths and cause of death were ascertained from NDI.

The study compared patients who were exposed to rosi versus those exposed to pio. Time-to-event analyses were performed from the first TZD prescription until the occurrence of the first CV event or procedure. Patients with no CV event were censored at the earliest of: date of last TZD prescription + days supply + 90 days, the date the

patient disenrolled from the HP, the last date of service in the administrative data, or TRIAD's administrative cut-off date. The Cox proportional hazard model was used for these analyses. Hazard ratios and 95% CI's were reported. The authors stated that the proportional hazards assumption was tested with graphical display and by examination of correlations between the ranked failure time variable and the Schoenfeld residuals of the independent variables.

The Cox model was adjusted for a number of study variables. Missing values for age, sex, race/ethnicity, income, and smoking were <15% and were imputed using single imputation. Separate analyses were performed on patients from (1) all 10 HPs and (2) 7 HPs with both TZD's in the formulary.

Reviewer's Comments:

- ***It is unclear why patients with age at diagnosis under 30 years were excluded in this study when the TRIAD study enrolled patients who were at least 18 years old.***
- ***As stated above, analyses were performed on patients from all 10 HPs and on patients from 7 HPs with both TZD's in the formulary. Among the 3 HPs that did not have both TZD's in the formulary, 2 HPs had pio accounting for 99% of TZD prescriptions while 1 HP had rosi accounting for 100% of all TZD prescriptions. The analyses on the 10 HPs might be biased because of the imbalances in the number of prescriptions to rosi and pio in the 3 HPs. This may be the reason that the study included analyses of the 7 HPs only.***
- ***There were patients in the rosi and pio comparison groups who were also exposed to insulin at baseline or during the study. It is unclear whether these patients were also exposed to other antidiabetes drugs e.g. metformin or sulfonylurea.***

6. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304(4):411-418.

This was a retrospective observational cohort study of the risk of CV adverse events and death in patients 65 years and older who were exposed to rosi and pio. Prescription and other data were obtained from Medicare from July 2006 through June 2009. The study used a new-user inception cohort design where patients with at least 6 months of continuous Medicare Part D (for prescription drugs) enrollment and at least 12 months of continuous Parts A (for hospitalization expenses) and B (for outpatient medical care) enrollment prior to the date of their first TZD prescription were included. Patients who were not resident in a hospital or long-term care facility or receiving hospice care formed the rosi and pio cohorts. Baseline patient data were collected on chronic medical conditions and their medical treatment prescriptions.

The outcomes of interest were AMI, stroke, heart failure, and ACM. CV outcomes were assessed by ICD-9 hospital discharge diagnosis codes. ICD-9 codes in the first and second position were used for AMI while ICD-9 codes in the first position only were used for stroke and heart failure. ACM was determined using the Social Security Master Beneficiary Record database which provides the date but not the cause of death.

Study patients were followed-up from cohort entry until the earliest of: the occurrence of a study endpoint, >7 days gap in TZD exposure, a switch to another TZD treatment, a non-endpoint hospitalization, or end of study period (June 30, 2009). Events occurring within 14 days following a gap in continuous treatment (except for TZD switching or end of study period) or admission to hospital, were included in the analysis.

The study compared patients exposed to rosi to patients exposed to pio. Time-to-event analyses were performed using Kaplan-Meier and Cox PH models stratified by prior history of the CV endpoint and cancer. Hazard ratios and their 95% CIs were reported. The PH assumption in the Cox model was assessed using a test of weighted Schoenfeld residuals.

Preplanned sensitivity analyses were performed including no follow-up after a gap of TZD therapy and restriction of analyses to strata defined by baseline treatment with insulin, metformin, sulfonylureas, or statins.

Reviewer's Comments:

- ***The causes of patient deaths in the study are unknown because the Social Security Master Beneficiary Record database provides the date but not the cause of death.***
- ***The study did not describe how missing data were handled.***

7. Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. *Circ Cardiovasc Qual Outcomes* 2010; 3:538-45.

This was a retrospective observational cohort study of the risk of acute AMI, acute heart failure (AHF), or all-cause death among rosi- and pio-treated patients who were members of WellPoint health plans in California, Georgia, Virginia, and Missouri. Administrative medical/pharmacy data were obtained from the HealthCore Integrated Research Database (HIRD) and mortality data was obtained from the National Death Index (NDI) Plus database. Patients at least 18 years old with a new rosi or pio claim during the period from January 1, 2000 to December 31, 2005 were included in the study, regardless of their history of AMI or AHF.

Patients who did not have continuous health plan eligibility for at least 365 days before the first rosi or pio claim date (the index date), or had a preindex date pharmacy claim for insulin were excluded from the study. Patients were considered to be on continuous therapy if the period between prescription refills was less than 1.5 times the days supply of the preceeding TZD claim. Patients were excluded from the study if they were exposed to both rosiglitazone and pioglitazone during follow-up. Patients who switched medication within 60 days after discontinuing the first drug were censored after the first period of continuous therapy.

There were three analyses performed in the study:

Primary analysis: TZD exposure was measured from index date until the earliest of the end of study period (December 31, 2005), termination from health plan, or occurrence of AMI, AHF, or death.

Sensitivity Analyses:

1. Patients were followed from index date until end of continuous therapy plus 60 days; occurrence of an AMI, AHF, or death; or end of health plan enrollment, whichever occurred first.
2. Patients were followed from the index date until the end of continuous therapy; occurrence of AMI, AHF, or death; or end of health plan enrollment, whichever occurred first.

An additional analysis was performed to study the subpopulation of patients who were at least 65 years of age.

PS matching was used to control for measured potential confounders which included demographic/clinical variables that were identified in the 12-month preindex period. PS were obtained using logistic regression controlling for the measured potential confounders. Patients were matched in a 1:1 fashion using Parsons 1:1 greedy 4→1 digit matching algorithm. The quality of the match was determined by comparing baseline characteristics on the matched sample and standardized differences.

The study compared patients exposed to rosi to patients exposed to pio. The Cox PH model was used to evaluate the effects of exposure to rosi and pio on time to cardiovascular event (AMI, AHF) and mortality using all patients, patients age 65 years and over, and the PS-matched patients. The regression analyses using all patients and patients age 65 years and over were adjusted for relevant covariates.

Reviewer's Comments:

- ***The publication presented the endpoints for all propensity matched patients (approximately 80% of the total patient sample) but did not do so for the unmatched patients. However, Table 5 (copied from the publication, page 542) below shows that when all patients are included (matched or unmatched), the risks of the composite outcome under various analyses are not statistically significant.***
- ***PS matching was not used in the subsample of patients who were at least 65 years old because of the small sample, although there were no significant differences observed in baseline characteristics between treatment groups except index year.***
- ***The publication did not discuss whether the PH assumption of the Cox model was satisfied or not.***
- ***The study did not describe how missing data were handled.***
- ***The publication stated a few strengths or improvements of the current study compared to previous studies such as Gerritts et al. (2007), Winkelmayer et al. (2008), and Juurlink et al. (2009): (1) The use of PS matching to ensure similarity at baseline between groups (2) The use of NDI to improve the accuracy of the results by potentially capturing deaths that occurred outside the hospital (3) The mean duration of therapy was longer by a few months compared to previous studies (e.g. 3 months longer than Winkelmayer et al., 2008 and 6 months longer than Juurlink et al., 2009) and (4) The population studied was not limited to older patients.***
- ***The following limitations were cited in the publication: (1) Even when the database is large, the study's statistical power may be limited by the rarity of the events in the population and the ability to detect small differences in cohorts. Furthermore, because the study database encompasses a commercially-insured population, elderly patients and those with substantial chronic illness who are at highest risk***

are underrepresented relative to the overall US population. (2) The study could not assess the length of time patients had diabetes because the preindex period was only 1 year, although diabetes severity was accounted for in the multivariate model by identifying claims for diabetes-related complications. Furthermore, patients who used insulin before TZD use were excluded because this may imply the disease has progressed to become a confounding factor related to AMI. However, because only a small subset of patients had electronic laboratory values available, no laboratory values (HbA1c, glucose) were evaluated to assess degree of diabetes control. (3) There were unmeasured confounders (e.g. body mass index, exercise, family history of CV disease, aspirin use) that could have affected the results.

III. Additional Reviewer Comments

- ***The 7 studies did not explicitly state the study designs, i.e. whether they were cohort or case-control studies. However, all 7 studies appeared to be retrospective cohort studies based on the study description.***
- ***The studies do not state whether endpoints and analyses were pre-specified in study protocols.***
- ***Among the 6 studies that used the Cox PH model (all except [3]), only studies [5] and [6] checked the PH assumption.***
- ***Among the 6 studies that studied death (all except [2]), only study [3] studied the cause of death.***
- ***Two studies [3, 7] did not explicitly state whether the antidiabetes drugs were administered as monotherapies or combination therapies.***
- ***All studies, except ([2, 6-7]), discussed how missing data were handled.***
- ***None of the studies provided adjustments for multiple comparisons.***
- ***Study [1] was co-funded by Pfizer.***

IV. Summary of Numerical Study Results

Table 5: Summary of Numerical Results

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[1] Tannen et al., 2012	Replication Studies: 709 (Pio) vs 1,654 (Control)	Death	C: 0.82 (0.63, 1.08)	Intention-to-Treat Analysis C: 0.90 (0.67, 1.21); PS: 0.81 (0.61, 1.08); P: NR As-Treated Analysis: C: 0.61 (0.41, 0.91); PS: NR; P: NR	None
		Stroke	C: 0.70 (0.41, 1.18)	Intention-to-Treat Analysis C: 0.75 (0.43, 1.32); PS: 0.69 (0.39, 1.21); P: 0.75 (0.39, 1.34) As-Treated Analysis: C: 0.85 (0.45, 1.61); PS: NR; P: 0.84 (0.41, 1.57)	
		AMI	C: 1.00 (0.63, 1.57)	Intention-to-Treat Analysis C: 0.86 (0.53, 1.40); PS: 0.83 (0.51, 1.35); P: 0.88 (0.49, 1.42) As-Treated Analysis: C: 0.74 (0.42, 1.31); PS: NR; P: 0.76 (0.38, 1.30)	
		CRV	C: 1.14 (0.75, 1.71)	Intention-to-Treat Analysis C: 1.01 (0.65, 1.55); PS: 0.97 (0.63, 1.51); P: 1.20 (0.70, 2.04) As-Treated Analysis: C: 1.11 (0.69, 1.77); PS: NR; P: 1.37 (0.76, 2.34)	
		CHF	C: 1 31 (0.91, 1.87)	Intention-to-Treat Analysis C: 1.25 (0.85, 1.85); PS: 1.20 (0.81, 1.77); As-Treated Analysis: C: 1.50 (0.99, 2.28); PS: NR; P: NR	
	Replication Studies: 2,001 (Rosi) vs 5,056 (Control)	Death	C: 0.85 (0.73, 0.99)	Intention-to-Treat Analysis C: 0.93 (0.79, 1.10); PS: 0.87 (0.74, 1.03); P: NR As-Treated Analysis: C: 0.74 (0.60, 0.92); PS: NR; P: NR	None
		Stroke	C: 0.75 (0.55, 1.02)	Intention-to-Treat Analysis C: 0.80 (0.58, 1.12); PS: 0.71 (0.51, 0.99); P: 0.88 (0.59, 1.24) As-Treated Analysis: C: 0.67 (0.45, 1.00); PS: NR; P: 0.71 (0.44, 1.06)	
		AMI	C: 1.21 (0.95, 1.55)	Intention-to-Treat Analysis C: 1.18 (0.89, 1.55); PS: 1.20 (0.91, 1.57); P: 1.31 (0.94, 1.74) As-Treated Analysis: C: 1.06 (0.77, 1.45); PS: NR; P: 1.17 (0.83, 1.61)	
		CRV	C: 1.34 (1.07, 1.67)	Intention-to-Treat Analysis C: 1.19 (0.93, 1.52); PS: 1.25 (0.98, 1.60); P: 1.30 (0.97, 1.70) As-Treated Analysis: C: 1.09 (0.83, 1.44); PS: NR; P: 1.20 (0.87, 1.62)	
		CHF	C: 1 22 (0.97, 1.53)	Intention-to-Treat Analysis C: 1.25 (0.97, 1.60); PS: 1.21 (0.95, 1.56); P: NR As-Treated Analysis: C: 1.14 (0.85, 1.51); PS: NR; P: NR	

C=Cox PH model; PS=propensity score; P=PERR adjustment; NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[1] Tannen et al., 2012…continued	Replication Studies: 2,001 (Rosi) vs 709 (Pio)	Death	NR	Intention-to-Treat Analysis C: 1.23 (0.93, 1.61); PS: 1.14 (0.87, 1.49); P: NR As-Treated Analysis: C: 1.38 (0.92, 2.08); PS: NR; P: NR	None
		Stroke		Intention-to-Treat Analysis C: 1.12 (0.65, 1.92); PS: 1.09 (0.64, 1.87); P: 1.36 (0.75, 2.75) As-Treated Analysis: C: 0.89 (0.46, 1.72); PS: NR; P: 1.05 (0.53, 2.54)	
		AMI		Intention-to-Treat Analysis C: 1.26 (0.81, 1.96); PS: 1.27 (0.82, 1.96); P: 1.55 (0.98, 2.65) As-Treated Analysis: C: 1.40 (0.80, 2.44); PS: NR; P: 1.62 (0.53, 2.54)	
		CRV		Intention-to-Treat Analysis C: 1.17 (0.79, 1.71); PS: 1.24 (0.85, 1.82); P: 1.16 (0.67, 1.88) As-Treated Analysis: C: 0.99 (0.64, 1.54); PS: NR; P: 0.95 (0.54, 1.65)	
		CHF		Intention-to-Treat Analysis C: 0.89 (0.63, 1.26); PS: 0.81 (0.58, 1.15); P: NR As-Treated Analysis: C: 0.73 (0.49, 1.09); PS: NR; P: NR	
	Expanded Studies: 3,844 (Pio) vs 11,090 (Control)	Death	C: 0.65 (0.57, 0.74)	Intention-to-Treat Analysis C: 0.70 (0.60, 0.81); PS: 0.76 (0.66, 0.88); P: NR As-Treated Analysis: C: 0.51 (0.42, 0.62); PS: NR; P: NR	None
		Stroke	C: 0.90 (0.69, 1.18)	Intention-to-Treat Analysis C: 0.95 (0.70, 1.29); PS: 1.01 (0.77, 1.42); P: 1.10 (0.77, 1.61) As-Treated Analysis: C: 0.81 (0.56, 1.17); PS: NR; P: 0.94 (0.59, 1.40)	
		AMI	C: 0.89 (0.70, 1.15)	Intention-to-Treat Analysis C: 0.94 (0.87, 1.49); PS: 1.01 (0.76, 1.34); P: 1.14 (0.82, 1.63) As-Treated Analysis: C: 0.89 (0.64, 1.24); PS: NR; P: 1.09 (0.74, 1.62)	
		CRV	C: 0.94 (0.73, 1.21)	Intention-to-Treat Analysis C: 0.93 (0.71, 1.24); PS: 0.93 (0.07, 1.23); P: 1.14 (0.77, 1.65) As-Treated Analysis: C: 0.89 (0.64, 1.23); PS: NR; P: 1.08 (0.71, 1.57)	
		CHF	C: 1 20 (0.99, 1.46)	Intention-to-Treat Analysis C: 1.40 (1.12, 1.75); PS: 1.52 (1.21, 1.92); P: NR As-Treated Analysis: C: 1.47 (1.15, 1.87); PS: NR; P: NR	

C=Cox PH model; PS=propensity score; P=PERR adjustment; NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[1] Tannen et al., 2012…continued	Expanded Studies: 10,862 (Rosi) vs 32,135 (Control)	Death	C: 0.67 (0.62, 0.72)	Intention-to-Treat Analysis C: 0.77 (0.70, 0.83); PS: 0.79 (0.73, 0.86); P: NR As-Treated Analysis: C: 0.63 (0.56, 0.70); PS: NR; P: NR	None
		Stroke	C: 0.85 (0.72, 1.00)	Intention-to-Treat Analysis C: 0.91 (0.76, 1.10); PS: 0.97 (0.80, 1.17); P: 1.33 (1.06, 1.68) As-Treated Analysis: C: 0.83 (0.67, 1.03); PS: NR; P: 1.22 (0.95, 1.57)	
		AMI	C: 0.88 (0.75, 1.02)	Intention-to-Treat Analysis C: 0.93 (0.79, 1.09); PS: 0.94 (0.80, 1.11); P: 1.24 (1.00, 1.52) As-Treated Analysis: C: 0.76 (0.62, 0.93); PS: NR; P: 1.06 (0.83, 1.32)	
		CRV	C: 0.90 (0.77, 1.05)	Intention-to-Treat Analysis C: 0.94 (0.78, 1.12); PS: 0.97 (0.81, 1.16); P: 1.04 (0.83, 1.28) As-Treated Analysis: C: 0.85 (0.69, 1.04); PS: NR; P: 0.93 (0.73, 1.18)	
		CHF	C: 1 11 (0.99, 1.25)	Intention-to-Treat Analysis C: 1.14 (1.00, 1.30); PS: 1.25 (1.09, 1.44); P: NR As-Treated Analysis: C: 1.03 (0.88, 1.19); PS: NR; P: NR	
	Expanded Studies: 10,862 (Rosi) vs 3,844 (Pio)	Death	NR	Intention-to-Treat Analysis C: 1.09 (0.94, 1.26); PS: 1.08 (0.94, 1.24); P: NR As-Treated Analysis: C: 1.23 (1.00, 1.51); PS: NR; P: NR	None
		Stroke		Intention-to-Treat Analysis C: 0.98 (0.74, 1.30); PS: 0.97 (0.74, 1.29); P: 1.13 (0.77, 2.67) As-Treated Analysis: C: 1.04 (0.72, 1.50); PS: NR; P: 1.20 (0.77, 1.86)	
		AMI		Intention-to-Treat Analysis C: 0.99 (0.76, 1.28); PS: 1.02 (0.79, 1.32); P: 1.05 (0.72, 1.50) As-Treated Analysis: C: 0.93 (0.67, 1.29); PS: NR; P: 0.95 (0.63, 1.43)	
		CRV		Intention-to-Treat Analysis C: 0.92 (0.70, 1.20); PS: 0.93 (0.72, 1.21); P: 0.95 (0.66, 1.40) As-Treated Analysis: C: 0.88 (0.63, 1.22); PS: NR; P: 0.88 (0.58, 1.35)	
		CHF		Intention-to-Treat Analysis C: 0.98 (0.80, 1.19); PS: 0.98 (0.81, 1.19); P: NR As-Treated Analysis: C: 0.84 (0.67, 1.06)	

C=Cox PH model; PS=propensity score; P=PERR adjustment; NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[2] Chou et al., 2011	7,695 (Rosi vs Pio)	MI	NR	0.539 (0.327, 0.889)	A total of 7,725 patients (6,048 rosi and 1,677 pio) were included in the final analysis. For each outcome, only the total number of patients was reported.
	7,494 (Rosi vs Pio)	CHF		0.820 (0.619, 1.086)	
	7,653 (Rosi vs Pio)	Angina		0.543 (0.293, 1.006)	
	7,410 (Rosi vs Pio)	CVA		0.949 (0.724, 1.244)	
[3] Gallagher et al., 2011	Insulin vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 2.40 (2.20, 2.61) Fully adjusted: 2.84 (2.60, 3.11)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.00 (1.54, 2.61) Fully adjusted: 1.68 (1.27, 2.21)	
		Stroke		Age, sex, calendar year adjusted: 1.91 (1.45, 2.52) Fully adjusted: 1.91 (1.43, 2.56)	
		CHF		Age, sex, calendar year adjusted: 2.23 (1.74, 2.87) Fully adjusted: 1.62 (1.25, 2.10)	
	Sulphonylurea vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 1.77 (1.72, 1.82) Fully adjusted: 2.18 (2.11, 2.26)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.38 (2.23, 2.54) Fully adjusted: 1.63 (1.51, 1.77)	
		Stroke		Age, sex, calendar year adjusted: 1.82 (1.68, 1.97) Fully adjusted: 1.60 (1.45, 1.76)	
		CHF		Age, sex, calendar year adjusted: 2.45 (2.30, 2.62) Fully adjusted: 1.42 (1.31, 1.54)	
	TZD vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 1.77 (1.66, 1.88) Fully adjusted: 3.04 (2.77, 3.33)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.47 (2.17, 2.81) Fully adjusted: 1.61 (1.31, 1.97)	
		Stroke		Age, sex, calendar year adjusted: 1.90 (1.61, 2.25) Fully adjusted: 1.89 (1.46, 2.45)	
		CHF		Age, sex, calendar year adjusted: 3.23 (2.80, 3.72) Fully adjusted: 1.75 (1.41, 2.17)	
	Metformin vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 2.01 (1.96, 2.07) Fully adjusted: 2.23 (2.15, 2.31)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.48 (2.32, 2.67) Fully adjusted: 1.55 (1.42, 1.68)	
		Stroke		Age, sex, calendar year adjusted: 2.05 (1.89, 2.22) Fully adjusted: 1.72 (1.56, 1.89)	
		CHF		Age, sex, calendar year adjusted: 2.97 (2.77, 3.19) Fully adjusted: 1.50 (1.38, 1.63)	
	Insulin vs Past Exposure of Metformin	Death	NR	Age, sex, calendar year adjusted: 1.38 (1.26, 1.50) Fully adjusted: 1.24 (1.12, 1.37)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 1.00 (0.76, 1.32) Fully adjusted: 1.04 (0.79, 1.37)	
		Stroke		Age, sex, calendar year adjusted: 0.99 (0.75, 1.32) Fully adjusted: 0.95 (0.71, 1.26)	
		CHF		Age, sex, calendar year adjusted: 0.94 (0.73, 1.22) Fully adjusted: 0.94 (0.73, 1.22)	

NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[3] Gallagher et al., 2011...continued	Sulphonylurea vs Past Exposure of Metformin	Death	NR	Age, sex, calendar year adjusted: 0.96 (0.89, 1.03) Fully adjusted: 0.97 (0.90, 1.04)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 1.23 (1.03, 1.48) Fully adjusted: 1.29 (1.08, 1.55)	
		Stroke		Age, sex, calendar year adjusted: 1.01 (0.82, 1.25) Fully adjusted: 1.04 (0.85, 1.29)	
		CHF		Age, sex, calendar year adjusted: 1.20 (0.99, 1.44) Fully adjusted: 1.34 (1.12, 1.62)	
	TZD vs Past Exposure of Metformin	Death	NR	Age, sex, calendar year adjusted: 0.81 (0.76, 0.85) Fully adjusted: 0.84 (0.79, 0.89)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 1.03 (0.91, 1.18) Fully adjusted: 1.05 (0.92, 1.20)	
		Stroke		Age, sex, calendar year adjusted: 0.91 (0.77, 1.07) Fully adjusted: 0.92 (0.79, 1.09)	
		CHF		Age, sex, calendar year adjusted: 1.12 (0.98, 1.28) Fully adjusted: 1.13 (0.99, 1.29)	
	Rosi vs Pio (Current Exposures)	Death (GPRD)	NR	Age, sex, calendar year adjusted: 1.15 (1.04, 1.28) Fully adjusted: 1.20 (1.08, 1.34)	Number of patients not reported.
		Death (ONS)		Age, sex, calendar year adjusted: 1.09 (0.90, 1.32) Fully adjusted: 1.07 (0.89, 1.29)	
		ACS (GPRD)		Age, sex, calendar year adjusted: 0.99 (0.84, 1.16) Fully adjusted: 1.03 (0.87, 1.21)	
		ACS (HES)		Age, sex, calendar year adjusted: 1.04 (0.79, 1.37) Fully adjusted: 1.02 (0.77, 1.35)	
		Stroke (GPRD)		Age, sex, calendar year adjusted: 1.00 (0.80, 1.26) Fully adjusted: 1.05 (0.83, 1.32)	
		Stroke (HES)		Age, sex, calendar year adjusted: 1.16 (0.77, 1.74) Fully adjusted: 1.12 (0.75, 1.68)	
		CHF (GPRD)		Age, sex, calendar year adjusted: 1.08 (0.92, 1.27) Fully adjusted: 1.14 (0.97, 1.34)	
		CHF (HES)		Age, sex, calendar year adjusted: 1.73 (1.19, 2.50) Fully adjusted: 1.73 (1.19, 2.51)	
	Rosi vs Pio (Current Exposures)	Death (age<65)	NR	Age, sex, calendar year adjusted: 1.08 (0.82, 1.41) Fully adjusted: 1.14 (0.87, 1.49)	Number of patients not reported.
		Death (age≥65)		Age, sex, calendar year adjusted: 1.17 (1.04, 1.31) Fully adjusted: 1.22 (1.09, 1.37)	
		ACS (age<65)		Age, sex, calendar year adjusted: 0.79 (0.61, 1.03) Fully adjusted: 0.82 (0.64, 1.07)	
		ACS (age≥65)		Age, sex, calendar year adjusted: 1.12 (0.92, 1.38) Fully adjusted: 1.17 (0.95, 1.43)	
		Stroke (age<65)		Age, sex, calendar year adjusted: 0.84 (0.52, 1.36) Fully adjusted: 0.90 (0.56, 1.46)	
		Stroke (age≥65)		Age, sex, calendar year adjusted: 1.05 (0.81, 1.36) Fully adjusted: 1.09 (0.84, 1.41)	

NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[3] Gallagher et al., 2011...continued	Rosi vs Pio (Current Exposures)	CHF (age<65)	NR	Age, sex, calendar year adjusted: 0.90 (0.61, 1.34) Fully adjusted: 0.95 (0.64, 1.42)	Number of patients not reported.
		CHF (age≥65)		Age, sex, calendar year adjusted: 1.12 (0.94, 1.34) Fully adjusted: 1.19 (0.99, 1.42)	
	Rosi vs Pio (Current Exposures)	Death (co-prescribing insulin: no)	NR	Age, sex, calendar year adjusted: 1.16 (1.05, 1.30) Fully adjusted: 1.22 (1.09, 1.35)	Number of patients not reported.
		Death (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 1.12 (0.63, 1.97) Fully adjusted: 1.20 (0.68, 2.13)	
		ACS (co-prescribing insulin: no)		Age, sex, calendar year adjusted: 0.98 (0.83, 1.15) Fully adjusted: 1.00 (0.85, 1.18)	
		ACS (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 1.70 (0.71, 4.08) Fully adjusted: 1.83 (0.76, 4.42)	
		Stroke (co-prescribing insulin: no))		Age, sex, calendar year adjusted: 0.98 (0.78, 1.23) Fully adjusted: 1.02 (0.81, 1.29)	
		Stroke (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 2.54 (0.49, 13.16) Fully adjusted: 2.66 (0.51, 13.84)	
		CHF (co-prescribing insulin: no)		Age, sex, calendar year adjusted: 1.11 (0.94, 1.31) Fully adjusted: 1.16 (0.98, 1.37)	
		CHF (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 0.73 (0.31, 1.75) Fully adjusted: 0.80 (0.33, 1.91)	
	Rosi vs Pio (Current Exposures)	Death (<2007)	NR	Age, sex, calendar year adjusted: 1.15 (0.98, 1.35) Fully adjusted: 1.20 (1.03, 1.41)	Number of patients not reported.
		Death (≥2007)		Age, sex, calendar year adjusted: 1.13 (0.98, 1.30) Fully adjusted: 1.19 (1.03, 1.37)	
		ACS (<2007)		Age, sex, calendar year adjusted: 1.04 (0.83, 1.30) Fully adjusted: 1.06 (0.84, 1.33)	
		ACS (≥2007)		Age, sex, calendar year adjusted: 0.90 (0.71, 1.13) Fully adjusted: 0.94 (0.75, 1.19)	
		Stroke (<2007)		Age, sex, calendar year adjusted: 1.33 (0.94, 1.87) Fully adjusted: 1.40 (0.99, 1.98)	
		Stroke (≥2007)		Age, sex, calendar year adjusted: 0.74 (0.54, 1.02) Fully adjusted: 0.76 (0.55, 1.06)	
		CHF (<2007)		Age, sex, calendar year adjusted: 1.04 (0.83, 1.29) Fully adjusted: 1.10 (0.88, 1.37)	
		CHF (≥2007)		Age, sex, calendar year adjusted: 1.13 (0.89, 1.43) Fully adjusted: 1.20 (0.94, 1.53)	
	Rosi vs Pio (Current Users)	ACM		Age, sex, calendar year adjusted: 1.09 (0.90, 1.32)	Number of patients not reported.

NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[4] Loebstein et al., 2011	745 (Rosi) vs 11,938 (Metformin)	AMI	NR	1.13 (0.6, 2.1)	HR were as reported in the text.
		ACS		0.85 (0.57, 1.26)	
		CRV		1.22 (0.82, 1.54)	
		CHF		2.23 (1.41, 3.53)	
		ACM		1.15 (0.85, 1.56)	
	2,753 (Rosi combo) vs 11,938 (Metformin)	AMI	NR	0.95 (0.5, 1.4)	HR were as reported in the text.
		ACS		1.08 (0.83, 1.40)	
		CRV		1.18 (0.94, 1.49)	
		CHF		1.33 (0.91, 1.95)	
		ACM		0.90 (0.69, 1.17)	
[5] Bilik et al., 2010	10 Health Plans: 773 (Rosi) vs 711 (Pio); 7 Health Plans: 564 (Rosi) vs 334 (Pio)	Nonfatal MI	0.71 (NR); 0.89 (NR)	10 Health Plans: 0.75 (0.33, 1.67); 7 Health Plans: 1.30 (0.31, 5.37)	95% CI for crude estimates were not reported.
		CRV	0.92 (NR); 0.80 (NR)	10 Health Plans: 1.08 (0.47, 2.45); 7 Health Plans: 0.82 (0.49, 1.37)	
		Nonfatal MI or CRV	0.80 (NR); 0.83 (NR)	10 Health Plans: 0.91 (0.46, 1.78); 7 Health Plans: 1.01 (0.38, 2.67)	
		Nonfatal Stroke	1.34 (NR); 1.18 (NR)	10 Health Plans: 1.42 (0.76, 2.62); 7 Health Plans: 1.33 (0.89, 1.98)	
		Nonfatal MI, CRV or Nonfatal Stroke	0 96 (NR); 0.93 (NR)	10 Health Plans: 1.08 (0.62, 1.88); 7 Health Plans: 1.11 (0.52, 2.36)	
		CV Mortality	0.54 (NR); 0.79 (NR)	10 Health Plans: 0.62 (0.22, 1.71); 7 Health Plans: 0.93 (0.21, 4.12)	
		ACM	0.26 (NR); 0.66 (NR)	10 Health Plans: 0.74 (0.39, 1.40); 7 Health Plans: 0.69 (0.28, 1.69)	
		Nonfatal MI or ACM	0.75 (NR); 0.81 (NR)	10 Health Plans: 0.83 (0.51, 1.35); 7 Health Plans: 0.99 (0.51, 1.91)	
		Nonfatal MI, Nonfatal Stroke or CV Mortality	0.90 (NR); 0.97 (NR)	10 Health Plans: 0.94 (0.63, 1.40); 7 Health Plans: 1.16 (0.61, 2.18)	
		Nonfatal MI, Nonfatal Stroke or ACM	0.88 (NR); 0.88 (NR)	10 Health Plans: 0.94 (0.67, 1.32); 7 Health Plans: 1.03 (0.67, 1.60)	
		Nonfatal MI, CRV, Nonfatal Stroke or ACM	0.90 (NR); 0.86 (NR)	10 Health Plans: 1.00 (0.63, 1.57); 7 Health Plans: 0.99 (0.54, 1.82)	
[6] Graham et al., 2010	67,593 (Rosi) vs 159,978 (Pio)	AMI	1.07 (0.97, 1.19)	1.06 (0.96, 1.18)	None
		Stroke	1.31 (1.15, 1.49)	1.27 (1.12, 1.45)	
		Heart Failure	1.27 (1.18, 1.37)	1.25 (1.16, 1.34)	
		ACM	1.17 (1.07, 1.27)	1.14 (1.05, 1.24)	
		AMI, Stroke, Heart Failure, or ACM	1.20 (1.14, 1.26)	1.18 (1.12, 1.23)	
[7] Wertz et al., 2010	14,469 (Rosi) vs 14,469 (Pio)	Composite (AMI, AHF, ACD): Matched Patients	NR	1.03 (0.91, 1.15)	Only primary analysis results are included here.
	2,558 (Rosi) vs 2,819 (Pio)	Composite (AMI, AHF, ACD): Patients ≥65 years		0.97 (0.83, 1.12)	
	18,319 (Rosi) vs 18,309 (Pio)	Composite (AMI, AHF, ACD): All Patients		1.00 (0.90, 1.11)	

NR=not reported

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/s/

JOHN S YAP
04/23/2013

MARK S LEVENSON
04/23/2013

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KATE GELPERIN
04/26/2013

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04/26/2013

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

POSTMARKET REVIEW

NDA Number:	21071 (Avandia), 21073 (Actos)
Drug Name:	Avandia (rosiglitazone maleate) and Actos (pioglitazone)
Indication(s):	Treatment of Type 2 Diabetes Mellitus
Sponsor:	GlaxoSmithKline (Avandia) and Takeda (Actos)
Date(s):	April 23, 2013 (review date)
Biometrics Division:	Division of Biometrics 7
Statistical Reviewer:	John Stephen Yap, PhD (DB7)
Concurring Reviewers:	Mark Levenson, PhD (Deputy Director, DB7)
Study Division:	Division of Epidemiology I, Office of Surveillance and Epidemiology
Study Team:	Kate Gelperin, MD, MPH; Esther Zhou, MD, PhD; Tarek Hammad, MD, PhD, MSc, MS
Project Manager:	Margarita Tossa

Keywords: Thiazolidinedione, TZD, Avandia, Actos, Rosiglitazone, Pioglitazone, Diabetes, Observational Study, Systematic Review

I. Introduction

A. Background

Avandia (rosiglitazone maleate) was originally approved in 1999 for the treatment of patients with type 2 diabetes mellitus (DM). Joint meetings of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Committees were held in 2007 and 2010 to assess the cardiovascular (CV) safety of Avandia. After the 2010 AC meeting, the FDA restricted the distribution of Avandia.

In April 2010, the Office of Surveillance and Epidemiology (OSE) requested the Division of Biometrics 7 (DB7) in the Office of Biostatistics (OB) to conduct an independent statistical review of the methodology described in each of 21 published observational studies that evaluated cardiovascular risks associated with thiazolidinediones (TZDs) (the class of drugs that includes Avandia and Actos) in patients with DM. The 21 studies were identified by OSE following a systematic review study protocol. The findings in the statistical review were referenced in a final OSE systematic review that was presented at the 2010 AC meeting.

Another AC meeting for Avandia is scheduled on June 5-6, 2013. The focus of the meeting will be the readjudication of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial. However, evidences presented at the 2010 AC will be reviewed and new evidences available after the 2010 AC will be evaluated. Among the new evidences are from published observational studies that were not available at the time of the 2010 OSE systematic review.

B. Scope of Statistics Review

This review will cover 7 published observational studies that evaluated CV risks associated with TZDs that were not available for the 2010 statistical review. Six of the 7 publications were identified in a literature search by Dr. Patricia Bright of the Division of Epidemiology I in OSE. Dr. Bright's literature search initially identified 13 publications. This number was reduced to 6 after the publications were subjected to the same inclusion/exclusion criteria that were used in the 2010 OSE systematic review. In summary, the reasons for inclusion/exclusion were: no appropriate comparator (1), meta-analysis of observational studies (1), spontaneous reports (2), randomized clinical trials (2), and study sample size was too small (1). See the 2013 OSE systematic review for more details regarding the study selection. The 7th publication is by Graham et al. (2010). Graham et al. (2010) was not included in 2010 OSE systematic review but was presented at the 2010 AC meeting.

This review will summarize and comment on the statistical methodology described in each of the 7 selected observational studies. An assessment or interpretation of individual study results and conclusions will not be included. However, this review will include a tabulation of the primary numerical results in each of the 7 studies, which will be used to create tabular and graphical summaries for the background package for the June 2013 AC.

Only published manuscripts were provided and no subject-level data were available for this review. From hereon, Avandia will be referred to as rosi and Actos will be referred to as pio.

II. Summary of Studies

A. Overview of Studies

Table 1 summarizes the studies included in this review.

Outcomes Evaluated

All 7 studies evaluated a subset of the following outcomes:

- acute myocardial infarction (AMI)
- stroke
- coronary revascularization (CRV)
- congestive heart failure (CHF)
- angina
- cerebral vascular accident (CVA)
- acute coronary syndrome (ACS)
- heart failure
- death or all-cause mortality (ACM)

All studies except one ([2]) studied ACM. Studies that evaluated cardiovascular (CV) outcomes used International Classification of Diseases version 9 (ICD-9) codes ([2, 4-7]) or the United Kingdom (UK) General Practice Research Database (GPRD) coding system ([3]). Studies that evaluated death used the National Death Index (NDI) ([5, 7]), GPRD coding system ([3]), Macabi Healthcare Services (Israel) coding system ([4]), or the Social Security Master Beneficiary Record Database ([6]). One study ([1]) did not describe how CV or death outcomes were assessed.

Antidiabetic Drugs Evaluated

All studies except one ([4]) evaluated both rosi and pio. Study [4] evaluated rosi and metformin. Study [3] evaluated insulin, metformin, and sulfonylurea in addition to rosi and pio.

Data Source

Table 2 shows a summary of the databases used in the 7 publications. Three of the 7 studies ([5-7]) used national databases in the United States. Other studies used databases in Israel ([4]), Taiwan ([2]), and United Kingdom ([1, 3]).

Table 1: Summary of Observational Studies

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Confounding Adjustment	Comparison Groups
[1] Tannen et al., 2012	Stroke, AMI, CRV, CHF; Death	Rosi, Pio	The Health Improvement Network Database (THIN) (UK)	12/1/2000-6/1/2008	709 (Pio) and 2,001 (Rosi) in replication studies; 3,844 (Pio), and 10,862 (Rosi) in expanded studies	Type 2 DM patients (by prescription) ages 35-75 years; with and without pre-existing ischemic CV diseases.	• Cox PH model • PS (stratification) • PERR adjustment	Cox model used in each PS quintile and combined into overall estimate; also used PERR adj.	Combo
[2] Chou et al., 2011	MI, CHF, Angina, CVA (ICD-9 codes)	Rosi, Pio	Longitudinal Health Insurance Database 2005 (Taiwan)	1/1/1998-12/31/2006	6,048 (Rosi); 1,677 (Pio)	Type 2 DM Taiwanese patients (by prescription and ICD-9 diagnosis codes).	Cox PH model	Controlled for multiple variables in Cox model.	Combo
[3] Gallagher et al., 2011	ACS, stroke, heart failure; ACM (including cause of death)	Rosi, Pio, Insulin, Metformin, Sulphonylurea	General Practice Research Database (GPRD) (UK)	Not stated (but covers the year 2007)	22,636 (Rosi); 18,953 (Pio); 121,637 (Metformin); 76,863 (Sulphonylurea); 26,458 (Insulin)	Type 2 DM patients age 40 years and over (from the UK GPRD).	• Poisson regression • Kaplan-Meier	Controlled for multiple variables in regression model.	Unclear (possibly combo)
[4] Loebstein et al., 2011	AMI, ACS, CRV, CHF (ICD-9 codes); ACM	Rosi, Metformin	Macabi Healthcare Services (MHS) (Israel)	1/1/2000-6/30/2007	745 (Rosi); 2,753 (Rosi-Metformin); 11,938 (Metformin)	Patients with American Diabetes Association defined criteria for diabetes (from Israel MHS); purchased Rosi, Metformin	Cox PH model	Controlled for multiple variables in Cox model.	Combo
[5] Bilik et al., 2010	NMI, CRV, Nonfatal Stroke (ICD-9 codes); CV Mortality, ACM (NDI)	Rosi, Pio	TRIAD (10 managed care health plans, 68 provider groups) (US)	1999-2003	773 (Rosi); 711 (Pio)	Type 2 diabetes patients (by prescription); exclude age at diagnosis <30 yrs and treatment with insulin only	Cox PH model	Controlled for multiple variables in Cox model.	Combo (some patients used insulin)
[6] Graham et al., 2010	AMI, Stroke, Heart failure (ICD-9 codes); ACM (SSMBR database)	Rosi, Pio	Medicare (US)	7/2006-6/2009	67,593 (Rosi); 159,978 (Pio)	TZD-exposed patients 65 yrs and older.	• Cox PH model • Kaplan-Meier	Controlled for multiple variables in Cox model.	Combo
[7] Wertz et al., 2010	AMI, AHF (ICD-9 codes); Death (NDI)	Rosi, Pio	Healthcore Integrated Research Database (HIRD) (Wellpoint) (US)	1/1/2001-12/31/2005	14,469 PS-matched Rosi and Pio patients	Patients ≥18 years of age, newly initiated on Rosi or Pio	• Cox PH model • PS (matching)	Included Cox model analysis of PS-matched sets of patients.	Unclear (possibly combo)

AMI=acute myocardial infarction; CHF=congestive heart failure; MI=myocardial infarction; CVA=cerebral vascular accident; ACM=all-cause mortality; ACS= acute coronary syndrome; CRV=coronary revascularization; NMI=nonfatal MI; CV=cardiovascular; AHF=acute heart failure; NDI=National Death Index; PS=propensity score; SSMBR= Social Security Master Beneficiary Record

Table 2: Summary of Study Databases

Country of Study	Database (Publication Number)
1. United States (National Databases)	Translating Research Into Action for Diabetes (TRIAD) ([5]); Medicare ([6]); Healthcore Integrated Research Database – Wellpoint ([7])
2. Israel	Macabi Healthcare Services ([4])
3. Taiwan	Longitudinal Health Insurance Database 2005 ([2])
4. United Kingdom	General Practitioner Research Database ([3]); The Health Information Network in United Kingdom ([1])

Reviewer's Comments: In the 2010 OSE systematic review, one study used the The Health Improvement Network Database (THIN) database and two studies used the General Practice Research Database (GPRD). These databases are from the United Kingdom. In this review, study [1] used the THIN database while study [3] used the GPRD. One study in the 2010 review also used the National Health Insurance (NHI) database in Taiwan. The same database was used in study [2] in this review. The studies in the 2010 OSE systematic review and the studies in the current review that use the same database overlap in the years exposure data were obtained as shown in Table 3.

Table 3: Overlap in Study Databases from 2010 and 2013 Systematic Reviews

	Overlap in Exposure Period (Calendar Years)	
Database	**2010 Review**	**2013 Review**
UK GPRD	Azoulay et al., 2009: 1988-2008	[3] Gallagher et al., 2011: not stated but covers the year 2007
	Tzoulaki et al., 2009: 1990-2005	
UK THIN	Margolis et al., 2008: 2002-2006	[1] Tannen et al., 2012: 2000-2008
Taiwan NHI	Hsiao et al., 2009: 2001-2005	[2] Chou et al., 2001: 1998-2006

Exposure Period

The study exposure periods ranged from 4-8 years:

- 4 years: [6]
- 5 years: [5], [7]
- 8 years: [1], [2], [4]
- Unknown: [3]

The earliest study start date was 1/1/1998 ([2]) which was a few months earlier than the marketing approval dates of rosi (5/25/1999) and pio (7/15/1999) in the United States. The latest study start date was 7/2006 ([6]).

The study end dates were mostly prior to the 2007 AC meeting except for [1] (12/1/2000-6/1/2008) and [6] (7/2006-6/2009). Study [3] did not specify an exposure period although it indicated that the year 2007 was within the study's exposure period.

Reviewer's Comment: The exposure periods for studies [1] and [6] include the date of the 2007 AC meeting that discussed the CV risks of rosi exposure. The outcome of the 2007 AC meeting may have led to a decrease in the number of rosi patients and/or an increase

in the number of pio patients in these two studies. Additionally, the characteristics of the patients taking these drugs may have changed after the 2007 AC meeting.

Number of Exposed/Unexposed

The numbers of exposed/unexposed patients ranged from small ([5]), moderate ([1-2, 4]), to large ([3, 6-7]) (see Table 1).

Reviewer's Comment: Study [5] may be underpowered to detect a clinically meaningful risk.

Population Details

The study populations were patients with type 2 DM. Generally, the patients were identified by their record of antidiabetes prescriptions in the databases. One study used ICD-9 diagnosis codes in addition to an antidiabetic prescription to identify diabetes patients ([2]). There were no age restrictions in two studies ([2, 4]) while other studies had the following age restrictions: 35-75 ([1]), ≥18 years ([7]), ≥30 years ([5]), ≥40 years ([3]), and ≥65 years ([6]). One study ([1]) performed analyses on patients with and without pre-existing ischemic CV diseases. Study populations varied by locations: US ([5-7]), Israel ([4]), Taiwan ([2]), and UK ([1, 3]).

Statistical Methods

All 7 studies, except [3], performed time-to-event analyses using the Cox proportional hazards (PH) model. Two of the studies that used the Cox PH model also used propensity scores (PS) to balance covariates between treatment groups: study [1] used PS stratification while [7] used PS matching. Study [3] used Poisson regression. The Cox PH model and Poisson regression estimate risk in the form of hazard ratio (HR) and relative rate, respectively. The statistical models in all studies included adjustments for multiple variables or covariates.

Other statistical methods that studies used include the Kaplan-Meier ([3, 6]) and prior event rate ratio ("PERR") adjustment for reducing bias from unmeasured confounders ([1]).

Confounding Adjustment

All studies included methods to address confounding. The typical approach was to include multiple variables that were potentially confounders into the Cox PH or Poisson regression models ([2-6]). Other studies ([1, 7]) used PS. Study [1] stratified patients into PS quintiles and used the Cox model in each quintile; an overall estimate of the hazard ratio was obtained by combining estimates from each quintile. Study [7] used PS matching and the Cox model was applied to the PS-matched sets of patients. Study [1] also performed analyses using the PERR adjustment to address unmeasured confounding.

Table 4: Summary of Study Drug Comparisons

Studies	Comparisons	Comments
[1] Tannen et al., 2012	(1) Rosi/Pio vs Control; (2) Rosi vs Pio	Some patients received other antidiabetes medication.
[2] Chou et al., 2011	(1) Rosi vs Pio	Rosi and pio were add-on antidiabetes medications.
[3] Gallagher et al., 2011	(1) Insulin, Sulphonylurea, TZD, Metformin (past exposures) vs Controls; (2) Insulin, Sulphonylurea, TZD (past exposures) vs past exposure to Metformin; (3) Rosi vs Pio (current exposures); (4) Rosi vs Pio (current exposures, stratified by age, co-prescribing of insulin, and calendar time); (5) Rosi vs Pio (mortality)	Study patients may have received other antidiabetes medications but it is not clear in the publication.
[4] Loebstein et al., 2011	(1) Rosi mono vs Rosi-Metformin combo (2) Rosi mono vs Metformin mono (3) Rosi-Metformin combo vs Metformin mono	Rosi mono was not strictly monotherapy but an overlap of <10% between the exposure period of the rosi and metformin. Some patients received insulin or sulphonylurea.
[5] Bilik et al., 2010	(1) Rosi vs Pio	Some patients used insulin.
[6] Graham et al., 2010	(1) Rosi vs Pio	Some patients received other antidiabetes medication.
[7] Wertz et al., 2010	(1) Rosi vs Pio	Study patients may have received other antidiabetes medications but it is not clear in the publication.

mono=monotherapy; combo=combination therapy

Comparison Groups

The comparisons differed among the studies. Table 4 summarizes the comparisons that were performed in each study. Studies [2, 5-7] compared rosi versus pio patients only. Other studies compared rosi versus pio in addition to comparing rosi/pio versus controls ([1, 3]) or rosi/pio versus past exposure to metformin ([3]). One study ([4]) compared rosi versus metformin only as either mono- or combination therapy. The study comparison groups were also classified in this review as to whether the antidiabetic drugs were administered alone (monotherapy) or in combination with (or add-on to) other antidiabetic drugs (combo). The 7 studies were classified as follows:

- Combo: [1, 2, 4, 5, 6]
- Unclear (possibly combo): [3, 7]

B. Review of Studies

The following is a detailed summary of the statistical review of each of the 7 observational studies. The studies are arranged according to the year of publication (starting with the most recent) and by last name of the first author (a-z). Each publication review includes a brief summary of the study followed by comments by the statistical reviewer.

1. **Tannen R, Xie D, Wang X, Menggang Y, Weiner MG. A new "Comparative Effectiveness" assessment strategy using the THIN database: Comparison of the cardiac complications of pioglitazone and rosiglitazone. *Pharmacoepidemio Drug Saf* 2012 Oct 16. doi: 10.1002/pds.3360. [Epub ahead of print]**

This was a retrospective observational study with a cohort design of type 2 DM patients using the The Health Improvement Network (THIN) database in the United Kingdom. THIN is a large database in the United Kingdom with approximately 7.5 million patient records. The study included replication and expanded studies (Figure 1). The replication studies used the same study design attributes of the Proactive trial (pio vs placebo) including study and enrollment duration, patient age (35 - 75 years), and inclusion/exclusion criteria. Like the Proactive trial, patients in the replication studies had ischemic CV disease. The expanded studies were similar to the replication studies except that patients were not required to have pre-existing ischemic CV diseases.

The replication and expanded studies included rosi- and pio- exposed groups of patients. These patients were initially selected based on their record of rosi and pio prescriptions during the recruitment period. Patients in each group were matched to unexposed patients (1 rosi/pio patient: 3 control patients) in the THIN database based on age, sex, and study start date. Within the replication and expanded studies, the rosi and pio exposure groups were each compared to their matched controls, and also with each other.

The study included simulated “intention-to-treat” and “as-treated” time-to-event analyses. In the “intention-to-treat” analyses, patients in the exposed and unexposed groups continued until death, loss to follow-up, or the study end date; a stop point occurred if one TZD treatment was switched to another. In the “as-treated” analyses,

patients in the exposed groups "…reached a stop point 90 days after the end of the last TZD prescription duration, and the unexposed group if TZD treatment was initiated." Time-to-event analyses were performed using the Cox PH model. The study also used PS quintiles as strata in the Cox model and the "PERR" adjustment technique, an adjustment method used to reduce bias from unmeasured confounders.

The study adjusted for various baseline confounders in the Cox PH model including histories of pre-existing ischemic CV diseases. Imputation for missing confounders was not performed because the percentage of missing data (systolic blood pressure, smoking, and/or body mass index) was less than 5%.

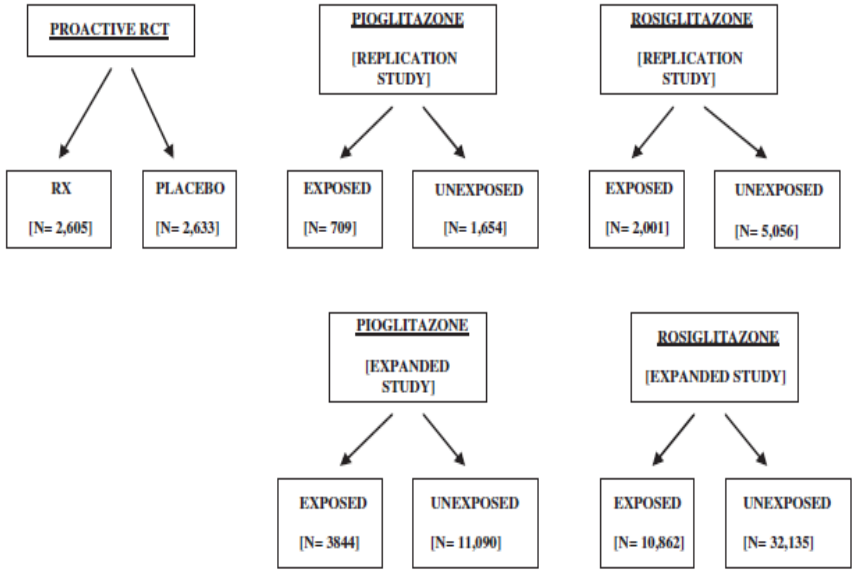

Figure 1. Overall study design. The overall study design, along with the number of subjects in each cohort, and in the Proactive RCT is shown
Figure 1 copied from page 2 of publication.

Reviewer's Comments:

- ***The study states that validation studies have been published about the THIN database.***
- ***Patients in the rosi and pio groups were exposed to other antidiabetic drugs.***
- ***The authors did not describe the study outcomes and how these outcomes were assessed e.g. via ICD-9 codes. However, the THIN database use Read codes.***
- ***The publication states that, in the "intention-to-treat" analysis, a stop point occurred if TZD treatment was switched from rosi to pio or vice versa. However, under the clinical trial meaning of "intention-to-treat", a switch from rosi to pio or vice versa is not considered a stop point. This definition appears to be consistent with an "as-treated" analysis instead.***
- ***The publication is unclear in its definition for "as-treated" analysis. In the reviewer's understanding of this definition, a stop point occurred 90 days after the last TZD prescription for patients in the exposed (to TZD) group or 90 days after the last non-TZD prescription for patients in the unexposed (to TZD) group who switched to TZDs. Under the strict meaning of "as-treated", the stop point should***

occur after zero (0) instead of 90 days; otherwise, this analysis more closely resembles an "intention-to-treat" analysis.

- ***The study did not state whether the PH assumption of the Cox model was satisfied or not.***
- ***The study period was from 12/1/2000 to 6/1/2008. This study period covers the 2007 AC meeting for Rosi.***

2. Chou CC, Chen WL, Kao TW, Chang YW, Loh CH, Wang CC. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. *Clin Ther* 2011; 33(12):1904-13.

This was a retrospective observational study of Taiwanese patients who were prescribed antihyperglycemic agents and diagnosed with diabetes (ICD-9 CM code 250.XX) from January 1, 1998 through December 31, 2006. Patients were required to have had diabetes medication for > 120 days within 180 days after the indexed date of inclusion and treated with only one kind of TZD (rosi or pio). Patients who switched medications were excluded. Medical data, including prescription medications were obtained from the Longitudinal Health Insurance Database 2005 of Taiwan which contains original claims data of 1 million beneficiaries which were sampled from the year 2005 Registry for Beneficiaries of the National Health Insurance Database.

The study focused on four CV events: MI, angina, CHF, and CVA. MI was defined by ICD-9 CM diagnosis codes (410, 411, and 413) during hospitalization or emergency contact. CHF was defined by ICD-9 CM diagnosis code (428) on outpatient or emergency contact and prescription of diuretics. Angina pectoris was defined by ICD-9 CM diagnosis code (413) and at least 3 emergency managements. CVA was defined by ICD-9 CM diagnosis codes (430-432, 434-437) and computer tomography or magnetic resonance image in the same record.

Comparisons were made between groups of patients exposed to rosi and pio. The study performed survival analyses including Cox regression. The study adjusted for multiple variables in the Cox model.

Reviewer's Comments:

- ***In the time-to-event analyses, the study did not define the event(s) and censoring.***
- ***The rosi and pio patients received other antidiabetic medications (e.g. metformin or sulfonylurea).***
- ***Univariate analyses showed that gender and stratified age were not statistically significantly different between the rosi and pio groups. It appears that in adjusted analyses, gender was excluded; stratified age was included but the subcategory of patients <40 years old was excluded. The authors did not provide any reason for these exclusions. The subcategory of patients <40 years old comprises 3.5% and 4.5% of the rosi and pio groups, respectively.***
- ***The study did not state whether the PH assumption of the Cox model was satisfied or not.***
- ***The study did not describe how missing data were handled.***

3. **Gallagher AM, Smeeth L, Seabroke S, Leufkens H, van Staa TP. Risk of death and cardiovascular outcomes with thiazolidinediones: A study with the general practice research database and secondary care data. *PLoS ONE* 2011; 6(12):e28157 [pages1-9].**

This was a retrospective observational study of the risk of death and CV outcomes from TZD exposure using the General Practice Research Database (GPRD) in the United Kingdom. The primary study objective was to describe the likely extent of confounding in evaluating the risks of CV events and mortality in patients using diabetes medication.

The study included an exposed cohort consisting of adults 40 years and older with a prescription for insulin or oral antidiabetic drugs (OAD) at least one year after start of data collection. Patients with type I diabetes were excluded. The index date was the first prescription for insulin or OAD one year after the start of GPRD data collection. The follow-up period was from the index date until censor date defined as transfer out of practice, last collection from the practice, or death.

Exposed patients were matched to control patients by age (within 5 years), sex, practice, and index date. The medications of interest in this study include TZD (rosiglitazone and pioglitazone), insulins, metformin, and sulphonylurea. Inception cohorts were identified for each class of diabetes medication. Two separate inception cohorts were also created for rosi and pio. The publication stated that, "Patients prescribed multi-constituent preparations were included in multiple classes of diabetes medication." Patients could belong to multiple inception cohorts and in comparisons between different diabetes medications, patients were censored at the start of treatment with medication of the reference group. The period of follow-up was divided into (a) current (from date of first prescription up to 3 months), (b) recent (the period from 3 to 12 months after the most recent prescription), and (c) past (the period after 12 months after the most recent prescription) exposure. Patients could move between exposure categories over time.

The outcomes of interest were death due to any cause, cause of death, acute coronary syndrome (ACS), stroke, and heart failure. Data for these outcomes were taken from the GPRD, death certificates, or Hospital Episode Statistics (HES).

There were four sets of analyses performed: (1) Comparison of various outcome incidences between past exposure for exposed versus matched control patients (using Poisson regression), (2) Comparison of outcome rates during current use of different diabetes medications (restricted to the types of diabetes medications that did not have major differences in risk during past use; stratified by age, co-prescribing of insulin and calendar time [before and after 2007]), (3) Description of the pattern of risks over duration of treatment for current exposure to diabetes medication, and (4) Estimation of the cumulative incidence over time with current use of various diabetes medications.

The main study comparisons were (1) insulin, sulphonylurea, TZD, metformin past exposures vs controls, (2) insulin, sulphonylurea, TZD past exposures vs metformin past exposure, (3) rosi vs pio current exposures (also stratified by age, co-prescribing of insulin, and calendar time, and (4) rosi vs pio mortality.

Time-to-event analyses were also performed via Kaplan-Meier. Regression models were adjusted for various covariates. Missing values for alcohol use, smoking status, and body mass index were included as separate categories in the statistical models.

Reviewer's Comments:

- ***Control patients were not clearly defined in the study.***
- ***The comparisons between different inception cohorts could be biased because, as stated in the study, patients could belong to multiple inception cohorts.***
- ***The study performed a comparison between exposed diabetic patients versus unexposed control patients without diabetes (analysis (1) above). A comparison between exposed diabetes patients versus unexposed diabetes patients would be a more appropriate comparison.***
- ***The comparison for current exposure may be inadequate to assess the effects of diabetes medications because, as defined above, current exposure is only a three month period. Additionally, patients may have been previously exposed to multiple antidiabetic medications or had concomitant antidiabetic exposures.***
- ***A potential issue when using Poisson regression is overdispersion where the variance of the data is much larger than the mean. The study did not state whether the Poisson model was assessed for overdispersion.***
- ***The study stated that missing data (for alcohol use, smoking status, and body mass index) were classified into a subcategory for the respective covariates in the statistical model. It is unclear how much missing data there was.***

4. **Loebstein R, Dushinat M, Vesterman-Landes J, Silverman B, Friedman N, Katzir, I, Kurnik D, Lomnicky Y, Kokia E, Halkin H. Database evaluation of long-term rosiglitazone treatment on cardiovascular outcomes in patients with Type 2 diabetes.** ***J Clin Pharmacol*** **2011; 51:173-180.**

This was a retrospective observational study of adverse CV outcomes in type 2 diabetes patients who were exposed to rosi and metformin. Patient data were obtained from the Maccabi Healthcare Services (MHS), one of the four public health insurers in Israel. MHS offers comprehensive health coverage to approximately 1,800,000 people nationwide.

Study patients were selected from the Maccabi diabetes mellitus registry and satisfied criteria defined by the American Diabetes Association (fasting plasma glucose > 126 mg/dL or a casual plasma glucose concentration of at least 200 mg/dL). These patients also had a record of purchase of rosi and/or metformin for a period of at least 6 months (between January 1, 2000 and June 30, 2007) with a medication possession ratio (no. of daily doses dispensed over x days divided by x days) of at least 0.7 and no gaps in treatment longer than 3 months. There were three study comparison groups: (1) rosi alone (<10% overlap in rosi exposure with metformin), (2) rosi and metformin combined (>50% overlap in rosi exposure with metformin), and (3) metformin alone.

The study outcomes were AMI, ACS, need for coronary revascularization (either by coronary artery bypass graft or coronary angioplasty with or without stent implantation), CHF, and ACM. Patients with these outcomes were determined from new entries in the Maccabi Heart Registry or from hospital ICD-9 discharge diagnosis codes. Only outcomes that occurred at least 1 month after the first drug purchase until 1 month after drug discontinuation were considered in the analyses.

Time-to-event analyses were performed using the Cox PH model comparing the three study groups (with the metformin group as the reference).

Reviewer's Comments:

- ***Patients with >10% and <50% overlap in rosi exposure with metformin were excluded in the analyses.***
- ***The comparison groups were rosi, metformin, or a combination of both drugs. However, some of the patients in either group were also exposed to insulin or sulfonylurea.***
- ***The study abstract suggests that covariates were included in the statistical models for adjustment only when univariate analyses found them to be significantly different between comparison groups. A variable selection procedure that accounts for correlations among multiple variables may be more appropriate.***
- ***The results tables for each study outcome are labeled "logistic regression" although the study stated that the Cox PH model was used in the analyses.***
- ***The study did not state whether the PH assumption of the Cox model was satisfied or not.***
- ***The study did not describe how missing data were handled.***

5. **Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, Hsiao VC, Tseng CW, Mangione CM, Lasser NL, Crosson JC, Herman WH. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD).** ***Pharmacoepidemiol Drug Saf*** **2010; 19:715-21.**

This was a study that analyzed survey, medical record, administrative, and National Death Index (NDI) data from 1999 through 2003 from the Translating Research Into Action for Diabetes (TRIAD) study, a prospective observational study of diabetes care in managed care. TRIAD involved six research centers collaborating with 10 managed care health plans (HP) and 68 provider groups. Patients were enrolled from July 2000 until August 2001 and included patients who were at least 18 years old, not pregnant, community-dwelling, English or Spanish speaking, and continuously enrolled in the HP for at least 18 months prior to a baseline patient survey. The study involved medical record review at baseline, collection of HP data from 1999 through 2003, and death searches in the National Death Index (NDI) occurring through 2003. This study analyzed type 2 diabetes patients from TRIAD who had complete data, excluding those with age at diagnosis under 30 years and with treatment with insulin only.

HP administrative data was used to determine TZD exposure. Among the 10 HPs, 7 HPs had both TZD's (rosiglitazone and pioglitazone) on formulary.

Insulin treatment at baseline was assessed using patient surveys and medical record reviews. Subsequent insulin treatment was determined using administrative data.

The study ascertained non-fatal AMI, stroke, or percutaneous or surgical CV intervention from HP administrative data. These outcomes were ICD-9 diagnosis codes. Deaths and cause of death were ascertained from NDI.

The study compared patients who were exposed to rosi versus those exposed to pio. Time-to-event analyses were performed from the first TZD prescription until the occurrence of the first CV event or procedure. Patients with no CV event were censored at the earliest of: date of last TZD prescription + days supply + 90 days, the date the

patient disenrolled from the HP, the last date of service in the administrative data, or TRIAD's administrative cut-off date. The Cox proportional hazard model was used for these analyses. Hazard ratios and 95% CI's were reported. The authors stated that the proportional hazards assumption was tested with graphical display and by examination of correlations between the ranked failure time variable and the Schoenfeld residuals of the independent variables.

The Cox model was adjusted for a number of study variables. Missing values for age, sex, race/ethnicity, income, and smoking were <15% and were imputed using single imputation. Separate analyses were performed on patients from (1) all 10 HPs and (2) 7 HPs with both TZD's in the formulary.

Reviewer's Comments:

- ***It is unclear why patients with age at diagnosis under 30 years were excluded in this study when the TRIAD study enrolled patients who were at least 18 years old.***
- ***As stated above, analyses were performed on patients from all 10 HPs and on patients from 7 HPs with both TZD's in the formulary. Among the 3 HPs that did not have both TZD's in the formulary, 2 HPs had pio accounting for 99% of TZD prescriptions while 1 HP had rosi accounting for 100% of all TZD prescriptions. The analyses on the 10 HPs might be biased because of the imbalances in the number of prescriptions to rosi and pio in the 3 HPs. This may be the reason that the study included analyses of the 7 HPs only.***
- ***There were patients in the rosi and pio comparison groups who were also exposed to insulin at baseline or during the study. It is unclear whether these patients were also exposed to other antidiabetes drugs e.g. metformin or sulfonylurea.***

6. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304(4):411-418.

This was a retrospective observational cohort study of the risk of CV adverse events and death in patients 65 years and older who were exposed to rosi and pio. Prescription and other data were obtained from Medicare from July 2006 through June 2009. The study used a new-user inception cohort design where patients with at least 6 months of continuous Medicare Part D (for prescription drugs) enrollment and at least 12 months of continuous Parts A (for hospitalization expenses) and B (for outpatient medical care) enrollment prior to the date of their first TZD prescription were included. Patients who were not resident in a hospital or long-term care facility or receiving hospice care formed the rosi and pio cohorts. Baseline patient data were collected on chronic medical conditions and their medical treatment prescriptions.

The outcomes of interest were AMI, stroke, heart failure, and ACM. CV outcomes were assessed by ICD-9 hospital discharge diagnosis codes. ICD-9 codes in the first and second position were used for AMI while ICD-9 codes in the first position only were used for stroke and heart failure. ACM was determined using the Social Security Master Beneficiary Record database which provides the date but not the cause of death.

Study patients were followed-up from cohort entry until the earliest of: the occurrence of a study endpoint, >7 days gap in TZD exposure, a switch to another TZD treatment, a non-endpoint hospitalization, or end of study period (June 30, 2009). Events occurring within 14 days following a gap in continuous treatment (except for TZD switching or end of study period) or admission to hospital, were included in the analysis.

The study compared patients exposed to rosi to patients exposed to pio. Time-to-event analyses were performed using Kaplan-Meier and Cox PH models stratified by prior history of the CV endpoint and cancer. Hazard ratios and their 95% CIs were reported. The PH assumption in the Cox model was assessed using a test of weighted Schoenfeld residuals.

Preplanned sensitivity analyses were performed including no follow-up after a gap of TZD therapy and restriction of analyses to strata defined by baseline treatment with insulin, metformin, sulfonylureas, or statins.

Reviewer's Comments:

- ***The causes of patient deaths in the study are unknown because the Social Security Master Beneficiary Record database provides the date but not the cause of death.***
- ***The study did not describe how missing data were handled.***

7. Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. *Circ Cardiovasc Qual Outcomes* 2010; 3:538-45.

This was a retrospective observational cohort study of the risk of acute AMI, acute heart failure (AHF), or all-cause death among rosi- and pio-treated patients who were members of WellPoint health plans in California, Georgia, Virginia, and Missouri. Administrative medical/pharmacy data were obtained from the HealthCore Integrated Research Database (HIRD) and mortality data was obtained from the National Death Index (NDI) Plus database. Patients at least 18 years old with a new rosi or pio claim during the period from January 1, 2000 to December 31, 2005 were included in the study, regardless of their history of AMI or AHF.

Patients who did not have continuous health plan eligibility for at least 365 days before the first rosi or pio claim date (the index date), or had a preindex date pharmacy claim for insulin were excluded from the study. Patients were considered to be on continuous therapy if the period between prescription refills was less than 1.5 times the days supply of the preceeding TZD claim. Patients were excluded from the study if they were exposed to both rosiglitazone and pioglitazone during follow-up. Patients who switched medication within 60 days after discontinuing the first drug were censored after the first period of continuous therapy.

There were three analyses performed in the study:

Primary analysis: TZD exposure was measured from index date until the earliest of the end of study period (December 31, 2005), termination from health plan, or occurrence of AMI, AHF, or death.

Sensitivity Analyses:

1. Patients were followed from index date until end of continuous therapy plus 60 days; occurrence of an AMI, AHF, or death; or end of health plan enrollment, whichever occurred first.
2. Patients were followed from the index date until the end of continuous therapy; occurrence of AMI, AHF, or death; or end of health plan enrollment, whichever occurred first.

An additional analysis was performed to study the subpopulation of patients who were at least 65 years of age.

PS matching was used to control for measured potential confounders which included demographic/clinical variables that were identified in the 12-month preindex period. PS were obtained using logistic regression controlling for the measured potential confounders. Patients were matched in a 1:1 fashion using Parsons 1:1 greedy 4→1 digit matching algorithm. The quality of the match was determined by comparing baseline characteristics on the matched sample and standardized differences.

The study compared patients exposed to rosi to patients exposed to pio. The Cox PH model was used to evaluate the effects of exposure to rosi and pio on time to cardiovascular event (AMI, AHF) and mortality using all patients, patients age 65 years and over, and the PS-matched patients. The regression analyses using all patients and patients age 65 years and over were adjusted for relevant covariates.

Reviewer's Comments:

- ***The publication presented the endpoints for all propensity matched patients (approximately 80% of the total patient sample) but did not do so for the unmatched patients. However, Table 5 (copied from the publication, page 542) below shows that when all patients are included (matched or unmatched), the risks of the composite outcome under various analyses are not statistically significant.***
- ***PS matching was not used in the subsample of patients who were at least 65 years old because of the small sample, although there were no significant differences observed in baseline characteristics between treatment groups except index year.***
- ***The publication did not discuss whether the PH assumption of the Cox model was satisfied or not.***
- ***The study did not describe how missing data were handled.***
- ***The publication stated a few strengths or improvements of the current study compared to previous studies such as Gerritts et al. (2007), Winkelmayer et al. (2008), and Juurlink et al. (2009): (1) The use of PS matching to ensure similarity at baseline between groups (2) The use of NDI to improve the accuracy of the results by potentially capturing deaths that occurred outside the hospital (3) The mean duration of therapy was longer by a few months compared to previous studies (e.g. 3 months longer than Winkelmayer et al., 2008 and 6 months longer than Juurlink et al., 2009) and (4) The population studied was not limited to older patients.***
- ***The following limitations were cited in the publication: (1) Even when the database is large, the study's statistical power may be limited by the rarity of the events in the population and the ability to detect small differences in cohorts. Furthermore, because the study database encompasses a commercially-insured population, elderly patients and those with substantial chronic illness who are at highest risk***

are underrepresented relative to the overall US population. (2) The study could not assess the length of time patients had diabetes because the preindex period was only 1 year, although diabetes severity was accounted for in the multivariate model by identifying claims for diabetes-related complications. Furthermore, patients who used insulin before TZD use were excluded because this may imply the disease has progressed to become a confounding factor related to AMI. However, because only a small subset of patients had electronic laboratory values available, no laboratory values (HbA1c, glucose) were evaluated to assess degree of diabetes control. (3) There were unmeasured confounders (e.g. body mass index, exercise, family history of CV disease, aspirin use) that could have affected the results.

III. Additional Reviewer Comments

- ***The 7 studies did not explicitly state the study designs, i.e. whether they were cohort or case-control studies. However, all 7 studies appeared to be retrospective cohort studies based on the study description.***
- ***The studies do not state whether endpoints and analyses were pre-specified in study protocols.***
- ***Among the 6 studies that used the Cox PH model (all except [3]), only studies [5] and [6] checked the PH assumption.***
- ***Among the 6 studies that studied death (all except [2]), only study [3] studied the cause of death.***
- ***Two studies [3, 7] did not explicitly state whether the antidiabetes drugs were administered as monotherapies or combination therapies.***
- ***All studies, except ([2, 6-7]), discussed how missing data were handled.***
- ***None of the studies provided adjustments for multiple comparisons.***
- ***Study [1] was co-funded by Pfizer.***

IV. Summary of Numerical Study Results

Table 5: Summary of Numerical Results

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[1] Tannen et al., 2012	Replication Studies: 709 (Pio) vs 1,654 (Control)	Death	C: 0.82 (0.63, 1.08)	Intention-to-Treat Analysis C: 0.90 (0.67, 1.21); PS: 0.81 (0.61, 1.08); P: NR As-Treated Analysis: C: 0.61 (0.41, 0.91); PS: NR; P: NR	None
		Stroke	C: 0.70 (0.41, 1.18)	Intention-to-Treat Analysis C: 0.75 (0.43, 1.32); PS: 0.69 (0.39, 1.21); P: 0.75 (0.39, 1.34) As-Treated Analysis: C: 0.85 (0.45, 1.61); PS: NR; P: 0.84 (0.41, 1.57)	
		AMI	C: 1.00 (0.63, 1.57)	Intention-to-Treat Analysis C: 0.86 (0.53, 1.40); PS: 0.83 (0.51, 1.35); P: 0.88 (0.49, 1.42) As-Treated Analysis: C: 0.74 (0.42, 1.31); PS: NR; P: 0.76 (0.38, 1.30)	
		CRV	C: 1.14 (0.75, 1.71)	Intention-to-Treat Analysis C: 1.01 (0.65, 1.55); PS: 0.97 (0.63, 1.51); P: 1.20 (0.70, 2.04) As-Treated Analysis: C: 1.11 (0.69, 1.77); PS: NR; P: 1.37 (0.76, 2.34)	
		CHF	C: 1 31 (0.91, 1.87)	Intention-to-Treat Analysis C: 1.25 (0.85, 1.85); PS: 1.20 (0.81, 1.77); As-Treated Analysis: C: 1.50 (0.99, 2.28); PS: NR; P: NR	
	Replication Studies: 2,001 (Rosi) vs 5,056 (Control)	Death	C: 0.85 (0.73, 0.99)	Intention-to-Treat Analysis C: 0.93 (0.79, 1.10); PS: 0.87 (0.74, 1.03); P: NR As-Treated Analysis: C: 0.74 (0.60, 0.92); PS: NR; P: NR	None
		Stroke	C: 0.75 (0.55, 1.02)	Intention-to-Treat Analysis C: 0.80 (0.58, 1.12); PS: 0.71 (0.51, 0.99); P: 0.88 (0.59, 1.24) As-Treated Analysis: C: 0.67 (0.45, 1.00); PS: NR; P: 0.71 (0.44, 1.06)	
		AMI	C: 1.21 (0.95, 1.55)	Intention-to-Treat Analysis C: 1.18 (0.89, 1.55); PS: 1.20 (0.91, 1.57); P: 1.31 (0.94, 1.74) As-Treated Analysis: C: 1.06 (0.77, 1.45); PS: NR; P: 1.17 (0.83, 1.61)	
		CRV	C: 1.34 (1.07, 1.67)	Intention-to-Treat Analysis C: 1.19 (0.93, 1.52); PS: 1.25 (0.98, 1.60); P: 1.30 (0.97, 1.70) As-Treated Analysis: C: 1.09 (0.83, 1.44); PS: NR; P: 1.20 (0.87, 1.62)	
		CHF	C: 1 22 (0.97, 1.53)	Intention-to-Treat Analysis C: 1.25 (0.97, 1.60); PS: 1.21 (0.95, 1.56); P: NR As-Treated Analysis: C: 1.14 (0.85, 1.51); PS: NR; P: NR	

C=Cox PH model; PS=propensity score; P=PERR adjustment; NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[1] Tannen et al., 2012…continued	Replication Studies: 2,001 (Rosi) vs 709 (Pio)	Death	NR	Intention-to-Treat Analysis C: 1.23 (0.93, 1.61); PS: 1.14 (0.87, 1.49); P: NR As-Treated Analysis: C: 1.38 (0.92, 2.08); PS: NR; P: NR	None
		Stroke		Intention-to-Treat Analysis C: 1.12 (0.65, 1.92); PS: 1.09 (0.64, 1.87); P: 1.36 (0.75, 2.75) As-Treated Analysis: C: 0.89 (0.46, 1.72); PS: NR; P: 1.05 (0.53, 2.54)	
		AMI		Intention-to-Treat Analysis C: 1.26 (0.81, 1.96); PS: 1.27 (0.82, 1.96); P: 1.55 (0.98, 2.65) As-Treated Analysis: C: 1.40 (0.80, 2.44); PS: NR; P: 1.62 (0.53, 2.54)	
		CRV		Intention-to-Treat Analysis C: 1.17 (0.79, 1.71); PS: 1.24 (0.85, 1.82); P: 1.16 (0.67, 1.88) As-Treated Analysis: C: 0.99 (0.64, 1.54); PS: NR; P: 0.95 (0.54, 1.65)	
		CHF		Intention-to-Treat Analysis C: 0.89 (0.63, 1.26); PS: 0.81 (0.58, 1.15); P: NR As-Treated Analysis: C: 0.73 (0.49, 1.09); PS: NR; P: NR	
	Expanded Studies: 3,844 (Pio) vs 11,090 (Control)	Death	C: 0.65 (0.57, 0.74)	Intention-to-Treat Analysis C: 0.70 (0.60, 0.81); PS: 0.76 (0.66, 0.88); P: NR As-Treated Analysis: C: 0.51 (0.42, 0.62); PS: NR; P: NR	None
		Stroke	C: 0.90 (0.69, 1.18)	Intention-to-Treat Analysis C: 0.95 (0.70, 1.29); PS: 1.01 (0.77, 1.42); P: 1.10 (0.77, 1.61) As-Treated Analysis: C: 0.81 (0.56, 1.17); PS: NR; P: 0.94 (0.59, 1.40)	
		AMI	C: 0.89 (0.70, 1.15)	Intention-to-Treat Analysis C: 0.94 (0.87, 1.49); PS: 1.01 (0.76, 1.34); P: 1.14 (0.82, 1.63) As-Treated Analysis: C: 0.89 (0.64, 1.24); PS: NR; P: 1.09 (0.74, 1.62)	
		CRV	C: 0.94 (0.73, 1.21)	Intention-to-Treat Analysis C: 0.93 (0.71, 1.24); PS: 0.93 (0.07, 1.23); P: 1.14 (0.77, 1.65) As-Treated Analysis: C: 0.89 (0.64, 1.23); PS: NR; P: 1.08 (0.71, 1.57)	
		CHF	C: 1 20 (0.99, 1.46)	Intention-to-Treat Analysis C: 1.40 (1.12, 1.75); PS: 1.52 (1.21, 1.92); P: NR As-Treated Analysis: C: 1.47 (1.15, 1.87); PS: NR; P: NR	

C=Cox PH model; PS=propensity score; P=PERR adjustment; NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[1] Tannen et al., 2012…continued	Expanded Studies: 10,862 (Rosi) vs 32,135 (Control)	Death	C: 0.67 (0.62, 0.72)	Intention-to-Treat Analysis C: 0.77 (0.70, 0.83); PS: 0.79 (0.73, 0.86); P: NR As-Treated Analysis: C: 0.63 (0.56, 0.70); PS: NR; P: NR	None
		Stroke	C: 0.85 (0.72, 1.00)	Intention-to-Treat Analysis C: 0.91 (0.76, 1.10); PS: 0.97 (0.80, 1.17); P: 1.33 (1.06, 1.68) As-Treated Analysis: C: 0.83 (0.67, 1.03); PS: NR; P: 1.22 (0.95, 1.57)	
		AMI	C: 0.88 (0.75, 1.02)	Intention-to-Treat Analysis C: 0.93 (0.79, 1.09); PS: 0.94 (0.80, 1.11); P: 1.24 (1.00, 1.52) As-Treated Analysis: C: 0.76 (0.62, 0.93); PS: NR; P: 1.06 (0.83, 1.32)	
		CRV	C: 0.90 (0.77, 1.05)	Intention-to-Treat Analysis C: 0.94 (0.78, 1.12); PS: 0.97 (0.81, 1.16); P: 1.04 (0.83, 1.28) As-Treated Analysis: C: 0.85 (0.69, 1.04); PS: NR; P: 0.93 (0.73, 1.18)	
		CHF	C: 1 11 (0.99, 1.25)	Intention-to-Treat Analysis C: 1.14 (1.00, 1.30); PS: 1.25 (1.09, 1.44); P: NR As-Treated Analysis: C: 1.03 (0.88, 1.19); PS: NR; P: NR	
	Expanded Studies: 10,862 (Rosi) vs 3,844 (Pio)	Death	NR	Intention-to-Treat Analysis C: 1.09 (0.94, 1.26); PS: 1.08 (0.94, 1.24); P: NR As-Treated Analysis: C: 1.23 (1.00, 1.51); PS: NR; P: NR	None
		Stroke		Intention-to-Treat Analysis C: 0.98 (0.74, 1.30); PS: 0.97 (0.74, 1.29); P: 1.13 (0.77, 2.67) As-Treated Analysis: C: 1.04 (0.72, 1.50); PS: NR; P: 1.20 (0.77, 1.86)	
		AMI		Intention-to-Treat Analysis C: 0.99 (0.76, 1.28); PS: 1.02 (0.79, 1.32); P: 1.05 (0.72, 1.50) As-Treated Analysis: C: 0.93 (0.67, 1.29); PS: NR; P: 0.95 (0.63, 1.43)	
		CRV		Intention-to-Treat Analysis C: 0.92 (0.70, 1.20); PS: 0.93 (0.72, 1.21); P: 0.95 (0.66, 1.40) As-Treated Analysis: C: 0.88 (0.63, 1.22); PS: NR; P: 0.88 (0.58, 1.35)	
		CHF		Intention-to-Treat Analysis C: 0.98 (0.80, 1.19); PS: 0.98 (0.81, 1.19); P: NR As-Treated Analysis: C: 0.84 (0.67, 1.06)	

C=Cox PH model; PS=propensity score; P=PERR adjustment; NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[2] Chou et al., 2011	7,695 (Rosi vs Pio)	MI	NR	0.539 (0.327, 0.889)	A total of 7,725 patients (6,048 rosi and 1,677 pio) were included in the final analysis. For each outcome, only the total number of patients was reported.
	7,494 (Rosi vs Pio)	CHF		0.820 (0.619, 1.086)	
	7,653 (Rosi vs Pio)	Angina		0.543 (0.293, 1.006)	
	7,410 (Rosi vs Pio)	CVA		0.949 (0.724, 1.244)	
[3] Gallagher et al., 2011	Insulin vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 2.40 (2.20, 2.61) Fully adjusted: 2.84 (2.60, 3.11)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.00 (1.54, 2.61) Fully adjusted: 1.68 (1.27, 2.21)	
		Stroke		Age, sex, calendar year adjusted: 1.91 (1.45, 2.52) Fully adjusted: 1.91 (1.43, 2.56)	
		CHF		Age, sex, calendar year adjusted: 2.23 (1.74, 2.87) Fully adjusted: 1.62 (1.25, 2.10)	
	Sulphonylurea vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 1.77 (1.72, 1.82) Fully adjusted: 2.18 (2.11, 2.26)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.38 (2.23, 2.54) Fully adjusted: 1.63 (1.51, 1.77)	
		Stroke		Age, sex, calendar year adjusted: 1.82 (1.68, 1.97) Fully adjusted: 1.60 (1.45, 1.76)	
		CHF		Age, sex, calendar year adjusted: 2.45 (2.30, 2.62) Fully adjusted: 1.42 (1.31, 1.54)	
	TZD vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 1.77 (1.66, 1.88) Fully adjusted: 3.04 (2.77, 3.33)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.47 (2.17, 2.81) Fully adjusted: 1.61 (1.31, 1.97)	
		Stroke		Age, sex, calendar year adjusted: 1.90 (1.61, 2.25) Fully adjusted: 1.89 (1.46, 2.45)	
		CHF		Age, sex, calendar year adjusted: 3.23 (2.80, 3.72) Fully adjusted: 1.75 (1.41, 2.17)	
	Metformin vs Control (Past Exposures)	Death	NR	Age, sex, calendar year adjusted: 2.01 (1.96, 2.07) Fully adjusted: 2.23 (2.15, 2.31)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 2.48 (2.32, 2.67) Fully adjusted: 1.55 (1.42, 1.68)	
		Stroke		Age, sex, calendar year adjusted: 2.05 (1.89, 2.22) Fully adjusted: 1.72 (1.56, 1.89)	
		CHF		Age, sex, calendar year adjusted: 2.97 (2.77, 3.19) Fully adjusted: 1.50 (1.38, 1.63)	
	Insulin vs Past Exposure of Metformin	Death	NR	Age, sex, calendar year adjusted: 1.38 (1.26, 1.50) Fully adjusted: 1.24 (1.12, 1.37)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 1.00 (0.76, 1.32) Fully adjusted: 1.04 (0.79, 1.37)	
		Stroke		Age, sex, calendar year adjusted: 0.99 (0.75, 1.32) Fully adjusted: 0.95 (0.71, 1.26)	
		CHF		Age, sex, calendar year adjusted: 0.94 (0.73, 1.22) Fully adjusted: 0.94 (0.73, 1.22)	

NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[3] Gallagher et al., 2011...continued	Sulphonylurea vs Past Exposure of Metformin	Death	NR	Age, sex, calendar year adjusted: 0.96 (0.89, 1.03) Fully adjusted: 0.97 (0.90, 1.04)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 1.23 (1.03, 1.48) Fully adjusted: 1.29 (1.08, 1.55)	
		Stroke		Age, sex, calendar year adjusted: 1.01 (0.82, 1.25) Fully adjusted: 1.04 (0.85, 1.29)	
		CHF		Age, sex, calendar year adjusted: 1.20 (0.99, 1.44) Fully adjusted: 1.34 (1.12, 1.62)	
	TZD vs Past Exposure of Metformin	Death	NR	Age, sex, calendar year adjusted: 0.81 (0.76, 0.85) Fully adjusted: 0.84 (0.79, 0.89)	Number of patients not reported.
		ACS		Age, sex, calendar year adjusted: 1.03 (0.91, 1.18) Fully adjusted: 1.05 (0.92, 1.20)	
		Stroke		Age, sex, calendar year adjusted: 0.91 (0.77, 1.07) Fully adjusted: 0.92 (0.79, 1.09)	
		CHF		Age, sex, calendar year adjusted: 1.12 (0.98, 1.28) Fully adjusted: 1.13 (0.99, 1.29)	
	Rosi vs Pio (Current Exposures)	Death (GPRD)	NR	Age, sex, calendar year adjusted: 1.15 (1.04, 1.28) Fully adjusted: 1.20 (1.08, 1.34)	Number of patients not reported.
		Death (ONS)		Age, sex, calendar year adjusted: 1.09 (0.90, 1.32) Fully adjusted: 1.07 (0.89, 1.29)	
		ACS (GPRD)		Age, sex, calendar year adjusted: 0.99 (0.84, 1.16) Fully adjusted: 1.03 (0.87, 1.21)	
		ACS (HES)		Age, sex, calendar year adjusted: 1.04 (0.79, 1.37) Fully adjusted: 1.02 (0.77, 1.35)	
		Stroke (GPRD)		Age, sex, calendar year adjusted: 1.00 (0.80, 1.26) Fully adjusted: 1.05 (0.83, 1.32)	
		Stroke (HES)		Age, sex, calendar year adjusted: 1.16 (0.77, 1.74) Fully adjusted: 1.12 (0.75, 1.68)	
		CHF (GPRD)		Age, sex, calendar year adjusted: 1.08 (0.92, 1.27) Fully adjusted: 1.14 (0.97, 1.34)	
		CHF (HES)		Age, sex, calendar year adjusted: 1.73 (1.19, 2.50) Fully adjusted: 1.73 (1.19, 2.51)	
	Rosi vs Pio (Current Exposures)	Death (age<65)	NR	Age, sex, calendar year adjusted: 1.08 (0.82, 1.41) Fully adjusted: 1.14 (0.87, 1.49)	Number of patients not reported.
		Death (age≥65)		Age, sex, calendar year adjusted: 1.17 (1.04, 1.31) Fully adjusted: 1.22 (1.09, 1.37)	
		ACS (age<65)		Age, sex, calendar year adjusted: 0.79 (0.61, 1.03) Fully adjusted: 0.82 (0.64, 1.07)	
		ACS (age≥65)		Age, sex, calendar year adjusted: 1.12 (0.92, 1.38) Fully adjusted: 1.17 (0.95, 1.43)	
		Stroke (age<65)		Age, sex, calendar year adjusted: 0.84 (0.52, 1.36) Fully adjusted: 0.90 (0.56, 1.46)	
		Stroke (age≥65)		Age, sex, calendar year adjusted: 1.05 (0.81, 1.36) Fully adjusted: 1.09 (0.84, 1.41)	

NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[3] Gallagher et al., 2011...continued	Rosi vs Pio (Current Exposures)	CHF (age<65)	NR	Age, sex, calendar year adjusted: 0.90 (0.61, 1.34) Fully adjusted: 0.95 (0.64, 1.42)	Number of patients not reported.
		CHF (age≥65)		Age, sex, calendar year adjusted: 1.12 (0.94, 1.34) Fully adjusted: 1.19 (0.99, 1.42)	
	Rosi vs Pio (Current Exposures)	Death (co-prescribing insulin: no)	NR	Age, sex, calendar year adjusted: 1.16 (1.05, 1.30) Fully adjusted: 1.22 (1.09, 1.35)	Number of patients not reported.
		Death (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 1.12 (0.63, 1.97) Fully adjusted: 1.20 (0.68, 2.13)	
		ACS (co-prescribing insulin: no)		Age, sex, calendar year adjusted: 0.98 (0.83, 1.15) Fully adjusted: 1.00 (0.85, 1.18)	
		ACS (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 1.70 (0.71, 4.08) Fully adjusted: 1.83 (0.76, 4.42)	
		Stroke (co-prescribing insulin: no))		Age, sex, calendar year adjusted: 0.98 (0.78, 1.23) Fully adjusted: 1.02 (0.81, 1.29)	
		Stroke (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 2.54 (0.49, 13.16) Fully adjusted: 2.66 (0.51, 13.84)	
		CHF (co-prescribing insulin: no)		Age, sex, calendar year adjusted: 1.11 (0.94, 1.31) Fully adjusted: 1.16 (0.98, 1.37)	
		CHF (co-prescribing insulin: yes)		Age, sex, calendar year adjusted: 0.73 (0.31, 1.75) Fully adjusted: 0.80 (0.33, 1.91)	
	Rosi vs Pio (Current Exposures)	Death (<2007)	NR	Age, sex, calendar year adjusted: 1.15 (0.98, 1.35) Fully adjusted: 1.20 (1.03, 1.41)	Number of patients not reported.
		Death (≥2007)		Age, sex, calendar year adjusted: 1.13 (0.98, 1.30) Fully adjusted: 1.19 (1.03, 1.37)	
		ACS (<2007)		Age, sex, calendar year adjusted: 1.04 (0.83, 1.30) Fully adjusted: 1.06 (0.84, 1.33)	
		ACS (≥2007)		Age, sex, calendar year adjusted: 0.90 (0.71, 1.13) Fully adjusted: 0.94 (0.75, 1.19)	
		Stroke (<2007)		Age, sex, calendar year adjusted: 1.33 (0.94, 1.87) Fully adjusted: 1.40 (0.99, 1.98)	
		Stroke (≥2007)		Age, sex, calendar year adjusted: 0.74 (0.54, 1.02) Fully adjusted: 0.76 (0.55, 1.06)	
		CHF (<2007)		Age, sex, calendar year adjusted: 1.04 (0.83, 1.29) Fully adjusted: 1.10 (0.88, 1.37)	
		CHF (≥2007)		Age, sex, calendar year adjusted: 1.13 (0.89, 1.43) Fully adjusted: 1.20 (0.94, 1.53)	
	Rosi vs Pio (Current Users)	ACM		Age, sex, calendar year adjusted: 1.09 (0.90, 1.32)	Number of patients not reported.

NR=not reported

First author/ Year of publication	Number of patients/ Drug therapy	Outcomes	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Comments
[4] Loebstein et al., 2011	745 (Rosi) vs 11,938 (Metformin)	AMI	NR	1.13 (0.6, 2.1)	HR were as reported in the text.
		ACS		0.85 (0.57, 1.26)	
		CRV		1.22 (0.82, 1.54)	
		CHF		2.23 (1.41, 3.53)	
		ACM		1.15 (0.85, 1.56)	
	2,753 (Rosi combo) vs 11,938 (Metformin)	AMI	NR	0.95 (0.5, 1.4)	HR were as reported in the text.
		ACS		1.08 (0.83, 1.40)	
		CRV		1.18 (0.94, 1.49)	
		CHF		1.33 (0.91, 1.95)	
		ACM		0.90 (0.69, 1.17)	
[5] Bilik et al., 2010	10 Health Plans: 773 (Rosi) vs 711 (Pio); 7 Health Plans: 564 (Rosi) vs 334 (Pio)	Nonfatal MI	0.71 (NR); 0.89 (NR)	10 Health Plans: 0.75 (0.33, 1.67); 7 Health Plans: 1.30 (0.31, 5.37)	95% CI for crude estimates were not reported.
		CRV	0.92 (NR); 0.80 (NR)	10 Health Plans: 1.08 (0.47, 2.45); 7 Health Plans: 0.82 (0.49, 1.37)	
		Nonfatal MI or CRV	0.80 (NR); 0.83 (NR)	10 Health Plans: 0.91 (0.46, 1.78); 7 Health Plans: 1.01 (0.38, 2.67)	
		Nonfatal Stroke	1.34 (NR); 1.18 (NR)	10 Health Plans: 1.42 (0.76, 2.62); 7 Health Plans: 1.33 (0.89, 1.98)	
		Nonfatal MI, CRV or Nonfatal Stroke	0 96 (NR); 0.93 (NR)	10 Health Plans: 1.08 (0.62, 1.88); 7 Health Plans: 1.11 (0.52, 2.36)	
		CV Mortality	0.54 (NR); 0.79 (NR)	10 Health Plans: 0.62 (0.22, 1.71); 7 Health Plans: 0.93 (0.21, 4.12)	
		ACM	0.26 (NR); 0.66 (NR)	10 Health Plans: 0.74 (0.39, 1.40); 7 Health Plans: 0.69 (0.28, 1.69)	
		Nonfatal MI or ACM	0.75 (NR); 0.81 (NR)	10 Health Plans: 0.83 (0.51, 1.35); 7 Health Plans: 0.99 (0.51, 1.91)	
		Nonfatal MI, Nonfatal Stroke or CV Mortality	0.90 (NR); 0.97 (NR)	10 Health Plans: 0.94 (0.63, 1.40); 7 Health Plans: 1.16 (0.61, 2.18)	
		Nonfatal MI, Nonfatal Stroke or ACM	0.88 (NR); 0.88 (NR)	10 Health Plans: 0.94 (0.67, 1.32); 7 Health Plans: 1.03 (0.67, 1.60)	
		Nonfatal MI, CRV, Nonfatal Stroke or ACM	0.90 (NR); 0.86 (NR)	10 Health Plans: 1.00 (0.63, 1.57); 7 Health Plans: 0.99 (0.54, 1.82)	
[6] Graham et al., 2010	67,593 (Rosi) vs 159,978 (Pio)	AMI	1.07 (0.97, 1.19)	1.06 (0.96, 1.18)	None
		Stroke	1.31 (1.15, 1.49)	1.27 (1.12, 1.45)	
		Heart Failure	1.27 (1.18, 1.37)	1.25 (1.16, 1.34)	
		ACM	1.17 (1.07, 1.27)	1.14 (1.05, 1.24)	
		AMI, Stroke, Heart Failure, or ACM	1.20 (1.14, 1.26)	1.18 (1.12, 1.23)	
[7] Wertz et al., 2010	14,469 (Rosi) vs 14,469 (Pio)	Composite (AMI, AHF, ACD): Matched Patients	NR	1.03 (0.91, 1.15)	Only primary analysis results are included here.
	2,558 (Rosi) vs 2,819 (Pio)	Composite (AMI, AHF, ACD): Patients ≥65 years		0.97 (0.83, 1.12)	
	18,319 (Rosi) vs 18,309 (Pio)	Composite (AMI, AHF, ACD): All Patients		1.00 (0.90, 1.11)	

NR=not reported

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/s/

JOHN S YAP
04/23/2013

MARK S LEVENSON
04/23/2013

OFFICE of DRUG EVALUATION I and DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS (DCaRP)

Memorandum

Date: May 14, 2013

From: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products

Ellis F. Unger, M.D., Director, Office of Drug Evaluation-I

Robert Temple, M.D., Deputy Director for Clinical Science, CDER

To: The File

The FDA background package for June 5-6, 2013, Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee includes a background document with two attachments written by Dr. Thomas Marciniak, a medical team leader in the Division of Cardiovascular and Renal Products. The title of his briefing document is "RECORD re-adjudication advisory committee briefing document, NDA 21-071." Attachments 1 and 2 are his "RECORD re-adjudication reviews" of April 23, 2013 and May 15, 2012, respectively.

Center for Drug Evaluation and Research (CDER) policies are intended to promote open scientific exchange while allowing for an orderly decision-making process. Consistent with this policy, CDER permits staff to file reviews on topics that are not formally assigned and to present their points of view to public advisory committees. Whether work is officially assigned or performed independently, reviews are expected to meet the highest standards and scientific principles. Dr. Marciniak's memoranda were neither assigned by his supervisors in the Division of Cardiovascular and Renal Products nor solicited by the Division of Metabolic and Endocrine Products, which manages NDA 21071. He did not seek supervisory review or concurrence prior to filing his memoranda in the FDA Document Archiving, Reporting and Regulatory Tracking System (DAARTS) – our electronic filing system. Thus, although Dr. Marciniak's documents are part of the official FDA record for NDA 21-071, rosiglitazone (Avandia), his views do not necessarily reflect official FDA positions.

This memorandum does not offer commentary on Dr. Marciniak's specific criticisms of particular findings. The Division of Cardiovascular and Renal Products and the Division of Metabolic and Endocrine Products have provided detailed reviews of the RECORD re-adjudication process, and we refer the reader to the review memoranda of Drs. Preston

Dunnmon, Karen Mahoney, and Mary Parks for commentary on the re-adjudication process and its findings. We do, however, have a number of thoughts about the overall tone and content of Dr. Marciniak's reviews.

At CDER, we encourage, even cherish, scientific debate. Although Dr. Marciniak did not request supervisory concurrence for his reviews, we support and respect his right to express his scientific views. Regrettably, however, some of the views expressed in his memoranda go beyond scientific and regulatory principles and issues. They include disparaging remarks about FDA staff and review units, as well as serious allegations regarding the competence and behavior of DCRI and GlaxoSmithKline, and, indeed, all investigations and organizations that are paid by a drug company for any clinical trial conduct or analysis activity. The Division of Cardiovascular and Renal Products and the Office of Drug Evaluation-I reject these personal remarks, and have the following specific concerns regarding Dr. Marciniak's review memoranda:

Limitations of academic research organizations; lack of independence from drug companies

Dr. Marciniak criticizes academic research organizations (AROs) in general, and the Duke Clinical Research Institute (DCRI) in particular, for both general (they are paid by drug companies) and specific potential biases. There is no support provided for this broad assertion about the biased conduct of essentially all studies. Clinical trials, as well as non-clinical studies, are conducted either by drug company personnel or by contractors, all of whom are remunerated for their efforts. There are important legal consequences for falsifying results, and we are aware of no evidence that AROs in fact regularly present intentionally biased or fraudulent results. Obviously, if being paid for work regularly induced bias, there could be essentially no credible data of any kind related to most medical treatments. We do not believe this represents an accurate picture of the current state of clinical investigation.

In addition to the overall bias, Dr. Marciniak asserts that AROs are not truly independent when dealing with data from drug company-sponsored trials, because the data are provided and controlled by the sponsor, and the ARO is ill-equipped to detect or report problems. In essence, Dr. Marciniak asserts that if an ARO analyzes only clinical documents and data provided by a company, then the outcome of any analysis is pre-determined by the company that provided this information. But when a study is complete, the only source of that data collected, the data to be re-adjudicated, is the sponsor. The plan for re-adjudication of RECORD was carefully reviewed by expert biostatisticians and clinical trial experts at FDA, and agreed to in advance.

The implication of Dr. Marciniak's assertions is that data should be collected, analyzed, and adjudicated only by entities independent of the company, and such entities should not be reimbursed by the company. We do not accept the view that every investigator or ARO that is paid to carry out a study or analysis should be assumed to be biased and will misinterpret or even falsely interpret results in order to favor the sponsoring drug company.

We recognize that drug companies have an interest in showing that their drugs are effective and that they will not cause unreasonable harm. Randomization and blinding are major mechanisms in place to protect against bias reflective of such interest. FDA

also requires pre-specified protocols and statistical analytical plans for studies of regulatory importance, and we follow up with careful review of the data, as well as and audits and inspections as warranted, all, again, devoted to assuring that interpretations are not influenced by preferred outcomes. We do not believe, however, that the well-established and well-recognized concerns about potential bias in interpretation of data, the primary stimulus to the development of the randomized clinical trial, reflect a belief that investigators will regularly engage in fraudulent behavior. We also recognize that RECORD was not blinded, and that the open-label design could raise concerns about the quality and consistency of event ascertainment. We doubt, however, that the open-label design would affect ascertainment of deaths, and the adjudication and re-adjudication of the clinical endpoints was blinded. The mortality analysis in particular is highly credible and shows no suggestion of a deleterious effect of rosiglitazone. Indeed there is a numerical trend in favor of, and not against, rosiglitazone. For details, we refer the reader to the numerous reviews, endorsed by supervisors, in this FDA background package, specifically the review memoranda of Dr. Preston Dunnmon from Division of Cardiovascular and Renal Products, and Drs. Karen Mahoney and Mary Parks from the Division of Metabolic and Endocrine Products. We also note that some of the comments provided for the FDA background package by Dr. Marciniak and referred to as the "Dunnmon, Grant & Stockbridge, DCRP consult regarding RECORD re-adjudication mortality findings, FDA, May 13-14, 2012" were taken out of context.

In essence, Dr. Marciniak alleges that parties involved in the sponsorship, the re-adjudication, the statistical review, and the inspection of RECORD were all unreliable because of contractual arrangements, flaws in some unrelated matter, or both. We disagree with his assessment.

Data Mishandling

Apart from his general skepticism about the reliability of any party paid to conduct a clinical trial or analysis, Dr. Marciniak gives various examples of what he refers to as "data mishandling," or "blunders," by DCRI, not only in RECORD, but also in the large registrational trials for ticagrelor (PLATO) and apixaban (ARISTOTLE).

Given that over 41,000 subjects were enrolled in these three trials and millions of individual data points were collected, and given the computing resources available to FDA, it is not surprising that a few errors and/or inconsistencies have been uncovered. Of note, however, Dr. Mahoney's review of the RECORD data filed May 6, 2013 (page 42 of 53) actually rebuts all but one of the cases of "data mishandling'' described by Dr. Marciniak. Subsequent review of the ARISTOTLE (apixaban) data (after the reports Dr. Marciniak referenced) showed that apparent dosing errors were almost all spurious and that the study was reliable. The study supported approval of apixaban for use in non-valvular atrial fibrillation.

Unprofessional Language

Apart from the content and basis for Dr. Marciniak's critique, we find much of the language used in his memoranda regrettable. A number of passages insult our own review staff (Dr. Preston Dunnmon), our Biostatistical staff, DCRI, and the applicant. We find this language unprofessional, inappropriate, and not commensurate with our standards.

As noted, we welcome and thrive on honest debate, but it is unprofessional to insult someone because he or she disagrees with you.

Summary

In summary, we stand by the reviews of Drs. Preston Dunnmon and Karen Mahoney, and agree that the re-adjudication of RECORD is acceptable. We do not believe there is evidence that being paid to perform an investigation (as all investigators are) or manage a trial (as all AROs and CROs are) inevitably leads to a biased study.

After re-adjudication, we do not find a cardiovascular "signal" of concern in RECORD. The mortality data are, in fact, reassuring.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 23, 2013

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (DCRP)

Subject: RECORD re-adjudication advisory committee briefing document, NDA 21-071

To: Jena Weber, Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

This review provides my background materials for the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on June 5 and 6, 2013, regarding the RECORD trial re-adjudication. While the materials are lengthy I am insisting that they be communicated intact, including all attachments, because many of the issues discussed are complex with detailed relevant histories.

Executive Summary

The RECORD trial re-adjudication does not provide reassurances regarding the cardiovascular (CV) safety of rosiglitazone but reinforces the flaws in RECORD that force us to conclude that RECORD can only provide suggestions of CV safety problems and can not confirm safety. The reasons for these conclusions are the following:

1. Academic research organizations (AROs), in particular the Duke Clinical Research Institute (DCRI) that performed the re-adjudication, have limitations when dealing with drug-companied sponsored activities and poor track records of detecting or reporting problems. Duke's poor track record of detecting fraud is highlighted by the Anil Potti fiasco and its poor track record of detecting or reporting trial problems is documented in recent FDA submissions such as the PLATO trial of ticagrelor and the ARISTOTLE trial of apixaban.

2. The re-adjudication was not independent. As the DCRI charter states simply, "2.0 Role of the DCRI RECORD CEC Group. The DCRI RECORD CEC group is responsible for the conduct of the CEC operations for the RECORD Re-Adjudication Protocol, in collaboration with the sponsor, GSK." While the charter and reports describe "collaboration", the descriptions of the activities in the reports document that GSK controlled the re-adjudication just as it controlled the original adjudication. We should

not find it surprising that the results of the two, non-independent adjudications are similar. Furthermore, DCRI and the other contractor, MediciGlobal, were not financially independent of GSK as documented by publically-available Web pages.

3. The re-adjudication provides minimal new information. The success rate of the 127 DCRI queries regarding "unknown" and "insufficient information" deaths was 5.5%, i.e., DCRI changed 7 causes of death from "unknown" to a known cause based on queries. The success rate for the 343 MediciGlobal vital status searches was about 10%, i.e., new follow-up beyond the study end date in 20 rosiglitazone and 9 control patients (>2:1 favoring rosiglitazone), and five death changes (4:1 favoring rosiglitazone.) The MediciGlobal follow-up is also suspect because of its black box nature.

4. While the DCRI re-adjudication, because of the three reasons discussed above, can not provide reassurances about the safety of rosiglitazone, it did confirm the extreme mishandling of cases by GSK. The DCRI re-adjudication agrees with my characterization of three of the four cases I highlighted as extreme mishandling in my review for the 2010 advisory committee meeting. DCRI adjudicated the fourth case, a stroke with a 36-day hospitalization reported by a family member, as "insufficient information." This case, as well as the second case involving a 46-day hospitalization with inadequate information, illustrates the vast missing data problem in RECORD that persists to this day.

5. The FDA epidemiology reviewer in 2007, the FDA cardiorenal reviewer in 2010, and the FDA cardiorenal reviewers in 2012 all described serious RECORD design flaws such that RECORD can not provide re-assurances regarding the safety of rosiglitazone. RECORD remains a broken RECORD.

Summary

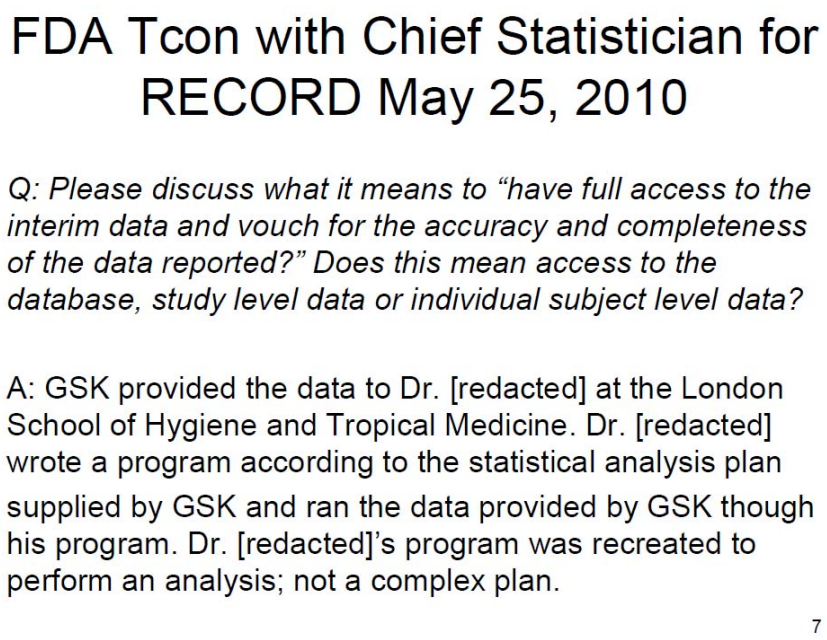
The summary below provides additional details regarding the five problems with the RECORD re-adjudication described above. The attachments provide all of the details and the summary provides references to specific discussions in the attachments.

1. Limitations of Academic Research Organizations

Drug companies, when sponsoring clinical trials, typically contract with academic physicians, organized as "academic research organizations" or "AROs", to participate in some aspects of the trials such as protocol design and publication of the trial results in an academic journal. The extent of the involvement in the trial of the ARO and the access to trial source documentation and raw data sets are typically not disclosed. Finally, the financial arrangements between the drug company and the ARO are not disclosed and the control of the drug company over release of trial information is also typically not detailed.

The experience of the ARO for RECORD, the London School of Hygiene and Tropical Medicine (LSHTM), illustrates well the limited involvement of an ARO in a trial. The FDA interviewed the chief statistician for RECORD from LSHTM on May 25, 2010. I have included the minutes of the interview in Appendix 2 of Attachment 1 and pertinent excerpts in Figure 1.

Figure 1:

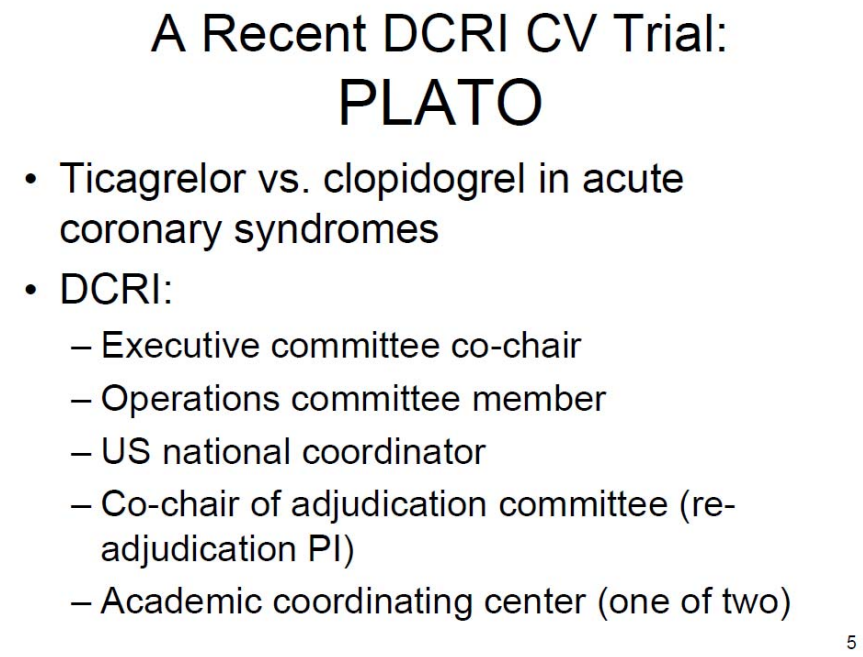


b. What analyses did you or your staff perform to verify the data? See 4a.
c. Were you provided access to RECORD data sets? If so, what type of datasets and when? All raw data sets? Analytical data sets only? Other? See 4a.
d. Were you provided access to and did you examine case report forms? Endpoint dossiers (dossiers and patients)? Data query forms, notes to record, data clarifications, etc. (patients)? No
e. Did you or your staff check the coding of adverse events? No
f. Did you or your staff check the CV endpoint adjudications? No
g. Did you or your staff cross-check data sets to verify that referrals for adjudication were complete? AEs vs. endpoints? Hospitalizations from the Medical Care Utilisation forms vs. AEs and endpoints? No

The role of LSHTM in RECORD appears to have been very limited regarding confirmation of data quality. On the other hand, a press release on the GSK website dated March 23, 2010, states "Both the interim and final analyses were independently verified at the London School of Hygiene and Tropical Medicine." The "independently verified" appears to have been limited to running the same statistical analyses against the GSK-provided, unverified datasets.

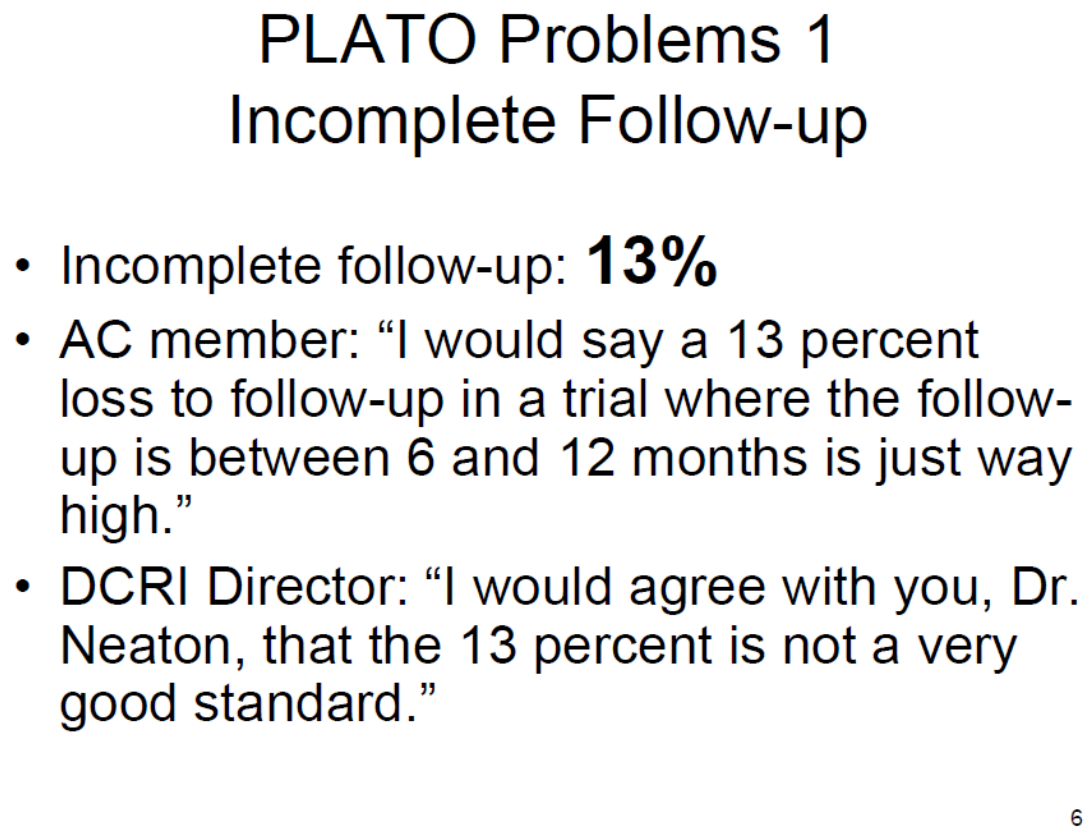
DCRI experiences with clinical trials appears to be similar to LSHTM's. Figure 2 lists DCRI's involvement in a recent CV outcomes trial, the PLATO trial of ticagrelor vs. clopidogrel in acute coronary syndromes.

Figure 2:



PLATO, like RECORD, had many trial conduct problems. PLATO, like RECORD, was plagued by incomplete follow-up as described in Figure 3.

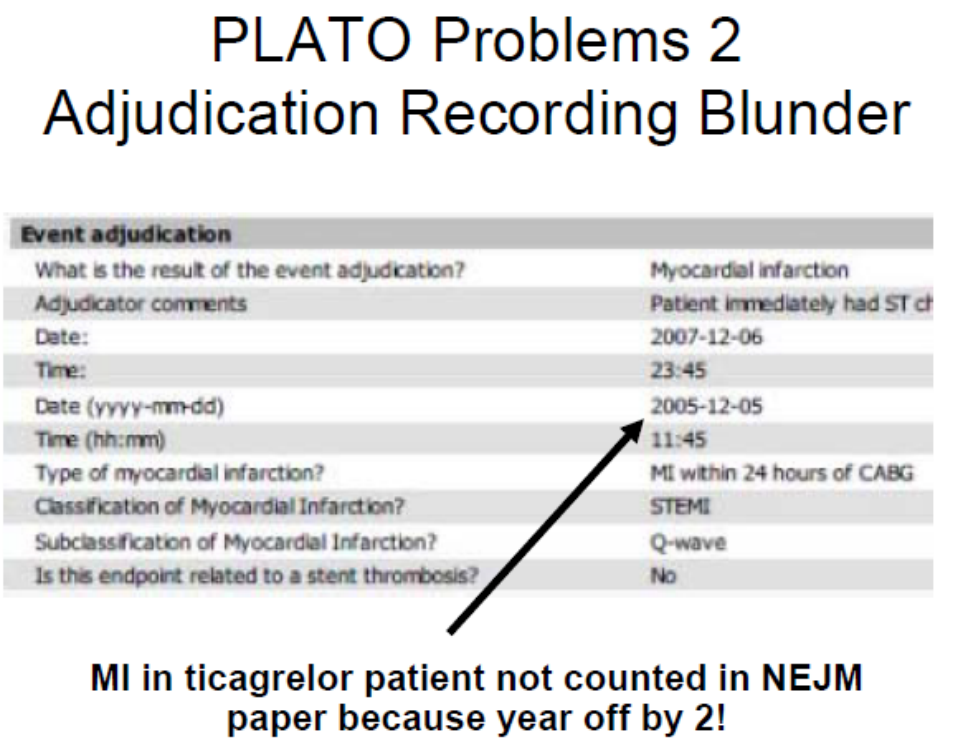
Figure 3:



The incomplete follow-up rate in PLATO, 13% for a trial with a median treatment duration of 277 days, is worse than that in RECORD. So we're to be reassured about the follow-up and data quality problems in RECORD by an ARO re-assessing the RECORD problems two to ten years later when that ARO has a poor track record of insuring good follow-up contemporaneously?

PLATO, like RECORD, had suspicious miscountings of events. I show in Figure 4 one flagrant example.

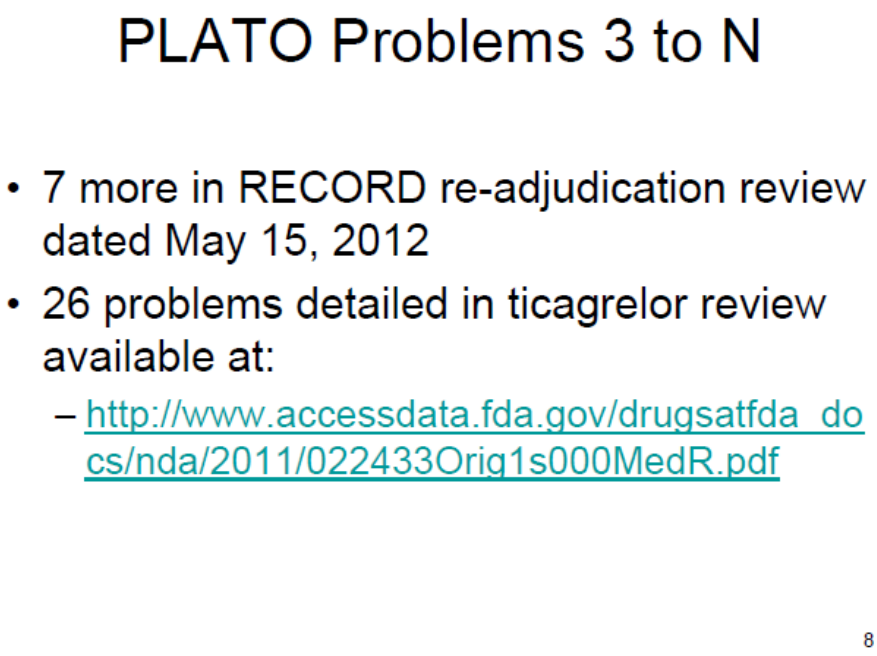
Figure 4:



The MI referenced in Figure 4 was correctly adjudicated except for the date. It was not counted in the NEJM paper presenting the PLATO results. If one wants to call this mistake an anomalous fluke, there were two other endpoints similarly not counted in the NEJM paper because of event timing blunders—all three in ticagrelor patients. These errors are the types of errors that one can identify in datasets—if one has the relevant datasets and one has experience with checking them.

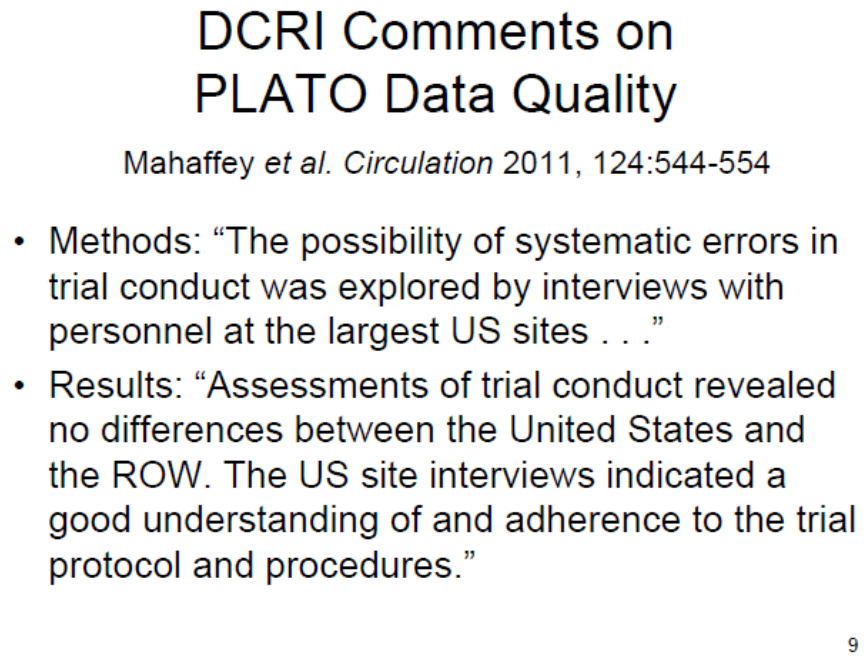
PLATO had many other study conduct problems. I described some of them in the references listed in Figure 5.

Figure 5:



We informed DCRI of the data quality problems at the July 28, 2010, advisory committee meeting. In a paper exploring regional variations in 2011 DCRI commented on trial conduct as quoted in Figure 6.

Figure 6:



Why did DCRI interview personnel at the largest US sites rather than examining source documents? How could they conclude that assessments of trial conduct revealed no differences between the United States and the ROW if they only interviewed US sites? Did they really expect sites to report that they didn't adhere to the protocol and trial procedures? Perhaps their concern with participants having a good understanding of the trial protocol is related to the fact the then DCRI director and PLATO co-principal investigator emphasized erroneously at the ticagrelor advisory committee meeting on July 28, 2010, that the randomization for PLATO was stratified by invasive intent—it was not.

I document problems with another recent trial participated in by DCRI, the ARISTOTLE trial of apixaban vs. warfarin in atrial fibrillation, in Attachment 1, pages 3 to 6. However, the most telling indictment of Duke regarding failure to detect trial conduct problems is conveyed by two words: Anil Potti. Anil Potti is the Duke researcher who falsified many study results leading to the retractions of many published papers. If Duke couldn't detect frank fraud concurrently at its own institution, how can we be confident that it can clear up the data quality problems for RECORD two to ten years later and an ocean away?

2. Lack of Independence in the Re-Adjudication

The supporters of RECORD persist in calling the re-adjudication "independent", i.e., the April 15, 2013, Federal Register notice for the advisory committee meeting states that "the committees will discuss the results of an independent readjudication of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial." However, the re-adjudication was clearly not independent of GSK. The Clinical Events Classification (CEC) Charter states the relationship of DCRI to GSK as a "collaboration" as shown in Figure 7.

Figure 7:

RECORD Re-Adjudication is NOT Independent

Clinical Events Classification (CEC) Charter

Re-Adjudication Protocol AVD115170
"RECORD"

2.0 Role of the DCRI RECORD CEC Group

The DCRI RECORD CEC group is responsible for the conduct of the CEC operations for the RECORD Re-Adjudication Protocol, in collaboration with the sponsor, GSK. The DCRI CEC group creates and maintains the CEC Charter and will develop the event

Version 1.0 2011May02 4

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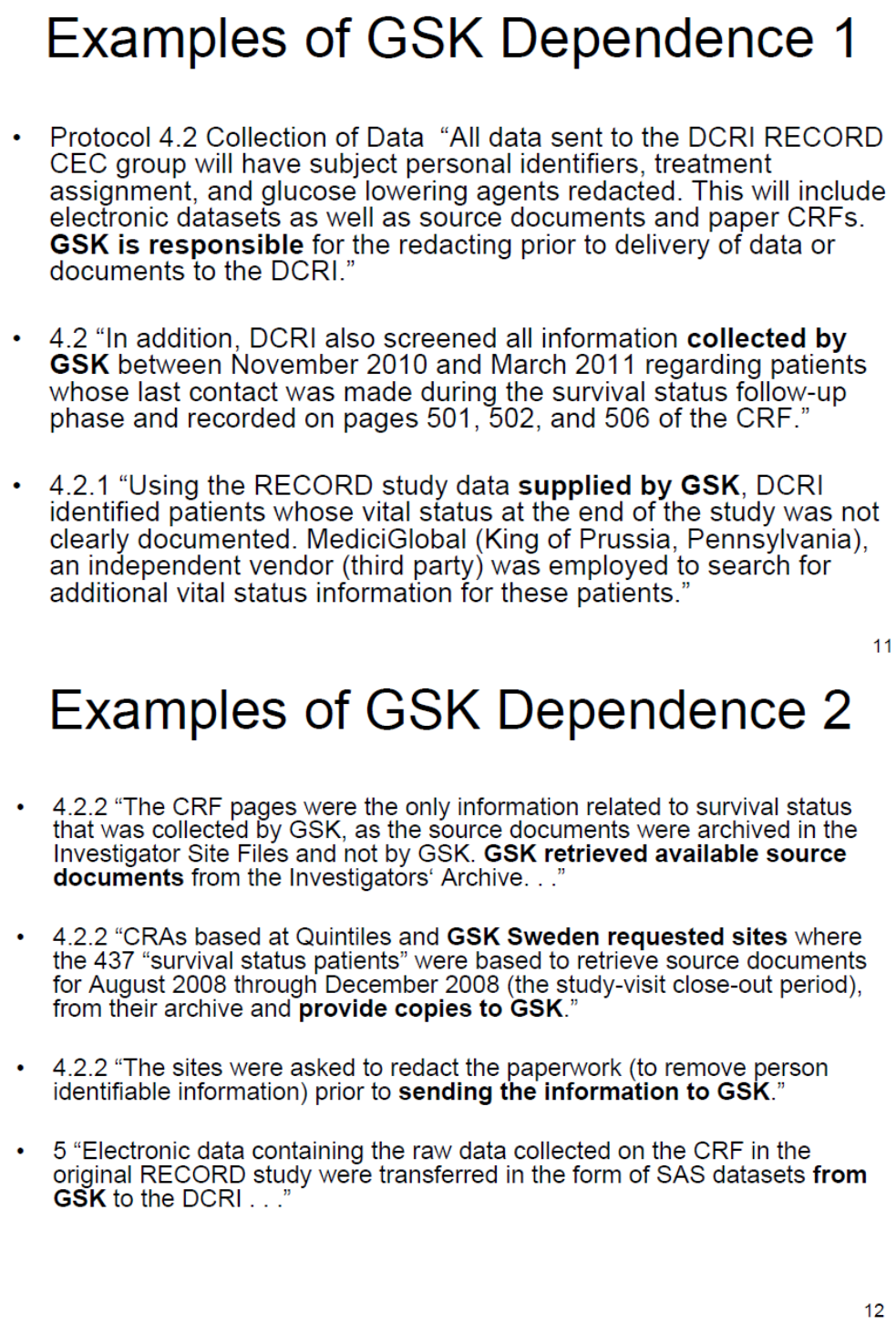
While DCRI called its relationship to GSK "collaboration", the relationship might be more accurately termed "controlled by GSK" based on the activities described in the DCRI reports quoted in Figure 8. I provide more details on the GSK involvement in the re-adjudication in Attachment 2, pages 3 to 5.

Figure 8:



Not only was the re-adjudication operationally dependent upon GSK, but the contractors were financially dependent upon GSK as well. The financial dependence of DCRI upon GSK is shown by the article from the Duke student newspaper excerpted in Figure 9.

Figure 9:

DCRI Was
NOT Financially Independent

The Chronicle

The Research Industrial Complex

By Caroline McGeough | April 23, 2010

In one tower of an nondescript, nine-story white building on Fulton Street, just across from Duke University Hospital, operates the world's largest academic clinical research institute, generating more than $125 million in revenue per year from the research grants and contracts it receives from both government sources and from industry. Its more than 218 clients in the pharmaceutical and medical device sectors include corporate giants Johnson & Johnson, Pfizer, GlaxoSmithKline and GE Healthcare. The Duke Clinical Research Institute, composed of more than 1,000 employees supporting the worldwide

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The DCRI re-adjudication PI received consulting fees directly from GSK as documented in Figure 10, from the PLATO article, and in the DCRI website conflict of interest pages.

Figure 10:

The PI Was
NOT Financially Independent

Mahaffey *et al. Circulation* 2011, 124:544-554

Dr Mahaffey has received consulting fees from AstraZeneca, Bayer, Boehringer Ingleheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmith-Kline, Johnson & Johnson, Merck, Ortho/McNeill, Sanofi-Aventis, and Schering-Plough (now Merck); he has also received research funding from Bayer, Boehringer Ingleheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Portola Pharmaceuticals, Pozen, Regado, Sanofi-Aventis, Schering-Plough (now Merck), and The Medicines Com-pany.

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The other contractor, MediciGlobal, does not post conflict of interest statements or client listings on its website. However, a former employee's new release confirms GSK as a MediciGlobal client as described in Figure 11.

Figure 11:

The MediciGlobal website does relate that the company suffered when a drug company was forced to withdraw its product from the market as described in Figure 12.

Figure 12:

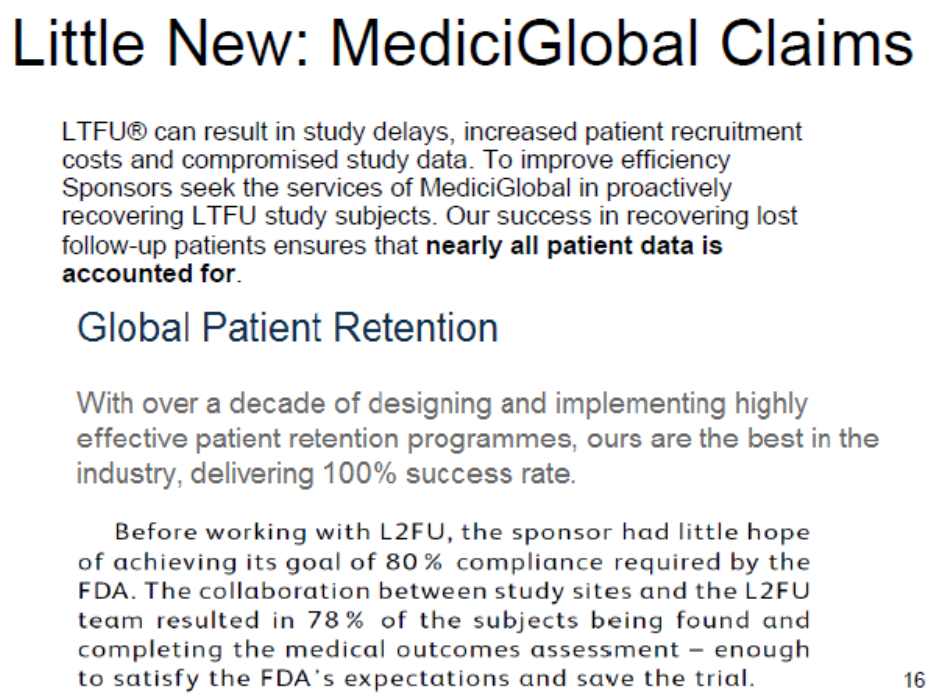
DCRI also suffered when Novartis discontinued its involvement in the elinogrel development program. DCRI also "adjusted headcount" earlier this year, cutting 56 jobs per the student newspaper at http://www.dukechronicle.com/articles/2013/04/04/duke-clinical-research-institute-cuts-56-jobs.

I provide additional details on the DCRI financial conflict of interest declarations in Attachment 2, pages 2-3. Both DCRI and MediciGlobal have financial reasons for wanting to keep their client GSK happy.

3. Minimal New Information

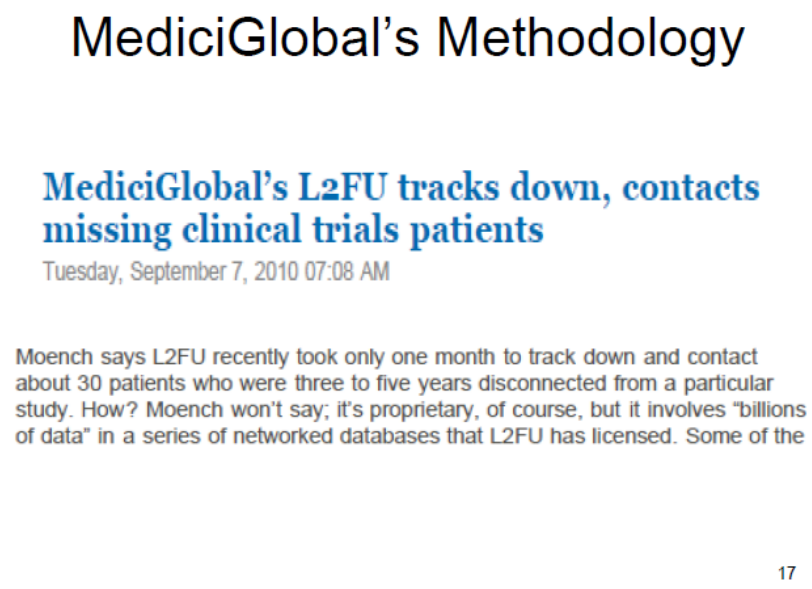
Before reviewing the reality of new information for the RECORD re-adjudication, I find it informative to examine the claims of success made by the MediciGlobal contractor. I show selected MediciGlobal claims from the web in Figure 13.

Figure 13:



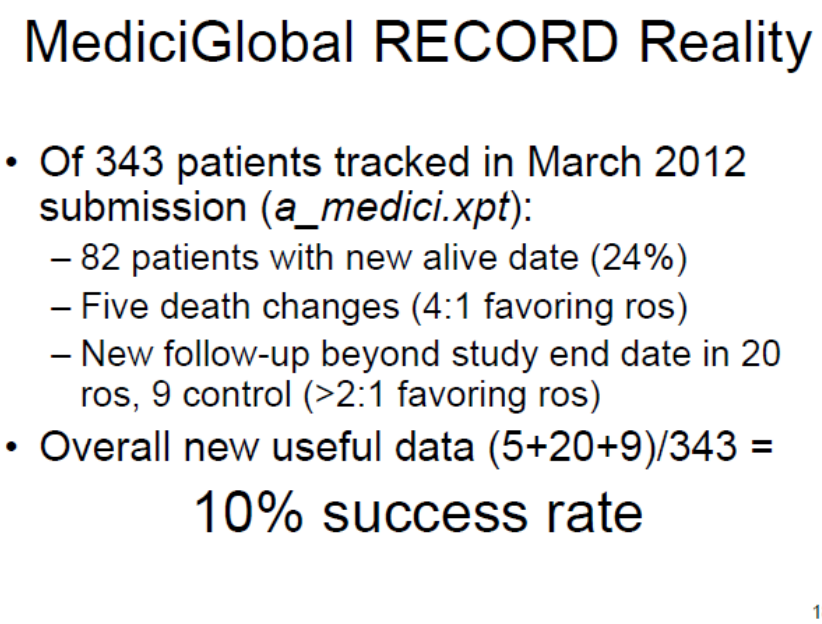
The first paragraph above claims that MediciGlobal is successful in recovering "nearly all patient data" for lost follow-up patients. The claim for patient retention in the second paragraph is perfection, i.e., "100% success rate." The claimed reality reported in an article allegedly describing real results for trial submitted to the FDA isn't quite as glowing but allegedly acceptable to the FDA, "78% of the subjects being found and completing the medical outcomes assessment" (but I don't consider 78% at all acceptable for CV outcome studies.) How MediciGlobal achieves these results is a black box, i.e., "proprietary, of course, but it involves 'billions of data'" as noted in Figure 14.

Figure 14:



The above example seems similar to the RECORD re-adjudication, i.e., "three to five years disconnected from a particular study" and yet "took only one month to track down and contact about 30 patients." The reality of what MediciGlobal achieved for RECORD is quite different. I show statistics for the initial RECORD vital status follow-up in Figure 15.

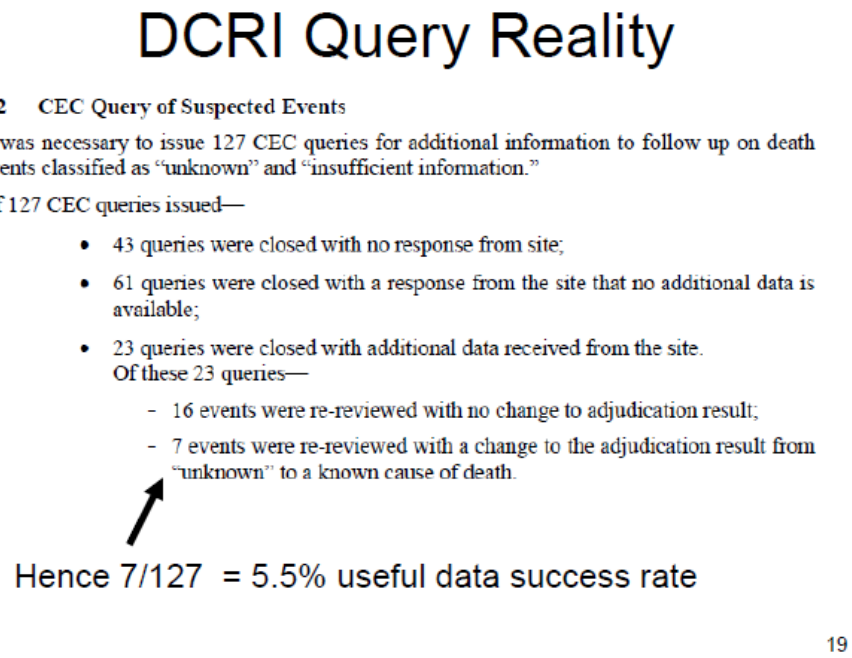
Figure 15:



Not only is the success rate low but the results appear to favor rosiglitazone highly. The point to consider is that GSK supplied the search data to MediciGlobal. I provide more details regarding the MediciGlobal follow-up in Attachment 2, pages 7 to 8.

The results for DCRI queries to sites regarding deaths classified as "unknown" or "insufficient information" were slightly worse. I show the query statistics in Figure 16.

Figure 16:



The DCRI queries produced useful information for only 7 patients regarding deaths. The MI/stroke queries were similarly unproductive: Of 70 queries only two resulted in adjudication changes, one from MI yes to no and one from MI no to yes. I provide additional discussion regarding problems with the DCRI queries and results in Attachment 2, pages 6 and 8 to 9.

The problems with missing data in RECORD are particularly concerning because we would expect differential informative censoring: We would expect rosiglitazone patients to discontinue prematurely because of worsening heart failure, such patients fare poorly, and many of them may have discontinued and been lost prior to having any cardiac event or death. I discussed this issue and presented the data confirming it at the second day (July 14) of the 2010 rosiglitazone advisory committee meeting, the minutes of which are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Endocrinologicand Metabolic DrugsAdvisoryCommittee/UCM222629.pdf, pages 249 to 250.

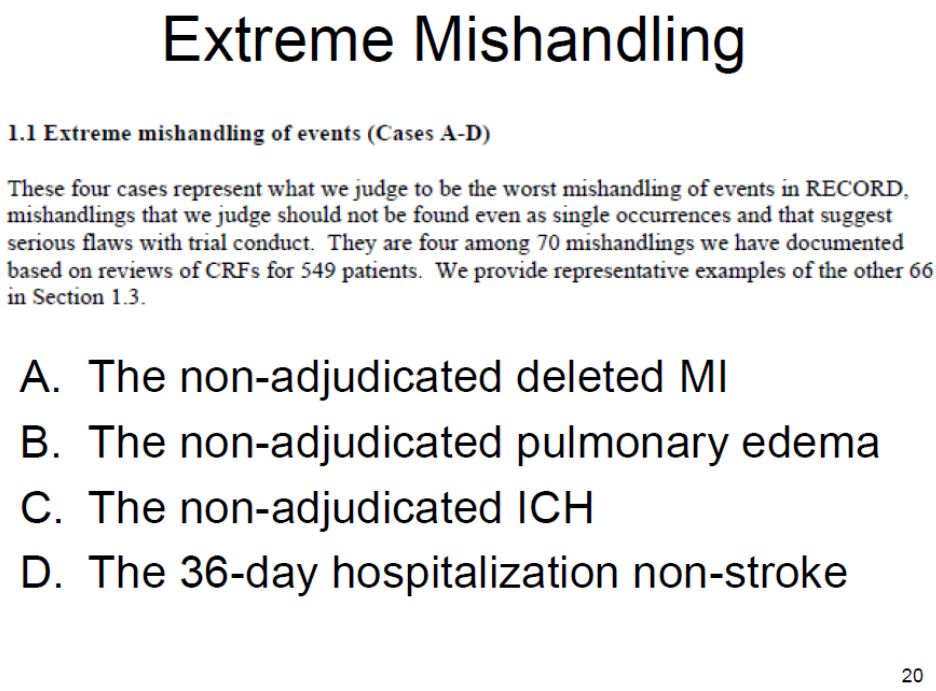
The re-adjudication generated very little new information. Lacking new information and controlled by GSK, the results are similar to GSK's original.

4. Extreme Mishandling Confirmed

Because GSK provided all of the documents and datasets to DCRI the RECORD re-adjudication can not determine whether RECORD confirms the safety of rosiglitazone; it can only suggest that the data as provided by GSK do not confirm safety problems. The problems I identified in RECORD in 2010 (and the problems I have identified in PLATO, ARISTOTLE, TRITON, ATLAS, and other recent CV outcome trials) were not primarily problems with the adjudications; they were primarily problems with referrals for adjudication and with missing data. Because GSK controlled the submissions to DCRI, I argue that examining the DCRI adjudications or auditing DCRI is futile. I would expect that the DCRI results are consistent with the documents GSK provided to them. The one value of examining the DCRI adjudications is to determine whether the DCRI adjudications confirmed the mishandling of cases that I identified in 2010.

In 2010 I identified four case of extreme mishandling listed in Figure 17.

Figure 17:

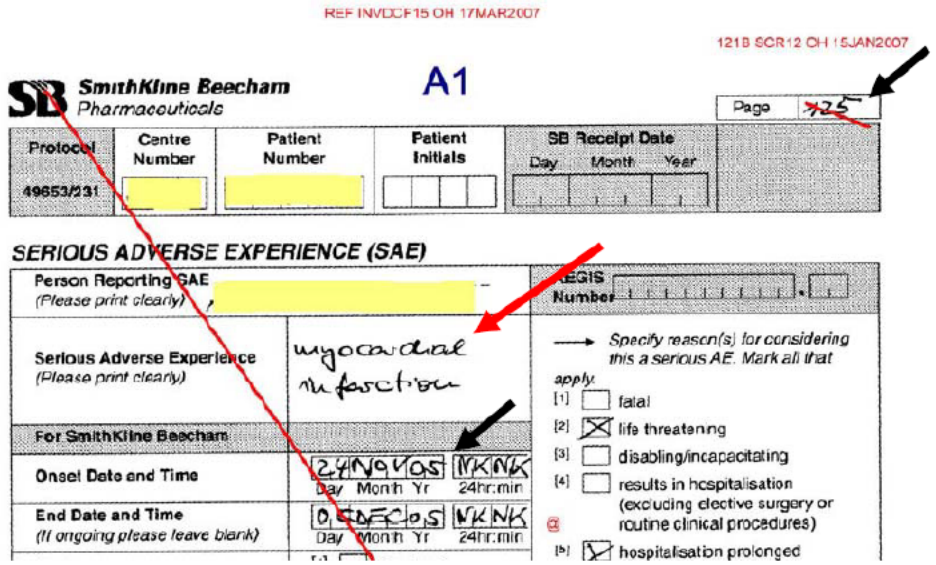


As Figure 17 describes, I identified these four cases of extreme mishandling among my reviews of CRFs for 549 patients, i.e., I reviewed about 12% of the 4,458 RECORD patients. There likely are other examples of extreme mishandling among the 3,909 patients I didn't review. Note also that the other problem cases in my 2010 review were representative examples, not egregious ones.

I summarize the four extremely mishandled cases below for convenience of reference. Case A, depicted in Figure 18 and Figure 19, was my sentinel case of an MI SAE that was deleted 15 months after the event.

Figure 18:

Case A: The Deleted MI

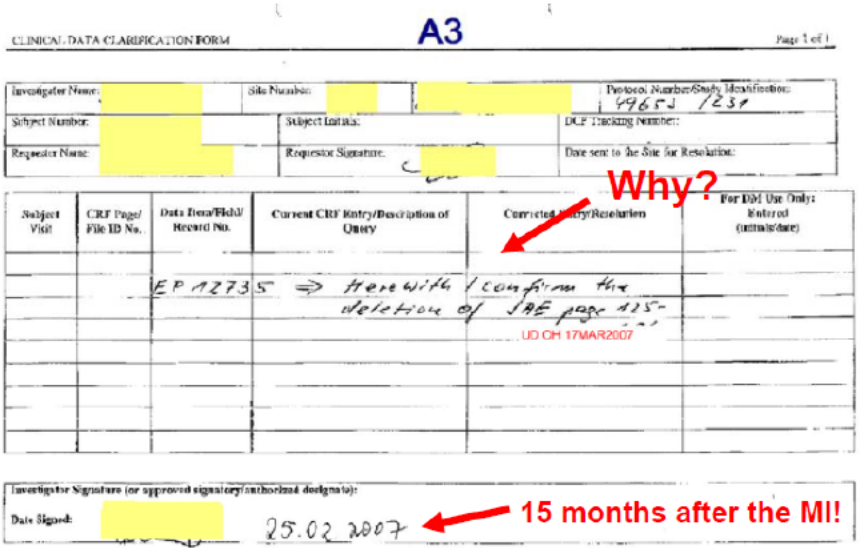


This patient had PTCA on [redacted] and died of HF on [redacted]

21

Figure 19:

Case A:The MI Vanishes!



The event was never referred for adjudication.

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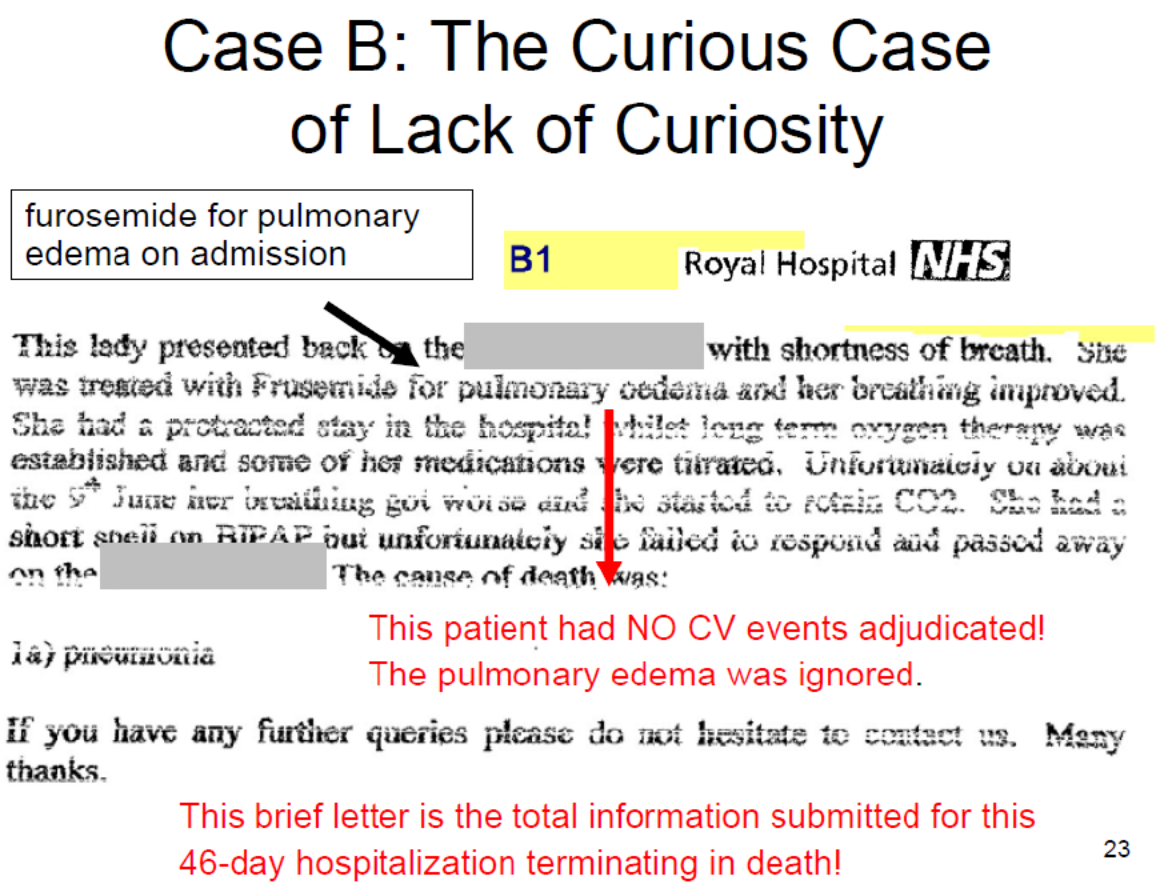
Case B was an unadjudicated 46-day pulmonary edema hospitalization with the minimal information shown in Figure 20. Was the cause of the pulmonary edema an MI? The death was adjudicated as pneumonia, non-CV. How long did the heart failure persist such that the cause of death should have been heart failure and hence CV?

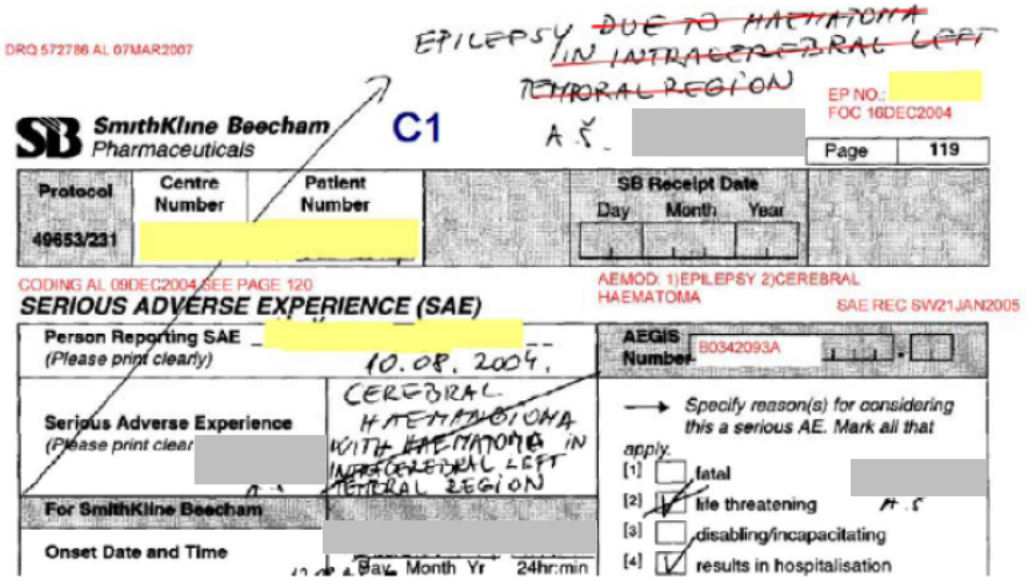
Figure 20:



Case C involved seizures related to an intracerebral hematoma that was reported only as epilepsy and not adjudicated. This patient also had a "worsening of hypertension" AE reported about five months prior to the intracerebral bleed.

Figure 21:

Case C: The Stroke Vanishes!



DRQ 572786 AL 07MAR2007

EPILEPSY ~~DUE TO HAEMATOMA IN INTRACEREBRAL LEFT TEMPORAL REGION~~

EP NO.: [redacted]
FOC 16DEC2004

SmithKline Beecham Pharmaceuticals C1

A.S. [redacted]

Page 119

Protocol	Centre Number	Patient Number	SB Receipt Date Day Month Year
49653/231	[redacted]		

CODING AL 09DEC2004 SEE PAGE 120

AEMOD: 1)EPILEPSY 2)CEREBRAL HAEMATOMA

SAE REC SW21JAN2005

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) [redacted] 10.08.2004.

AEGIS Number B0342093A

Serious Adverse Experience (Please print clear) [redacted] CEREBRAL HAEMATOMA ~~WITH HAEMATOMA IN INTRACEREBRAL LEFT TEMPORAL REGION~~

A.S.

Specify reason(s) for considering this a serious AE. Mark all that apply.

[1] ☐ fatal
[2] ☐ life threatening
[3] ☐ disabling/incapacitating
[4] ☑ results in hospitalisation

For SmithKline Beecham

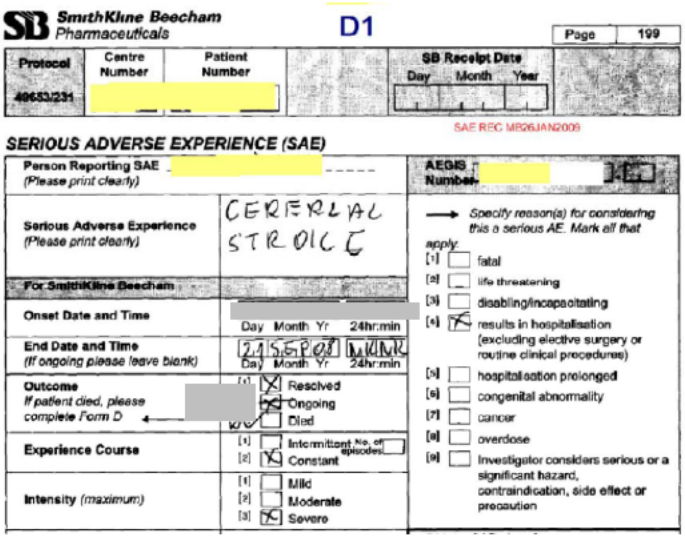
Onset Date and Time [redacted] Day Month Yr 24hr:min

24

Case D was a stroke SAE that was adjudicated as a non-stroke, despite a 36-day hospitalization, because the only information allegedly obtained from the family was regarding the occurrence of a stroke and the dates of the hospitalization.

Figure 22:

Case D: A Stroke SAE



SmithKline Beecham Pharmaceuticals — D1 — Page 199

Protocol	Centre Number	Patient Number	SB Receipt Date Day Month Year
49653/231	[redacted]		

SAE REC MR26JAN2009

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly): [redacted] — AEGIS Number: [redacted]

Serious Adverse Experience (Please print clearly)	CEREBRAL STROKE	→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] ☐ fatal; [2] ☐ life threatening; [3] ☐ disabling/incapacitating; [4] ☒ results in hospitalisation (excluding elective surgery or routine clinical procedures); [5] ☐ hospitalisation prolonged; [6] ☐ congenital abnormality; [7] ☐ cancer; [8] ☐ overdose; [9] ☐ Investigator considers serious or a significant hazard, contraindication, side effect or precaution
For SmithKline Beecham		
Onset Date and Time	[redacted] Day Month Yr 24hr:min	
End Date and Time (If ongoing please leave blank)	21 SEP 08 Day Month Yr 24hr:min [redacted]	
Outcome If patient died, please complete Form D	[1] ☒ Resolved; [2] ☒ Ongoing; [3] ☐ Died	
Experience Course	[1] ☐ Intermittent No. of episodes; [2] ☒ Constant	
Intensity (maximum)	[1] ☐ Mild; [2] ☐ Moderate; [3] ☒ Severe	

25

Figure 23:

Case D: Another Stroke Vanishes!

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

Patient was admitted to hospital due to stroke cerebral from [redacted] to [redacted]

Information obtained from family member and document not available

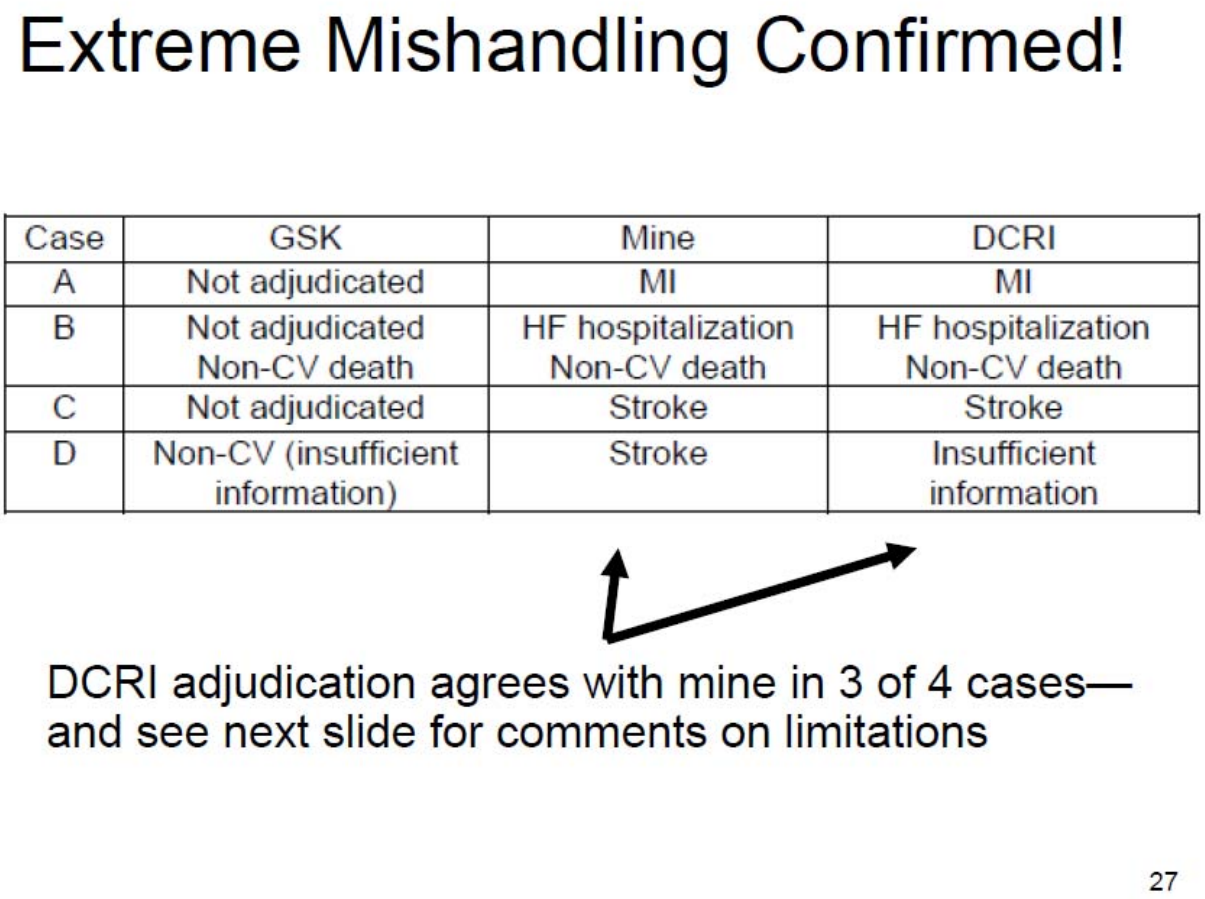
Adjudicated non-CV insufficient information

For a severe stroke with 36-day hospitalization, the site couldn't have queried the family member about onset? Paralysis? Speech?

26

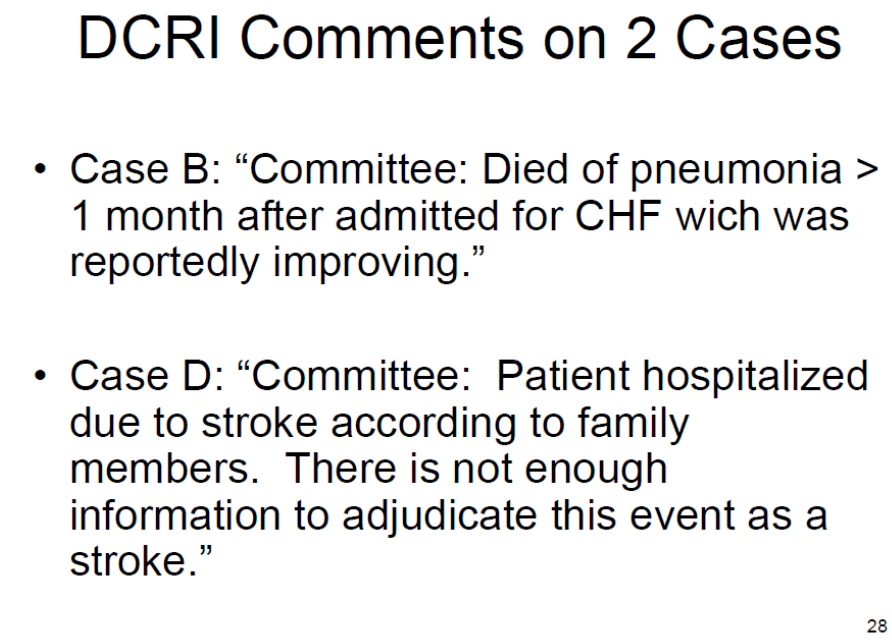
I show the adjudications of these four cases by GSK, DCRI, and myself in Figure 24.

Figure 24:



The DCRI adjudication agrees with mine in all but one of the cases. For two of the cases (A and C) both DCRI and I disagree unequivocally with GSK. The other two cases warrant further discussion. DCRI commented on both of these cases as shown in Figure 25.

Figure 25:



For both cases involving prolonged hospitalizations, the amount of information collected was appalling. For Case D, while DCRI adjudicated it as "insufficient information", I classified it as a stroke. I believe lay persons understand sufficiently the findings of a stroke to provide reasonable diagnostic confirmation for a patient hospitalized for 36 days. Regardless, these four cases confirm the extreme mishandling of cases by GSK in RECORD regarding both failure to adjudicate obvious events and missing data on other high likelihood events. Both of these problems persist to this day.

5. Study Design Flaws

The epidemiology reviewers in 2007 and all cardiology reviewers from 2010 on have concluded that RECORD had too many study design flaws to confirm safety from it. I show the findings and conclusions of the epidemiology reviewers from 2007 in Figure 26, those of the cardiorenal consultant (mine) from 2010 in Figure 27, and those of the cardiorenal consultants from 2012 in Figure 28.

Figure 26:

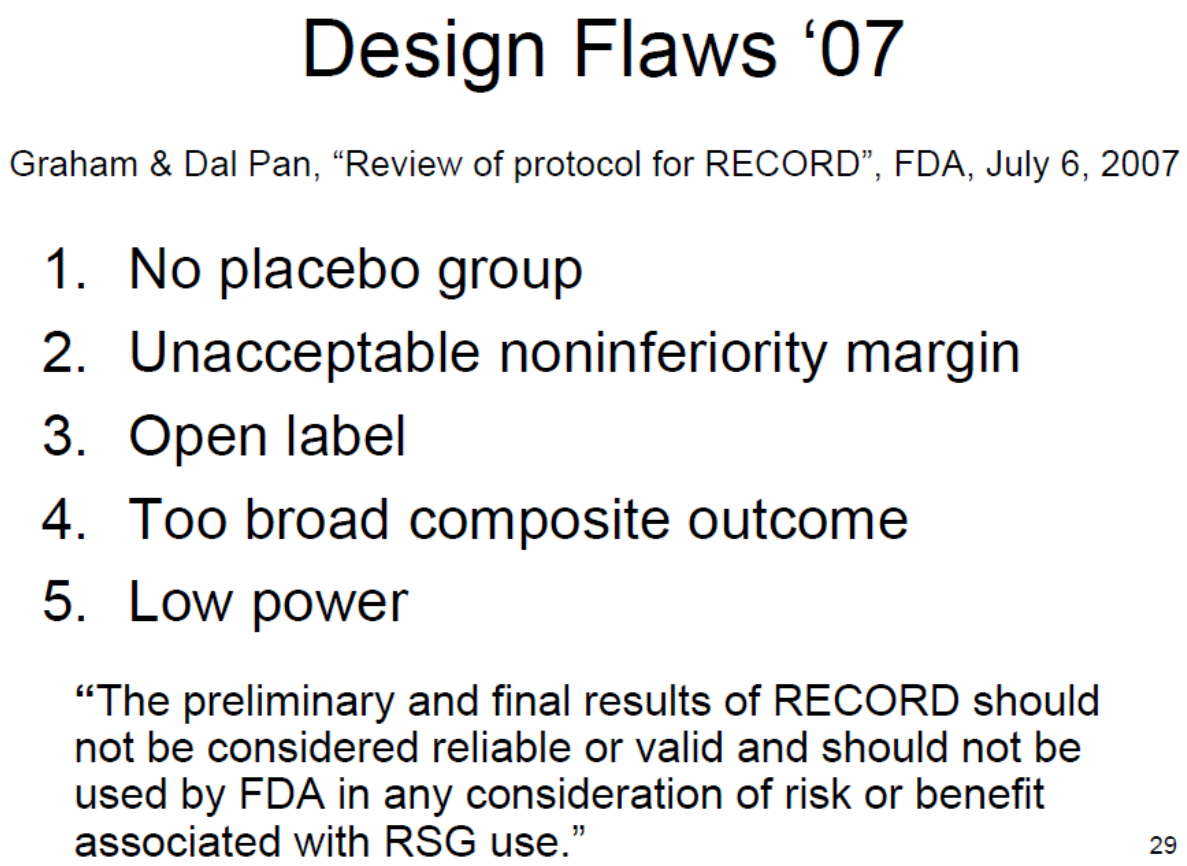


Figure 27:

Design Flaws '10

Red shading indicates key issue

#	Issue	Bias
1	Open label	rosiglitazone
2	Two studies	null
3	Active controls	null
4	Post-randomization determination of treatment phases	null
5	Treatment crossovers	null
6	Investigator determination of visit frequencies and types	rosiglitazone
7	Lower CV risk population	null
8	CV hospitalizations in primary endpoint	null
9	Ambiguities regarding endpoint definition of amputations	null
10	Strict MI definition	null

The potential biases favoring rosiglitazone all stem from the open label design of RECORD.

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Design Flaws '10
(Continued)

#	Issue	Bias
11	Primary endpoint not reflecting suspected problems	null
12	Endpoint date definition	null
13	Minimal documentation on rationale for adjudication of cases	neutral
14	Analysis populations	null
15	Endpoint reporting	null
16	SAE reporting	neutral
17	Concomitant medication reporting	null
18	Handling of withdrawals	rosiglitazone

If consulted in advance, I would have rejected this study design as inappropriate and biased.

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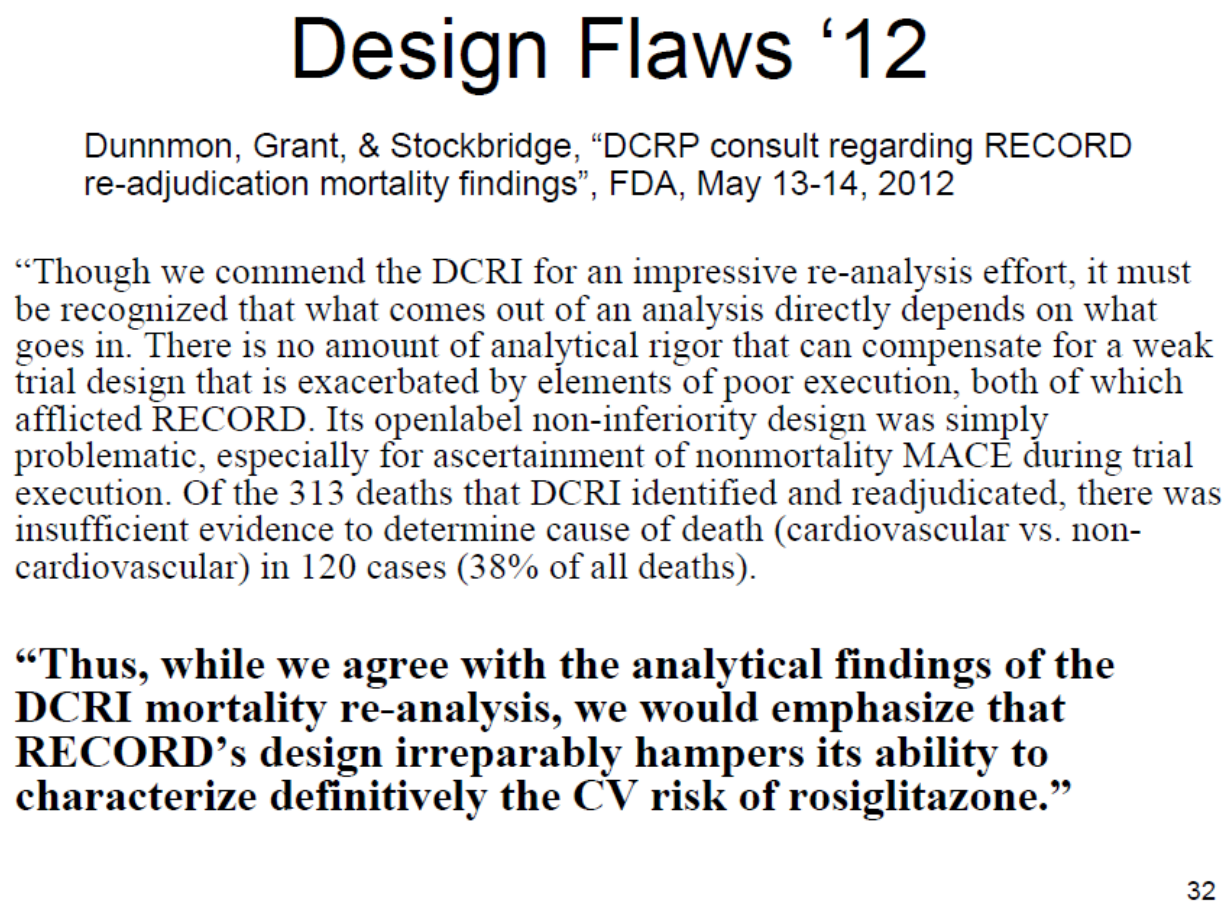
Figure 28:

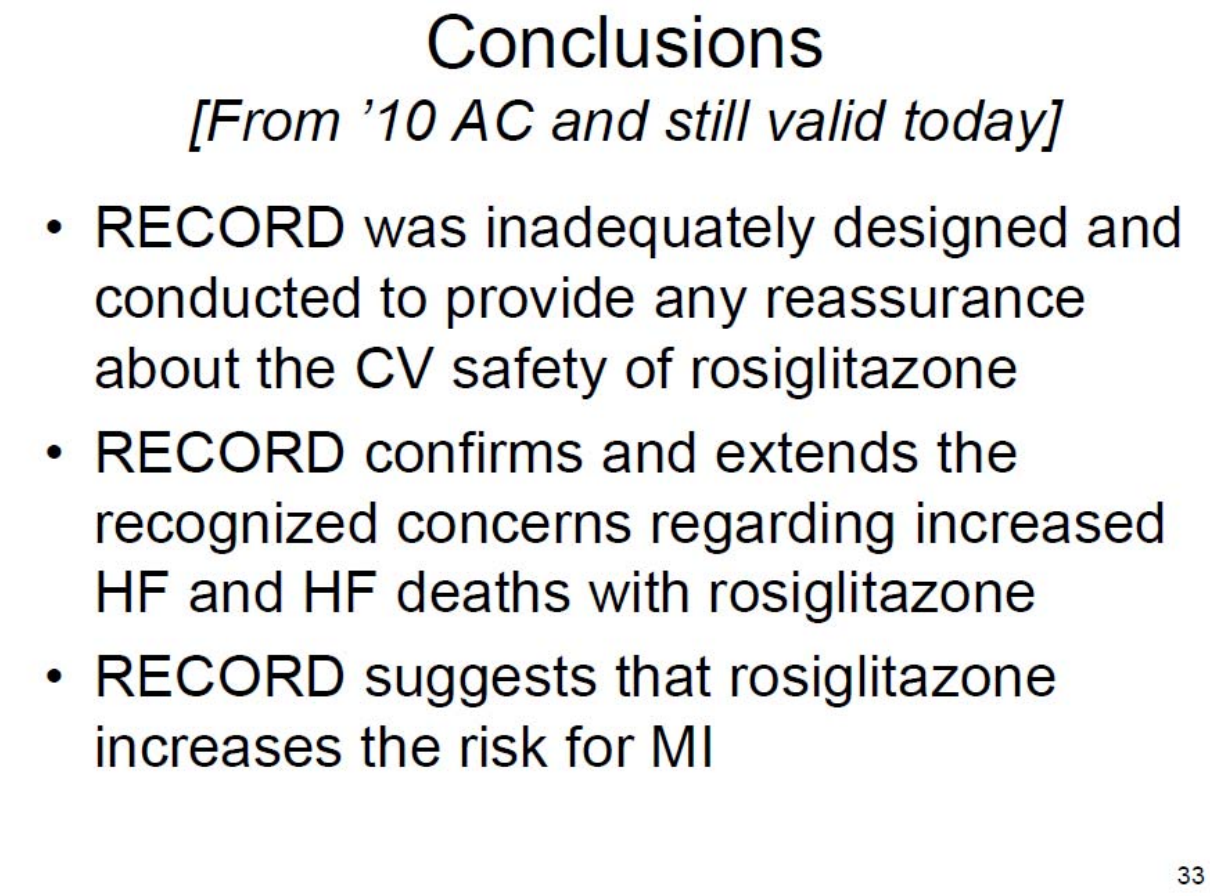


All three sets of FDA internal consultants over a span of five years consistently communicated to DMEP and FDA management that RECORD can not confirm the CV safety of rosiglitazone. I think that it has been a huge waste of FDA resources and federal tax dollars to devote so much attention to a seriously flawed study.

Conclusions

My conclusions from 2010, reproduced in Figure 29, remain valid today.

Figure 29:



The one contribution of the re-adjudication is that it has confirmed the extreme mishandling of cases by GSK. RECORD remains a broken RECORD.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 23, 2013

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (DCRP)

Subject: RECORD re-adjudication review update, NDA 21-071

To: Jena Weber, Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

This review updates my evaluation filed May 15, 2012, of the "Final study report of the first phase of the independent re-adjudication of the RECORD endpoints as provided by Duke Clinical Research Institute (DCRI)". Since I filed my original review two reviews have been filed and a Center Director Briefing presented commenting on my review, so I address inaccuracies and misinterpretations in those reviews and the presentation. In addition more information is now available on the performance of the re-adjudication contractor in conducting other cardiovascular (CV) outcomes trials. The new reviews and information do not change my original conclusions but rather reinforce them:

"These problems are substantial such that the re-adjudication contributes little to our understanding regarding cardiovascular risks in RECORD. These problems are not remedial by a site audit of DCRI. All that we can say about the overall results of the re-adjudication is that they were not independent and that the execution of the re-adjudication was flawed."

Performance of Duke Clinical Research Institute (DCRI) in Recent CV Outcomes Trials

I would have thought that the two words "Anil Potti" are sufficient for convincing anyone that Duke University is a poor choice for a contractor whose task it is to confirm the integrity of scientific research. If Duke couldn't detect blatant fraud on its own campus contemporaneously how can we have any confidence that they can detect problems with research performed across the Atlantic years ago with all information filtered through the study sponsor? While Anil Potti was an oncologist, recent DCRI participation in CV outcomes trials has not been reassuring. I documented in my previous re-adjudication review the substantial errors made, undetected, or unreported by DCRI in the recent PLATO CV outcomes trial. Some examples of the problems are the following (and I provide more details in the Appendix 1 on two of them for which CRFs were submitted):

- The percentage of patients with incomplete follow-up in PLATO for the primary endpoint was 13%. As one Cardiovascular and Renal Drugs Advisory Committee member commented, "I would say a 13 percent loss to follow-up in a trial where the follow-up is between 6 and 12 months is just way high." The DCRI Director responded "I would agree with you, Dr. Neaton, that the 13 percent is not a very good standard." Note that incomplete follow-up is one of the major limitations of RECORD.

- A ticagrelor patient had a PCI with stent on day 1 followed by hypotension and mild pulmonary edema. On day 2 he suffered bradycardia and complete AV block treated with a temporary pacemaker and resolving by day 6. On day 12 he was rehospitalized for "syncope)before hospitalization, Ventricular tarchycardia, seizure,v-fib and Asystole after hospitalization"; ticagrelor was discontinued. Treatment included CPR, cardioversion, and an IABP. This event was not submitted for adjudication. His last visit was on day 42 but the sponsor counted him as completing the study through day 391 without an endpoint. The DCRI co-authors did not count the event as an endpoint.

- A ticagrelor patient was hospitalized on day 22 with a coronary thrombosis. A troponin T was reported as >5x and an echo showed hypokinesis of the inferior wall with ejection fraction 55%. No other information on symptoms, physical findings, lab, treatment (of this event, prior concomitant medications are listed), or hospital course are provided. The event was not submitted for adjudication and the DCRI co-authors did not count the event as an MI.

- A ticagrelor patient had a scheduled visit on day 91 then suffered an NSTEMI on day 96. The last study drug day was day 97 and the patient withdrew consent on day 97. An NSTEMI SAE was "inactivated" and the NSTEMI event was not submitted for adjudication. The DCRI co-authors did not count the MI.

- A ticagrelor patient without a prior history of heart disease has an NSTEMI as the index event followed by a routine CABG on day 10, having discontinued study drug on day 4. A triggered MI (i.e., based on biomarker reports) at the CABG is adjudicated as not an MI because of "Minor increaes in mb ~2 days post cabg. no evidnence of clinical event. will not call endpoint MI." He is discharged on day 13. He then suffers a cardiac arrest on day 44 apparently with successful resuscitation, but the cardiac arrest is not adjudicated. He later develops heart failure. The DCRI co-authors do not count him as having a cardiac event.

- A ticagrelor patient had a CABG on day 4. After sternal closure but before leaving the operating room he arrested. The surgeons reopened the chest, instituted cardiac massage, successfully resuscitated him, and re-closed. The patient was noted to be severely anemic post-op and was transfused with four units of packed red cells. While the cardiac arrest could be related to the anemia or a reperfusion arrhythmia, an intraoperative MI should also be considered. This case was adjudicated regarding the bleeding but not regarding the possible MI. The adjudicator for the bleeding was given the discharge summary describing the cardiac arrest but did record any consideration of also adjudicating for MI.

No CK-MB values were reported after day 2. The DCRI co-authors do not count him as having a cardiac event. (Example 1 in Appendix 1)

- One ticagrelor patient had an adjudicated "myocardial infarction within 24 hours of CABG". However, the adjudicated date and time were recorded as [redacted] despite the facts that all hospital documents and data sets record the CABG as [redacted], the biomarker rises were on [redacted] and [redacted] and the date of randomization was [redacted]. Another ticagrelor patient had an adjudicated MI but the year of the adjudicated date of the event was recorded as 2005 despite the facts that the site-reported event date and all other related dates in the adjudication package were in 2007. (Example 2 in Appendix 1) The DCRI co-authors did not count either event as an MI. Note that the DCRI clinical faculty leader for the PLATO adjudication committee is also the principal investigator for the RECORD re-adjudication.

PLATO, like RECORD, was plagued by incomplete follow-up and incomplete referral of cases for adjudication. I document more examples in my previous re-adjudication review and in my review of PLATO. (FDA 2011)

Some may argue that I was the major critic of PLATO—as I am the major internal FDA critic of RECORD. However, another recent submission having a pivotal trial with DCRI involvement also showed major data problems documented by other FDA primary reviewers. The trial was the ARISTOTLE trial of apixaban in atrial fibrillation. The opening sentence in the clinical review of it regarding "Data Quality" is "We are concerned that the trial datasets do not match the information in the CRF." (FDA 2012) The primary reviewers recommended a "complete response" rather than a first-round approval because of the data quality issues; the decision authority concurred. The primary reviewers justified the complete response as follows:

> "We do not have sufficient confidence in the ARISTOTLE study data to approve the application. ARISTOTLE was a double dummy study in which subjects randomized to apixaban received active apixaban and placebo warfarin, and subjects randomized to warfarin received active warfarin and placebo apixaban. We discovered a substantial issue involving medication errors in ARISTOTLE, whereby subjects received either two active drugs or two placebos for varying amounts of time. The former would primarily increase the risk of bleeding, while the latter would primarily increase the risk of ischemic stroke and other thrombotic events. Some of the data indicate that the medication error rate, affecting up to about 8% of subjects in each arm, were driven by errors in the dispensing of warfarin/placebo (refers to active warfarin or placebo warfarin) bottles. If this is the case, one would expect that some warfarin arm subjects might receive placebo warfarin and placebo apixaban, and that some apixaban arm subjects might receive active apixaban and active warfarin. The potential consequence of these errors is a higher ischemic stroke rate in the warfarin arm, and a higher bleeding and or hemorrhagic stroke rate in the apixaban arm.
>
> "We are still not sure of the number and type of errors that occurred, despite considerable effort on the parts of the Applicant and the review team. Similarly, we are not sure of how these errors affected study outcomes.

> "The Applicant has told us that they were unaware of the scope of the medication errors during the trial or even when they submitted the NDA. This was due in part to deficiencies in centralized monitoring while data were accruing and less than diligent monitoring at the sites. Notably, there is no evidence that the sponsor initiated effective procedural changes to ameliorate the rate of medication errors, such as increasing the intensity of monitoring or the intensity of its centralized data checking procedures."

While the primary responsibility for the problems rests with the Applicant, it is not reassuring that DCRI participated extensively in the trial. One of the two co-investigators was from DCRI; he was the lead author on the NEJM publication of the trial. (Granger, Alexander et al. 2011) That publication contains the following statement: "All the authors assume responsibility for the accuracy and completeness of the data and the analyses and for the fidelity of the study to the protocol." A supplementary appendix to the publication lists five DCRI staff as members of the "Operations Team", a DCRI co-chair for the Clinical Events Committee (CEC), and 13 DCRI staff as CEC reviewers.

While the problems documented by the FDA primary reviewers for ARISTOTLE are different than those I documented for RECORD, I analyzed ARISTOTLE for completeness of follow-up and filed my findings in a review dated December 17, 2012. (FDA 2012) I documented problems with completeness of follow-up for ARISTOTLE similar to those for RECORD. The details are in my review but I summarize some examples of the problems below for ease of reference:

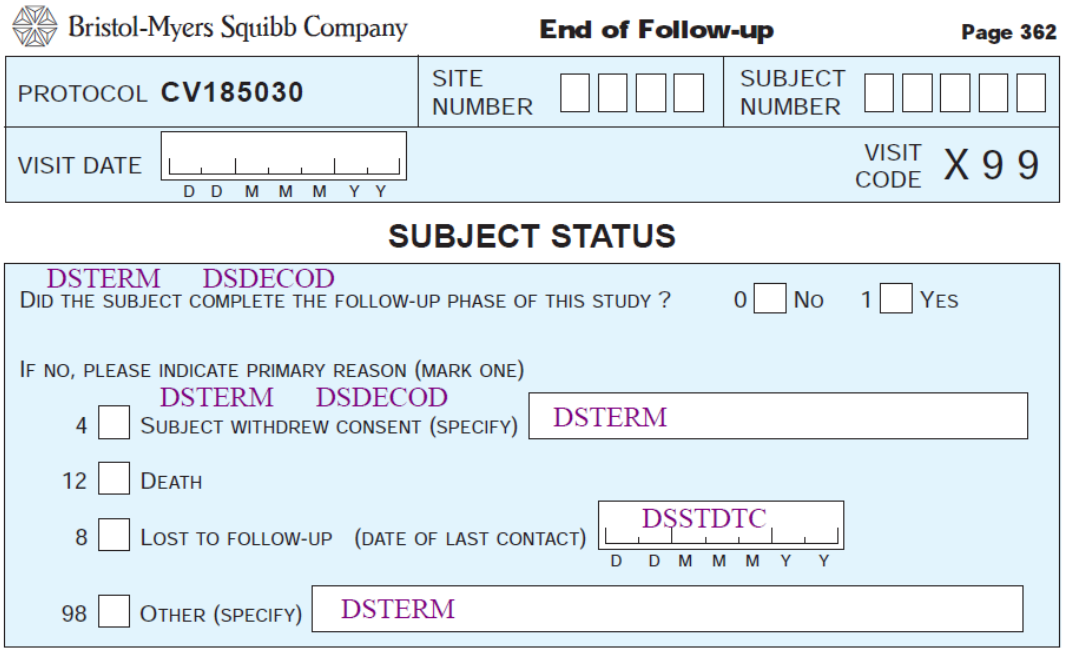
- The clinical study report (CSR) for the ARISTOTLE trial of apixaban vs. warfarin in atrial fibrillation states that vital status could not be determined for 2.0% in the apixaban group and 2.2% in the warfarin group (380 patients in both groups total). The main study publication reported the same vital status statistics. However, the rates of discontinuation from the study were much higher, 25.3% in the apixaban group and 27.5%, with 10.1% of apixaban patients and 10.0% of warfarin patients discontinuing at their own request.

  Furthermore, I could not confirm the reported vital status follow-up rates from the datasets. For one estimate of completeness of vital status follow-up in ARISTOTLE I used the sponsor's variable *e_cddn* described as "Censor Date for Death ITT Period" from the sponsor's ADEFS.XPT ("Efficacy Summary") dataset. Counting good vital status as either known dead at any time or a censor date of January 30, 2011, or later, 3.2% of patients (589) are missing vital status. For a second estimate I also analyzed all of the datasets for the maximum dates of events, procedures, vital sign recordings, and status reports to estimate a date of last follow-up for every patient. By this latter analysis of the raw data 3.6% of patients (659) are missing vital status. Either number, 589 or 659, greatly exceeds the sponsor's and DCRI investigator's reports of 380 missing vital status follow-up.

- A serious problem in ARISTOTLE, as in RECORD, was that the "visit date" may have little connection to a date on which the patient was actually observed or contacted. In many cases there is no way of determining whether the "visit date" is an observation date or the date of recording or something else. However, both I and the sponsor based our

dates of last vital status partially on "visit dates". In particular a critical form for follow-up, the End of Follow-up CRF shown in Figure 1, has this ambiguity regarding "visit date".

Figure 1: ARISTOTLE End of Follow-up CRF


Bristol-Myers Squibb Company

End of Follow-up Page 362

PROTOCOL **CV185030** | SITE NUMBER | SUBJECT NUMBER

VISIT DATE (D D M M M Y Y) VISIT CODE X 9 9

SUBJECT STATUS

DSTERM DSDECOD
DID THE SUBJECT COMPLETE THE FOLLOW-UP PHASE OF THIS STUDY ? 0 ☐ NO 1 ☐ YES

IF NO, PLEASE INDICATE PRIMARY REASON (MARK ONE)

DSTERM DSDECOD
4 ☐ SUBJECT WITHDREW CONSENT (SPECIFY) DSTERM

12 ☐ DEATH

8 ☐ LOST TO FOLLOW-UP (DATE OF LAST CONTACT) DSSTDTC (D D M M M Y Y)

98 ☐ OTHER (SPECIFY) DSTERM

What does the "visit date" on the End of Follow-up CRF represent? Only for lost to follow-up is the date of last contact to be recorded on this CRF. For death there is the death form with a field for date of death, but what about "withdrew consent" or "other" or even "complete"? It is easy to document that "visit date" for "withdrew consent" likely does not represent the date on which the patient visited the site or withdrew consent. For example, one patient discontinued treatment on 16jul00 with the last verifiable events on 18jun00. However, the disposition (DS) dataset has a "Start Date/Time of Disposition Event" for withdrew consent of 12apr11 and the sponsor counts the patient as completing follow-up, censoring on 30jan11. Withdrawing consent on 12apr11, long after the trial ended, is not rational and would not represent a withdrawal of consent during the ITT period, as the sponsor classifies this patient. Another patient is similar, with end of treatment and last events on 06may10 but withdrawal of consent allegedly on 24feb11 with sponsor's censoring on 30jan11. I count both of these patients (and other similar ones) as having incomplete vital status follow-up, partially explaining and justifying why my estimate of incompleteness of vital status follow-up is higher than the sponsor's.

- The problem of completeness of follow-up is not limited to vital status. I estimated completeness of event follow-up based on events, procedures, vital sign recordings, and last direct contacts with the patient (i.e., the types of reports relevant to events, endpoint or adverse, or the absence thereof) but not counting the flawed status report visit dates. For these reports about 15% of patients, or over 2,700 patients, have incomplete follow-

> up. Compare 1,349, the number of apixaban patients with incomplete follow-up, to 53, the difference in primary endpoints. There is a vast amount of missing follow-up in which endpoints may be hidden or missed.

I provide other examples in my full review documenting why follow-up was poor in ARISTOTLE. That ARISTOTLE and RECORD may share some problems could be related to some personnel involvement: the chief statistician for RECORD was also a member of the Data Monitoring Committee for ARISTOTLE.

COMMENT: I find it completely unacceptable that, in critical, multi-million dollar (or Euro) CV outcomes trials such as ARISTOTLE and RECORD, we have to guess at when and how the patients were last contacted. We can not have confidence in any positive efficacy or negative safety results if we don't know how all patients fared.

The Duke Vice Chancellor for Clinical and Translational Research and founder of DCRI tried to explain on the February 12, 2012, airing of the television news show 60 Minutes (Pelley 2012) how Duke missed Dr. Potti's fraud:

> *60 Minutes:* "How could they have found nothing wrong, nothing suspicious about the work at that point?"
>
> DCRI founder: "They were analyzing a data set that had been prepared by Dr. Potti. So, the data set they got was one that produced the same results that had been seen in our own analyses."

When Bristol-Myers Squibb/Pfizer announced that we had sent them a complete response letter requesting additional information on "data management and verification" in ARISTOTLE, the DCRI founder blogged on June 25, 2012 (Califf 2012):

> DCRI founder: "While DCRI did not do the data management or monitoring for this trial, we have a copy of the database and our statisticians have performed the independent analyses."

So, how can the DCRI founder explain Duke missing fraud because of a data set prepared by someone else while expressing confidence in trial results similarly based on a database prepared by someone else? How can the DCRI first author of the ARISTOTLE publication (Granger, Alexander et al. 2011) "assume responsibility for the accuracy and completeness of the data and the analyses and for the fidelity of the study to the protocol" if he did not know intimately the data management and monitoring for the trial? Given the long list of DCRI staff involved with ARISTOTLE the truth is likely somewhere between only having a third party-prepared database and having primary responsibility for data management and monitoring of ARISTOTLE. Regardless, the problems with ARISTOTLE and with PLATO do not generate confidence that DCRI has resolved the similar problems with RECORD.

The problem with trial monitoring academicians having access only to sponsor-prepared databases—and not even analyzing them completely—is not limited to DCRI and ARISTOTLE

and PLATO. It was a major limitation in RECORD as well during the conduct of the study. I've included as Appendix 2 a copy of the minutes of a teleconference with the chief statistician for RECORD. I've also reproduced below the most pertinent discussion:

> "c. Please discuss what it means to "have full access to the interim data and vouch for the accuracy and completeness of the data reported?" Does this mean access to the database, study level data or individual subject level data? GSK provided the data to Dr. [redacted] at the London School of Hygiene and Tropical Medicine. Dr. [redacted] wrote a program according to the statistical analysis plan supplied by GSK and ran the data provided by GSK though his program. Dr. [redacted]'s program was recreated to perform an analysis; not a complex plan.
>
> "4. With regard to the RECORD data:
> a. How would you describe the activities you, your staff, or your co-authors have taken to insure the quality of the RECORD data and your analyses thereof? Dr. [redacted] had the full trial database set to recreate the analysis. We had more of a scientific advisory role, not detailed activities in data management.
> b. What analyses did you or your staff perform to verify the data? See 4a.
> c. Were you provided access to RECORD data sets? If so, what type of datasets and when? All raw data sets? Analytical data sets only? Other? See 4a.
> d. Were you provided access to and did you examine case report forms? Endpoint dossiers (dossiers and patients)? Data query forms, notes to record, data clarifications, etc. (patients)? No
> e. Did you or your staff check the coding of adverse events? No
> f. Did you or your staff check the CV endpoint adjudications? No
> g. Did you or your staff cross-check data sets to verify that referrals for adjudication were complete? AEs vs. endpoints? Hospitalizations from the Medical Care Utilisation forms vs. AEs and endpoints? No"

The response above from the RECORD chief statistician seems identical to the blogging of the DCRI founder, i.e., they superficially analyzed the datasets from the sponsor and didn't find any problems. Compare the above to the attestation to data quality from the RECORD interim analysis paper (Home, Pocock et al. 2007):

> "Members of the steering committee (seven academic investigators and one representative of the sponsor) developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported."

The chief statistician was a member of the RECORD steering committee and a co-author of NEJM paper. Regardless of the outstanding reputations of academic institutions like Duke University and the London School of Hygiene and Tropical Medicine their staff are not doing an adequate job of monitoring the clinical trials that they publish. From my review of clinical outcome studies in recent years this problem is a universal problem. Addressing this problem would be a far more valuable topic for an FDA advisory committee meeting than rehashing a flawed study on a drug of questionable value.

This problem also documents that all of the recent press regarding clinical trial data transparency and sponsor's (first of all GSK) releasing clinical trial data will not resolve the trial data quality issues and will likely obscure them more effectively. If the medical community assumes that having scrubbed datasets that agree with publications solves the problem then we will have taken a step backwards in solving this issue: Most of the problems that I have identified in my reviews are not detectable from the supposedly "raw" datasets.

One can argue that, for RECORD, DCRI had access to case report forms as well as data sets—but DCRI has had access to adjudications packages for the other studies and adjudication packages provide much more detail on events than CRFs. The case report forms, like the datasets and adjudication packages, were filtered through a biased party, i.e., GSK, as described in the DCRI study report and documented in my previous review. The re-adjudication was not an independent effort.

Statistical Review and Evaluation Avandia (The RECORD Trial) Filed June 7, 2012
This review is a mixture of incomplete references to my review, sweeping generalizations, and conclusions not justified by the data presented. I summarize examples of its problems as follows:

- One major point of the Executive Summary is the following: "The DCRI re-adjudicated a considerable percentage of deaths in both treatment arms as 'undetermined' or with insufficient information to complete adjudication (43.8% in RSG and 37.9% in MET/SU). The high percentage of 'undetermined' deaths was caused by insufficient data to properly adjudicate these deaths. Overall, there was no evidence to suggest that deaths in either treatment arm were more likely to have missing information and be classified as 'undetermined'." Later the review later states that "There was no pre-specified definition of what constitutes 'sufficient information'." With "insufficient information" to be able to adjudicate a cause of death, the conclusion that "there was no evidence to suggest that deaths in either treatment arm were more likely to have missing information" would be better worded as "there is insufficient information to judge whether the missing information is missing at random."

- Regarding "3 Independent re-adjudication of deaths", the review does not provide an explanation of how the re-adjudication was "independent". As I documented in my review, most or all data were provided by GSK, so how was the re-adjudication "independent"?

- Regarding "3.1 Submitted datasets", the review states "The provided documentation was adequate and allowed the review team to assess data quality and conduct the required statistical analyses." How does documentation allow one to assess most aspects of data quality?

- Regarding "3.4 Assessment of re-adjudication process", the opening sentence states "The DCRI had access to all the information collected during the conduct of RECORD." Having all information is impossible because trial records should be redacted for privacy

concerns. DCRI had access to information as provided by GSK. There is no practical way of determining whether that constitutes "all the information".

- Section 3.4 states later: "Even though the results of the DCRI re-adjudication process have limitations due to the available data, the re-adjudication addresses some of the issues raised in Dr. Marciniak's review: Most, or all, deaths in RECORD are likely to have been captured by the original RECORD team and the additional efforts of the DCRI." How is it "likely" that all deaths have been captured? Similarly, "The DCRI reviewed the subject-specific follow-up time and date of death for all subjects. Any remaining errors in follow-up time or date of death are unlikely to favor any treatment arm systematically." How does the fact of any review make it "unlikely" that there is a systematic bias, particularly given that there are insufficient information and much missing data?

- The concluding paragraph of the Executive Summary starts "The re-adjudication of deaths conducted by the DCRI addressed some of the concerns raised by Dr. Marciniak regarding event capture, adjudication and dating." If only some of my concerns are addressed, how can one conclude anything with confidence? Some unaddressed concerns are quoted incompletely later in the review:

  > "Dr. Marciniak completed a review of RECORD in June, 2010. In his review, Dr. Marciniak criticized some of the trial's design features as well as the original endpoint definition and adjudication process. His main criticism of RECORD's design was that it was an open-label trial and therefore susceptible to ascertainment bias. We recognize this design limitation of RECORD. As this limitation has been addressed in the literature and in FDA reviews, it is not discussed further in this review."

  In my review I detailed not one but eighteen trial design issues. Other reviews have discussed the design issues and no review has negated them. The most relevant quotes are from the closing two paragraphs of the Division of Cardiovascular and Renal Products' consultative review on the mortality re-adjudication:

  > "There is no amount of analytical rigor that can compensate for a weak trial design that is exacerbated by elements of poor execution, both of which afflicted RECORD."
  >
  > "Thus, while we agree with the analytical findings of the DCRI mortality re-analysis, we would emphasize that RECORD's design irreparably hampers its ability to characterize definitively the CV risk of rosiglitazone."

COMMENT: The re-adjudication and this statistical review of it have not addressed my concerns regarding event capture, adjudication, and completeness of follow-up and treatment. To the contrary, the re-adjudication reinforces some of my concerns as I discuss below. Additionally, there appears to be agreement among the primary cardiology consultants that the design flaws in RECORD preclude it from assuring the CV safety of rosiglitazone.

The fundamental problems with RECORD are not mathematical issues so we may not be surprised that a statistical review fails to elucidate them. In addition, the statisticians responsible for this review were also responsible for serious non-mathematical blunders in another recent review. The latter was a meta-analysis of cancers in trials of angiotensin receptor blockers (ARBs) and was the primary evidence for a FDA Safety Announcement dated June 2, 2011, concluding that treatment with an ARB does not increase the risk of cancer. I have described the many problems with the meta-analysis in reviews filed to Tracked Safety Issue 935 on May 28, 2012, and August 31, 2012. The most egregious blunders in the meta-analysis are the following:

- *The meta-analysis did not define either cancer incidence or the censoring period.*

- *The original meta-analysis did not count lung cancers coded as the MedDRA term "lung carcinoma" as lung cancers, erroneously limiting lung cancers to "malignant lung neoplasm".*

- *After I identified the lung carcinoma error, the statisticians redid their meta-analysis but persisted in not counting lung cancers coded as the MedDRA term "lung cancer metastatic".*

- *The statisticians performed sensitivity analyses double-counting some trials, apparently because they failed to match trials referenced by acronyms in publications with the same trials referenced by trial numbers in NDA submissions.*

If these statisticians can not count simple MedDRA terms correctly, how can we have confidence that they can elucidate the more complex issues of adjudication of CV death or of MI?

Memo regarding DCRP Consult on RECORD death readjudication by Duke Clinical Research Institute (DCRI) filed October 12, 2012

This memo does not provide any new analyses or data regarding the readjudication so it is not very helpful in understanding the problems. However, it does make some misleading comments regarding my review so I address them below for the official record:

- On page 3 the memo states that "We do not have, to my knowledge, examples of academic contractors improperly manipulating study results (which does not, of course, mean it could not happen)." While this statement may be carefully worded regarding "contractors", we have a recent egregious example of an academic grantee improperly manipulating study results undetected by the FDA, i.e., Duke's Dr. Anil Potti—also a past consultant to GSK. (Tracer 2010)

- Later on page 3 the memo references my review (p. 5) and states that "The fact that GSK had to supply the data (and thus "collaborated with DCRI") seems simply unavoidable, as they possessed the data; concerns therefore need to be quite specific." The statement on my review page 5 is not my wording but an exact quote from the DCRI report that they conducted the CEC operations "in collaboration with the sponsor, GSK." Mere provision of data would not usually be interpreted as collaboration. Furthermore I do provide many

specific examples of how GSK was extensively involved in the re-adjudication. It would not seem "unavoidable", for example, to have sites send the "paperwork" directly to DCRI, rather than to GSK. A neutral party—FDA staff—rather than GSK could have redacted the datasets—or we could have easily provided to DCRI (with GSK consent) copies of datasets, CRFs, and trial documentation that GSK had submitted to the NDA. Similarly, FDA could have funded the re-adjudication through a research contract rather than allowing financial conflicts of interest to be of concern.

While I argue that many aspects of the re-adjudication should have been handled differently to avoid the "collaboration" that makes the re-adjudication as performed of limited value, I also agree that, in 2010 and later, it was impossible to perform a truly independent, valid re-adjudication. It is simply unavoidable for GSK to be involved with new data, particularly "new" because not previously submitted to the NDA. However, "unavoidable" does not mean that the resulting effort is worth doing. The Agency appears to have wasted a considerable amount of tax dollars, i.e., reviewer time and site audit and advisory committee expenses, on an effort that was destined for inadequacy at its design stage—just as RECORD was destined for inadequacy at its design stage.

- On page 4 the memo states that "Dr. Marciniak devotes a good deal of attention to what he thinks was poor performance by DCRI as a contractor for the PLATO trial of ticagrelor, citing a 13% loss to follow-up, and failure to refer certain cases for adjudication. Most of the latter cases, however, were not DCRI's responsibility and only ticagrelor cases non-referral were included." How were the cases not DCRI's responsibility when the DCRI Director co-chaired the Executive Committee, the DCRI coordinated the clinical events committee (the DCRI clinical faculty leader for the PLATO CEC is also the principal investigator for the RECORD re-adjudication), and the DCRI Director wrote and co-authored and the DCRI principal investigator for this RECORD re-adjudication also co-authored the PLATO NEJM article? (Wallentin, Becker et al. 2009) The PLATO NEJM article has the following statement regarding responsibility: "The manuscript was drafted by the chairs of the executive and operations committee, who were academic authors and who vouch for the accuracy and completeness of the reported data."

  The memo is also misleading regarding "only ticagrelor cases non-referral were included." In my re-adjudication review I included examples only of ticagrelor cases, but my ticagrelor review includes both the ticagrelor and control cases and statistics. (FDA 2011) Regarding failures to referral only one of the cases was a control case. The unpleasant truth is that, in PLATO as in RECORD, the vast majority of mishandled cases favor the study drug.

Center Director Briefing October 15, 2012

I was invited to attend this briefing but not to present. The majority of this briefing was devoted to presentations on the design of the re-adjudication and the results as summarized in the DCRP consult responses. Because I have already commented on these topics in my previous review I will not repeat those comments here. However, some of the slides attempted to reconcile my

findings of mishandled cases with the DCRI re-adjudications. Because these slides are erroneous, I explain the misrepresentations below.

On slide 47 my original review is quoted as "In original Cardiology review, 8 cases identified for 'failure to refer events for adjudication'; 3 of these also cited for 'extreme mishandling of events' while on slide 48 the 3 extreme cases become 8 per "Again examining the 8 cases of extreme concern". Slide 48 concludes "Blinded readjudication reached the same MACE result in most (6/8) cases, even in this sample of cases identified as having the most egregious problems."

In fact I identified 4 cases as "extreme mishandling", i.e., my Cases A-D documented in Appendix 1 of my original review. (FDA 2010) I show how I, GSK, and DCRI classified these cases in Table 1.

Table 1: Adjudication Results for My Four Cases of Extreme Mishandling

Case	GSK	Mine	DCRI
A	None (MI SAE deleted)	MI	MI
B	(Hospitalization not adjudicated) non-CV death	HF hospitalization, non-CV death	(HF hospitalization) non-CV death
C	None (intracerebral hematoma SAE deleted)	Stroke	Stroke
D	Non-CV (insufficient information)	Stroke	Insufficient information

DCRI agreed with my assignments in 3 of the 4 cases and with GSK's in only 1 of the 4. It is also informative to examine the reasons behind the agreements and disagreements. For the two cases (A and C) that both DCRI and I classify as MACE there were definite CV SAEs recorded that GSK or its agents deleted. Sufficient information had been collected at the time of the study to enable a reasonable adjudication. For the other two cases (B and D) there was scanty data collection at the time of the study—and no apparent success in rectifying the scanty data collection for the re-adjudication.

The first paragraph from my original RECORD review describing case B is the following:

> **"Case B**: This patient had one referred endpoint event, his death on [redacted], adjudicated as non-CV, pneumonia. While the patient was hospitalized for 46 days starting on [redacted], the only a brief letter summarizing the hospitalization was obtained. (B1) Note that the admission was for pulmonary edema improved with furosemide. The details of this hospitalization should have been obtained—and note that the letter closes "If you have any further queries please do not hesitate to contact us." Note also that this was not at a remote Eastern European or Australian hospital but at a UK NHS hospital. This pulmonary edema hospitalization should have been adjudicated. All hospitalizations for unexplained pulmonary edema or acute heart failure should also have been scrutinized for MI."

DCRI adjudicated only the death but did provide the following comment: "Committee: Died of pneumonia > 1 month after admitted for CHF wich was reportedly improving." DCRI was not tasked to adjudicate heart failure and did not adjudicate the hospitalization for acute pulmonary edema. However, I assert that the recommendation from my review that all hospitalizations for unexplained pulmonary edema should also have been scrutinized (i.e., adjudicated) for MI

remains valid. Regardless, GSK did include heart failure hospitalizations in its primary CV endpoint and failed to count the heart failure hospitalization for this patient.

The first paragraph from my original RECORD review describing case B is the following:

> **"Case D**: This patient was hospitalized for 67 days for a severe stroke starting on [redacted]. The investigator obtained minimal information from a family member about the stroke (D1-D2) and a discharge summary was stated to be not available. (D3) However, the investigator was successful about contacting the patient's husband for survival information on 22dec08. The hospitalization was adjudicated as non-CV, insufficient information. The CEC Charter does not require a discharge summary. All the investigator or someone else had to do was to verify that the onset was rapid, that the symptoms of the severe stroke, e.g., hemiparesis, were clinical signs of focal disturbances of cerebral function, that there were no other apparent causes, and that the symptoms were persistent (> 24 hours, which the investigator did check off on a TIAS1 CRF.)"

The comment on this case by DCRI is the following: "Committee: Patient hospitalized due to stroke according to family members. There is not enough information to adjudicate this event as a stroke." So, despite an extended hospitalization stay for the patient, GSK was not able to collect more information regarding this case (or case B)? GSK does not appear to have exhibited due diligence in following up on the suspicious rosiglitazone cases. Finally, given a prolonged hospitalization for stroke and non-medical individuals' understandings of stroke, I'll argue that adjudicating this case as a stroke is reasonable despite GSK's failure to obtain a discharge summary, scans, or even a simple description of the event.

The four cases of extreme mishandling—all rosiglitazone—remain as extremely mishandled by GSK today as they were in 2010 when I filed my original review. The one reliable result of the re-adjudication is that it confirms GSK's mishandling of cases.

Office of Scientific Investigations (OSI) Audits

At the Center Director Briefing on October 15, 2012, OSI staff presented a summary of their audits of the DCRI re-adjudication. Because I have not discussed or presented previously the limitations of the OSI audits, I will do so here.

I would not have expected OSI to identify any problems at DCRI. The problems with RECORD, and with many other recent CV outcome trials, have not been the accuracy of the adjudications; the problems have been what was not sent in for adjudication, well documented for completely omitted events but also likely for completeness of individual patient submissions. These latter problems are not detectable at an audit of a central site.

RECORD was a European trial. Hence OSI audits of the clinical sites are constrained by the fact that the FDA has no legal authority in Europe. Furthermore, OSI audits are paper audits. If the "books" are in order and consistent, OSI will not identify any problems regardless of the veracity of the records. Only the sloppy get caught. This latter limitation, of course, is also true of US site audits.

There is another limitation of OSI audits: OSI auditors audit a variety of different trials and other activities. An OSI auditor has to be a Jack (or Jill) of all trades and a master of none. For a high profile trial like RECORD one would have thought OSI would select auditors with the most appropriate backgrounds available or even bring in specialists for the RECORD site audits—I volunteered to participate but was turned down.

However, OSI does not appear to have selected auditors for RECORD clinical sites with appropriate backgrounds. For a site in Germany the credentials of the auditor are given by his degree: DDS. I do not consider it to be appropriate to have a CV outcomes trial audited by a dentist. For the other two RECORD clinical sites the auditor does not have an advanced degree listed in the FDA directories. Hence I queried DSI (former name for OSI) about the second auditor's credentials. I've included in Appendix 3 the email thread documenting my attempt to elicit the qualifications of the second RECORD clinical site auditor. DSI and ORA (Office of Regulatory Affairs) refused to answer my question. The qualifications of the second RECORD clinical site auditor remains a mystery, as does the extent of the problems with the RECORD data.

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Appendix 1: Documentation of Adjudication Failures in Other Studies

Example 1: Adjudication for bleeding but not for MI

A ticagrelor patient had a CABG on day 4 that ended as follow:

In the immediate postoperative period prior to the patient leaving the operating room, after sternal closure the patient underwent a cardiac arrest. The chest was reopened and a cardiac massage was instituted and the patient was successfully resuscitated. He was able to be re-closed and taken to the cardiovascular intensive care unit in stable condition. However, he was on inotropic support including epinephrine, Levophed, and Primacor for 24 hours. He had no further cardiac complications throughout the postoperative. He was seen by

The patient was noted to be severely anemic post-op and was transfused with four units of packed red cells. While the cardiac arrest could be related to the anemia or a reperfusion arrhythmia, an intraoperative MI should also be considered. This case was adjudicated regarding the bleeding but not regarding the possible MI. The adjudicator for the bleeding was given the discharge summary including the text above but did record any consideration of also adjudicating for MI. No CK-MB values were reported after day 2. Ticagrelor was discontinued on day 11 and the last event recorded was moderate hypotension on day 12. The last vital signs for this patient were recorded on day 93 although he has visits recorded through day 366.

Example 2: An uncounted MI because the adjudicated date was off by two years

Figure 2: Chronology Submitted by Site

Description	Date and time
Randomisation	2007-12-05
Index event	2007-12-05 07:00
Sampling-Enzymes	2007-12-05 08:22
Sampling-Enzymes	2007-12-05 09:18
Sampling-Enzymes	2007-12-05 09:18
Sampling-Enzymes	2007-12-05 09:18
Sampling-Enzymes	2007-12-05 09:18
Sampling-Enzymes	2007-12-05 09:18
Sampling-Enzymes	2007-12-05 09:18
Coronary angiography	2007-12-05 09:20
Cardiac surgery	2007-12-05 11:45
Sampling-Enzymes	2007-12-05 15:33
Sampling-Enzymes	2007-12-06 06:00
Sampling-Enzymes	2007-12-06 06:00
Sampling-Enzymes	2007-12-06 06:00
Sampling-Enzymes	2007-12-06 07:14
Sampling-Enzymes	2007-12-06 14:00
Sampling-Enzymes	2007-12-06 14:00
Sampling-Enzymes	2007-12-06 14:00
Cardiac ischaemic event	**2007-12-06 23:45**

Figure 3: Adjudication

Event adjudication	
What is the result of the event adjudication?	Myocardial infarction
Adjudicator comments	Patient immediately had ST changes after surgery and was later found to have 2 SVG's occluded, so this is a peri-CABG infarct
Date:	2007-12-06
Time:	23:45
Date (yyyy-mm-dd)	2005-12-05 ← **Year off by 2!**
Time (hh:mm)	11:45
Type of myocardial infarction?	MI within 24 hours of CABG
Classification of Myocardial Infarction?	STEMI
Subclassification of Myocardial Infarction?	Q-wave
Is this endpoint related to a stent thrombosis?	No

Because the adjudicated year was off by two years and prior to the randomization, this MI (in the ticagrelor arm) was not counted in either the NEJM publication or the NDA submission. There are two other endpoints, both in ticagrelor patients, with date or time errors not counted in the NEJM publication or the NDA submission.

Appendix 2: Meeting Minutes of Interview with RECORD Chief Statistician

MEMORANDUM OF MEETING
MINUTES

MEETING DATE:	Tuesday May 25, 2010
TIME:	9 – 10 am
LOCATION:	Bld. 22 3270
APPLICATION:	NDA 21-071
DRUG NAMES:	Avandia
TYPE OF MEETING:	T-con with Professor Pocock (in UK)

FDA ATTENDEES:

Susan Leibenhaut, M.D.	Leslie Ball, M.D.	Karen Mahoney, M.D.
Mary Parks, M.D.	Ellis Unger, M.D.	Jena Weber,
BS David Hoberman, Ph.D.	Tom Marciniak, M.D.	

BACKGROUND: Discussion with Prof. Pocock on Avandia (see attached questions from DSI).

ACTION ITEMS: None at this time.

Questions for statistician Stuart Pocock

Introductions of participants, purpose of call to interview Prof. Pocock on his role and activity in the RECORD study:

1. Please describe your involvement in the RECORD trial. Specifically, how were you recruited to serve on the Steering Committee? How would you describe your contractual duties and activities regarding RECORD?
    a. Contractual duties? Prof. Pocock may have only partial recall for these events that occurred in 1999 or 2000. He was invited to become a member of the Steering Committee by either GSK or Professor Home. He was the only statistician on the committee. His understanding of the mission of the committee was to ensure that the RECORD study was conducted according to good clinical practice.
    b. Activities? Meetings took place in London approximately every six months to discuss trial design and analyses, such as review glycemic control and patient subset analyses, to oversee progress of the trial, and to write manuscripts concerning the trial.
    c. Were you requested to provide any financial conflict of interest forms to GSK? Prof. Pocock had no recollection, although he does not hold any financial interests in GSK.

2. What are your current contractual duties and activities regarding RECORD? He remains on the Steering Committee and is consulted by GSK from time to time.

3. The article published in the NEJM in July 2007 describing the interim analysis in the section tiled "Study Oversight", states, "Members of the Steering Committee developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported." First I would like you to discuss the events surrounding the decision to conduct and publish the interim safety analysis and then address "accuracy and completeness of the data."

    a. Please describe the events that surrounded the interim analysis. When did you first learn of the plan for an interim analysis and what conversations did you have concerning this? What conversations did you have concerning the performance of the analysis, the publication of the analysis? Dr. Pocock had distant recall here. The Steering Committee was informed of possible concerns of cardiovascular safety concerning Avandia. This became an urgent matter; t-con with GSK senior management ensued. Publicity and public concern suggested that there was a need for a balanced approach presenting the totality of the evidence, and that an interim analysis of the ongoing trial should be conducted. Although it was considered unusual to publish, it was considered of interest to the public. Prior to the formal interim analysis, the safety results were known only to the DSMB using the DSMB analysis performed by Quintiles. Prof. Pocock does not recall a conversation with Dr. Murray Stuart, so it was probably with Dr. Home. He was unaware of the results of the interim analysis at the time of decision to publish, but assumed that the DSMB were aware.

    b. Concerning the events surrounding the steering committee meeting on May 24, 2007: Your name is not on either the attendees or the apologies list. Do you recall whether you participated in the telecon? Were you contacted prior to the steering committee meeting to discuss the agenda for the meeting or any other items concerning conducting an interim analysis of the safety data? If so, who contacted you and when, and what was the nature of the discussion? Do you remember if anyone, yourself or Prof. Home, reviewed and approved the RAP? He recalls that he participated in the telecon of May 24, 2007, and does not recall prior telecons.

    c. Please discuss what it means to "have full access to the interim data and vouch for the accuracy and completeness of the data reported?" Does this mean access to the database, study level data or individual subject level data? GSK provided the data to (b) (6) at the London School of Hygiene and Tropical Medicine. (b) (6) wrote a program according to the statistical analysis plan supplied by GSK and ran the data provided by GSK though his program. (b) (6) program was recreated to perform an analysis; not a complex plan.

4. With regard to the RECORD data:
    a. How would you describe the activities you, your staff, or your co-authors have taken to insure the quality of the RECORD data and your analyses thereof? (b) (6) had the full trial database set to recreate the analysis. We had more of a scientific advisory role, not detailed activities in data management.
    b. What analyses did you or your staff perform to verify the data? See 4a.
    c. Were you provided access to RECORD data sets? If so, what type of datasets and when? All raw data sets? Analytical data sets only? Other? See 4a.
    d. Were you provided access to and did you examine case report forms? Endpoint dossiers (dossiers and patients)? Data query forms, notes to record, data clarifications, etc. (patients)? No
    e. Did you or your staff check the coding of adverse events? No
    f. Did you or your staff check the CV endpoint adjudications? No
    g. Did you or your staff cross-check data sets to verify that referrals for adjudication were complete? AEs vs. endpoints? Hospitalizations from the Medical Care Utilisation forms vs. AEs and endpoints? No

5. A press release on the GSK website dated March 23, 2010, states that, "Both the interim and final analyses were independently verified at the London School of Hygiene and Tropical Medicine. The methodology and baseline characteristics and design were published well in advance of any analysis." Please provide details of these verifications (confirmatory analyses). Who performed the verification? What is involved in "independently verifying"? (b) (6) involved in publication that appeared in Lancet. See reply to 3c.

6. Were you involved in preparation of the NDA submission? No involvement. a. What was your involvement? No
    b. Did you have any reservations regarding, the NDA submission? Did you report any reservations to GSK? No

7. The August 3, 2007, RECORD Steering Committee Meeting minutes, item 8 indicated that you raised concerns about some data issues that were discovered during the recent interim analysis work. "Jackie to liase with Stuart to find out more on this issue; target to present an overview at the face to face SC meeting on 9 October." What were your concerns regarding data issues? Why was nothing on this topic described in the October SC meeting minutes? Please provide the documentation on these data issues. He does not recall. He assumed that minor issues were usually discussed and if it had been something major it would have been brought up again.

8. The "Final Draft minutes 8th Steering Committee Meeting – September 10, 2003," records state that "The Steering Committee members were informed of the unrestricted availability of unblinded treatment code within Quintiles and GSK: no concerns raised." What was your understanding of the availability of unblinded treatment code within Quintiles and GSK? Do you have any recollection of how this item was reported, by whom and what discussion, if any, occurred?

a. Did you have any concerns? If so, what were they, and if no concerns, why not? Prof. Pocock does not have any recall concerning this. Maybe this was related to the GSK safety committee?

9. The paper published in the Lancet in June 2009, discussion section on page 2133 states," Although this study was open-label, in-depth site and data inspections in some countries did not suggest any bias in reporting." Can you provide any specifics concerning the nature of these "in-depth site and data inspections?" He doesn't recall specifically. He believes that there were presentations to the Steering Committee concerning this issue; he believes that GSK may have conducted physical inspections and analysis due to high profile public awareness and that no major flaws documented.

10. The following is a quote from Dr. Steve Nissen's article, "Setting the RECORD Straight" in the March 24/31, 2010, issue of JAMA:

"There are 2 general approaches to academic governance. In one approach, the steering committee is composed of academic investigators and has full access to all of the study data and reports. In another approach, the steering committee is appointed by the company, but the clinical trial database is exclusively controlled by the company and "access" provided to the investigators. In general, this means that the authors can send queries to the company, but the steering committee does not have a copy of the database and no outside statistician has independent access to the raw data." Please describe the approach to academic governance used in the RECORD trial.

(b) (6) had the full trial database made available to him. This was the channel by which the steering committee had access to the database. Dr. Pocock expressed that GSK seemed more forthcoming with information and more open to suggestions than other sponsors with whom he has worked.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENA M WEBER
07/09/2010

Appendix 3: Email Thread Attempting to Elicit Qualifications of the Second RECORD Clinical Site Auditor

From: Marciniak, Thomas
Sent: Wednesday, September 08, 2010 8:58 AM
To: Laska, Susan F
Cc: Glasgow, David K
Subject: RE: DSI field inspections

I can't have an issue with an investigator's training or abilities because you have not told me specifically what the specified investigator's qualifications are. As a clinical reviewer who depends upon DSI inspections I am trying to understand the basis for them, in particular for the RECORD trial. I would still like my simple request answered. I do not understand your reluctance to answer.

Tom

[no response]

From: Laska, Susan F
Sent: Wednesday, September 01, 2010 3:27 PM
To: Marciniak, Thomas
Cc: Glasgow, David K
Subject: RE: DSI field inspections

Tom

If you have an issue or concern about an Investigators training or abilities please let me know. We will evaluate and inform the District management.

Susan Laska
Deputy Director, Division of Domestic Field Investigations
301 827 5662
Fax 301 443 3757

From: Marciniak, Thomas
Sent: Wednesday, September 01, 2010 2:29 PM
To: Laska, Susan F
Cc: Glasgow, David K
Subject: RE: DSI field inspections

Would you answer the questions below regarding Laura Garcia? She did the audits for a particularly sensitive study.

Would you provide the educational background, years of field experience, and identities of other CV outcome trials (NDA numbers would be ideal) for Laura Garcia?

Tom

From: Laska, Susan F
Sent: Wednesday, September 01, 2010 2:07 PM
To: Marciniak, Thomas
Cc: Glasgow, David K
Subject: RE: DSI field inspections

Tom

Field investigators selected for foreign inspections are experienced investigators, endorsed by their management as operating independently and proficiently in a certain program area. The field investigators are in the consumer safety officer (CSO) series. The basic qualifications for a CSO are listed below. The field force that has been hired in the last couple of years typically have advanced degrees and industry experience.

- a full course of study at an accredited college or university leading to a bachelor's or higher degree, including 30 semester hours in one or a combination of biological sciences, chemistry, pharmacy, physical sciences, food technology, nutrition, medical science, engineering, epidemiology, veterinary medical science, or related scientific fields that provide knowledge directly related to consumer safety officer work

- or 30 semester hours of course work as described above plus appropriate experience or additional education. The required 30 semester hours can include up to 8 semester hours in statistics or course work that includes the principles, theory, or practical application of computers or computer programming.

Susan Laska
Deputy Director, Division of Domestic Field Investigations
301 827 5662
Fax 301 443 3757

From: Marciniak, Thomas
Sent: Wednesday, September 01, 2010 8:19 AM
To: Laska, Susan F
Subject: FW: DSI field inspections

Please see my request at the start of this thread.

Tom

From: Purohit-Sheth, Tejashri
Sent: Tuesday, August 31, 2010 11:32 AM
To: Marciniak, Thomas
Cc: Leibenhaut, Susan
Subject: RE: DSI field inspections

Hi Tom,

As the field investigators work for Office of Regulatory Affairs, outside of CDER, DSI doesn't have the type of information that you are requesting. I can tell you, in general, that the educational background of the field investigator is variable. They are CSOs, and most will have some basic science degree. They do not, in general, have advanced degree, although there are very rare investigators with an advanced degree.

The best person to ask is ORA. The POC is Susan Laska from ORA (she is in FDA Global). Thanks.

Tejashri

Tejashri Purohit-Sheth, M.D.
CDR, Medical Category, USPHS
Branch Chief, Good Clinical Practice 2
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tejashri.purohit-sheth@fda.hhs.gov

From: Marciniak, Thomas
Sent: Tuesday, August 31, 2010 8:59 AM
To: Purohit-Sheth, Tejashri
Cc: Leibenhaut, Susan
Subject: RE: DSI field inspections

The answers?

Tom

From: Leibenhaut, Susan
Sent: Wednesday, August 25, 2010 9:36 AM
To: Purohit-Sheth, Tejashri
Cc: Marciniak, Thomas
Subject: FW: DSI field inspections

Tejashri,
Please see Tom's request below.
Thanks,
Susan

From: Marciniak, Thomas
Sent: Wednesday, August 25, 2010 8:58 AM
To: Leibenhaut, Susan
Subject: DSI field inspections

One aftermath of RECORD is that I'm trying to understand how field investigators do inspections in Europe. Would you provide the educational background, years of field experience, and identities of other CV outcome trials (NDA numbers would be ideal) for Laura Garcia?

Tom

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/s/

THOMAS A MARCINIAK
04/23/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 15, 2012

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (DCRP)

Subject: RECORD re-adjudication, NDA 21-071

To: Jena Weber, Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

This review provides my evaluation of the "Final study report of the first phase of the independent re-adjudication of the RECORD endpoints as provided by Duke Clinical Research Institute (DCRI)" that you requested DCRP to review and comment on both all-cause and CV deaths in your consult request dated January 11, 2012. I am the team leader for the DCRP clinical reviewer, Dr. Preston Dunnmon, assigned to this consult. Because there is substantial background regarding RECORD and the re-adjudication about which I am more knowledgeable than Dr. Dunnmon, I am filing the following review:

The re-adjudication cannot address many of the trial design flaws documented previously
The re-adjudication cannot correct the RECORD design flaws such as its open-label nature, active controls, and treatment crossovers. As the synopsis of the re-adjudication report declares "The independent CEC re-adjudication of all-cause mortality and cardiovascular mortality for the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study was designed to address **some** of the critical FDA concerns detailed in the FDA briefing document: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf; Woodcock, 2010) [emphasis added].

COMMENT: The referenced document UCM218493.pdf provides the details of all of the trial design flaws that this re-adjudication cannot address.

The re-adjudication is not independent
During early discussions of the proposed protocol for the readjudication I emailed to your staff on January 18, 2011, the following comment about the proposed methodology:

> "But, if GSK is doing the redacting, there is the possibility for differential dropping of critical information. I documented with hard examples how differential dropping of patients and events prior to adjudication is found in RECORD. I believe that argues that GSK involvement in this readjudication should be minimized: Any activity that can be carried out by another group should be. However, no group funded by GSK is completely independent of GSK."

I was not involved with or consulted about later discussions of the protocol or of the conduct of the re-adjudication. However, my comment from January 18, 2011, raised many issues with the proposed protocol that the report confirms as severe limitations of the re-adjudication. The first such issue is that the re-adjudication is not independent.

The re-adjudication is not independent of the sponsor GlaxoSmithKline (GSK) in two important regards: (1) The parties carrying out the re-adjudication have received other financial support from GSK; and (2) GSK itself carried out activities critical for unbiased conduct. I document these two problems below.

1. The parties carrying out the re-adjudication are not financially independent of GSK
GSK used two contractors, Duke Clinical Research Institute (DCRI) and MediciGlobal, to assist with the re-adjudication. (It is possible that MediciGlobal was a subcontractor of DCRI.) Both contractors have received other financial support from GSK.

Regarding DCRI and GSK, *The Chronicle*, Duke University's daily independent newspaper, published on April 23, 2010, an article entitled "The Research Industrial Complex" that starts as follows: "In one tower of an nondescript, nine-story white building on Fulton Street, just across from Duke University Hospital, operates the world's largest academic clinical research institute, generating more than $125 million in revenue per year from the research grants and contracts it receives from both government sources and from industry. Its more than 218 clients in the pharmaceutical and medical device sectors include corporate giants Johnson & Johnson, Pfizer, **GlaxoSmithKline** and GE Healthcare." [emphasis added]

That GSK provided prior and ongoing financial support for the DCRI staff involved with the re-adjudication can be confirmed from their conflict of interest (COI) disclosure statements available at https://www.dcri.org/about-us/conflict-of-interest. The most revealing are the following (accessed April 30, 2012):

- The COIs for the principal investigator document GSK support for both salary and research projects since 2008, the earliest COIs currently posted. The also document GSK payments for "Consulting or Other Services (Including CME) for this Company Generates Personal Income" of "<$10K" in 2008-2009 and "$10-25K" in 2009-2011.

- The COIs for the "faculty lead" document GSK support for both salary and research projects since 2009.

- The COI for the "Faculty Reviewing Statistician (Unblinded) for review of Mortality Report" documents GSK support for salary in 2008-2009 but there are no later COIs posted for this individual.

The MediciGlobal website does not provide COIs or reveal the identities of its clients. However, a news release available on the Web regarding a former MediciGlobal employee who moved to a different company confirms that GSK is a MediciGlobal client: "[redacted]'s previous position was Vice President of Operations for MediciGlobal, a clinical trials marketing company. There, she led the project team in the implementation of patient recruitment and retention programs for major pharmaceutical companies such as **GlaxoSmithKline**, Pfizer and Sepracor." [emphasis added]

The MediciGlobal website at http://mediciglobal.com/press/category/company_history/ (accessed April 30, 2012) did provide the following relevant information regarding the company's history:

> "2008 EMEA orders a major Pharma Company (and Medici client) to withdraw its product from the market. The company removes the product from 47 countries. MediciGlobal adjusts headcount as a result of this regulatory decision and the loss of two global studies and one domestic one."

There appears to be a reason why MediciGlobal might be supportive of another client threatened with drug withdrawals.

COMMENT: The major issues here are not that GSK paid DCRI and MediciGlobal to perform the work related to the re-adjudication but the natures of the financial relationships between GSK and both contractors both for contracts related to the re-adjudication and for other relationships. It would be informative to know how much GSK paid them for re-adjudication work, the terms of payment, the deliverables from the contractors provided to GSK, and what control GSK retained over the work (see next section) and the reports to the FDA.

Both contractors appear to have continuing financial relationships with GSK that could be jeopardized if the re-adjudication results were not satisfactory to GSK. Having the details of the contracts would facilitate evaluating the potential for conflict of interest. The continuing financial relationships make the re-adjudication not financially independent of GSK.

The GSK personal payments to the DCRI principal investigator are concerning.

2. Critical re-adjudication activities were not independent of GSK
The DCRI report describes in Section 6.1 the sources it used: "In the process of identifying suspected death events, the DCRI RECORD CEC group accessed the following:
- Original RECORD data set
- Original RECORD paper case report forms
- Original RECORD serious adverse event (SAE) reports
- Source documents contained in original RECORD event packets
- Original RECORD queries and query responses

- DCRI CEC query responses
- Correspondence from GSK
- Correspondence from MediciGlobal"

All of these, with the possible exception of the DCRI CEC query responses (but see next section), were supplied or potentially influenced by GSK. For example, the summary above describes DCRI accessing the "Original RECORD data set". However the report provides more details on how DCRI acquired the datasets in this summary from the report synopsis:

> **Database transfers**
>
> SAS datasets containing the raw data collected in the original RECORD trial were transferred from GSK to the DCRI in three phases as follows. Redaction of specific data was done in order to blind DCRI personnel to treatment and event adjudication results.
>
> Phase 1 transfer included raw CRF datasets needed to provide electronic identification of events for referral to the DCRI CEC. Treatment information was redacted from this dataset. The phase 1 dataset transfer was completed on 26 January 2011. An additional dataset containing GSK population flags was delivered on 04 February 2011.
>
> Phase 2 transfer included AE and cardiovascular (CV) procedure endpoint numbers, dummy randomization data, treatment start and stop dates, subgroups reported in original study (eg use of particular concomitant medications at baseline), and a dataset containing the ID numbers of patients whose deaths had been reported in the original study. The phase 2 data transfer was performed in several phases and completed on 12 August 2011.
>
> Phase 3 transfer included treatment information and re-delivery of all previously delivered datasets with redacted information unredacted. These data were placed in a secure folder on the DCRI server (completed 01 November 2011) and access was granted only to the unblinded statistical team members responsible for producing the Mortality report.

Note that GSK provided all datasets to DCRI and, in fact, explicitly redacted information. We do not know whether GSK—knowing all treatment assignments and the impact of dropping relevant information—also dropped completely relevant information.

The report documents that GSK supplied or intervened in all data sources for which the report documents the ultimate source (as opposed to "were also provided".) Other examples are the following [emphasis added]:

- 4.2 "In addition, DCRI also screened all information **collected by GSK** between November 2010 and March 2011 regarding patients whose last contact was made during the survival status follow-up phase and recorded on pages 501, 502, and 506 of the CRF."

- 4.2.1 "Using the RECORD study data **supplied by GSK**, DCRI identified patients whose vital status at the end of the study was not clearly documented. MediciGlobal (King of Prussia, Pennsylvania), an independent vendor (third party) was employed to search for additional vital status information for these patients."

- 4.2.2 "The CRF pages were the only information related to survival status that was collected by GSK, as the source documents were archived in the Investigator Site Files

and not by GSK. **GSK retrieved available source documents** from the Investigators' Archive. . ."

- 4.2.2 "CRAs based at Quintiles and **GSK Sweden requested sites** where the 437 "survival status patients" were based to retrieve source documents for August 2008 through December 2008 (the study-visit close-out period), from their archive and **provide copies to GSK**."

- 4.2.2 "The sites were asked to redact the paperwork (to remove person identifiable information) prior to **sending the information to GSK**."

COMMENT: The topic sentence for Section 4.1, CEC Review and Adjudication Process, correctly states the relationship between DCRI and GSK:

> *"The DCRI RECORD CEC Group is responsible for the conduct of the CEC operations for the RECORD Re-Adjudication Protocol, **in collaboration with the sponsor, GSK**." [emphasis added]*

This was not an independent re-adjudication.

The re-adjudication is impossible to blind completely

The document UCM218493.pdf referenced in the re-adjudication report synopsis and in the second paragraph of this review includes a copy of my review of the 2009 RECORD study submission including appendices providing clinical details on all patients for whom my evaluation of a death, myocardial infarction, or stroke differed from GSK's as well as details, including CRF copies (redacted for patient and site IDs), of other patients whose data had been mishandled. Another appendix contains the treatment assignments for all of these patients. If one has, as DCRI did, the RECORD datasets and CRFs, it is a simple matter to match the clinical details of the patients and treatment assignments to their study IDs.

COMMENT: The patients whom anyone with blinded study data can unblind represent the ones of greatest concern, i.e., the ones predominantly that GSK failed to adjudicate or that had missing data making adjudication difficult. The report describes in great detail how other aspects of the blind were maintained (see the Database transfers box above) but fails to discuss that the blind for many patients could be broken easily by anyone with blinded study data and Internet access. I would not be greatly concerned about blinding for this re-adjudication if the evaluators were truly independent of GSK. Unfortunately they were not.

Additional follow-up was minimal and possibly biased

Follow-up and documentation thereof during the conduct of RECORD was poor for many cases, so it should not be surprising that follow-up in 2011, 10 years after the earliest lost-to-follow-up dates, is difficult or impossible. Section 6.2, the DCRI description of their query of suspected events, is informative:

6.2 CEC Query of Suspected Events

It was necessary to issue 127 CEC queries for additional information to follow up on death events classified as "unknown" and "insufficient information."

Of 127 CEC queries issued—

- 43 queries were closed with no response from site;
- 61 queries were closed with a response from the site that no additional data is available;
- 23 queries were closed with additional data received from the site.
  Of these 23 queries—
  - 16 events were re-reviewed with no change to adjudication result;
  - 7 events were re-reviewed with a change to the adjudication result from "unknown" to a known cause of death.

Note that the response rate for any additional data was only 18% and the response rate for meaningful information (excluding the 16 patients with no change to the adjudication result of "unknown" or "insufficient information") was only 5.5%.

COMMENT: The report does not clearly state whether GSK was involved in these queries but I would be concerned about bias in the response rate or biased responses regardless of current GSK involvement: If a site had either inadvertently or intentionally misreported data during the study, I would expect that such a site would be more likely not to respond or to respond with incomplete information. Regardless, with the extremely low response rate we can have no confidence that we have obtained any unbiased information.

The additional DCRI follow-up from their CRF review was similarly limited: For patients not known to be dead (from the review of the CRFs in the FDA UCM218493.pdf document referenced by DCRI) the DCRI CRF review extended follow-up to or beyond the earliest study end date for only 10 patients, 4 rosiglitazone and 6 control. The CRF entries for one of these patients show the uncertainty of these determinations: A rosiglitazone patient had a last visit with vital signs on 16nov07. The end of study survival CRF listed the patient as alive on 18aug08 with name of contact originally blank but added later in a data query as "patient". A documentation of third party survival CRF dated mar09 listed the patient as alive on 18oct08 from "site sourcedocs". The CRFs do not provide any other information regarding these late contacts. How can we be certain that the correct date is 18oct08 (a Saturday) rather than 18aug08 (a Monday)? If DCRI obtained copies of the "site sourcedocs" such as a clinic visit progress note or hospital summary for the 2008 contacts then we would judge the late follow-up to be valid (but this submission does not include copies of source documents.) The conservative estimate for last follow-up would be to use 16nov07; DCRI used 18oct08.

COMMENT: The DCRI CRF review extended the follow-up minimally and with uncertainty. The numbers do not suggest a bias for this part of the re-adjudication.

There are multiple problems with the follow-up by MediciGlobal:

1. The report does not state who provided data to MediciGlobal and what was provided. We have no idea of the accuracy or completeness of the data MediciGlobal used to perform its searches.

2. The report does not describe the methodology MediciGlobal employed or its reliability. The MediciGlobal president described her firm's methodology in an article entitled "MediciGlobal's L2FU tracks down, contacts missing clinical trials patients" and dated September 7, 2010:

   > "[redacted] says L2FU recently took only one month to track down and contact about 30 patients who were three to five years disconnected from a particular study. How? [redacted] won't say; it's proprietary, of course, but it involves "billions of data" in a series of networked databases that L2FU has licensed."

   COMMENT: Proprietary data base matching is not error free. We would need to understand completely the methodology used by MediciGlobal and have complete access to its inputs and outputs before we could rely upon its results. However, the following facts suggest that there are substantial problems with it regardless of the methodology.

3. The submission does not provide any information on the MediciGlobal output except a "Last Alive Date from 3rd Party Search". The following case illustrates that there likely are problems with the output: One rosiglitazone patient was 75 years old at entry in June 2002 with a history of hypertension and stroke and receiving digoxin and lasix for "prophylaxis for heart failure". GSK submitted an adjudication package to the NDA for this patient with errors in patient identity, i.e., the PDF file was named with this patient's number but included a different patient number on some of the included documents including a different gender on a cath report from a country at the opposite end of the globe from the patient's site. The patient apparently moved to another city in 2004 and was lost to follow-up, although the site reported the patient as dead in 2004, year and month of death unknown. In the December 2011 death re-adjudication report the MediciGlobal follow-up for this patient is absent. However, in the March 2012 CV re-adjudication report the MediciGlobal follow-up lists the patient as alive on October 25, 2011. (Per the March 2012 report MediciGlobal did do additional searches after the December 2011 report was finalized.) The March 2012 report does not otherwise comment on the status of this patient.

   COMMENT: While it is possible that a 75-year-old hypertensive diabetic with a stroke and heart failure is alive more than 9 years later, this type of third party follow-up report requires confirmation and specific scrutiny. For this particular patient there is the additional concern that GSK had previously made a mistake about the patient's identity. That DCRI did not specifically address this patient's results in either report is problematic and indicates a limited understanding of the RECORD data or limited access to them.

4. The success rate of the MediciGlobal effort was low. I could not find one number anywhere confirming how many cases were referred to MediciGlobal. My best estimate is 46 patients with inadequate documentation of follow-up plus 43 patients with unknown or partial date of death plus 252 additional patients who failed several criteria, or 341 patients in total. (The a-medici.xpt dataset in the March 2012 submission has 343 entries.) The a_medici.xpt file in this submission has a "Last Alive Date from 3rd Party Search" for 82 patients, or a crude success rate of about 24%.

   However, the MediciGlobal search results have additional limitations:

   - Changes in deaths prior to the earliest study end date (24aug2008) were limited from all sources: In addition to the original on-study rosiglitazone death described above with late follow-up alive, another rosiglitazone patient originally reported as dead per a newspaper report in jul08 is now counted as dead on 21oct2009. Three deaths prior to 24aug2008 were added for one rosiglitazone and two control patients. Hence the changed deaths favor rosiglitazone 4:1.

   - For patients not known to be dead (from the review of the CRFs in the FDA UCM218493.pdf document referenced by DCRI) the MediciGlobal effort extended follow-up to or beyond the earliest study end date for only 29 patients, 20 rosiglitazone and 9 control. Hence the changed follow-up favors rosiglitazone about 2:2:1.

   The MediciGlobal effort appears to have provided some (but not necessarily accurate) information for about 5 + 29 = 34 patients, yielding an unverified "success" rate of about 10%.

   COMMENT: While the MediciGlobal results favoring rosiglitazone 4:1 and greater than 2:1 do not prove that the results are biased, they are suspicious. The unknown methodology, suspicious case of late live follow-up, low success rate, and possible bias favoring rosiglitazone all suggest that the MediciGlobal results are not trustworthy.

   Finding three additional deaths eliminates little missing data and does not add appreciable to our understanding of the results reported by GSK in 2009. How many deaths could be missing? DCRI provided the following estimate of missing vital status in RECORD:

> For purposes of the re-adjudication of mortality in the RECORD trial, patients were considered to have completed follow-up if any of the following conditions was met:
>
> - Patient died
> - Patient had a face-to-face visit (vital signs recorded) on or after 24 August 2008
> - Patient had a face-to-face visit in 2008 and a phone visit (a visit with no vital signs recorded) after 24 August 2008
>
> On this basis, 3,843 patients were initially designated as completing follow-up. The remaining 604 patients included 127 patients who were reported in the original RECORD trial to have unknown vital status at study end. The DCRI RECORD CEC group issued CEC queries to these patients' sites for additional information.

So DCRI classified 604 patients as having incomplete vital status and not known to be dead. About 6.5% of RECORD patients with complete vital status died before the earliest study end date (24 August 2008 used above.) We would expect that the death rate in patients with incomplete vital status should be equal to or greater than that for patients who completed follow-up because death is one reason for being lost to follow-up. Hence we can estimate that at least 604 x 6.5% ≈ 39 deaths are missing—far greater than the 3 new deaths found. The ≈ 39 deaths is likely a low estimate. In addition to the belief that dead patients are more likely to be lost to follow-up, rosiglitazone patients who withdrew were more likely to have died than control patients: There is evidence in RECORD of differential informative censoring, i.e., rosiglitazone patients withdrew more frequently because of heart failure and heart failure patients fared poorly. (Pages 249 to 250 in http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM222629.pdf) The vast majority of missing follow-up in RECORD remains missing. The re-adjudication effort does not clarify RECORD results but, because of the problems documented above, likely confounds them more.

DCRI's handling of a recent CV outcomes trial was questionable

While some might point to the recent scandal regarding a Duke cancer trial as evidence that Duke is lax regarding clinical trial monitoring, there is another recent, more relevant example of problems with DCRI's handling of CV outcome trial data similar to those seen in RECORD. DCRI was a contractor for the PLATO CV outcomes trial evaluated in the following review http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000MedR.pdf and described in a *New England Journal of Medicine* (NEJM) article co-authored by both the DCRI Director at the time and the DCRI principal investigator for this RECORD re-adjudication. (Wallentin, Becker et al. 2009) DCRI co-coordinated the clinical events committee (CEC) that adjudicated events in PLATO; the DCRI clinical faculty leader for the PLATO CEC is also the principal investigator for the RECORD re-adjudication.

PLATO, like RECORD, was plagued by incomplete follow-up and incomplete referral of cases for adjudication. (Note that, while PLATO was "double-blind", the blind could easily be broken by opening a study drug capsule that contained either a commercial clopidogrel tablet or filler.) The referenced review provides the details of these problems but I've summarized some of them below for ease of reference:

Regarding incomplete follow-up, even by the sponsor's counting confirmed by the DCRI principal investigator at the Cardiovascular and Renal Drugs Advisory Committee meeting on July 28, 2010, the percentage of patients with incomplete follow-up for the primary CV death, myocardial infarction, or stroke primary endpoint was 13%. As one committee member commented, "I would say a 13 percent loss to follow-up in a trial where the follow-up is between 6 and 12 months is just way high." The DCRI principal investigator responded, "I would agree with you, [redacted], that the 13 percent is not a very good standard." (Page 193 of the transcript available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM223579.pdf)

The problem of incomplete referral of cases for adjudication was similar in PLATO to that in RECORD. The referenced review summarizes about 26 problems cases. The following are some examples of failures to refer for adjudication:

- A ticagrelor patient had a PCI with stent on day 1 followed by hypotension and mild pulmonary edema. On day 2 he suffered bradycardia and complete AV block treated with a temporary pacemaker and resolving by day 6. On day 12 he was rehospitalized for "syncope( )before hospitalization, Ventricular tarchycardia, seizure,v-fib and Asystole after hospitalization"; ticagrelor was discontinued. Treatment included CPR, cardioversion, and an IABP. This event was not submitted for adjudication. His last visit was on day 42 but the sponsor counted him as completing the study through day 391 without an endpoint. The DCRI co-authors did not count the event as an endpoint.

- A ticagrelor patient was hospitalized on day 22 with a coronary thrombosis. A troponin T was reported as >5x and an echo showed hypokinesis of the inferior wall with ejection fraction 55%. No other information on symptoms, physical findings, lab, treatment (of this event, prior concomitant medications are listed), or hospital course are provided. The event was not submitted for adjudication and the DCRI co-authors did not count the event as an MI.

- A ticagrelor patient had a scheduled visit on day 91 then suffered an NSTEMI on day 96. The last study drug day was day 97 and the patient withdrew consent on day 97. An NSTEMI SAE was "inactivated" and the NSTEMI event was not submitted for adjudication. The DCRI co-authors did not count the MI.

Not only was referral for adjudication problematic in PLATO but missing data needed for adjudication were also problematic. The following are examples from the referenced review:

- A ticagrelor patient on day 8 had chest pain, called an acute myocardial infarction (MI) by the site, and a stent thrombosis on angiography. No biomarkers or ECGs were provided and the event was adjudicated as severe recurrent ischemia, not an MI. The DCRI co-authors did not count the event in the primary endpoint.

- A ticagrelor patient was hospitalized on day 68 with ischemic chest pain, and ST changes and had an angiography showing three vessel disease and vein graft ostium obstruction. He had an adverse event of ventricular fibrillation. No biomarkers were reported and the adjudication was recurrent ischemia. The DCRI co-authors did not count the event in the primary endpoint.

There were other variations on eliminating events in PLATO study drug patients:

- A ticagrelor patient was randomized at 11:09, received first study drug at 11:20, and then had an urgent angiography at "12:00". Relatives allegedly withdrew consent on day 1 because "patient no longer responsive after surgery" (likely a stroke and hence an endpoint occurring before the withdrawal of consent.) The surgery is not described and the time of withdrawal is recorded as "12:00". Some additional information was

collected, including a multiorgan failure SAE and a sudden death on day 18 that were "inactivated", although the death was adjudicated as unknown—cardiovascular by the PLATO endpoint rules. The sponsor censored the patient on day 1 and the DCRI co-authors did not count an endpoint.

- A ticagrelor patient had an adjudicated "myocardial infarction within 24 hours of CABG". However, the adjudicated date and time were recorded as [redacted] despite the facts that all hospital documents and data sets record the CABG as [redacted], the biomarker rises were on [redacted] and [redacted] and the date of randomization was [redacted]. The DCRI co-authors did not count the MI.

- Another ticagrelor patient had an adjudicated MI. However, the year of the adjudicated date of the event was recorded as 2005 despite the fact that the site-reported event date and all other related dates in the adjudication package were in 2007. The DCRI co-authors did not count the MI.

COMMENT: While the primary responsibility for the above problems rests with the sponsor, I do not find it reassuring that DCRI staff were unable to catch and correct many of these problems either when they reviewed cases for adjudication or when they reviewed the data files to assure the accuracy of the publications that they co-authored. The last two errors above, impossible adjudicated dates, are likely data entry blunders whose detection would appear clearly to be the responsibility of the staff monitoring the adjudications, i.e., DCRI. In general (and in PLATO and in RECORD) the problems with adjudication have not been problems with what the CEC physicians adjudicate but in manipulations before or after the adjudications, particularly before.

The types of the other problems described above are the same types of problems found in RECORD. If DCRI could not detect them concurrently in PLATO, why should we have any confidence that they have in RECORD up to 10 years after the patients were lost?

I am sympathetic that large, international, multicenter CV outcomes trials are difficult to conduct and some errors will be avoidable. However, RECORD and PLATO stand out in my experience as worst cases for documented problems with referrals for adjudication. I am also sympathetic to the position of academic research organizations who have limited clout in getting sponsors to release all of the raw data and documents needed to evaluate completely trial quality and results. However, while I am sympathetic, limited or controlled access does not insure that the RECORD re-adjudication is independent and unbiased.

This submission does not include any source documents needed for verification of the results

This submission includes a study report and "raw" CRF, CEC, and analysis datasets. I did confirm that the allegedly "raw" CRF datasets have similar limitations to the ones that GSK submitted in 2009, e.g., a myocardial infarction SAE that was deleted from the CRFs (Case A in Appendix 1 of the prior DCRP consult in the referenced UCM218493.pdf) was not included in the adverse event datasets in 2009 and is not included in the ace.xpt dataset in this submission. Missing entirely from this submission are any of the source documents needed for verification of

the alleged results, i.e., the source documents providing the details on the new follow-up, such as materials provided to DCRI and MediciGlobal and the results of the MediciGlobal searches and the DCRI CEC queries. Missing also are the source documents used by the CEC, i.e., the adjudication packages, needed to verify that the adjudication packages were as complete as those submitted in 2009.

COMMENT: While having source documents would be helpful in addressing some issues, even having all source documents we would not be able to verify the accuracy of this entire submission. For example, even if GSK could ignore privacy concerns and provide patient identifiers used in the follow-up searches, we have no practical means of verifying that the patient identifiers have not been manipulated to miss follow-up on rosiglitazone deaths.

Recommendation

I have documented the following problems with the re-adjudication:

- The re-adjudication cannot address many of the trial design flaws documented previously.
- It is neither financially nor operationally independent of GSK.
- It is impossible to blind completely.
- The success rates for the CEC query, CRF, and vital status searches were extremely low and the amount of new information obtained was minimal.
- The methodology for the MediciGlobal vital status searches was not provided and there is evidence for bias in the search results.
- DCRI failed to detect in a recent CV outcomes trial problems like those documented in the 2009 RECORD submission.
- Source documents needed for verification were not submitted and are not verifiable.

These problems are substantial such that the re-adjudication contributes little to our understanding regarding cardiovascular risks in RECORD. These problems are not remedial by a site audit of DCRI. All that we can say about the overall results of the re-adjudication is that they were not independent and that the execution of the re-adjudication was flawed.

The most independent re-adjudication and estimation of follow-up rates for RECORD is the one included in the prior DCRP consult in the referenced UCM218493.pdf. Regarding mortality and CV mortality, the missing vital status follow-up in the rosiglitazone arm (estimated 70 to 320 cases depending upon the strictness of criteria used for validating follow-up) greatly exceeds the expected difference in CV deaths between arms (about 30) estimated based on the 1.64 odds ratio in the original published rosiglitazone meta-analysis. (Nissen and Wolski 2007) RECORD did not have enough deaths and complete follow-up to provide reliable estimates of the effects of rosiglitazone on mortality or CV mortality.

References

Nissen, S. E. and K. Wolski (2007). "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes." N Engl J Med **356**(24): 2457-71.

Wallentin, L., R. C. Becker, et al. (2009). "Ticagrelor versus clopidogrel in patients with acute coronary syndromes." N Engl J Med **361**(11): 1045-57.

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THOMAS A MARCINIAK
04/23/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 25, 2013

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Summary of Inspection of Duke Clinical Research Institute for NDA 21-071

Executive Summary:
Duke Clinical Research Institute (DCRI) processes for the re-adjudication of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes)" were evaluated during inspection. No regulatory violations were noted. Overall, DCRI procedures appear to have been implemented adequately. There were isolated failures of redaction of the paper subject records received by DCRI from GSK, and one of these was not detected by the DCRI staff during preparation of the re-adjudication package for the physician adjudicators. This failure of redaction was detected by the DCRI physician adjudicator, and the file was returned for complete redaction and re-adjudication.

I. Background

The Endocrinologic and Metabolic Drugs Advisory Committee held July 13 and 14, 2010 discussed cardiovascular safety risk related to the use of Avandia. The Committee raised concerns about the design and conduct of RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes). In order to address these concerns, FDA notified GlaxoSmithKline (GSK) of the post marketing requirement (PMR) to commission an independent readjudication of RECORD under FD&C Act Section 505(o). GSK contracted with DCRI to conduct the readjudication. DCRI designed and

conducted Protocol AVD 115170, entitled "Re-adjudication Protocol AVD115170, for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes)", an independent Clinical Endpoint Committee (CEC) readjudication of all-cause mortality and cardiovascular mortality to fulfill this PMR. The readjudication was to proceed step-wise starting with review of the mortality findings for Phase 1 and then review of the major adverse cardiovascular events (MACE) for Phase 2.

For Protocol AVD115170, DCRI responsibilities included:

- Developing the CEC charter and processes
- Designing event triggers consisting of automatic (computer) and manual terms in order to prioritize records for review by DCRI staff
- Developing processes, forms, and databases for tracking the adjudication process and its results
- Developing and implementing quality control procedures

For the electronic trigger development, DCRI received electronic datasets from GSK that had been redacted by GSK and then had a secondary review by a DCRI unblinded statistician to remove any other data that would potentially unblind DCRI study staff. For the manual trigger process, DCRI developed a list of terms to alert the CEC staff so that these records could be reviewed manually in a priority fashion.

For the readjudication process, DCRI received the subject files from PPD who had been contracted by GSK to conduct additional redaction of the paper files and provide the files to DCRI. These records consisted of case report forms, endpoint dossiers (CEC endpoint packages with endpoint forms, source documents, and e-mail correspondence between data management and sites), SAE case files and narratives, and any survival status data. DCRI tracked receipt and review process for each subject record.

Previous Inspectional History for the RECORD Trial

For the actual RECORD clinical study, OSI inspected the following sites in 2010:

Inspected Entity	Inspection Program
GlaxoSmithKline	Sponsor*
Quintiles	Contract Research Organization (CRO)*
Croatia – Tertiary Referral Center	Clinical Investigator
Sweden – Primary care	Clinical Investigator
Germany- Dedicated research site	Clinical Investigator

* Participation by Office of Scientific Investigations (OSI) and Office of New Drugs (OND) subject matter experts at the request of the review division

During these 2010 inspections, no evidence of systemic or pervasive findings that would undermine the reliability of the data was found; however there were limitations to the inspections outlined in the original OSI review of June 18, 2010 included in the AC

briefing document for the July 13 and 14, 2010 meeting. These limitations included the limited ability of inspections to detect bias in referral for adjudication in an open label trial and the small percentage of subject records examined during inspections (less than 1%).

II. Inspection Rationale and Scope

At the request of the review division, CDER's Office of Scientific Investigations (OSI) completed an inspection of DCRI's conduct of Protocol AVD 115170.This inspection took place from August 20 to 24, 2012. The scope of the inspection was to evaluate DCRI's compliance with the CEC (Clinical Endpoint Committee) charter and associated procedures.

Specifically, the inspection focused on the following:

- Procedures for blinding of the DCRI adjudication committee and staff including adequacy of redaction of clinical files and of the Phase 1 (mortality) report from the CEC members and reviewers and analysts for the Phase 2 (MACE) report
- Tracking and review of files for the re-adjudication process and entry of results into the databases
- Review of DCRI documentation and training of personnel
- Review of quality control procedures
- Verification of primary endpoint: compare DCRI source with eCRF and data submitted to the NDA (DCRI source was the adjudication sheets completed by the adjudicators).

The inspection scope did not include the appropriateness of the original study design, correctness of protocol-specified definitions of endpoints, timing and appropriateness of statistical analyses, and appropriateness of the CEC adjudications, all of which are review issues.

III. Inspection Results

<u>Transfer of data and documents from GSK to DCRI:</u>
GSK sent electronic datasets to DCRI. An unblinded DCRI statistician reviewed the data for any information that could unmask treatment assignment and recommended additional redactions. After redaction the datasets were sent to the statistics department for development of the electronic triggers and set up of dummy data tables for the study report.

Additionally, DCRI received individual study subject files from a contract research organization, PPD. PPD was contracted by GSK to conduct additional redaction of the paper files prior to providing the files to DCRI. These subject files consisted of case report forms, endpoint dossiers from the prior adjudication (e.g., CEC endpoint packages

with endpoint forms, source documents, and e-mail correspondence between Quintiles data management and clinical investigator sites), serious adverse event (SAE) case files and narratives, and any survival status data. Most subject records were received as paper compiled into a binder for each subject with an accompanying CD containing the scanned images. The binders and CDs were shipped in approximately 15 to 20 installments from March to August 2011. DCRI requested that the records for subjects who died be shipped first so that the mortality review could commence review. Later in the transfer, records were received only as CDs, and no paper copies were provided.

Tracking, Review, and Re-adjudication

DCRI developed specific systems and databases to support implementation of the RECORD re- adjudication. These included:

- DCRI's Data Management team developed electronic triggers designed to prioritize the review of files
- An Excel database was created and used by CEC coordinators to track all individual subject triggers. This is the usual practice of the CEC coordinators and is not unique to this study. In addition to all triggers, this tracking database contained a listing for each subject, whether or not this subject had a trigger, because, ultimately, the records of all subjects in the study were reviewed by a CEC coordinator who was a nurse with specialty training in screening records for adjudication.
- A CEC tracker system was developed to track subject records that were sent to the adjudication committee.
- An InForm database was used to store the adjudication results.

When a subject record was identified as requiring adjudication, the CEC coordinators compiled an adjudication package and distributed the package to assigned adjudicators. The actual adjudication processes for each of the endpoints (death, stroke and myocardial infarction (MI)) are outlined in the protocol and the CEC charter.

Database lock and unblinding for the mortality database was completed according to DCRI standard procedures. Statisticians and cardiologists that reviewed the results of the re-adjudication were divided into Phase 1 (mortality) and Phase 2 (major adverse cardiac events or MACE) teams and, once the results of Phase 1 were unblinded, contact was limited between the review teams. Data and documents concerning analysis and report writing for Phase 1 were located in a limited access database.

End of study vital status

GSK recommended that DCRI contract with MediciGlobal to conduct the third party search for end-of study documentation of vital status that had been requested by FDA. If the case was referred to MediciGlobal then, as per MediciGlobal usual practice, data concerning subjects was posted by MediciGlobal on a website and retrieved by a clinical research assistant. This data was usually in the form of a death certificate or information from a registry if the subject had died, or was in the form of an e-mail confirming vital status.

Review of training of personnel and quality control procedures

Training was required of all adjudicators and key staff. The training covered protocol overview, CEC charter, study cases, definitions, review conventions and adjudication forms, source records and guidelines. This was reviewed and appeared complete. The CEC Charter outlined the quality control program based on a "historical strategy" to collect a random sample of 5 % of the cases at various intervals during the review process. This strategy was used for both mortality events and MI or stroke events. There was review of the manual trigger outcomes and also the adjudication outcomes.

Endpoint verification

An audit of a total of 60 subjects' records was conducted. These subjects were chosen either from a list of subjects that had discrepant findings between the original adjudication and readjudication or were on a list of subjects that had been discussed in previous reviews and presentations as having not been referred for the original adjudication. No discrepancies between the DCRI source data and the datasets provided by the FDA statistical reviewer were noted.

Subjects discussed previously because of concern for lack of referral

Below are the results for six subjects discussed in Dr. Khin U's review in the previous briefing document as not having been referred for adjudication or having a delay in adjudication. In the OSI review, lack of referral for only Subject 98364 was considered a violation. Note that of the six examples below, five were sent to the adjudication committee by the DCRI CEC coordinators and one (Subject 31427) was not referred to the adjudication committee, indicating that, at least for these subjects, there was a lower threshold for referral for adjudication in the readjudication protocol than the original study.

Subject 18215:

- Cardio-renal reviewer concerns regarding lack of referral for initial hospitalization and adequacy of adjudication concerning hospitalization and death.
- Readjudication Outcome: DCRI adjudicated death is non-CV (unchanged), hospitalization listed as pneumonia in CEC spreadsheet.

Subject 19079:

- MI was initially withdrawn from consideration as an endpoint at the discretion of investigator, no source documents at GSK or Quintiles to refute.
- Readjudication Outcome: DCRI re-adjudicated the event as an MI; cause of death adjudicated by DCRI as heart failure or cardiogenic shock.

Subject 20930

- Event of collapse attributed to atrial fibrillation was not sent for

adjudication by the CI. Subject was demented and non-compliant.
- Readjudication Outcome: Two MI triggers adjudicated by DCRI as no MI; death adjudicated by DCRI as unknown.

Subject 31427
- Hospitalization for facial paralysis not referred for adjudication because CT scan ruled out a stroke.
- Readjudication Outcome: At DCRI, diagnosis on CEC spreadsheet was peripheral facial paralysis, and the event was not sent to DCRI CEC for adjudication.

Subject 43697
- CI withdrew this event from consideration as an endpoint of TIA or stroke. Hospital discharge stated "probable hemangioma recommend surgical evacuation".
- Readjudication Outcome: DCRI adjudicated as hemorrhagic stroke.

Subject 98364
- Hospitalization for CHF removed from consideration as an endpoint by the CI; this was cited by FDA in original inspections as failure to adhere to protocol
- Readjudication Outcome: DCRI adjudicated as no MI (unchanged)

Issue Noted During Inspection Concerning Redaction

Concerning the issue of redaction of paper records, Section 4.2 "Collection of Data" of the CEC Charter states:
"If during the course of DCRI activities it is noted that information that should have been redacted was not, then DCRI RECORD CEC Coordinators, Clinical Data Assistant, and/or Clinical Trial Assistants will redact the information, document the event and notify GSK."

There was one documented instance in which the DCRI did not follow its own procedure. During the adjudication of Subject 97703, it was noted by one of the physician adjudicators that the word "insulin" had not been redacted from the subject medical record. The physician returned the file to the staff for redaction and readjudication; however, GSK was not notified.

According to the DCRI staff there were three to five cases of source records received from GSK that required additional redaction by DCRI staff prior to review by the adjudication committee. However, these were not documented and could not be confirmed at the time of inspection.

It is noted that during the inspection of the Quintiles Clinical Event Validation and Adjudication Committee (CEVA) in 2010, the FDA investigators reviewed 53 subject

records and noted one instance of inadequate redaction. We concluded at that time that "failure to redact treatment information occurred rarely."

IV. Summary of Inspection Results and Recommendations

No significant noncompliance was noted. The DCRI established and appropriately implemented procedures for the blinding of data received electronically, for tracking, review and re-adjudication of the records, as well as for training of staff and auditing of the triggering and adjudication procedures.. There were also adequate procedures in place for the blinding of the staff who wrote the Phase 1 report as well as for the DCRI staff who conducted the Phase 2 adjudication and wrote the Phase 2 report. For sixty subjects, the primary endpoint (DCRI adjudication results) was verified by a comparison of the source documents (DCRI adjudication outcome) to the data submitted in the NDA. No discrepancies were noted. DCRI did not follow the procedure concerning reporting to GSK failure of the one case of redaction that went to adjudication. However, because the file was returned by the originally designated adjudicator, then adequately redacted and sent to newly designated adjudicators, there is no evidence that this had any impact on the overall outcome of the study. The data generated by DCRI is considered reliable in support of the performance and fulfillment of the post marketing requirement by GSK.

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 22, 2013
To:	Members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM)
From:	Division of Risk Management Office of Medication Error Prevention and Risk Management Office of Surveillance and Epidemiology (OSE)
Subject:	Risk Evaluation and Mitigation Strategy (REMS) for Rosiglitazone-Containing Products
Products:	NDA 021071 Avandia (rosiglitazone maleate) Tablets NDA 021410 Avandamet (rosiglitazone maleate and metformin hydrochloride) NDA 021700 Avandaryl (rosiglitazone maleate and glimepiride) ANDA 076747 Rosiglitazone Maleate

1 INTRODUCTION

This memorandum from the Division of Risk Management (DRISK) presents the risk evaluation and mitigation strategy (REMS) in place for rosiglitazone-containing drugs.

2 BACKGROUND

The Food and Drug Administration Amendments Act (FDAAA) provides FDA authority to require risk evaluation and mitigation strategies (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks [FDAAA Section 505-1(a)]. A REMS is a required risk management plan that uses risk minimization strategies beyond professional labeling.

REMS may include one or more of the following: a Medication Guide (MG) or patient package insert for patients, a communication plan (CP) for health care providers (HCPs), and elements to assure safe use (ETASU), which often involve some form of restricted distribution and or evidence of safe-use conditions.

A communication plan consists of FDA-approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. For example, "Dear Healthcare Professional" letters, dissemination of risk information by professional societies, brochures focusing on the important risk messages, and/or other educational materials have been required to alert prescribers to serious risks associated with the use of certain drugs and biologics.

ETASU can include one or more of the following requirements:

- HCPs who prescribe the drug have particular training or experience, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings;
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Each patient using the drug is enrolled in a registry.

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling [FDAAA Section 505-1 f(1)(A)]. The statute [FDAAA Section 505-1(d)] also requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

In September 2010, the Agency determined that a restricted distribution REMS was needed for rosiglitazone-containing products to ensure that the benefits of these products outweigh the risk of myocardial infarction.

The Agency determined that the REMS should provide complete risk information to each patient and document that the information has been received and understood, and document that each patient receiving rosiglitazone falls into one of two categories:

1. patients currently taking a rosiglitazone-containing drug, or
2. patients not already taking a rosiglitazone-containing drug who are unable to achieve glycemic control on other medications and, in consultation with their health care professional, decide not to take pioglitazone for medical reasons.

The REMS for rosiglitazone-containing products, the Avandia-Rosiglitazone Medicines Access Program, was approved on May 18, 2011. A six-month phase-in period from the time of approval was implemented to allow patients and prescribers to transition to the REMS. Removal of rosiglitazone-containing products from retail pharmacies was accomplished by November 18, 2011.

On January 25, 2013, the FDA approved a single shared system REMS to allow generic manufacturers to participate in the REMS.

3 ROSIGLITAZONE REMS PROGRAM

Goals

The goals of the Rosiglitazone REMS Program for the rosiglitazone-containing products (RCPs) are:

1) To restrict access to rosiglitazone so that only prescribers who acknowledge the potential increased risk of myocardial infarction associated with the use of rosiglitazone are prescribing rosiglitazone.

2) To restrict access to patients who have been advised by a healthcare provider about the potential increased risk of myocardial infarction associated with the use of rosiglitazone and are one of the following:

   • either already taking rosiglitazone or

   • if not already taking rosiglitazone, they are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons

REMS Elements

Medication Guide
A Medication Guide will be dispensed with each rosiglitazone prescription in accordance with 21 CFR 208.24.

Elements to Assure Safe Use

1. Healthcare providers who prescribe rosiglitazone for outpatient or long-term care use are specially certified

To become specially certified to prescribe rosiglitazone, prescribers are required to enroll in the Rosiglitazone REMS Program and must:

- Review the Rosiglitazone REMS *Prescriber Overview* and the Full Prescribing Information, including the Medication Guide.
- Complete and sign the Rosiglitazone REMS *Prescriber Enrollment Form* and submit it to the Rosiglitazone REMS Program.
- Agree to complete and sign a Rosiglitazone REMS *Patient Enrollment Form* for each patient enrolled.
- Agree to provide and review the Medication Guide for the prescribed rosiglitazone medicine with the patient or caregiver.
- Agree to provide a completed, signed copy of the Rosiglitazone REMS *Patient Enrollment Form* to the patient, retain a copy for your records, and submit a copy to the Rosiglitazone REMS Program.

2. Rosiglitazone will be dispensed only by specially certified pharmacies.

Rosiglitazone is only be dispensed by certified pharmacies. To become certified to dispense rosiglitazone, each pharmacy must be enrolled in the Rosiglitazone REMS Program**.** To be certified, the pharmacy must agree to the following:

- To have a system in place to be able to verify that the prescriber (if the prescriber has prescribed rosiglitazone for outpatient or long-term care use) and patient are enrolled in the Rosiglitazone REMS Program prior to dispensing each time rosiglitazone is prescribed. If the patient and prescriber are not enrolled, rosiglitazone cannot be dispensed.
- To educate all pharmacy staff involved in the dispensing of rosiglitazone on the program requirements of the Rosiglitazone REMS Program.
- To provide a Medication Guide each time rosiglitazone is dispensed.
- To be audited to ensure that all processes and procedures are in place and are being followed for the Rosiglitazone REMS Program.

3. Rosiglitazone will only be dispensed to patients with evidence or other documentation of safe-use conditions

Rosiglitazone will only be dispensed if there is documentation in the Rosiglitazone REMS Program system that the dispensing pharmacy, prescriber (if the prescriber will prescribe rosiglitazone for outpatient or long-term care use), and patient are all enrolled in the Rosiglitazone REMS Program. To become enrolled, each patient must review the

Medication Guide and sign the Rosiglitazone REMS *Patient Enrollment Form* or with their prescriber.

The Rosiglitazone REMS also has an Implementation System to establish the operational framework of the REMS, and a Timetable for Submission of Assessments to submit REMS assessments to FDA 6 months, 12 months, and annually from the date of initial approval of this REMS with ETASU (May 18, 2011).

4 SUMMARY OF REMS ASSESSMENTS

The timetable for submission of assessments of the REMS to the Agency is 6 months, 12 months, and annually from the date of initial approval of this REMS with ETASU (May 18, 2011). A summary of the of the first two REMS Assessment reports covering the period May 19, 2011 through March 12, 2012 is provided below. Since the Sponsor is expected to submit their 24-month assessment plan in May 2013 which is after FDA's backgrounder is to be finalized, information from the May 2013 report will be summarized in slides to be presented at the Advisory Committee meeting.

Enrollment Statistics and Drug Utilization Data

Data for the number of patients, prescribers, and certified pharmacies enrolled in the REMS as of March 12, 2012 is as follows:

- 2,231 total prescribers enrolled
- 2,758 total patients enrolled
    - 96% were receiving rosiglitazone products upon enrollment
- 4 certified mail-order pharmacies are enrolled

Data on prescribed rosiglitazone products:

- 63% Avandia
- 31% Avandamet
- 6% Avandaryl

Table 1 on the following page compares prescription and dispensation data from the two Assessment Reports that cover the time period from REMS approval to March 19, 2012. Since the most recent assessment report includes the November 19, 2011 milestone date when patients could no longer receive rosiglitazone products from their local pharmacy, the data for this reporting are split into pre-November 18th and post-November 18th time spans.

Table 1: Prescription and Dispensation Data for the Two Assessment Periods Covering the Time Period of May 18, 2011 (REMS Initiation) to March 19, 2012

Parameter	1st Assessment Report	Most Recent Assessment Report	
	May 18 2011 to SEP 19 2011	SEP 20 2011 to NOV 18 2011	NOV 19 2011 to MAR 19 2012
Total Prescriptions written	257,223	93,285	3,661
Prescriptions/month	64,306	46,463	915
Prescriptions written by non-enrolled prescribers	257,075	93,279	37
Total number of prescriptions written for non-enrolled patients	257,075	93,279	308
Number of times specialty pharmacies dispensed RCPs from a prescription written by a non-enrolled prescriber	23,009	3	**0**[a]
Number of times specialty pharmacies dispensed RCPs to non-enrolled patients	23,088	10,086	**0**[a]

a - Prescriptions were written and received by Specialty Pharmacies but not filled; however, the Sponsor reports that one non-certified pharmacy (parent company of a certified pharmacy) inadvertently dispensed 40 prescriptions after November 18, 2011, 9 of which were intercepted prior to patient receipt.

The total number of prescriptions written decreased dramatically from 257,223 in the initial reporting period to 3,661 since November 18, 2011. Normalizing to prescriptions/month, the average number of prescriptions written per month has decreased from 64,306 to 915. Likewise, there has been a substantial decrease in the number of prescriptions written by non-enrolled prescribers or for non-enrolled patients. Prior to November 18, 2011, 99%+ of prescriptions were written by non-enrolled prescribers for non-enrolled patients. Following November 18th, non-enrolled prescribers and patients comprised at most 9.4% of prescriptions written. Lastly, since November 18, 2011, specialty pharmacies are appropriately not dispensing prescriptions written by either non-enrolled prescribers or for non-enrolled patients.

Prescriber and Patient Knowledge Surveys:

Prescriber and patient knowledge surveys are a part of the assessment plan. In general, both prescribers and patients demonstrated good knowledge regarding the risks of RCPs especially myocardial infarction (MI). In addition, patients have a good understanding of MI symptoms as well as understand the need to seek immediate medical attention should they experience those symptoms. However, prescribers and patients did demonstrate some knowledge deficits such as the fact that that insulin co-administration is not recommended**.**

Conclusions Regarding the REMS

The most recent assessment report indicates that the REMS is effective in meeting its goals of restricting RCP access to prescribers and patients who understood the potential increased risk of MI associated with the use of RCPs.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	May 6, 2013
Reviewer:	Justin Mathew, Pharm.D. Drug Use Data Analyst Division of Epidemiology II
Team Leader:	Hina Mehta, Pharm.D. Drug Use Data Analysis Team Leader Division of Epidemiology II
Deputy Director:	Laura Governale, Pharm.D., MBA Deputy Director for Drug Utilization Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
Drug Name(s):	Rosiglitazone- and Pioglitazone-Containing Products
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
OSE RCM #:	2013-427

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information in this document has been cleared for public release.

CONTENTS

EXECUTIVE SUMMARY

In preparation for the joint meeting of the Endocrine and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee scheduled on June 5 and 6, 2013, this review examines drug utilization patterns for rosiglitazone-containing products as well as pioglitazone-containing products for three different time periods, post AC1, post AC2, and post REMS, during July 2007 through December 2012. Because the majority of rosiglitazone-containing products were sold to U.S. outpatient retail pharmacies and mail-order/specialty pharmacies, this review focused on the outpatient retail pharmacy and mail-order/specialty pharmacy drug utilization patterns.

Summary of findings:

Utilization Data, July 2007 through December 2012

- Approximately 8.1 million prescriptions for rosiglitazone- and pioglitazone-containing products were dispensed to outpatient retail and mail order/specialty pharmacies during year 2012.
    - Dispensed prescriptions for pioglitazone-containing products were the market lead accounting for 76% to greater than 99% of dispensed prescriptions during each year examined.
    - The number of dispensed prescriptions of rosiglitazone-containing products has decreased by over 99% during the time examined from 5.1 million prescriptions dispensed during year 2008 to about 12,600 prescriptions dispensed during year 2012.
    - During year 2012, approximately 7,000 single-ingredient rosiglitazone prescriptions were dispensed followed by about 5,000 rosiglitazone/metformin prescriptions and about 1,000 rosiglitazone/glimepiride prescriptions.
- The majority of single-ingredient rosiglitazone, rosiglitazone/metformin, and rosiglitazone/glimepiride prescriptions were dispensed through outpatient retail pharmacies during years 2008 through 2011. By year 2012, there was a switch to dispensing from mail-order/specialty pharmacies (due to the implementation of the REMS).
- Approximately 1.6 million patients received a dispensed prescription for rosiglitazone-containing product during July 2007 through July 2010, the post AC1 period; approximately 249,000 patients received a dispensed prescription for rosiglitazone-containing products during August 2010 through June 2011, the post AC2 period; and 45,000 patients had a prescription claim for rosiglitazone-containing products during July 2011 through December 2012, the post REMS approval period.
- During each time period examined, Family Practice/General Practice specialist were the top prescribing specialty accounting for approximately 51%-53% of total rosiglitazone-containing prescriptions dispensed followed by Internal Medicine specialists accounting for approximately 32%-34% of total prescriptions dispensed.
- "Diabetes Mellitus Uncomp" (ICD-9 code 250.0) accounted for the highest proportion of rosiglitazone-containing product uses among the three time periods with 96% of uses during July 2007 through July 2010 (post AC1), 81% of uses during August 2010 through April 2011 (post AC2), and 100% of uses during May 2011 through December 2012 (post REMS approval).

1 INTRODUCTION

A joint meeting of the Endocrine and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee will be held to discuss the results of an independent re-adjudication of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial. In preparation for the meeting, the Division of Epidemiology II (DEPI II) was requested to provide drug utilization patterns for rosiglitazone-containing products, Avandia® (rosiglitazone), Avandamet® (rosiglitazone/metformin), and Avandaryl® (rosiglitazone/glimepride) for calendar years 2008 through 2012, and three distinct time periods: July 2007-July 2010 (post AC1), Aug 2010-April 2011 (post AC2), May 2011-Dec 2012 (post REMS approval). As a comparator, pioglitazone-containing products, Actos® (pioglitazone), Actoplus Met®, Actoplus Met® XR (pioglitazone/metformin), and Duetact® (pioglitazone/glimepride) were also included in the analysis.

2 BACKGROUND

2.1 REGULATORY HISTORY

Rosiglitazone (Avandia®) is a thiazolidinedione anti-diabetic agent initially approved under NDA 021071 on May 25th 1999. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] The first FDA advisory committee meeting on the potential risks of rosiglitazone (Avandia®) occurred on July 30th 2007, and recommendations by the committee included adding the following additions/changes to the label[2]:

- Black box warning for use in patients with heart failure.
- Contraindication for use with insulin,
- Warning about the use [of Avandia®] with anti-anginals.
- Monitoring and patient education
- Statement regarding ongoing research of the risk of Avandia® is in progress.

A second advisory committee meeting was held on July 13/14, 2010, to discuss the cardiovascular safety of rosiglitazone (Avandia®). Among the advisory committee members, the majority concluded that rosiglitazone should be either to "allow [for]continued marketing, revise the current label to add additional warnings, and add additional restrictions on use (such as restricting prescribing to certain physicians or requiring special physician and patient education) or withdrawal [of rosiglitazone] from the U.S. market.[3]"

The Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing products was implemented on May 18th, 2011, and a six month phase in period was established to allow for the transition for both patients and physicians. The REMS requires healthcare providers who prescribe rosiglitazone for outpatient or long-term care use be specially certified and that rosiglitazone will only

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[1] U.S. Food and Drug Administration: Drugs@FDA. Avandia Approval History. Accessed: April 2013. Available at: http://www.accessdata fda.gov/drugsatfda_docs/label/2012/021071s041lbl.pdf

[2]U.S. Food and Drug Administration: Advisory Committees. Endocrinologic and Metabolic Drugs Advisory Committee July 30, 2007. Accessed: April 2013. Available at: http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4308m1-final.pdf

[3]U.S. Food and Drug Administration: Advisory Committees. Endocrinologic and Metabolic Drugs Advisory Committee July 13/14, 2010. Accessed: April 2013. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM241505.pdf

be dispensed to patients with evidence or other documentation of safe-use conditions. Rosiglitazone will also only be dispensed by specially certified pharmacies.

2.2 BRAND/GENERIC PRODUCTS INCLUDED AND LABELING

The boxed warning section for all rosiglitazone-containing products includes the following:

- It may cause or exacerbate congestive heart failure in some patients.
- It is not recommended in patients with symptomatic heart failure.
- Based on 52 clinical trails, Avandia® has been associated with a statistically significant increased risk of myocardial infarction.

Due to these risks, Avandia®, as well all rosiglitazone-containing products (Avandaryl® and Avandamet®), is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program in which both prescribers and patients are required to be enrolled in.

Summary of regulatory history and product labeling[4]			
Product Name	**Formulations/Strengths**	**Approval Date**	**Indications**
Avandia® (rosiglitazone)	Oral Tablet: 2mg; 4mg; 8mg	May 25, 1999	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Avandaryl® (glimepride: rosiglitazone)	Oral Tablet: 1:4mg; 2:4mg; 4:4mg; 2:8mg; 4:8mg	November 23, 2005	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Avandamet® (metformin: rosiglitazone)	Oral Tablet: 500mg:1mg; 500mg:2mg; 500mg:4mg; 1000mg:2mg; 1000mg:4mg	October 10, 2002	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Actos® (pioglitazone)	Oral Tablet: 15mg; 30mg; 45mg	July 15, 1999	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Duetact® (glimepride: pioglitazone)	Oral Tablet: 2mg:30mg; 4mg:30mg	July 28, 2006	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Actoplus Met® (metformin: pioglitazone)	Tablet oral: 500mg:15mg; 850mg:15mg	August 29, 2005	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Actoplus Met XR® (metformin: pioglitazone)	Oral Solution: 1000mg:15mg; 1000mg:30mg	May 12, 2009	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

3 METHODS AND MATERIAL

[4] Drug Facts and Comparisons. Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health, Inc; March 2005. Accessed April 11, 2013

3.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives™ (see Appendix 2 for full database description) was used to determine the various retail and non-retail channels of distribution for rosiglitazone-containing products. During year 2011, approximately 59% of rosiglitazone-containing products were distributed to outpatient retail pharmacy settings; 34% to mail-order/specialty pharmacies; and 7% were to non-retail pharmacies.[5] During year 2012, following the implementation of the REMS for all rosiglitazone-containing products, 97% of bottles of rosiglitazone-containing products were distributed to mail-order/specialty pharmacies. Based on the distribution patterns of rosiglitazone-containing products, outpatient retail pharmacy and mail-order/specialty pharmacy utilization data were examined. Non-retail pharmacy setting data was excluded from this analysis.

3.2 DATA SOURCES USED

Proprietary drug use databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, IMS National Sales Perspectives™ was used to obtain the nationally estimated number of rosiglitazone- and pioglitazone-containing bottles sold from manufacturers to various channels of distribution for years 2008 through 2012. These sales data represent the amount of product being sold from manufacturers into the "back door" of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; it does not reflect what is being sold to or administered to patients directly.

The utilization analysis of rosiglitazone- and pioglitazone-containing products was conducted for calendar years 2008 through 2012, and the following three distinct time periods:

- July 2007 through July 2010: post 1st Advisory Committee meeting (AC1)
- August 2010 through April 2011: post 2nd Advisory Committee meeting (AC2)
- May 2011 through December 2012: post REMS approval

For the *dispensed prescription* analysis, Source Health Analytics' Source® PHAST Prescription database was used to obtain the estimated number of prescriptions dispensed for rosiglitazone- and pioglitazone-containing products for the above mentioned time periods.

For the *patient-level* analysis, the IMS Health, Vector One®: Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients receiving dispensed prescriptions for rosiglitazone- and pioglitazone-containing products for years 2008 through year 2012. This database was also used to obtain the nationally estimated number of patients receiving dispensed prescriptions for rosiglitazone-containing products stratified by patient age (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ years) and patient sex, for the two distinct time periods mentioned above: post AC1 (July 2007 through July 2010), and post AC2 (August 2010 through June 2011).

Source Health Analytics' Source® Prometis database was used to provide the number of unique patients with a pharmacy prescription claim for rosiglitazone-containing products, stratified by patient age (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ years) and patient sex, for the third time period: post REMS approval (July 2011 through December 2012). These data are not projected nationally and only represent this sample because nationally projected patient-level data are not available for products used in mail-order/specialty pharmacy settings. Patient selection was based on

[5] IMS Health, IMS National Sales Perspectives™. Extracted April 2013. File: NSP 2013-427 Rosiglitazone AC 4-5-2013.xlsx

the presence of pharmacy claims using the National Drug Code (NDC) for rosiglitazone-containing products (NDC codes listed in Appendix 3).

The analysis of the top ten *prescribing specialties*, and *diagnoses* associated with the use of rosiglitazone-containing products were examined from the Source Health Analytics' Source® PHAST Prescription, and the Encuity Research, LLC. Treatment Answers™ databases, respectively, for the three above distinct time periods: post AC1, post AC2, and post REMS.

4 RESULTS

4.1 SALES DISTRIBUTION OF ROSIGLITAZONE-CONTAINING AND PIOGLITAZONE-CONTAINING PRODUCTS

Figure 1 in Appendix 1 shows the total number of bottles sold for rosiglitazone- and pioglitazone-containing products for years 2008 through 2012. Throughout the time period examined, sales of pioglitazone-containing products have been the market lead. Rosiglitazone-containing products have seen a greater than 99% decrease in sales from approximately 5.4 million bottles sold during year 2008 to 21,000 bottles sold in year 2012. Pioglitazone-containing products have seen a decrease of 43% from 15.9 million bottles sold during year 2008 to 9 million bottles during year 2012.

4.2 PRESCRIPTIONS DISPENSED FOR ROSIGLITAZONE- AND PIOGLITAZONE-CONTAINING PRODUCTS THROUGH OUTPATIENT AND MAIL-ORDER/SPECIALTY PHARMACY CHANNELS

Figure 2 and Table 1 in Appendix 1 displays the nationally estimated number of dispensed prescriptions for rosiglitazone- and pioglitazone-containing products from U.S. outpatient retail and mail-order/specialty pharmacies from year 2008 through 2012. Dispensed prescriptions for rosiglitazone- and pioglitazone-containing products have been decreasing prior to the establishment of the REMS for rosiglitazone-containing products. The total number of prescriptions dispensed for the entire market of rosiglitazone- and pioglitazone-containing products decreased by 62% during the time examined from approximately 21 million prescriptions dispensed during year 2008 to about 8.1 million prescriptions dispensed during year 2012. Dispensed prescriptions for pioglitazone-containing products were the market lead throughout the time period, accounting for 76% of the market in year 2008 and increasing to over 99% of the market in year 2012.

The number of dispensed prescriptions of rosiglitazone-containing products has decreased by over 99% during the time examined from 5.1 million prescriptions dispensed during year 2008 to about 12,600 prescriptions dispensed during year 2012. Of the rosiglitazone-containing products dispensed, single-ingredient rosiglitazone accounted for the majority of prescriptions dispensed (53%-67%) followed by the combination products rosiglitazone/metformin (26%-39%) and rosiglitazone/glimepride (7%-9%) during the time examined. During year 2012, approximately 7,000 single-ingredient rosiglitazone prescriptions were dispensed followed by about 5,000 rosiglitazone/metformin prescriptions, and about 1,000 rosiglitazone/glimepiride prescriptions.

Pioglitazone-containing products decreased by approximately 49% from approximately 16 million prescriptions dispensed during year 2008 to 8.1 million prescriptions dispensed during year 2012. Of the pioglitazone-containing products dispensed, single-ingredient pioglitazone accounted for the majority of prescriptions dispensed (84%-87%), followed by pioglitazone/metformin (12%-15%) and pioglitazone/glimepiride (1%) during the time examined. During year 2012, approximately 6.8 million single-ingredient pioglitazone prescriptions were dispensed followed by about 1.2 million pioglitazone/metformin prescriptions, and about 82,000 pioglitazone/glimepiride prescriptions.

Throughout the time examined, the majority of single-ingredient pioglitazone, pioglitazone/metformin, and pioglitazone/glimepiride prescriptions were dispensed primarily through outpatient retail pharmacies accounting for greater than 85% of dispensed prescriptions. For rosiglitazone-containing products, prescriptions were dispensed primarily through outpatient retail pharmacies during years 2008 through 2011 until year 2012; there was a shift toward mail-order/specialty pharmacy dispensing for rosiglitazone-products during year 2012 after the approval and eventual implementation of the REMS.

4.3 NUMBER OF PATIENTS RECEIVING DISPENSED PRESCRIPTIONS FOR ROSIGLITAZONE- AND PIOGLITAZONE-CONTAINING PRODUCTS

Table 2 in Appendix 1 illustrates the nationally estimated number of patients who received a dispensed prescription for rosiglitazone- and pioglitazone-containing products from U.S. outpatient retail pharmacies during years 2008 through 2012. The patient count data were similar to the dispensed prescription data. Even prior to the establishment of the REMS, the total number of patients receiving a dispensed prescription for rosiglitazone- and pioglitazone-containing products has been decreasing. The total number of patients receiving dispensed prescriptions for rosiglitazone- and pioglitazone-containing products decreased by approximately 61% from 3.25 million patients during year 2008 to about 1.3 million patients during year 2012. During each year examined, approximately 77% to greater than 99% of patients received dispensed prescriptions for pioglitazone-containing products in this market.

The total number of patients receiving dispensed prescriptions for rosiglitazone-containing products has decreased by over 99% during the time examined from approximately 821,000 patients during year 2008 to less than 1,000 patients during year 2012. Of the rosiglitazone-containing products, patients receiving single-ingredient rosiglitazone accounted for the majority of patients (53%-69%) followed by patients receiving rosiglitazone/metformin (26%-39%) and rosiglitazone/glimepiride (7%-9%) combination products during the time examined.

Patients receiving dispensed prescriptions for pioglitazone-containing products decreased by approximately 49.5% from approximately 2.5 million patients in year 2008 to 1.3 million patients in year 2012. Of the pioglitazone-containing products, patients receiving dispensed prescriptions for single-ingredient pioglitazone accounted for the majority of patients (86%-88%) during the time examined followed by patients receiving pioglitazone/metformin (12%-14%) and pioglitazone/glimepiride (1%) combination products. During year 2012, approximately 1.1 million patients received dispensed prescriptions for single-ingredient pioglitazone followed by about 181,000 patients receiving dispensed prescriptions for pioglitazone/metformin, and about 11,000 patients receiving prescriptions for pioglitazone/glimepiride.

4.4 NUMBER OF PATIENTS WHO RECEIVED DISPENSED PRESCRIPTIONS FOR ROSIGLITAZONE-CONTAINING PRODUCTS BY PATIENT SEX AND AGE

Table 3 in Appendix 1 provides the nationally estimated number of unique patients, stratified by patient age (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years) and sex, who received a prescription for rosiglitazone-containing products from July 2007 through July 2010. Approximately 1.6 million patients received a dispensed prescription for rosiglitazone-containing products during the cumulative time period from July 2007 through July 2010. There was an even split among males (50%, 794,000 patients) and females (50%, 785,000 patients) that received a dispensed prescription for rosiglitazone-containing products. Adults aged 60-69 years accounted for the largest proportion of patients who received a dispensed prescription for rosiglitazone-containing products with

approximately 30% (469,000 patients) followed by patients aged 50-59 years with approximately 29% (455,000 patients) and 70-79 years with approximately 20% (315,000 patients) of the total.

Table 4 provides the nationally estimated number of unique patients, stratified by patient age (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years) and sex, who received a prescription for rosiglitazone-containing products from August 2010 through June 2011. There were a total of approximately 249,000 patients who received a dispensed prescription for rosiglitazone-containing products during the cumulative time examined. A slightly higher proportion of males (53%, 132,000 patients) received dispensed rosiglitazone-containing products as compared to females (47%, 117,000 patients). Adults aged 60-69 years accounted for the largest proportion of patients who received a dispensed prescription for rosiglitazone-containing products with approximately 30% (75,000 patients) followed by patients aged 50-59 years with approximately 28% (70,000 patients) and 70-79 years with approximately 20% (49,000 patients) of the total.

Table 5 in Appendix 1 provides the number of unique patients, stratified by patient age (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years) and sex, with a pharmacy prescription claim for rosiglitazone-containing products from a *sample* of U.S. outpatient retail and mail-order pharmacies from the first full month of implementation of REMS in July 2011 through December 2012. During the study period, approximately 45,000 patients had a prescription claim for rosiglitazone-containing products. The majority of patients with a prescription claim for rosiglitazone-containing products were males with 54% (24,500 patients) compared to females with 46% (20,900 patients) of the total. Adults aged 60-69 years accounted for the largest proportion of patients with a prescription claim for rosiglitazone-containing product with approximately 31% (14,000 patients) followed by patients aged 50-59 with approximately 27% (12,000 patients) and 70-79 years with approximately 20% (9,000 patients) of the total.

4.5 TOP PRESCRIBING SPECIALTY GROUPS FOR ROSIGLITAZONE-CONTAINING PRODUCTS

Table 6 in Appendix 1 provides the nationally estimated number of prescriptions for rosiglitazone-containing products by the top 10 prescribing specialty groups dispensed through U.S. outpatient retail and mail-order/specialty pharmacies during three separate time periods: post AC1 (July 2007 through July 2010), post AC2 (August 2010 through April 2011), and post REMS (May 2011 through December 2012). During each time period examined, Family Practice/General Practice specialist were the top prescribing specialty accounting for approximately 51%-53% of total rosiglitazone-containing prescriptions dispensed. Internal Medicine specialists followed accounting for approximately 32%-34% of total prescriptions dispensed. Endocrinology/Diabetes/Metabolism specialists accounted for approximately 4%-5% of total rosiglitazone-containing prescriptions dispensed.

4.6 INDICATIONS FOR ROSIGLITAZONE-CONTAINING PRODUCTS USE

The top diagnoses associated with the use of rosiglitazone-containing products were expressed in terms of *drug use mentions*.[6] Diagnoses were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were calculated for the estimates (**Table 7 in Appendix 1**). "Diabetes Mellitus Uncomp" (ICD-9 code 250.0) accounted for the highest proportion of rosiglitazone-containing product uses among the three time periods with 96% or with 4.3 million uses

[6] The term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

(95% CI 4 million-4.65 million) during the post AC1 period (July 2007 through July 2010), 81% or with 207,000 uses (95% CI 139,000-275,000) during the post AC2 period (August 2010 through April 2011), and 100% or 118,000 uses (95% CI 67,000-170,000 uses) during the post REMS period (May 2011 through December 2012.

5 DISCUSSION

The analyses in this review indicate that even prior to the establishment of the REMS the total number of patients receiving a dispensed prescription for rosiglitazone- and pioglitazone-containing products has been decreasing. The single-ingredient rosiglitazone and pioglitazone products accounted for the majority of use, followed by the combination product pioglitazone/metformin and rosiglitazone/metformin. The majority of rosiglitazone-containing product use was during July 2007 through July 2010. The implementation of the REMS called for rosiglitazone-containing products to have restricted distribution which is shown in the drug utilization data in this review.

Throughout each time period examined, the age group of 60-69 years accounted for the highest proportion of rosiglitazone-containing product use. There was an even distribution of use among males and females during each time period. During each time period examined, Family Practice/General Practice specialist were the top prescribing specialty accounting for approximately 51%-53% of total rosiglitazone-containing prescriptions dispensed followed by Internal Medicine specialists with 32%-34% of the total. Among all three time periods examined, "Diabetes Mellitus Uncomp" (ICD-9 code 250.0) was the top diagnosis associated with the use of rosiglitazone-containing products. Although the utilization of rosiglitazone-containing products dramatically decreased over the time period, the patient and prescriber characteristics did not appear to change over the three time periods.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2011 showed that approximately 59% of rosiglitazone-containing products were distributed to outpatient retail pharmacies while 97% was distributed to mail-order/specialty pharmacies during year 2012. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Data from Source Healthcare Analytics' ProMetis Lx® provides *unprojected* patient counts with a prescription claim from outpatient retail and mail-order/specialty pharmacies for rosiglitazone containing products**.** Due to the sample size and the unreported pharmacy information, there are limitations in the ability to identify national trends in the data. In addition, the universe of mail-order and specialty pharmacies contributing to these data are unknown, therefore, nationwide projections are not available at this time.

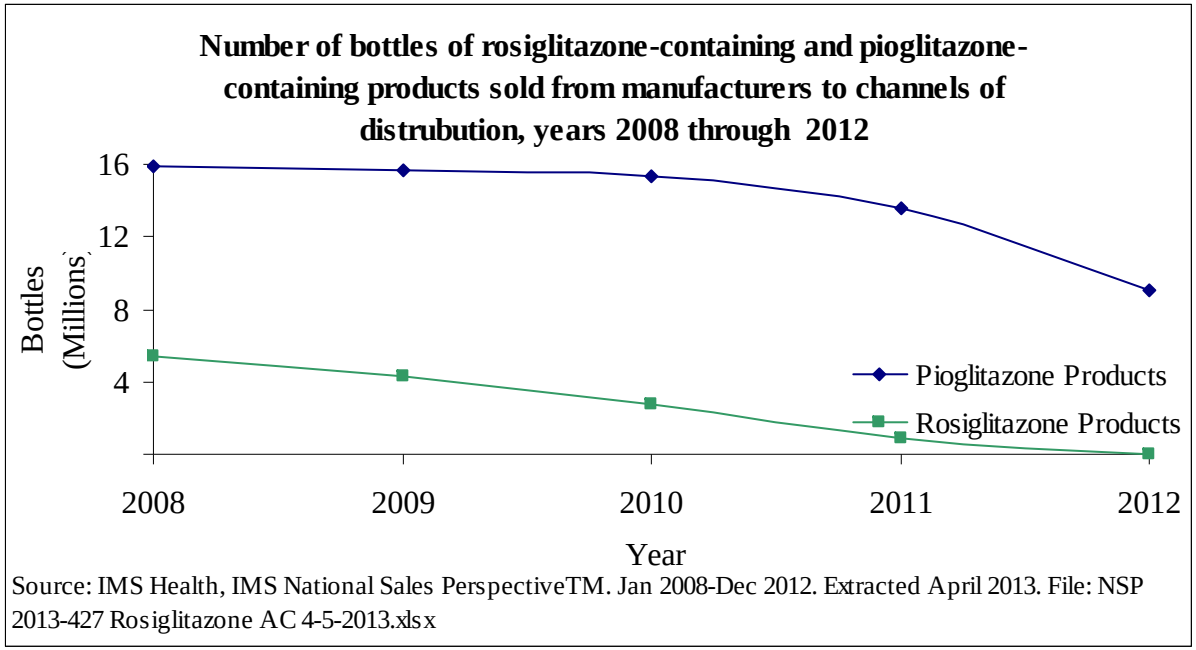
Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

6 CONCLUSIONS

There were approximately 8.1 million dispensed prescriptions and 1.3 million patients who received a dispensed prescription for rosiglitazone- or pioglitazone-containing products in 2012. The use of both the rosiglitazone- and pioglitazone-containing products has decreased since year 2008. The implementation of the REMS for rosiglitazone-containing products on May 2011 resulted in utilization of these agents only through mail-order/specialty pharmacies. While the utilization of rosiglitazone-containing products dramatically decreased over the time period, the patient and prescriber characteristics did not change appreciably over the time. During the entire study period, the greatest proportion of use for rosiglitazone-containing agents was among patients aged 60-69 year old, with a slight majority toward male patients; Family Practice/ General Practice was the top prescribing specialty of rosiglitazone-containing products; and "Diabetes Mellitus Uncomp" was the most common diagnosis associated with the use of rosiglitazone-containing products.

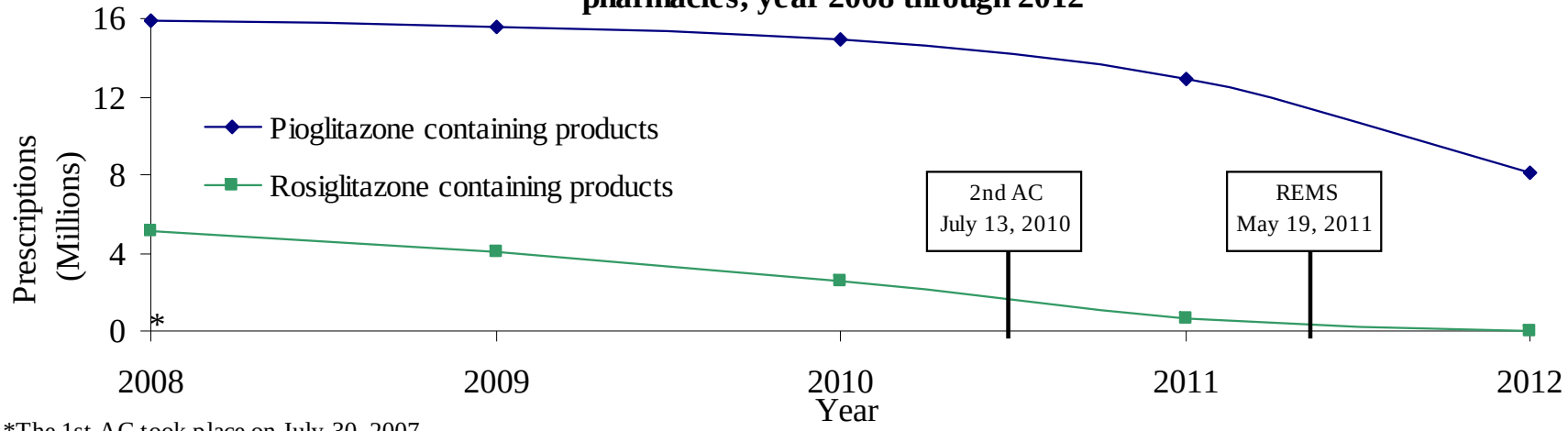
APPENDIX 1: TABLES AND FIGURES

FIGURE 1.



Source: IMS Health, IMS National Sales PerspectiveTM. Jan 2008-Dec 2012. Extracted April 2013. File: NSP 2013-427 Rosiglitazone AC 4-5-2013.xlsx

FIGURE 2.



*The 1st AC took place on July 30, 2007

Source:Source: Source Health Analytics' Source® PHAST PrescriptionTM. Jan 2008-December 2012. Extracted: April 2013. File: PHAST 2013-427 TRx Rosiglitazone and Pioglitazone 4-4-13.xlsx

Table 1.

Nationally estimated number of prescriptions dispensed for rosiglitazone-containing and pioglitazone-containing products dispensed through U.S. retail and mail-order/specialty pharmacies, year 2008 through 2012

		2008		2009		2010		2011		2012	
		TRx Count	*% Share*	TRx Count	*% Share*	TRx Count	*% Share*	TRx Count	*% Share*	TRx Count	*% Share*
Total Market		**21,013,553**	***100.0%***	**19,558,594**	***100.0%***	**17,543,044**	***100.0%***	**13,649,913**	***100.0%***	**8,078,574**	***100.0%***
Pioglitazone containing products		15,898,857	*75.7%*	15,520,275	*79.4%*	14,974,828	*85.4%*	12,957,398	*94.9%*	8,065,977	*99.8%*
Pioglitazone	Total	13,832,428	*87.0%*	13,363,150	*86.1%*	12,875,109	*86.0%*	11,047,020	*85.3%*	6,784,823	*84.1%*
	Mail Order	1,860,722	*13.45%*	1,813,847	*13.57%*	1,719,376	*13.35%*	1,522,925	*13.79%*	976,049	*14.39%*
	Retail	11,971,706	*86.55%*	11,549,303	*86.43%*	11,155,733	*86.65%*	9,524,095	*86.21%*	5,808,774	*85.61%*
Pioglitazone/Metformin	Total	1,906,806	*12.0%*	1,983,065	*12.8%*	1,947,275	*13.0%*	1,789,884	*13.8%*	1,198,851	*14.9%*
	Mail Order	249,365	*13.08%*	266,164	*13.42%*	257,805	*13.24%*	253,274	*14.15%*	178,944	*14.93%*
	Retail	1,657,441	*86.92%*	1,716,901	*86.58%*	1,689,470	*86.76%*	1,536,610	*85.85%*	1,019,907	*85.07%*
Pioglitazone/Glimepiride	Total	159,623	*1.0%*	174,060	*1.1%*	152,444	*1.0%*	120,494	*0.9%*	82,303	*1.0%*
	Mail Order	17,574	*11.01%*	19,852	*11.41%*	17,476	*11.46%*	15,600	*12.95%*	12,051	*14.64%*
	Retail	142,049	*88.99%*	154,208	*88.59%*	134,968	*88.54%*	104,894	*87.05%*	70,252	*85.36%*
Rosiglitazone containing products		5,114,696	*24.3%*	4,038,319	*20.6%*	2,568,216	*14.6%*	692,515	*5.1%*	12,597	*0.2%*
Rosiglitazone	Total	3,404,754	*66.6%*	2,578,605	*63.9%*	1,552,401	*60.4%*	373,566	*53.9%*	6,721	*53.4%*
	Mail Order	425,104	*12.49%*	341,456	*13.24%*	210,810	*13.58%*	57,961	*15.52%*	5,702	*84.84%*
	Retail	2,979,650	*87.51%*	2,237,149	*86.76%*	1,341,591	*86.42%*	315,605	*84.48%*	1,019	*15.16%*
Rosiglitazone/Metformin	Total	1,335,782	*26.1%*	1,172,362	*29.0%*	825,606	*32.1%*	255,992	*37.0%*	4,864	*38.6%*
	Mail Order	151,500	*11.34%*	142,400	*12.15%*	101,406	*12.28%*	36,736	*14.35%*	4,017	*82.59%*
	Retail	1,184,282	*88.66%*	1,029,962	*87.85%*	724,200	*87.72%*	219,256	*85.65%*	847	*17.41%*
Rosiglitazone/Glimepiride	Total	374,160	*7.3%*	287,352	*7.1%*	190,209	*7.4%*	62,957	*9.1%*	1,012	*8.0%*
	Mail Order	39,544	*10.57%*	34,072	*11.86%*	23,333	*12.27%*	9,312	*14.79%*	815	*80.53%*
	Retail	334,616	*89.43%*	253,280	*88.14%*	166,876	*87.73%*	53,645	*85.21%*	197	*19.47%*

Source: Source Health Analytics' Source® PHAST Prescription™. Jan 2008-December 2012. Extracted: April 2013. File: PHAST 2013-427 TRx Rosiglitazone and Pioglitazone 4-4-13.xlsx

TABLE 2.

Nationally estimated number of patients who received a dispensed prescription for rosiglitazone- or pioglitazone-containing products dispensed to U.S. retail pharmacies from year 2008 thorugh 2012

	2008		2009		2010		2011		2012	
	Patient Count (N)	% Share	Patient Count (N)	% Share	Patient Count (N)	% Share	Patient Count (N)	% Share	Patient Count (N)	% Share
Total	**3,253,732**	**100.0%**	**2,867,244**	**100.0%**	**2,802,411**	**100.0%**	**2,128,694**	**100.0%**	**1,265,106**	**100.0%**
Pioglitazone containing products	**2,506,457**	**77.0%**	**2,305,670**	**80.4%**	**2,448,119**	**87.4%**	**2,038,366**	**95.8%**	**1,264,628**	**>99.9%**
Pioglitazone	2,201,153	87.8%	2,006,482	87.0%	2,130,389	87.0%	1,763,894	86.5%	1,084,129	85.7%
Pioglitazone/Metformin	313,479	12.5%	304,773	13.2%	321,672	13.1%	277,946	13.6%	180,851	14.3%
Pioglitazone/Glimepiride	29,118	1.2%	27,811	1.2%	24,504	1.0%	17,619	0.9%	11,412	0.9%
Rosiglitazone containing products	**820,699**	**25.2%**	**603,402**	**21.0%**	**458,510**	**16.4%**	**132,278**	**6.2%**	**665**	**0.1%**
Rosiglitazone	563,642	68.7%	397,824	65.9%	293,580	64.0%	74,331	56.2%	350	52.7%
Rosiglitazone/Metformin	216,478	26.4%	175,723	29.1%	139,477	30.4%	47,428	35.9%	260	39.1%
Rosiglitazone/Glimepiride	58,953	7.2%	41,239	6.8%	30,825	6.7%	11,500	8.7%	62	9.3%

*Due to the possibility of double counting patients who are receiving treatment over multiple periods in the study, unique patient counts may not be added across time periods

Source: IMS Health Vector One® Total Patient Tracker. Jan 2008-December 2012. Extracted: April 2013. File: TPT TOTAL 2013-427 Rosiglitazone 2008-2012.xlsx

TABLE 3.

Nationally estimated number of patients who received a dispensedprescription for rosiglitazone-containing products, stratified by patient age and sex, from U.S. outpatient retail pharmacies during the post AC1 period, July 2007–July 2010

July 2007-July 2010

	Total		Male			Female			Unspecified		
	Total Patients (N)	%Share	Total Patients (N)	%Share	Horz. %Share	Total Patients (N)	%Share	Horz. %Share	Total Patients (N)	%Share	Horz. %Share
Total Rosiglitazone containing products*	**1,580,506**	***100.0%***	**793,903**	***100.0%***	***50.2%***	**785,075**	***100.0%***	***49.7%***	**1,515**	***100.0%***	***<0.1%***
0-9 years	576	*<0.1%*	349	*<0.1%*	*60.7%*	204	*<0.1%*	*35.5%*	20	*1.3%*	*3.5%*
10-19 years	2,346	*0.1%*	842	*0.1%*	*35.9%*	1,492	*0.2%*	*63.6%*	14	*0.9%*	*0.6%*
20-29 years	13,899	*0.9%*	5,272	*0.7%*	*37.9%*	8,578	*1.1%*	*61.7%*	49	*3.2%*	*0.4%*
30-39 years	74,060	*4.7%*	37,823	*4.8%*	*51.1%*	36,082	*4.6%*	*48.7%*	113	*7.5%*	*0.2%*
40-49 years	241,895	*15.3%*	134,449	*16.9%*	*55.6%*	107,077	*13.6%*	*44.3%*	320	*21.1%*	*0.1%*
50-59 years	454,688	*28.8%*	245,725	*31.0%*	*54.0%*	208,426	*26.5%*	*45.8%*	470	*31.0%*	*0.1%*
60-69 years	469,348	*29.7%*	241,697	*30.4%*	*51.5%*	227,293	*29.0%*	*48.4%*	375	*24.8%*	*0.1%*
70-79 years	315,358	*20.0%*	143,821	*18.1%*	*45.6%*	171,333	*21.8%*	*54.3%*	188	*12.4%*	*0.1%*
80+ years	138,364	*8.8%*	51,611	*6.5%*	*37.3%*	86,655	*11.0%*	*62.6%*	61	*4.0%*	*0.0%*
Unknown Age	171	*<0.1%*	52	*<0.1%*	*30.5%*	120	*<0.1%*	*69.7%*	--	--	--

**Rosiglitazone containing products = Avandia®, Avandamet®, and Avandaryl®*

Due to the possibility of double counting patients who are receiving treatment over multiple periods in the study, unique patient counts may not be added across time periods. Summing across patient age bands is not advisable and will result in overestimates of patient counts.

IMS Health Vector One® Total Patient Tracker, extracted April 2012, File: 2013-427 TPT Total Rosiglitazone containing products for 3 periods

TABLE 4.

Nationally estimated number of patients who received a dispensed prescription for rosiglitazone-containing products, stratified by patient age and sex, from U.S. outpatient retail pharmacies during the post AC2 period, August 2010 – June 2011

August 2010-June 2011

	Total		Male			Female			Unspecified		
	Total Patients (N)	%Share	Total Patients (N)	%Share	Horz. %Share	Total Patients (N)	%Share	Horz. %Share	Total Patients (N)	%Share	Horz. %Share
Total Rosiglitazone containing products*	**248,877**	***100.0%***	**131,913**	***100.0%***	***53.0%***	**116,857**	***100.0%***	***47.0%***	**113**	***100.0%***	***<0.1%***
0-9 years	81	*<0.1%*	55	*<0.1%*	*67.8%*	23	*<0.1%*	*28.4%*	3	*2.7%*	*3.8%*
10-19 years	206	*0.1%*	89	*0.1%*	*43.2%*	118	*0.1%*	*57.2%*	--	--	--
20-29 years	1,292	*0.5%*	497	*0.4%*	*38.4%*	795	*0.7%*	*61.5%*	--	--	--
30-39 years	8,393	*3.4%*	4,686	*3.6%*	*55.8%*	3,690	*3.2%*	*44.0%*	6	*5.1%*	*0.1%*
40-49 years	32,415	*13.0%*	19,138	*14.5%*	*59.0%*	13,250	*11.3%*	*40.9%*	21	*18.7%*	*0.1%*
50-59 years	69,759	*28.0%*	40,128	*30.4%*	*57.5%*	29,595	*25.3%*	*42.4%*	28	*25.0%*	*0.0%*
60-69 years	74,657	*30.0%*	39,872	*30.2%*	*53.4%*	34,754	*29.7%*	*46.6%*	29	*25.8%*	*0.0%*
70-79 years	49,073	*19.7%*	23,824	*18.1%*	*48.5%*	25,234	*21.6%*	*51.4%*	15	*13.1%*	*0.0%*
80+ years	21,335	*8.6%*	8,259	*6.3%*	*38.7%*	13,052	*11.2%*	*61.2%*	13	*11.2%*	*0.1%*
Unknown Age	68	*<0.1%*	23	*<0.1%*	*33.8%*	45	*<0.1%*	*65.6%*	--	--	--

**Rosiglitazone containing products = Avandia®, Avandamet®, and Avandaryl®*

Due to the possibility of double counting patients who are receiving treatment over multiple periods in the study, unique patient counts may not be added across time periods. Summing across patient age bands is not advisable and will result in overestimates of patient counts.

IMS Health Vector One® Total Patient Tracker, extracted April 2012, File: 2013-427 TPT Total Rosiglitazone containing products for 3 periods

TABLE 5.

Total number of patients with a pharmacy claim for rosiglitazone -containing products, stratified by patient age and sex, from a sample of U.S. outpatient retail and mail-order/specialty pharmacies during the post REMS period, July 2011 – December 2012

July 2011-December 2012								
	Total		Male			Female		
	Total Patients (N)	%Share	Total Patients (N)	%Share	Horz. %Share	Total Patients (N)	%Share	Horz. %Share
Total Rosiglitazone containing products*	**45,453**	***100.0%***	**24,560**	***100.0%***	***54.0%***	**20,893**	***100.0%***	***46.0%***
0-9 years	1	*<0.1%*	1	*<0.1%*	*100.0%*	--	--	--
10-19 years	21	*<0.1%*	7	*<0.1%*	*33.3%*	14	*0.1%*	*66.7%*
20-29 years	136	*0.3%*	55	*0.2%*	*40.4%*	81	*0.4%*	*59.6%*
30-39 years	1,028	*2.3%*	579	*2.4%*	*56.3%*	449	*2.1%*	*43.7%*
40-49 years	5,026	*11.1%*	2,974	*12.1%*	*59.2%*	2,052	*9.8%*	*40.8%*
50-59 years	12,414	*27.3%*	7,134	*29.0%*	*57.5%*	5,280	*25.3%*	*42.5%*
60-69 years	14,149	*31.1%*	7,682	*31.3%*	*54.3%*	6,467	*31.0%*	*45.7%*
70-79 years	8870	*19.5%*	4546	*18.5%*	*51.3%*	4324	*20.7%*	*48.7%*
80+ years	3808	*8.4%*	1582	*6.4%*	*41.5%*	2226	*10.7%*	*58.5%*

**Rosiglitazone containing products = Avandia®, Avandamet®, and Avandaryl*

Source: Source Health Analytics Prometis Lx CPA Analyzer, extracted April 2012, File: CPA Patient Count 2013-427 Rosiglitazone Jul-2011-Dec 2012.xlx

TABLE 6.

Nationally estimated number of prescriptions dispensed for rosiglitazone-containing products from U.S. outpatient retail and mail-order/specialty pharmacies by top 10 prescribing specialties from July 2007 – December 2012

Rosiglitazone Containing Products						
	Post AC1 July 2007- July 2010		Post AC2 August 2010-April 2011		Post REMS May 2011 - Dec 2012	
	TRx (N)	Share %	TRx (N)	Share %	TRx (N)	Share %
Total	**14,651,961**	**100.0%**	**1,090,955**	**100.0%**	**364,714**	**100.0%**
FAMILY PRACTICE/GENERAL PRACTICE	7,497,053	51.2%	579,695	53.1%	191,916	52.6%
INTERNAL MEDICINE	4,987,291	34.0%	353,001	32.4%	120,055	32.9%
ENDOCRINOLOGY-DIABETES-METABOLISM	721,036	4.9%	50,289	4.6%	14,051	3.9%
OTHER	407,584	2.8%	30,870	2.8%	11,306	3.1%
EMERGENCY MEDICINE	207,806	1.4%	16,884	1.5%	6,072	1.7%
CARDIOLOGY	202,986	1.4%	14,006	1.3%	5,268	1.4%
RESIDENT	134,142	0.9%	10,361	0.9%	3,576	1.0%
GERIATRICS	86,433	0.6%	5,912	0.5%	2,115	0.6%
SURGERY	71,278	0.5%	4,722	0.4%	1,641	0.4%
PEDIATRICS	66,988	0.5%	4,972	0.5%	1,683	0.5%
All Others	269,364	1.8%	20,243	1.9%	7,031	1.9%

Source: Source Health Analytics' Source® PHAST PrescriptionTM. Jan 2008-December 2012. Extracted: April 2013. File: PHAST Prescriber Specialty 2013-427 Rosiglitazone.xls

TABLE 7.

Top Diagnoses Associated with the Use of Rosiglitazone-Containing Products by U.S. Office-Based Physician Surveys, from July 2007 to December 2012

	Post AC1 July 2007 - July 2010			Post AC2 August 2010 - April 2011			Post REMS May 2011 - December 2012		
	Uses	95% Confidence Interval	Share% Uses	Uses	95% Confidence Interval	Share% Uses	Uses	95% Confidence Interval	Share% Uses
Total Market	4,511,000	4,194,000 - 4,828,000	100.0%	255,000	180,000 - 330,000	100.0%	118,000	67,000-170,000	100.0%
2500 DIABETES MELLITUS UNCOMP	4,343,000	4,032,000 - 4,654,000	96.3%	207,000	139,000 - 275,000	81.3%	118,000	67,000-170,000	100.0%
4019 HYPERTENSION NOS	18,000	<500 - 37,000	0.4%	--	--	--	--	--	--
4140 CORONARY ATHEROSCLEROSIS	15,000	<500 - 34,000	0.3%	--	--	--	--	--	--
5838 NEPHRITIS NOS W OTH LES	13,000	<500 - 29,000	0.3%	--	--	--	--	--	--
5854 CHRONIC KIDNEY DIS IV	--	--	--	13,000	<500 - 31,000	5.3%			
5818 NEPHROTIC SYN W OTH LES	--	--	--	13,000	<500 - 31,000	5.3%			
2504 DIAB W RENAL MANIFEST	13,000	<500 - 29,000	0.3%	13,000	<500 - 31,000	5.3%	--	--	--
2506 DIAB W NEUROLOGIC MANIF	11,000	<500 - 27,000	0.3%	7,000	<500 - 20,000	2.9%	--	--	--
2714 RENAL GLYCOSURIA	10,000	<500 - 25,000	0.2%	--	--	--	--	--	--
2509 DIABETES W COMPLIC NOS	10,000	<500 - 25,000	0.2%	--	--	--	--	--	--
2512 HYPOGLYCEMIA NOS	8,000	<500 - 22,000	0.2%	--	--	--	--	--	--
3572 NEUROPATHY IN DIABETES	8,000	<500 - 21,000	0.2%	--	--	--	--	--	--
All Others	62,000	25,000 - 99,000	1.4%	--	--	--	--	--	--

Source: Encuity Research, LLC, Physician, Drug and Diagnosis Audit (PDDA). July 2007 - December 2012 Extracted April 2012.File Encuity Total Diagnosis 2013-427 Rosiglitazone.xls

APPENDIX 2: DATABASES DESCRIPTION

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Source Healthcare Analytics' PHAST Prescription™

The Source Healthcare Analytics' PHAST Prescription Monthly is a syndicated view of U.S. retail and mail order pharmacy prescription activity, updated on a monthly basis. ProMetis PHAST Prescription Monthly covers over 42,000 retail pharmacies in the sample including mail order and specialty pharmacies. The dispensed prescriptions in the sample represent approximately 82% of all U.S. retail prescriptions (cash, Medicaid, commercial) as well as 60% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

Source Healthcare Analytics' ProMetis Lx®

The Source Healthcare Analytics' ProMetis Lx® database is a longitudinal patient data source which captures adjudicated prescription claims across the United States across all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The database contains approximately 4.8 billion prescriptions claims linked to over 190 million unique prescription patients, of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents nearly 30,000 pharmacies, 1,000 hospitals, 800 outpatient facilities, and 80,000 physician practices.

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases

encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

APPENDIX 3: NDC NUMBERS

NDC numbers for the selection of rosiglitazone containing for CPA analyzer

NDC Drug Name	NDC Code	NDC Drug Name (Cont.)	NDC Code
AVANDIA	29315818	AVANDIA	67544011360
AVANDIA	29315900	AVANDIA	67544011370
AVANDIA	29315913	AVANDIA	67544011380
AVANDIA	29315918	AVANDIA	67544011415
AVANDIA	29315920	AVANDIA	67544011445
AVANDIA	29316013	AVANDIA	67544011460
AVANDIA	29316020	AVANDIA	67544011482
AVANDIA	29316059	AVANDIA	68115068430
AVANDIA	173083418	AVANDIA	68115071260
AVANDIA	173083513	AVANDIA	68258911601
AVANDIA	173083613	AVANDARYL	7314813
AVANDIA	12280006200	AVANDARYL	7314913
AVANDIA	12280006230	AVANDARYL	7315113
AVANDIA	12280006290	AVANDARYL	7315213
AVANDIA	12280007830	AVANDARYL	7315313
AVANDIA	35356027160	AVANDARYL	173084113
AVANDIA	49999030430	AVANDARYL	173084213
AVANDIA	49999093530	AVANDARYL	173084313
AVANDIA	54569480100	AVANDARYL	173084513
AVANDIA	54569480200	AVANDARYL	54868573900
AVANDIA	54569480300	AVANDAMET	7316318
AVANDIA	54868419800	AVANDAMET	7316418
AVANDIA	54868419801	AVANDAMET	7316618
AVANDIA	54868422100	AVANDAMET	7316620
AVANDIA	54868524900	AVANDAMET	7316718
AVANDIA	54868524901	AVANDAMET	7316720
AVANDIA	55289093830	AVANDAMET	7316818
AVANDIA	57866006908	AVANDAMET	7316820
AVANDIA	57866006909	AVANDAMET	173083718
AVANDIA	57866126402	AVANDAMET	173083818
AVANDIA	57866136403	AVANDAMET	173083918
AVANDIA	58016008100	AVANDAMET	173084018
AVANDIA	58016008130	AVANDAMET	12280000360
AVANDIA	58016008160	AVANDAMET	12280000460
AVANDIA	58016008190	AVANDAMET	54569560300
AVANDIA	58016008200	AVANDAMET	54868496500
AVANDIA	58016008230	AVANDAMET	54868496501
AVANDIA	58016008260	AVANDAMET	54868496502
AVANDIA	58016008290	AVANDAMET	54868515700
AVANDIA	58864068730	AVANDAMET	54868526200
AVANDIA	58864068760	AVANDAMET	54868526201
AVANDIA	58864082730	AVANDAMET	54868537600
AVANDIA	58864082760	AVANDAMET	54868537900
AVANDIA	65243019509	AVANDAMET	68115089160
AVANDIA	65243019512		

Source: Source Health Analytics' Source® CPA Analyzer, extracted April 2012, File: CPA NDC #for 2013-427 Rosiglitazone Jun-2011-Dec 2012.xlx

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUSTIN A MATHEW
05/06/2013

HINA S MEHTA
05/06/2013
Drug use data cleared

LAURA A GOVERNALE
05/07/2013

DATE: September 22, 2010

TO: NDA 021071

FROM: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

SUBJECT: Decision on continued marketing of rosiglitazone (Avandia, Avandamet, Avandaryl)

I. Summary of Decision

This memorandum documents my decision on the continued marketing of rosiglitazone (Avandia, Avandamet, Avandaryl). After considering the available data on the cardiovascular risks of the drug, I have determined that rosiglitazone may be permitted to remain on the market if the following actions are taken:

1. GSK is directed to undertake a restricted access program under a REMS with elements to assure safe use, including:

    a. Provision of complete risk information to each patient and documentation in their medical record that the information has been received and understood.
    b. Documentation from health care providers that each patient receiving rosiglitazone falls into one of two categories:
        i. patients currently taking rosiglitazone, or
        ii. patients not already taking rosiglitazone who are unable to achieve glycemic control on other medications and, in consultation with their health care professional, decide not to take pioglitazone for medical reasons[1]
    c. Documentation from health care providers that the risk information has been shared with each patient
    d. Physician, patient, and pharmacist enrollment

2. GSK is required to commission an independent re-adjudication of the RECORD study. This could be conducted in a stepwise manner with initial examination of the mortality finding (see Discussion of Available Safety Data below); if the mortality finding is determined to be valid, then the other MACE[2] elements should be re-adjudicated. Considering the time and effort spent by the thousands of volunteers who participated in RECORD, I believe every effort should be made to learn as much as possible from its results.

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[1] This can be a one-time decision made by the patient and provider. Requiring repetitive documentation of these discussions in the absence of new information seems excessively burdensome on patients and providers.

[2] MACE is a combined measure of nonfatal myocardial infarction, nonfatal stroke, and CV death.

3. The TIDE trial is placed on full clinical hold and the regulatory deadlines for its conduct are rescinded. If reliable information on ischemic risk can be obtained from the re-adjudication of RECORD, the benefit-risk information for rosiglitazone should be re-evaluated and the conduct of further safety studies (including studies versus pioglitazone) re-considered.

II. Basis for Decision

In reaching my decision, I have reviewed the extensive documentation available on this issue, including the materials provided to the Endocrinologic and Metabolic and Drug Safety and Risk Management Advisory Committees in preparation for the July 13-14 meeting on this subject, the proceedings of that Advisory Committee, and subsequent memoranda from multiple members of OND (summarized by Dr. Jenkins' memo of September 2, 2010), OSE (summarized by Dr. Dal Pan on September 12, 2010) and from Dr. Temple, who has contributed a critical analysis of the relevant safety data. I have also reviewed information that became available subsequent to the Advisory Committee meeting, including an observational study by Wertz et al.[3] based on Wellpoint data, published in August 2010.

The evidence pointing to a cardiovascular ischemic risk with rosiglitazone is not robust or consistent (see Discussion of Available Safety Data below). Nevertheless, there are multiple signals of concern, from varied sources of data, without reliable evidence that refutes them. Additionally, evidence available to date, including a randomized trial in high-risk individuals[4], does not reveal a signal of cardiovascular ischemic risk with the other thiazolidinedione (TZD)-class drug available on the US market, pioglitazone. Therefore, based on this safety information, it is necessary to restrict access to rosiglitazone until more substantial evidence of its safety becomes available. The reasons for restriction rather than market removal include:

> (1) the cardiovascular safety profile of rosiglitazone is still an open question because there are conflicting data on the existence and magnitude of the risk, and a detailed re-adjudication and analysis of data from the RECORD study needs to be conducted;
> (2) there are individuals with Type 2 diabetes who may benefit from therapy with a TZD because they are unable to achieve glycemic control on other medications but who cannot tolerate pioglitazone or for whom it may not be the best medical choice (e.g., individuals with Type 2 diabetes and prior bladder cancer); and
> (3) there are individuals currently taking rosiglitazone who, with full knowledge of the potential risk and in consultation with their health care providers, may wish to remain on the drug rather than revise their treatment regimens.

[3] Wertz DA, Chang C-L, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circ Cardiovasc Qual Outcomes 2010;3:538-545.
[4] Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive: a randomized controlled trial. Lancet 2005;366:1279-1289.

My recommended actions are generally congruent with the recommendations of the Advisory Committee; although it must be pointed out that various members of the Committee had quite disparate opinions on these matters. These differences of opinion stem from varied conclusions about the existing data. A majority of the Advisory Committee members voted that the TIDE trial should continue should the drug remain on the market; however, they did not provide any guidance on how continuation of TIDE would be ethically or practically feasible if drug access in the United States were restricted (a majority voted for either restricted access or withdrawal).

Similarly, several CDER Offices have different recommendations. The Office of Surveillance and Epidemiology, as represented by Dr. Dal Pan, recommends market withdrawal (possibly with a Treatment IND program), or restricted access through a REMS. My reasons for not proceeding to market withdrawal are laid out above. I agree with Dr. Dal Pan's recommendation for restricted access. The purpose of this restriction is to limit initiation of rosiglitazone therapy to individuals for whom it is the preferable TZD option (e.g., for pioglitazone intolerance), to allow patients currently treated with rosiglitazone to continue on the drug if they so choose, and to provide prescribers and patients in both cases with full risk information. I do not support Dr. Dal Pan's proposal to require prescribers to submit extensive documentation of response to treatment, nor do I agree that monitoring of the patients should be stipulated as part of the REMS. I don't find that either of these steps would add any additional safety to a restricted distribution program for rosiglitazone, and I believe they would be excessively burdensome. Diabetes is a complex disorder; patients taking TZDs are usually taking multiple oral hypoglycemic agents; and current treatment guidelines stipulate monitoring procedures and treatment targets. It seems unlikely that a restricted access program could convey meaningful additional directions for individual patients.

CDER's Office of New Drugs recommends additional warnings on the drug label, without restrictions on marketing, and continuation of the TIDE trial, with appropriate modifications to informed consent. The basis of these recommendations is the uncertainty about the existence of the cardiovascular ischemic safety risk. While Dr. Temple does not make a recommendation, his memo clearly lays out some of the inconsistencies and weaknesses in the data signaling such risk.

Despite the lack of clarity in the data, I believe it is most prudent, given the current uncertainty about the safety risk, to restrict access to the product, and ensure that patients and prescribers are fully informed of the evidence of risk, until and unless more information is obtained. The FDA's current "Guidance on Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" calls for achieving an upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio (test drug versus comparators) for major adverse cardiovascular events (MACE) for marketed drugs of less than 1.3, along with a point estimate that is not close to the upper bound. These data can be derived from a prospectively planned meta-analysis of properly designed trials, or from a single large safety trial. Clearly, this level of assurance of cardiovascular safety is not achieved in the FDA meta-analysis for rosiglitazone. The RECORD study was intended be the large cardiovascular safety study to assess this risk,

but we are not currently able to rely on all the data from RECORD. It is possible that the re-adjudication of RECORD may provide evidence that supports the cardiovascular safety of rosiglitazone; however, at this time, the safety data base for rosiglitazone does not achieve the level of assurance of safety set out in the guidance, which is our current target for marketed anti-diabetic drugs.[5]

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[5] Because cardiovascular disease is the leading cause of death in individuals with type 2 diabetes, some have asserted that demonstrating a positive impact on cardiovascular outcomes (using MACE or a similar endpoint) should be required for approval of new anti-diabetic drugs. In fact, no current anti-diabetic drug has been definitively shown to reduce macrovascular complications in type 2 diabetes patients. While it might be possible for a new therapy to show improved MACE outcomes versus a no-treatment arm, such a trial is not ethical; longer-term trials must evaluate new therapies against the best standard care. Thus, showing that a new therapy reduces MACE would require a long-term superiority trial against current therapy. The recent ACCORD trial (New Engl J Med 2008, 358: 24: 2545-59) evaluated, among other things, the effect of more intensive diabetes control (compared to current guidelines) on cardiovascular outcomes in higher-risk patients with type 2 diabetes. The intensive glycemic control arm—which used standard therapies but targeted tighter glycemic control-- was halted after 3.5 years of follow-up due to higher mortality in the intensive therapy group. The factors leading to this result are not known. The ACCORD trial results demonstrate some of the uncertainties around the relationship between level of glycemic control and macrovascular outcomes.

However, since many diabetics have, or will develop, cardiovascular disease, it is important to make sure that new diabetic therapies do not have cardiovascular toxicities. This safety evaluation is distinct from demonstration of efficacy, which can be accomplished by evaluating effects on glycemic control, using HgA1c and other measures. In 2008, FDA issued a Guidance on conducting a cardiovascular safety evaluation of new therapies for Type 2 diabetes. This establishes guidelines for ruling out increases in cardiovascular risk, both at the time of marketing, and to be achieved after marketing. Thus new antidiabetic therapies will have been evaluated for cardiovascular toxicities prior to marketing, and will continue to undergo such evaluation, if very robust assurance of safety has not been achieved at the time of marketing.

Type 2 diabetes mellitus is a progressive metabolic disorder that is very often accompanied by other metabolic disturbances, particularly hypertension and dyslipidemia, frequently in individuals who are overweight or obese, are sedentary, and may smoke. Thus many type 2 diabetic patients have multiple risk factors for cardiovascular disease. In early stages of the disorder, the metabolic abnormalities can be mitigated or even eliminated in many people by (fairly radical) changes in diet, weight loss, salt restriction, and vigorous exercise. Unfortunately many are unable to undertake or maintain these behavioral changes, and have progressive disease. Although drug therapy can treat hyperglycemia, hypertension, and dyslipidemia, it does not follow that medical treatment will have the same benefit as elimination of the inciting factors. However, simultaneous intervention on multiple risk factors is likely required to improve cardiovascular outcomes. The follow-up Steno 2 study (New Engl J Med 2008 358; 6: 580-91) randomized patients with type 2 diabetes to intense lipid, blood pressure and glucose control, along with behavioral modification and other medications. They were then followed for another 13 years without differential recommendations for treatment. For this small but long term study of multifactor intervention, the hazard ratio for death was 0.54 in the treatment group, and the hazard ratio for cardiovascular events was 0.41, with large numerical differences in stroke, MI, PCI, and amputation. It is not possible to sort out which of the interventions were responsible for these effects, but this trial does illustrate that, over the long term, multi-factor intervention in type 2 diabetics can reduce severe cardiovascular outcomes. The issue of how "tight" glycemic control should be, at any given stage of disease, and how this impacts long-term microvascular and macrovascular diabetic complications, still remains an open question. This question is severable from the issue of standards for approval of new anti-diabetic drugs.

While both a majority of the Advisory Committee members and OND recommend continuation of TIDE, I do not believe it should proceed at this time, given the restrictions I have determined are necessary for rosiglitazone and the level of concern about its cardiovascular safety. In many cases, when a drug safety issue arises, conduct of a randomized trial is an appropriate step to resolve the question. However, the results of RECORD, which are currently in question, directly affect the ethics of conducting TIDE. I believe that re-adjudication of RECORD is the appropriate next step, with decisions on whether to conduct further studies or take additional regulatory actions to be based on the results of the re-adjudication and any other data that may become available in the interim. FDA is not rescinding the post-market requirement for the sponsor to study the safety of rosiglitazone compared to pioglitazone, if feasible and appropriate, but is stopping the current trial until all existing information is evaluated, including the data from RECORD, if possible.

This regulatory action places the burden of demonstrating cardiovascular safety on the drug sponsor. The RECORD trial was intended to provide the relevant safety information. The RECORD trial has certain built-in limitations, particularly its open-label design, its relatively small size (for a cardiovascular trial), the choice of primary endpoint, and the provision for investigator option in referring potential events for adjudication. Additionally, during its conduct, fewer events than anticipated were encountered and an unplanned interim analysis was conducted after publication of the meta-analyses regarding cardiovascular safety. Despite these limitations, it is the only large, randomized, long-term trial of the cardiovascular safety of rosiglitazone compared to other drug interventions for Type 2 diabetes—an inquiry that is highly relevant to the findings of the meta-analyses. During the FDA review of RECORD, questions arose about the potential for bias in influencing the results of this open-label study. Whereas the other limitations of the RECORD study can be taken into account when evaluating its results, the unresolved concern about biased referral currently limits the weight that can be placed on evidence from RECORD—for example, its ability to address the standards set forth in the FDA guidance. The questions about bias could not be fully addressed during the limited time period leading up to the Advisory Committee meeting. Therefore, it is reasonable to restrict drug access while further evaluation of RECORD is attempted. It must be noted that, even if all data points are fully verified, RECORD will not answer all questions about rosiglitazone safety, both for the reasons stated above, and because a comparison to pioglitazone was not a part of the study. However, if valid conclusions can be obtained from RECORD (within its known limitations), these findings will contribute more reliable information on the cardiovascular risk of rosiglitazone compared to standard anti-diabetic therapies than is currently available from the meta-analyses that have been done.

In summary, there are multiple and conflicting signals of cardiovascular ischemic risk related to rosiglitazone. The current cardiovascular safety database for rosiglitazone does not provide an assurance of safety at the level set out in FDA's guidance for marketed anti-diabetic drugs. There are not similar signals pertaining to the only other drug in the TZD class available in the US, pioglitazone. Marketing of rosiglitazone will be restricted

and the sponsor will be required to commission an independent verification of the RECORD data.

III. Discussion of Available Safety Data

Detailed analyses of extant data on the cardiovascular safety of both rosiglitazone and pioglitazone were presented at the July 2010 Advisory Committee meeting and are summarized in the memoranda from OSE and OND, and in Dr. Temple's analysis of the evidence. Many highly experienced clinical trialists and methodologists, both within and external to the FDA, who have examined these data find it hard to arrive at definitive conclusions about the cardiovascular ischemic risk of rosiglitazone, yet they agree that pioglitazone's data do not suggest such a signal of risk. This uncertainty about the risk of rosiglitazone is overwhelmingly the most important reason for the differing opinions on what regulatory action should be taken.

A. Data Directly Addressing the Meta-analysis Results

The original findings generating concern in 2006 and 2007 were from a group of related meta-analyses of cardiovascular ischemic events and deaths in efficacy trials of varying design evaluating rosiglitazone against placebo or other non-TZD anti-diabetic drugs. Such meta-analyses are often done to look for rare or uncommon problems that would not be detected in individual trials. The FDA 2010 meta-analysis, an update of the 2007 FDA meta-analysis, includes 52 trials. This meta-analysis finds a nominally significant odds ratio (OR) of 1.80 for non-fatal MI, with OR of 1.44, 1.46 and 1.38 for MACE (a combined measure of nonfatal MI, nonfatal stroke, and CV death), cardiovascular death, and all-cause death, respectively, that are not statistically significant but also not reassuring. The OR for non-fatal stroke is 0.86. Thus, the recent meta-analytic findings (which incorporate trials included in the prior analyses and add more) support the original concern that rosiglitazone increases the risk of heart attacks, and thereby might increase the risk of cardiovascular death and all-cause death, when compared to placebo or non-TZD diabetes drugs. Additionally, the vast majority of these events in the meta-analysis come from trials of 12 months duration or less; and the sparse data after 12 months are not revealing (see Table 1 in Dr. Parks' review of August 19, 2010). Therefore, the hypothesis raised by the meta-analysis includes the idea that the risk of MI, and potentially other serious cardiovascular events, occurs promptly after exposure to rosiglitazone, during the first year of therapy.

It has been shown repeatedly that hypotheses generated by meta-analyses may not be verified when studied in randomized controlled trials. (For example, see the recent Perspective article on tiotropium[6] and FDA's 2009 safety communication on cefepime[7].) Other available evidence must also be used to evaluate whether or not rosiglitazone

[6] Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. N Engl J Med 2010; 363:1097-99. [http://www.nejm.org/doi/pdf/10.1056/NEJMp1008502]

[7] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm167254.htm

increases the risk of heart attacks compared to placebo or standard diabetes drugs. After publication of the original meta-analyses, a number of epidemiologic studies evaluated the risk of ischemic CV events in populations where patients with diabetes were taking rosiglitazone or other standard, non-TZD therapies. These studies did not show any consistent increase or decrease in ischemic cardiovascular events (see slide 8 in Dr. Gelperin's AC presentation, or her review) in rosiglitazone treated patients compared to non-TZD treated patients. There were similar results for all-cause death. These findings diminish the likelihood that the meta-analytic results are correct, but do not have enough weight to dismiss them (because of the well-known limitations of epidemiologic studies).

The most reliable evidence about clinical outcomes comes from well-conducted, randomized trials. Two longer-term randomized, controlled, double-blind trials of rosiglitazone (DREAM and ADOPT) were completed around the time of the original meta-analysis. These trials did not show any signal of increased mortality, but had numerically (not statistically significant) higher rates of MI in the rosiglitazone arms. Neither of these trials had a substantial number of cardiovascular events: this limits how much information they contribute to the question at hand. Dr. Temple finds the post-hoc analyses from the more recently completed BARI-2D trial to weigh against a risk of ischemic CV events due to rosiglitazone, but the results are by no means definitive because of the non-randomized nature of the analysis. This leaves the RECORD trial, a randomized, controlled trial which evaluated the CV safety of rosiglitazone compared to metformin or sulfonylureas (standard diabetes drugs). Although the RECORD study looked at additional endpoints, it included prospective evaluation of heart attacks, CV death, and all-cause death. The problems with RECORD have already been discussed. However, I fully agree with Drs. Temple and Unger that there is every indication that the mortality results of RECORD are reliable, based both on trial retention rates and FDA inspections. These results trend favorably for rosiglitazone and thus pretty strongly (along with the results of ADOPT, DREAM and BARI-2D) weigh against the point estimate for all-cause death or cardiovascular death in the meta-analyses, although the RECORD mortality findings are within the confidence limits of those meta-analytic results. However, without re-adjudication, the results of RECORD cannot be used to help evaluate the risk of excess myocardial infarction.

While not directly addressing the meta-analytic results, a number of published observational studies compared various cardiovascular outcomes of patients taking either rosiglitazone or pioglitazone.(see below) These studies included evaluations of the occurrence of myocardial infarction. Most of these were presented by Dr. Gelperin in her systematic review (see Table 9.3.1.1). Dr. Gelperin points out that many of the studies found a numerical advantage for pioglitazone in rate of MI; however, the majority showed no statistically significant difference between the two drugs. Similarly, the very large FDA/CMS study, and the recent study by Wertz et al. did not detect a difference in the occurrence of myocardial infarction in patients taking rosiglitazone or pioglitazone. Several of the large studies found a statistically significant mortality advantage in favor of pioglitazone, but this was in the absence of a finding of a relative increase in myocardial infarction.

In summary, the main question raised by the various meta-analyses of rosiglitazone—does the drug increase the risk of heart attacks when compared to placebo or non-TZD diabetes drugs?—is still not clearly answered. The updated meta-analysis completed by FDA in 2010 still shows the myocardial infarction risk, but most observational studies completed to date do not find this risk. It also seems less likely, based on current data, that rosiglitazone increases cardiovascular or all-cause death compared to non-TZD diabetes drugs. More information on these questions may be achieved by a re-adjudication of RECORD.[8]

B. Comparisons of rosiglitazone and pioglitazone

As a result of the concerns about rosiglitazone's safety, the question naturally arises: what is the cardiovascular safety profile of pioglitazone, the other drug in the TZD class? Pioglitazone had been studied in a cardiovascular safety trial (PROactive) that enrolled patients at high risk for cardiovascular events. The trial added pioglitazone or placebo to underlying therapy. This trial recorded a large number of cardiovascular events. There was differential dropout due to edema in this trial, mirroring a criticism leveled at the RECORD trial by Dr. Marciniak (see his briefing document for the July 13-14, 2010 advisory committee meeting); such results are likely when a TZD is studied against a non-TZD therapy. FDA review of the study found that it failed to meet its primary endpoint, although a secondary endpoint of MACE had a favorable result, but could not be considered as statistically proven. The MACE result was driven by differences in non-fatal MI and in stroke. There was no difference in CV death or all-cause death between the groups. Thus, pioglitazone, added to background therapy, appeared to have a relatively favorable result on ischemic events, and a neutral effect on death, in a randomized controlled cardiovascular safety trial, when compared to placebo.

A number of observational studies comparing cardiovascular outcomes or mortality in patients prescribed either pioglitazone or rosiglitazone were conducted prior to 2010 and published in the literature. These were presented by Dr. Gelperin at the 2010 Advisory Committee meeting and are discussed in detail in Dr. Gelperin and Graham's June 15,

[8] The data relating to rosiglitazone's cardiovascular safety profile can be confusing even to experts. For example, some people have concluded that the FDA meta-analysis results mean that rosiglitazone causes an 80% increase in heart attacks when compared to standard therapy. This could be the case, but is not established by the meta-analysis, because the results are based on very few MI events (65 total) that were collected from trials that were not designed or executed in a manner to assess cardiovascular risk, and the confidence limits on the 1.8 OR are wide. To illustrate these points, it is generally agreed that there is no signal suggesting that pioglitazone has an ischemic cardiovascular risk. The OR for cardiovascular death in FDA's meta-analysis of pioglitazone trials is 1.18; nevertheless, it is not asserted that pioglitazone increases such deaths by 18%. This is because of the limitations of these particular meta-analyses, and because the 95% confidence limits (roughly speaking, the upper and lower numbers that have a 95% chance of containing the true OR within them) range from 0.6 to 2.34. Obviously, these confidence limits include very good outcomes (life saving) and very poor ones (increased mortality), so they signify a large amount of uncertainty about the actual effect. The 95% confidence limits on the OR for non-fatal heart attacks in the FDA meta-analysis of rosiglitazone are 1.03-3.25.

2010 briefing document to the Advisory Committee. In addition, a very large study[9] conducted by FDA and CMS in the Medicare database was published in June 2010 and was also presented. An additional study by Wertz et al.[10] appeared in the literature soon after the AC meeting. Dr. Gelperin presented forest plots summarizing the results of the published studies looking at MI, congestive heart failure, stroke and death. The point of this presentation was that, in many studies done by many authors, pioglitazone use was fairly uniformly associated with a lower rate of these events than rosiglitazone use--a "weight of the evidence" argument (see slides 13-15 in Dr. Gelperin's AC presentation). However, I find that not all these studies contribute the same weight of evidence. For example, the Hsiao study, while very large overall, included only 495 patients taking pioglitazone. Some of the published observational studies include large numbers of patients on rosiglitazone and pioglitazone (Walker, Winkelmayer, Gerrits, Juurlink, Ziyadeh, Graham and Wertz). The studies by Juurlink, Winkelmayer and Graham found statistically significant increases in all-cause mortality and congestive heart failure in rosiglitazone patients compared to those taking pioglitizone, but no increase in MI. The results of these studies were consistent. Wertz found no difference between the drugs on a composite endpoint of AMI, acute heart failure or all cause mortality. The most striking finding in the very large FDA/CMS (Graham et al) study was an increased rate of stroke in people treated with rosiglitazone compared to pioglitazone. As Dr. Temple explains in his analysis of the data, drawing conclusions from non-randomized comparisons of drugs is difficult, because small differences in the reasons people were treated with each drug can create undetected biases that influence the results. There is more concern with the influence of bias when the differences that are detected are proportionately small.

There are also challenges in interpreting studies that compare two drugs where the performance of the comparator drug is not completely known. For example, if two therapies show equivalent results for some outcome (for example, mortality), it may not be clear if both are better, both worse, or both no different than, for example, a placebo or standard therapy. If one therapy is superior on some outcome (for example, MI), it may not be clear whether that treatment prevents MIs or the other therapy causes them (i.e., compared to placebo if it had been used in a third arm.) This is why it is common to use well-understood drugs as active comparators in clinical trials. Of course, from the point of view of the treating clinician, the question of which drug in a class to use is of utmost importance: this is the point of "comparative effectiveness research" on drugs. However, for the purposes of advancing knowledge (to build the evidence base for disease therapy), and for regulatory purposes, the question of whether (in this case) one drug is superior, or the other has a specific toxicity, or there is really no difference, needs to be determined.

Dr. Gelperin makes the point that several of the epidemiologic studies in younger patients found a statistically significant increase in MI in rosiglitazone-treated patients compared to pioglitazone treated patients. This finding reinforces the concern about rosiglitazone

[9] Graham DJ, OUellet-Hellstrom R, Macurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010;304(4):411-8. Epub 2010Jun28.
[10] Wertz DA, et al; op.cit.

but of course these studies are not able to distinguish between a toxicity of rosiglitazone or a benefit of pioglitazone on myocardial ischemia as suggested in PROactive. Studies in older patients, who are at much greater risk of MI, did not find a difference. The FDA/CMS study, by Graham et al, was very large (over 227,000 patients exposed), was well conducted, and had a very large number of MI events (1746). No statistically significant increase in MI risk was found, and the study primarily looked at early treatment, e.g., the first 18 months, which includes the period of concern raised by the meta-analyses. Moreover, the large Winklemayer and Juurlink studies had similar results. Therefore, although these studies were not positive for rosiglitazone overall, they do not support the idea that there is a specific, early acting toxicity of rosiglitazone that increases myocardial infarction.

The large epidemiologic studies do raise additional concerns about the cardiovascular outcomes of rosiglitazone compared to pioglitazone use, outside of the MI finding. The FDA/CMS study (Graham et al) found a statistically increased rate of stroke (adjusted HR 1.27), heart failure (adjusted HR 1.25) and death (adjusted HR 1.14) in users of rosiglitazone versus pioglitazone. The heart failure finding, if verified, would represent a clear differential toxicity: since no one thinks that pioglitazone prevents CHF, it would suggest that pioglitazone use results in less heart failure than rosiglitazone. The stroke finding is a new one: the meta-analyses and trial results have not suggested that rosiglitazone increases stroke. Winkelmayer found a non-significant difference in stroke in his comparative study. The mortality findings seen in the Juurlink, Winkelmeyer and Graham studies (with hazard ratios between 1.14 and 1.16) are obviously of concern. Of note, the hazard ratios for these outcomes are often referred to as "small." This means there is a proportionally small difference (for example, a 10% increase rather than a three fold increase) that may be more vulnerable to hidden biases in non-randomized data (i.e., in epidemiologic studies). As Dr. Graham has pointed out, it does not mean that the impact would be "small" on a population basis—it could be very significant. Rather, it means that the "small" size of the observed difference makes it more difficult to rely on nonrandomized studies to reach conclusions. In addition, the differences found in these comparative studies (outside of the CHF finding) could have occurred because pioglitazone has a beneficial effect on, for example, mortality, greater than the effect of rosiglitazone (which could also theoretically have had a beneficial effect, albeit smaller). Such comparative superiority claims for survival benefits are usually established by the results of very large, randomized outcome studies; FDA usually requires rigorous evidence to support such comparative claims. If, on the other hand, these findings represent a toxicity of rosiglitazone, perhaps resulting from the fact that it causes more heart failure or from its effects on lipids, then there would be great concern for the use of the drug even in patients who are not candidates for pioglitazone. It is certainly reasonable, as Dr. Gelperin points out, to prefer the use of pioglitazone based on these epidemiologic findings, in the absence of controlled trial data. Interestingly, the Advisory Committee did not seem to place much weight on these data, perhaps because of continuing concerns about the reliability of non-randomized studies. They did not seem to weigh the MI findings from these studies very heavily, and, when explicitly asked about mortality, only 7 voted that they felt the data were sufficient to "raise significant safety concerns for mortality…relative to pioglitazone." (12 voted that the

data were not sufficient, and 14 voted that they were not able to make a make a finding). These votes may reflect ongoing concern about the reliability of results of "small" differences from observational studies. It is for all these reasons that the Office of New Drugs, and Dr. Temple, support continuation of the TIDE trial, which would have the capacity to address all these questions definitively, given that it has a standard therapy arm.

In summary, the existing data from observational studies comparing rosiglitazone to pioglitazone suggest that pioglitazone use may be associated with better cardiovascular outcomes. However, it is difficult to draw definite conclusions from these studies, both because of the small size of the observed effects, and because it is not clear whether the findings, if valid, represent beneficial effects of pioglitazone or toxicities of rosiglitazone.

D. Conclusions Regarding Available Safety Data

The sponsor has not submitted information on rosiglitazone that achieves the standards for assurance of cardiovascular safety set out in FDA's guidance. In addition, existing data raise concerns about a cardiovascular risk. Re-adjudication of RECORD may provide information directly relevant to questions raised by results of the meta-analyses.

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/s/

LINA ALJUBURI
09/23/2010

JANET WOODCOCK
09/23/2010

Memorandum

Date: August 8, 2010

From: Robert Temple

To: Janet Woodcock

Subject: Data on Rosiglitazone

The recent July 13, 14 AC meeting to consider rosiglitazone's cardiovascular risk was in many ways thoughtful but in my view left critical questions unaddressed. In particular, it did not really consider the weight of the various lines of evidence in much detail nor did it focus on the particular findings that were most critical in view of the initial stimulus that led to our concern (the Nissen meta-analysis). The following is an attempt to describe all the data, touch on its limitations, and suggest potential additional efforts (mostly related to RECORD). I am not here attempting to propose a decision; it is perfectly clear that there are grounds for concern about risks of rosiglitazone (as there were in 2007) and the question will be whether that concern exceeds the threshold for action beyond what we have already done in rosiglitazone's labeling. This clearly involves particular attention to what new information we have and how it affects our conclusions. What I am hoping to do is to lay out the data so we can be sure we're all considering the same information, identify and resolve disagreements about the data (as distinct from what to do about it), and, where appropriate, see what further analyses might be useful. In most cases, I am not doing new analyses but will be relying on a good deal of work already done.

There can be no doubt that the available data are not all we might wish for. The potentially important comparisons with pioglitazone are either indirect (known to be treacherous) or based on observational data (with recognized limitations, especially when relative risks are close to one). With respect to the rosiglitazone studies, there are seriously inconsistent findings among the controlled studies (here counting single trials and meta analyses as "controlled").

I will divide this discussion into the following segments:

I. Meta-analyses of rosiglitazone RCTs

II. Larger single RCTs of rosiglitazone (ADOPT, DREAM, RECORD, BARI 2D)

III. Meta-analyses and a single large RCT of pioglitazone

IV. Epidemiologic studies comparing rosi and "others" and studies comparing rosi and pio.

V. Conclusions

Let me note two critical premises: MACE and its components are the endpoints of interest, and lack of adjudication of potential endpoints should not create a false positive safety finding.

The endpoints of interest here are CV death, non-fatal MI (NFMI), and non-fatal stroke (also known, when combined, as MACE, major adverse cardiac events), because it is those endpoints (actually, not including stroke) about which concerns were raised by the Nissen meta-analysis. These endpoints can be reasonably well-assessed in clinical trials, even without an events evaluation/adjudication committee (such committees were not used in the short-term rosiglitazone studies included in the meta-analyses and not used in the current epidemiologic studies). Although the individual components are plainly of interest, and were critical in the Nissan meta-analysis, it is MACE that seems like the most informative endpoint and it is the one regularly used to assess favorable CV effects of drugs and drug risks (e.g., in the diabetes guidance). Thus, although RECORD was designed with CV hospitalizations and CV mortality as its primary endpoint, reflecting an important concern with heart failure, our major interest, given the meta-analysis that raised the issue under discussion, should be MACE and its components, leaving heart failure to other considerations.

The lack of an adjudication process for endpoints in the studies going into the meta-analysis has been noted, and is certainly of some concern, but this should not be over-emphasized. As a general matter, in blinded studies (which the meta-analysis studies were) one would expect imprecise endpoint assessment (a potential consequence of non-adjudication) to create “noise”, and a bias toward the null (finding no difference). The unplanned and generally poorly and variably specified endpoint assessments in the studies going into the meta-analyses and epi studies therefore should not create a finding, so long as the observations are unbiased. Such “noise” will not, I believe, be a major problem for a positive finding. I recognize the irony of this: the not very precise, not well-specified findings in the meta-analysis are held to a lower standard than the later trials that seek to examine the concerns stimulated by the meta-analysis. The studies and data in the meta-analysis have, for example, never been analyzed the way the RECORD findings have been scrutinized by Drs. Marciniak and Unger. Unfortunately, the kind of evidence needed to give a persuasive “no finding,” and to overcome the potential “bias toward the null” in any trial intended to show no effect, forces this approach.

I. Meta-analyses of Rosiglitazone

A. Nissen analysis

Nissen’s meta-analysis results are shown in the table below, taken from his NEJM publication. As can be seen, he pooled 40 relatively small studies, most of them 6 months or shorter, with ADOPT and DREAM, a step with important consequences to the outcome and one that is not fully explained in the paper. Among the 40 studies, 32 were either comparisons with placebo or placebo-controlled “add-on” studies. The remaining 8 were comparisons with other oral hypoglycemics. These design features are described in the publication.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

As can be seen, the small studies alone showed a nominally significant (p = 0.02), and rather large (OR point estimate 2.4) effect on cardiovascular mortality, with a trend, but not a significant effect, on NFMI (p = 0.15). Stroke is not mentioned at all, a strange omission as almost all CV event trials include it, and in the absence of a prior or mechanistic hypothesis, it would seem almost obvious to include stroke. It is possible Nissen had no access to stroke data (and, apparently, did not seek it), but, as we will see from FDA's analyses, rosiglitazone treatment was in fact associated with fewer strokes. MACE, obviously, was not considered by Nissen, nor was the combined endpoint of CV death and AMI, because (as explained in the paper) Nissen could not tell from available data whether a patient had more than one event. I will focus on FDA's updated analysis of these trials (not including ADOPT and DREAM, discussed in Section II) as the most pertinent analysis, but a few points should be noted as relevant to Nissen's analysis and to meta-analyses in general.

1. The overall analysis was carried out with results clearly knowable before it was done.

The decision to do the analysis was apparently (Nissen AC presentation) provoked by DREAM, with its finding of more AMIs, and the decision to include ADOPT/DREAM, etc. were all made with the consequences largely known. Specifically, the interest in AMI arose, according to Nissen, from the excess of AMI in DREAM (a difference of 6 events) and the results of ADOPT had been published, so that the effect of combining these studies with the smaller ones was clear. That is, of course, not what we expect in designing and evaluating RCTs, where we stress the need to make all analytic plans before results are in hand to avoid bias. It is one of the reasons many trialists have noted the "observational" qualities of meta-analyses and the need to interpret their results cautiously. Peto, for example, has emphasized the need to find critical missing data (strokes, for example, or time of events) and in a DIA talk, at least (I can't find a paper saying this) has suggested that only statistically very strong findings, e.g., p-values in the neighborhood of 0.001, should be interpreted as convincing, although he was not focused on safety, where perhaps a lesser degree of "certainty" might suffice.

The very important decision to include ADOPT and DREAM with the small studies is particularly interesting. It clearly took the mortality finding from nominally significant (p = 0.02 for the small studies) to NS (p = 0.06) overall. This might be taken as evidence of "fairness" and caution in interpretation, but there are other interpretations. Presenting only the small study mortality finding would have made the whole finding promptly rebuttable by the lack of a mortality effect in ADOPT/DREAM, perhaps leading to loss of credibility of the meta-analysis. Focusing on AMIs (which were not significantly more frequent on rosiglitazone in the small studies) avoided that outcome. In any event, speculation aside, this was not a blinded effort and the results were obtained with full knowledge of the effect of various analytic decisions on the outcome by the analysts, a very common situation with meta-analyses. As noted above, in his presentation at the July 2010 AC meeting, Nissen made it clear that it was DREAM, with its adverse trends on AMI as well as other endpoints (especially CHF), that provoked the meta-analysis. In such a case one could ask whether DREAM should have been included in the meta-analysis. In any event, although the history here is of interest, the current meta-analysis, whatever its etiology, is what we must consider.

2. In presenting results, both Nissen, and Psaty and Furburg in the accompanying NEJM editorial, emphasized the need for caution in interpreting the meta-analytic results.

Nissen and Wolski stressed certain limitations of the data.

> "However, these findings are based on limited access to trial results from publicly available sources, not on patient level source data. Furthermore, results are based on a relatively small number of events, resulting in odds ratios that could be affected by small changes in the classification of events. Nonetheless, our findings are worrisome. . . [and] the public health impact of an increase in cardiovascular risk could be substantial <u>if our data are borne out by further analysis and the results of larger controlled trials</u> (my emphasis).
>
> Although [we could not] construct a composite outcome that included AMI and CV death, the increase in the odds ratios for both of these endpoints suggests that observed effects associated with rosiglitazone were probably not due to chance alone."

The "dual" "finding" (AMI and mortality) was thus considered a critical strength of the meta-analysis, enhancing both its clinical importance and, of particular importance for this discussion, its credibility. That is, with BOTH critical endpoints showing (or strongly suggesting) an adverse effect, chance was an unlikely explanation.

Nissen also noted that the odds ratios for the short-term studies were similar to the overall results, suggesting that the adverse effects might occur rapidly. This is a somewhat odd point, as the short term studies, with a large fraction of the events, would obviously be expected to influence the overall result. Nonetheless, it is true that the finding occurs early. In fact, for CV death, as the above table shows, the striking, nominally significant, finding of increased mortality in the short-term studies (n about 10,000) is not present at all in the longer term studies (n about 9000). As described below, (IB) FDA's meta-analysis shows a similar result.

Nissen, later in the paper, reemphasized the limitations of the analysis, but his concern was mainly about the true magnitude of the risk, not whether or not the risk was present

or absent. He also hoped that ongoing RECORD would provide useful insight into the risks, citing, apparently with approval, the study design and protocol paper of 2005.

Nissen and Wolski also noted results on overall mortality (OR 1.18; 95% CI 0.89-1.55, p = 0.24), pointing out that this endpoint was "not prespecified," unlike, one supposes, all the rest of the analytic decisions.

In commenting on the Nissen meta-analysis, Psaty and Furburg noted that the weaknesses of the study were substantial and that "a few events either way might have changed the findings for myocardial infarction or death from cardiovascular causes. In this setting, the possibility that the findings were due to chance cannot be excluded." They noted with approval that in their discussion, Nissen and Wolski properly emphasized the "fragility" of their findings.

And they are in fact fragile, only marginally statistically significant, even without any correction for multiplicity or a more demanding standard for meta-analyses. A strength, on the other hand, as Nissen pointed out, is the finding on two highly pertinent endpoints.

Whatever the limitations of the original Nissen meta-analysis, FDA was able to conduct a more complete analysis and it seems most useful to focus on it, principally the 52-trial updated analysis presented at the July 2010 AC meeting.

B. FDA's Updated Meta-analysis

FDA's updated meta-analyses, presented to the 2010 Avandia Advisory Committee meeting, should be taken as the best available meta-analytic assessment of the studies of at least 2 months duration (but see below regarding a published meta-analysis with far more studies that has not yet been carefully scrutinized), as we had more data available. I note that we still lack detailed assessment of cases and we have not shown a K-M curve.

The 52-trial analysis, focused on MACE and its components and on all-cause mortality, showed the following results:

Outcome	Rosiglitazone # events (%)	Control # events (%)	Stratified Exact OR (CI)
	n = 10,039	n = 6956	
MACE *	70 (0.7)	39 (0.56)	1.44 (0.95-2.20)
CV Death	17 (0.17)	9 (0.13)	1.46 (0.60-3.77)
NFMI	45 (0.45)	20 (0.29)	1.80 (1.03-3.25)
NF Stroke	18 (0.18)	16 (0.23)	0.86 (0.40-1.83)
All-cause death	29 (0.29)	17 (0.24)	1.38 (0.72-2.72)

* Only one per patient, so that CVD, NFMI, and NF stroke are > MACE

I am displaying the stratified exact analysis, the analysis preferred by Biometrics. The 52- trial results are fairly similar to the 42-trial analysis done by FDA in 2007 (Mele

analysis) for MACE, AMI and stroke, except that the AMI finding is now nominally significant (same OR, however), but the mortality findings (both CV and overall) are much weaker, albeit still troublesome. The OR's had been 1.9 for all cause death and 2 for CV death, using the same analysis as used for the 52-trial analysis.

Note I am not looking at subsets, such as insulin users or NTG users, or analyzing by comparator treatment. I believe these subanalyses are too small to rely on very much, although they perhaps illustrate the variability of the data. In fact, most trials compared rosiglitazone to placebo, either alone (i.e., with no other therapy) or with each added to a common background treatment.

C. Interpreting the Initial and Updated Meta-analyses.

As Nissen and Psaty/Furburg emphasize, the Nissen and Wolski meta-analysis is not definitive, although it is surely grounds for concern and the CI upper bounds are impressive. Nonetheless, it must be recognized that there was potential bias in its development (or at least the analysis was done with knowledge of what would emerge) and the findings are statistically marginal in terms of the specific case and marginal in terms of expectations for a meta-analysis ($p = 0.05$ would generally not be enough). The FDA 52-study analysis generally has similar limitations. A few further observations:

1. The AMI finding (in the 52-study analysis) is now nominally statistically significant, but MACE is not, CV and overall mortality are not close, and stroke trends favorably for rosiglitazone. Any sort of correction for multiplicity leaves the finding well short of nominal statistical significance.

2. The patron saint of meta-analysis, Richard Peto, who helped bring the approach back from what we used to dismiss as "unplanned pooling," stressed approaches that would avoid bias and error, including selection of endpoints before the trials are analyzed and a reasonably high level of statistical significance.

The reason for such concern is that meta-analyses can give strikingly incorrect results (to be fair, so can individual RCTs). There are a few well-recognized examples cited in a letter to Dr. Parks from Dr. Salim Yusuf, such as the apparent survival benefit (statistically quite strong) of post-infarction Mg treatment, never confirmed (indeed, strongly rebutted) in a large trial. Dr. Yusuf notes the particular problem when the number of events is small. Very recently, FDA [Kim, et al. Meta-analysis of a possible signal of increased mortality associated with cefapine use. Clin Infect. Diseases. 2010; 51: 381-389] reported on our own experience with a cefapine meta-analysis after a published analysis found in a 41-trial, trial level analysis, a statistically significant 26% increase in 30-day mortality in patients with a variety of infections treated with cefapine compared to other beta-lactams. Our analyses, including a trial level analysis based on 88 reports, and a patient level analysis based on 35 trials, found no significant effect on survival.

Others, notably LeLorier [LeLorier, et al. Discrepancies between meta-analysis and subsequent large randomized controlled trials. NEJM, 1997;337;536-542] and Bailar, have discussed discrepant results between meta-analyses and large trials, discrepancies often not explained, and sometimes very substantial. They uniformly urge a cautious approach. LeLorier, for example, compared 12 large RCTS with 19 previous meta-analyses addressing the same questions, a total of 40 primary and secondary outcomes. They found that the RCT results were not correctly predicted by the meta-

analyses about 35% of the time, although the direction of the effects was generally similar.

These kinds of concerns have led us to treat meta-analytic findings very cautiously when it comes to an effectiveness conclusion. I cannot think of any novel claim we have accepted based on such analyses, although we certainly use them to calculate margins for NI trials, (where, of course, we believe we already know about effectiveness) and we use the ISS and ISE in NDAs to examine demographic and other subsets in NDAs for both safety and effectiveness. But we do regularly use meta-analyses to assess safety, where low event rates and the substantial delay and difficulty that would result from trying to rely on new large trials leave us little choice.

3. The findings of the 2010 meta-analysis can be compared with the expectations we have put forth for new antidiabetic drugs in our recent guidance. At initial approval, generally presuming a database of several thousand patients, we would expect the 95% CI upper bound for the MACE OR to be < 1.8. This has clearly NOT been achieved in this case. The post-approval OR goal of ≤ 1.3 for MACE with a larger database, is, obviously, also not close to having been met in the 52-trial meta-analysis, despite some 17,000 patients and is probably not met even if the meta-analysis is expanded to include all of the longer trials, including RECORD. Nissen showed an analysis for AMI including RECORD (but I presume this had both fatal and NFMI for RECORD) with the upper bound still 1.63 and for CV death, where the upper bound was still 1.36, although the point estimate is only 1.03). Although MACE was not analyzed, I would expect the AMI rate to push the upper level above 1.3. This means that a new drug with these results would not be approved and an approved drug (with OR < 1.8 at time of approval), having conducted its post-marketing effort with results like the meta-analysis, would, presumably, be considered for withdrawal, assuming that these were the only data available. Of course, these conclusions do not consider consistency. What would we do, for example, if a single large study substantially "rebutted" an initial concern, e.g., by being well within the 1.3 upper bound for MACE on its own, even if total data were not (i.e., what RECORD may well show, depending on results of further re-analysis)?

4. In his presentation at the July 2010 Advisory Committee, Nissen noted the lipid effects of rosiglitazone, an approximately 20% increase in LDL cholesterol, with larger effects in people closer to normal. He did not believe change in cholesterol would have an early effect, and that seems correct, based on a quick inspection of statin trials (4S, WOSCOPS). In these lipid-lowering trials, differences emerged only after at least a year. As will be described below (#5), it is largely trials of ≤ 6 months duration that drive the results here and any effect can probably not be attributed to LDL changes.

Certainly, however, the increased LDL caused by rosiglitazone is a long-term concern. It could, of course, be readily dealt with in most cases, but that could mean an extra drug in some patients. It has been noted that statin use in RECORD was greater in the rosiglitazone group; I would consider that good sense, not a problem.

5. I note the recent publication of a meta-analysis by Mannucci, et al [Mannucci E, et al. Cardiac safety profile of rosiglitazone: A comprehensive meta-analysis of randomized clinical trials. Int J Cardiol 2010; 143:35-140] of 164 short-term (> 4 week) rosiglitazone trials with a total of almost 43,000 patients. It reported an OR for CV and total death of 0.93 and 0.94 and for NFMI of 1.14, results similar to RECORD (below). I had not seen any prior reference to this analysis, and it is certainly not a patient level analysis, but I believe it deserves examination. We have no idea what rosiglitazone's mechanism of effect is (if indeed there is one), and trials of 4-26 weeks appear pertinent. Indeed, I

note, as others have pointed out, that in the 52-study FDA meta-analysis, the shorter trials (2-6 months) largely generate the MACE findings, the AMI findings, and the mortality findings. The following table, from the Biometrics' meta-analysis, grouping trials by duration, shows this:

	2-6 Months			> 6 mos - ≤ 1 yr			> 1 yr		
	Rosi n = 7068	Control N = 4716	OR (CI)	Rosi n = 2524	Control n = 1792	OR (CI)	Rosi n = 447	Control n = 448	OR (CI)
MACE	45 (0.64)	18 (0.38)	1.76 (0.98-3.27)	14 (0.55)	11 (0.61)	1.17 (0.48-2.89)	11 (2.46)	10 (2.23)	1.10 (0.42-2.92)
CV Death	14 (0.2)	2 (0.04)	4.71 (1.05-43.33)	3 (0.12)	3 (0.17)	1.01 (0.13-7.58)	0	4 (0.89)	0
MI	29 (0.41)	8 (0.17)	2.62 (1.15-6.73)	9 (0.36)	6 (0.33)	1.28 (0.4-4.44)	7 (1.57)	6 (1.34)	1.16 (0.33-4.22)
Stroke	12 (0.19)	10 (0.21)	0.78 (0.3-2.07)	2 (0.08)	4 (0.22)	0.50 (0.05-3.54)	4 (0.89)	2 (0.45)	2.02 (0.29-22.46)
All-cause	20 (0.28)	5 (0.11)	2.75 (0.98-9.51)	5 (0.2)	5 (0.28)	1.02 (0.23-4.46)	4 (0.89)	7 (1.56)	0.57 (0.12-2.27)

6. Part of the strength of the Nissen meta-analysis was the strong trend on two distinct, independent, albeit potentially mechanistically related, endpoints, CV death and NFMI. This was specifically emphasized by Nissen and Wolski as a significant reason for believing the statistically borderline individual results, and it is clearly a reasonable point. As quoted above they said: "the increase in the odds ratios for both of these endpoints suggests that observed effects associated with rosiglitazone were probably not due to chance alone." What this says is that, apart from the increased clinical concern that would arise from an effect on mortality, the two findings together greatly enhance the credibility of the finding, i.e., the likelihood that the finding is not the result of chance. That noted, the conclusion is surely weakened by the fact that ADOPT and DREAM, the 2 largest studies available at the time, do not support the dual findings. And, as will be described below, it seems clear, whatever reservations reviewers may have about the study, that RECORD does not support the mortality finding, especially the early finding that is prominent in the meta-analysis. Also, as described below, the BARI 2D study shows no suggestion of a mortality effect.

II. Larger Trials of Rosiglitazone

1. ADOPT/DREAM

The Nissen meta-analysis showed results of ADOPT and DREAM as follows

	Rosi	Control	OR/(CI)
AMI			
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)
ADOPT	27/1,456 (1.85)	41/2895 (1.44)	1.33 (0.80–2.21)
CV Death			
DREAM	12/2,635 (0.51)	10/2634 (0.38)	1.20 (0.52–2.78)
ADOPT	2/1,456 (0.14)	5/2895 (0.18)	0.80 (0.17–3.86)

There have been additional analyses of these trials and DREAM is a complex factorial study, but I have not examined these further. It seems clear, however, that, overall, these trials do not support the CV mortality trend in the meta-analysis, but they are consistent with an effect on AMI; indeed, they heavily influence that outcome. The distinction is critical. Both mortality and AMI matter, of course, but as both Nissen and Furburg noted, the survival data are what are really frightening and the consistency of the effect on the two endpoints enhanced the credibility of the meta-analytic findings.

2. RECORD

I will comment relatively briefly on RECORD, as Drs. Unger and Marciniak, and Drs. Parks and Mahoney have addressed it at length. I want to separate the RECORD mortality results, which I believe are relatively clear, and the AMI results, which need further assessment. First, like ADOPT and DREAM, RECORD is clearly inconsistent with the meta-analysis finding of increased CV and overall mortality, even without further adjudication, and no matter which of the various analyses one prefers. Second, we cannot fully assess effects on AMI without further review, although they seem on face nowhere close to the nearly 80% increase seen in the meta-analysis, nor the smaller, but still troublesome, increases in ADOPT and DREAM.

RECORD was a study in 4447 patients with type 2 diabetes mellitus. It was conducted outside the US, and was a response to an EMA (then EMEA) request. It was an open label comparison of rosiglitazone added to metformin (n=1117) or a sulfonylurea (n=1103), for a total n of 2220, with the combination of metformin plus a sulfonylurea (n=2227). Other drugs could be added to gain adequate HbA1c control. The planned endpoint was time to first occurrence of CV hospitalization or CV death. Deaths and possible events were identified by a CRO, Quintiles, from adverse event reporting or direct questioning of participants, and sent to a blinded adjudication committee. The study was open-label because of different insulin programs that could be used in the event of poor control in each group. Although the events reviewed by the blinded adjudication committee are not the major concern, there is a legitimate concern about

whether the unblinded referral process could have been biased by awareness of treatment assignment. This cannot yet be resolved fully but findings on CV mortality, and particularly all-cause mortality, would not be materially influenced by such biases, especially for the on-therapy population (or on-therapy plus 30-60 days), which I believe is generally the best analysis in a safety setting.

a. Reported results (without further adjudication), using ITT analysis:

First Event	Rosiglitazone	Control	HR (CI)
CV Death or Hosp'n	321 (14.5)	323 (14.5)	0.99 (0.85-1.16)
CV Hosp'n	288 (13)	284 (12.8)	
CV Death	33 (1.5)	39 (1.8)	
Total Events			
CV Death	60 (2.7)	71 (3.2)	0.84 (0.59-1.18)
CV Hosp'n	483 (21.8)	490 (22)	
All cause mortality	136 (6.1%)	157 (7.0)	0.86 (0.68-1.08)

I note the upper bound for the protocol-specified endpoint was 1.16 (i.e., very tight), but given the meta-analysis that stimulated our interest in heart attacks and CV death and the well-established ability of rosiglitazone to cause heart failure and consequent hospitalization, the RECORD planned study endpoint is not our major interest. Rather, we have a major interest in MACE (CV death, NFMI and NF stroke).

In general, use of an ITT analysis with many patients no longer on randomized treatment in a setting where demonstration of no difference is of interest tends to bias toward the desired finding of "no difference," and I believe the preferred analysis is on-treatment, or perhaps on-treatment plus 30-60 days (to capture anyone dropped because he or she was doing badly), but the ITT analysis also needs to be considered.

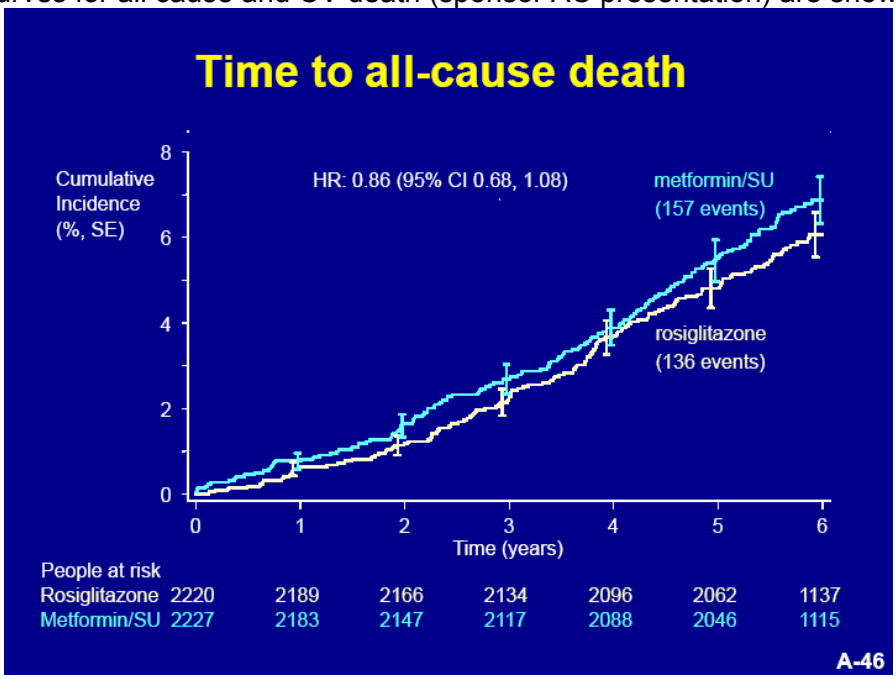
ITT Results for MACE and components, and all cause death

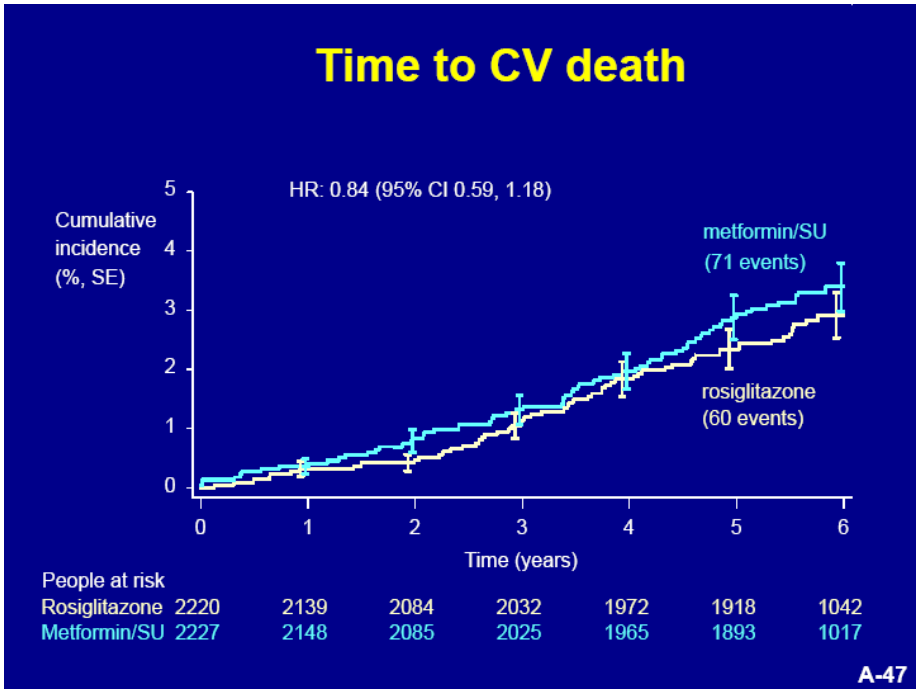
	Rosiglitazone	Control	HR (CI)
All cause death	136	157	0.86 (0.68-1.08)
CV Death	60	71	0.84 (0.59-1.18)
AMI (fatal & NF)	64	56	1.14 (0.8-1.63)
Stroke (fatal & NF)	46	63	0.72 (0.49-1.06)
CV death, MI, Stroke (MACE)	154	165	0.93 (0.74-1.15)

The all cause death, CV death, and MACE results can be examined readily, but assessing NFMI and NF stroke is more difficult because these rates were not presented separately, but were combined with fatal events. The idea of combining fatal and non-fatal MI and stroke is a poor one, in my view, as many CV deaths are not well-characterized with respect to cause (in fact, about half of the CV deaths are "unattributed"). That noted, however, only 7 rosi and 10 control CV deaths are attributed to AMI, so that subtracting them will leave 57 rosi and 46 control NFMI's, not very different from the fatal and NF numbers. All in all, these are very reassuring results with respect to mortality, and they show nothing like the 50% or so increase in AMI reported in the meta-analysis (but see below for concerns about this analysis related to the unblinded nature of the trial). There is, once again, a reduction in stroke. [I also note an additional "finding" that to date has elicited no comment. The published results show a marked reduction in pancreatic cancer, from 13 to 2 (p=0.0074), in rosiglitazone-treated patients. This is of course, either 1) another example of how, if you look at enough endpoints you will surely find something, or 2) a spectacular effect on one of our major tumors. One can only imagine the discussion of this "risk" had it favored the control treatment. At a minimum, these cases deserve a close look.]

(1) Mortality Results - ITT

The K-M curves for all cause and CV death (sponsor AC presentation) are shown below:





It should be noted that over the first 2-3 years, a time when most patients are still in the trial and accounted for (even if no longer taking drug), there is no suggestion of an adverse effect on mortality in the ITT analysis. Any concerns about follow up, especially regarding survival status, as expressed by Dr. Marciniak, should be minimal here.

Moreover, overall follow up for vital status appears to be quite good (Unger review of June 15, 2010), totaling 97.3% for rosiglitazone and 96.9% for control, i.e., all but 127 of the 4447 patients in RECORD, and there is clearly no excessive loss in the rosiglitazone group. As discussed by Dr. Unger, the analysis does depend on the sponsor's determination of the vital status of 394 people said to be alive. Dr. Marciniak has expressed concern about the reliability of these determinations. This can, of course, be checked, and the basis for determination of vital status verified. But I note again that over the first several years of the 5 year trial, the time when problems emerged in the meta-analysis, there was good and equivalent follow up in the two groups, and no suggestion of any excess mortality. I therefore conclude, as Dr. Unger did, that for overall and CV mortality, there is a strong finding of no adverse effect (actually a trend toward a favorable one). The determination by the adjudication committee of whether a death was CV or not has not been challenged in any major way (although one can always find specific cases to debate), so that whether the deaths need to be readjudicated seems open to question. Given the nature of public discussion of RECORD, however, it might be reasonable to do this, even if it is not really necessary, and even though total mortality is itself reassuring and favors rosiglitazone.

(2) Non-fatal event results (particularly AMI) – ITT
The critical question for the non-fatal events is whether there could have been biased referral, i.e., under-referral of the hospitalization events for adjudication in the rosiglitazone group. Dr. Marciniak found 8 rosiglitazone cases he thought should have been referred that were not referred, vs. no such control cases. A possible referral bias is surely a real concern in an open-label study and the 8 vs. 0 finding proved to have a

considerable effect on the advisory committee, which did not give RECORD much weight. In fact, Dr. Unger has now found similar "non-referral cases" in control patients (I note Dr. Marciniak does not think they meet the definition of possible CV events, but DSI did not agree with all of Dr. Marciniak's 8 referable cases. This is a debate for a later time). The question of possible referral bias clearly needs further evaluation. The best protection against such a bias, as Dr. Unger notes in his June 15, 2010 review, would have been a very broad referral requirement, essentially adjudicating any hospitalization. At this stage the only real remedy is a full readjudication.

Discussion of the "referral problem" at the AC meeting also contributed, I believe, to an impression of general sloppiness in the conduct of RECORD, but that impression is not supported by DSI's evaluation, in my view. DSI (helped by Dr. Khin U of the DCaRP) inspected many of the cases of "non-referral" (review of June 11, 2010) at GSK and Quintiles, finding some cases that could have merited transmission to the adjudication committee, but these were few and in most cases Dr. U thought the protocol requirements for transmission had been followed (See Appendix 1 of Dr. U's June 11 review). He did note, however, some very delayed transmissions to the adjudication committee, a troubling finding given the purpose of the study. Dr. Liebenhaut's presentation to the AC of DSI's findings did not identify problems that would suggest that the RECORD data were unreliable, although she noted the limitations of any on- site inspections.

Apart from the referral problem, Dr. Marciniak was not satisfied with the AMI criteria and recalculated the results for AMI based on his assessments, finding a somewhat higher risk than reported (but still not close to the meta-analysis result). I believe we must treat this as a "sensitivity analysis," not a revised result, as he was not blinded and used new AMI criteria, so that this approach can not be considered a valid readjudication. To evaluate the AMI finding properly we will need to adjudicate essentially all hospitalizations. We should do this because, although RECORD (together with ADOPT and DREAM) greatly weakens (really, essentially eliminates) the meta-analysis mortality finding, an increase in non-fatal AMI, even if not accompanied by death, would remain a concern.

b. As treated, on therapy

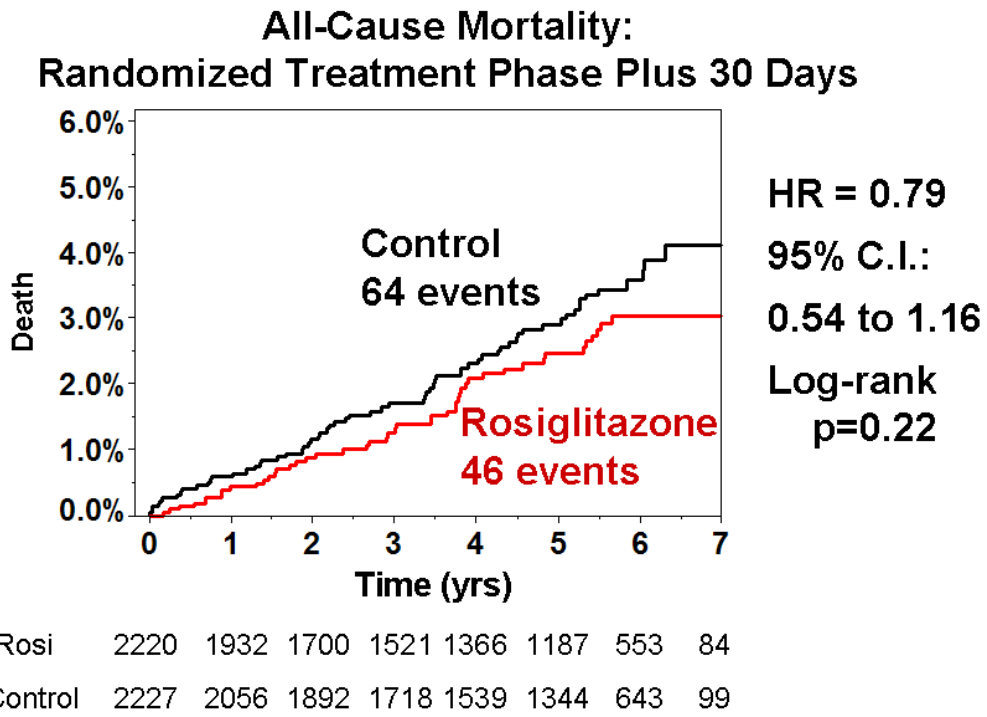
As noted above, in a safety evaluation, there is reason to consider "on therapy" results, as adverse effects should diminish once a drug is stopped. There may be reason to look at ITT as well, notably because of Dr. Marciniak's concern that patients might, especially in an unblinded study, be dropped when doing badly in anticipation of an event. A plausible possibility, e.g., is that exacerbated CHF might lead to discontinuation and that such discontinued patients might be at increased risk of death.

In any case, the sponsor's per protocol analysis, presented in Dr. Mahoney's June 9, 2010 review, p 50, shows:

Endpoint	Rosiglitazone	Control	HR (CI)
All-cause death	29 (1.3)	46 (2.1)	0.69 (0.44, 1.11)
CV death	23 (1.0)	34 (1.5)	0.75 (0.44, 1.27)
CV death, MI or stroke ("MACE")	94 (4.2)	117 (5.3)	0.89 (0.68, 1.17)
Myocardial infarction (fatal or nonfatal)	47 (2.1)	44 (2.0)	1.18 (0.78, 1.78)
Stroke (fatal or nonfatal)	32 (1.4)	51 (2.3)	0.69 (0.45, 1.08)

Note that this is "extreme per protocol," counting only patients still on randomized treatment without any added therapy to gain glucose control. It has many fewer events than other analyses but does address the earlier part of the study. All in all, results are similar to the ITT results shown above.

Another analysis, perhaps preferable because it should capture any patients leaving the study in anticipation of a bad outcome, would be on-therapy plus 30 days. Dr. Unger presented this analysis (confirmed by Dr. David Hoberman) to the AC and his K-M curve is shown below. Again, results are similar to the ITT and per protocol analyses.



RECORD has its limitations, mainly lack of blinding, but its mortality data appear credible and are completely at odds with the meta-analytic results, which show a near 50% increase in CV death. In RECORD, point estimates for OR for total and CV mortality are well below 1.0 and upper bounds for all-cause and CV death, stoke, and MACE are all below 1.2. Only AMI has an OR point estimate >1.0 (1.14), with an upper bound of 1.6.

It is also important to recognize that RECORD had far more overall and CV fatalities (all cause deaths 110 in the randomized plus 30 days analysis, and 293 in the sponsor's ITT analysis) than the meta-analysis (46 all cause fatalities in FDA's meta-analysis), so that these neutral or slightly favorable results are powerful findings against the adverse mortality effect seen in the meta-analysis.

The lack of blinding in RECORD has received extensive comment. We have good and obvious reasons for concern about blinding in any study where endpoints are subjective, and there are less obvious concerns as well, such as differential use of other treatments, different levels of effort to retain patients in the study, etc. ITT analyses may help with the retention issue, but these analyses are not optimal for safety studies or NI studies more generally. As noted earlier, one protection in RECORD would have been to forward essentially all hospitalizations for adjudication any reanalysis should consider all hospitalizations.

It should be appreciated that unblinded studies with MACE endpoints are fairly common, especially in device and surgical trials, but in others as well. The GISSI study of streptokinase and the GUSTO study comparing TPA regimens and SK were open-label (although the primary endpoint in those studies was survival, perhaps less of a problem), but a recent comparison of angioplasty and stenting for carotid stenosis (endpoint MACE) [Brott, et al, stenting vs. endarterectomy for treatment of carotid artery stenosis. NEJM 2010; 363:11-23] was open and used adjudication procedures that sound a lot like RECORD. We know, of course, that many oncologic RCTs are open-label for fairly obvious reasons, even where the endpoint is subjective (PFS), not just mortality. It is possible, of course, that the whole matter needs a re-look, but RECORD is not so exceptional.

4. BARI 2D

BARI 2D was not a randomized comparison of rosiglitazone with other treatments. Rather, it was a comparison of insulin sensitization (IS) approaches (metformin, glitazones) with insulin provision (IP) approaches (insulin, sulfonylureas, or other insulin secretion stimulators). About 55% of patients in the sensitization group got rosiglitazone vs. 3% of patients in the insulin provision group. Assignment to rosiglitazone was not randomized, limiting the interpretability of the study, but two analyses are of interest nonetheless. First, the overall neutral or slightly favorable result of the IS (containing rosiglitazone) group vs. IP is informative, suggesting no adverse effect of rosiglitazone if one assumes a neutral or favorable effect on CV endpoints of the comparators (insulin, sulfonylureas, and secretion stimulators) and no substantial favorable effect of metformin. The IS vs. IP showed (Brooks Presentation before Advisory Committee) the following results:

	K-M Est'd 5 Year Rate		Cox Prop Hazard	
	IS	IP	RR (CI)	P
	n = 1183	n = 1185		
Death	11.8%	12.1%	0.98 (0.79-1.23)	0.89
MI	12.2%	13.6%	0.86 (0.08-1.09)	0.21
Stroke	2.5%	3.7%	0.72 (0.44-1.16)	0.18
Death, MI, Stroke	22.3%	24.6%	0.88 (0.74-1.04)	0.13
CHF (in baseline CHF)	17.7%	13.5%	1.34 (1.07-1.68)	0.011

Obviously, interpretation is complex, but the other IS treatments (about 8% pioglitazone, the rest metformin) are likely, based on existing data, to be more or less neutral, and do not appear beneficial enough to overcome a substantial adverse effect of rosiglitazone. Given that, if the IP treatments are not adverse, it seems clear that rosiglitazone, given to more than half the patients, did not have an adverse effect on endpoints. The credibility of these results is enhanced by the finding of the anticipated adverse effect of rosiglitazone on CHF.

The study was also analyzed as rosiglitazone vs. no TZD, taking patients from both groups (i.e., not a randomized comparison). This analysis found an advantage for rosiglitazone.

	Rate per 100 patient-years			
Outcome	Rosiglitazone	No T2D	RR	P
Death	1.88	2.56	0.77	0.08
MI	2.16	3.16	0.76	0.06
Stroke	0.28	0.77	0.37	0.008
Death, MI, Stroke	3.79	5.81	0.71	0.002

It must be emphasized that this latter analysis needs cautious treatment, as it is not a randomized comparison and pools data from the 2 randomized groups, etc, giving it distinctly epidemiologic qualities, but there is certainly no hint of any adverse direction.

5. Overall Conclusions from Large Studies

We will need to review at least the non-fatal events in RECORD before reaching a complete conclusion, but the overall results of the larger trials are very reassuring with respect to any mortality effect of rosiglitazone – there is in fact no suggestion of such an effect in any of the 4 trials, a result completely at odds with the strong trend seen in the meta-analysis, raising major doubt about the validity of that finding. There is, however, a reason for our focus on MACE and not solely survival. All 3 components are of interest (although one would generally consider death and stroke more important) and an

adverse effect on heart attacks alone would be important. Re-analysis of RECORD therefore seems very much in order, to see whether in fact RECORD is as reassuring as its reported results suggest.

There have been suggestions that the OR > 1 (1.14) for fatal and NFMI seen in RECORD, with the OR upper bound of 1.63, is not "incompatible" with FDA's updated meta-analytic results (NFMI OR point estimate of 1.80, with upper bound of 3.25) but I disagree. Whether they overlap at some CI margin is not really the point. The meta-analytic hypothesis is of a "significant" and substantial (an 80% increase by point estimate) effect on MI, with a very unnerving MACE and mortality "lean." The results of the large studies appear entirely incompatible with any mortality effect, and RECORD, if verified, shows at worst a very modest effect on AMI and a favorable trend on MACE. The results of the meta-analysis and the larger individual studies are a world apart.

III. Meta- analysis and large single trial of pioglitazone.

The meta-analysis of pioglitazone has stimulated a variety of analyses and sub-analyses (trials vs. placebo, trials vs. active, trials of varying duration), but as is usually the case, it is not clear what to make of them. Overall, the pioglitazone meta-analysis raises far fewer "red flags" than the meta-analysis of rosiglitazone.

The results from the A.C. presentation are:

	Pio	***Control***	***Stratified Exact OR***
	N=6132 n(%)	*N=5642 n(%)*	*(95% CI)*
MACE	54 (0.9)	63 (1.1)	0.83 (0.56-1.21)
CV Death	22 (0.4)	18 (0.3)	1.18 (0.60-2.34)
NFMI	31 (0.5)	33 (0.6)	0.91 (0.53-1.53)
NF Stroke	10 (0.2)	16 (0.3)	0.61 (0.24-1.43)
All Cause Death	31 (0.5)	28 (0.5)	1.06 (0.61-1.85)

The rosiglitazone and pioglitazone meta-analyses differed in a number of ways. Unlike the largely short (69% of patients in trials $\leq$ 6 months) trials of rosiglitazone, which is where essentially all of the findings arose, the pioglitazone trials were generally longer (only 47% of patients in trials $\leq$ 6 months). The K-M curve shown by Dr. McEvoy at the AC (slide No 11), however, shows no suggestion of early adverse effect on MACE. There were also differences in control groups (placebo vs. comparator). To our best knowledge, however, none of the control treatments have known MACE effects, so I doubt these differences were important.

The pioglitazone meta-analysis does not, overall, suggest an effect on NFMI or mortality, as the rosiglitazone meta-analysis did. This is <u>not</u> a direct comparison, of course, and if there were some reason (other than that it is a true effect) for the rosiglitazone finding, it might not have been present for pioglitazone. Nonetheless, whatever the explanation, we have an <u>absence</u> of the troublesome rosiglitazone finding in the pioglitazone data. At the same time, and pertinent to the epidemiologic data, there is no real evidence here of any advantage over other treatments. That is, with respect to CV mortality, NFMI, it looks like the other drugs. Only for stroke, with few events, does it lean toward an advantage, and this seems well "rebutted" by the PROacitve trial (below).

The large (n = 5210) 3 year PROactive study compared pioglitazone to placebo, each added to background, and focused on CV risk in patients with a history of microvascular disease. Dr. Parks summarizes the 6 month results in her August 19 memo to Dr. Rosebraugh and Jenkins:

	Pio	***Placebo***	***HR***
Event	*N=2605 n(%)*	*N=2133 n(%)*	
CV Mortality	20 (0.8)	27 (1.0)	0.8
All Cause Mortality	25 (1.0)	30 (1.1)	0.9
NFMI	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	1.3

Dr. Parks notes some suggestions of an adverse direction on NFMI and stroke, and indeed there is a "lean," although CV mortality leans favorably. Later data on Proactive actually border on a favorable result, as shown in slide 13 of the Dr. Parks' AC presentation. PROACTIVE failed to show an effect on its primary endpoint (a composite of all cause mortality, NFMI, NF stroke, ACS, cardiac intervention, major leg amputation, or need for leg bypass), but some of the secondary endpoints looked reasonably good.

Endpoint	***Add on Pio***	***Add on Placebo***	***HR (CI)***
"MACE"(total, not CV, Mortality)	301 (11.0%)	358 (13.6%)	0.84 (0.72-0.98) p=0.0277
CV Mortality	127 (4.9%)	136 (5.2%)	0.94 (0.74-1.20) p=0.6163

I believe any way you look at all of the pioglitazone data they lack any real basis for concern about increased CV risk. It cannot be emphasized too strongly that they do not represent a comparison with rosiglitazone, but they allow one to say that an apparent alternative to rosiglitazone is "concern- free" with respect to MACE. This means that what still remains critical is the strength of the rosiglitazone signal. As noted above, since the first meta-analysis, that signal has weakened, weakened to the point of absence for mortality (and it was never there for stroke) and weakened considerably for NFMI, but the NFMI conclusion will depend on RECORD re-adjudication.

IV. Epidemiologic Data

There seems little doubt that the Advisory Committee was impressed by one particular aspect of what seemed to be epidemiologic consistency: the apparent advantage of pioglitazone over rosiglitazone for important endpoints, notably CV mortality, stroke, and heart failure, in 3 epidemiologic studies, including Dr, Graham's CMS study. A fourth study, the WellPoint study, recently published [Wertz, et al. Qual Cardiovascular Circulation Outcomes. 2010; 3:538-45], was minimally presented at the AC meeting by a presenter who did not know much about the study, and the presentation had little impact. That study has now been published and as presented it clearly does not support any advantage for pioglitazone. Our recent detailed review of it, however, raises important questions about it.

I am in no position to assess the quality of the various epidemiologic studies, but will consider what these studies can tell us about the concerns that have arisen about rosiglitazone. Epidemiologists are well aware of the uncertain meaning of studies reporting very small differences between treatments, i.e. odds ratios of less than 1.5, which is what all of these studies report. Moreover, it is critical to note that the rosiglitazone vs. pioglitazone findings (which have received the most attention) fail to confirm the strongest finding of the meta-analysis, the 80% increase (i.e., OR=1.8) for MFMIs, an effect large enough to allow us to hope that an epidemiologic study might have detected it. The studies did not defect that effect. Instead, they have raised a set of wholly new concerns.

A. What are the epidemiologic findings.

1. Rosiglitazone vs. Other Antidiabetics

Remembering that the hypothesis of interest was generated by a meta-analytic comparison of rosiglitazone with other drugs (drugs not known to have adverse CV effects) and placebo, the most obvious studies of interest are comparisons of rosiglitazone with other drugs (not including pioglitazone for the moment). Dr. Gelperin has analyzed these in great detail and displayed overall results at the AC meeting. In her slides and in her detailed review it is clear that for AMI and all cause mortality, rosiglitazone does not appear worse than other antidiabetic agents (Gelperin AC slides 8,10); that is, the meta-analytic finding is not supported by the epidemiologic studies. Of some interest, however, is that for CHF, rosiglitazone is considerably inferior (slide 9) to other drugs, as we would expect it to be, giving the studies some credibility; i.e., they WERE able to detect a known effect of rosiglitazone. These studies show somewhat more favorable results for pioglitazone, but they are directionally similar. These epidemiologic studies do not support the meta-analytic findings.

2. Rosiglitazone vs. Pioglitazone

It is the epi findings comparing rosiglitazone and pioglitazone (note, no controlled trial data on this) that raised a new issue: whether for critical endpoints pioglitazone was superior to rosiglitazone. Three studies were described: Wickelmayor, Juurlink, and Graham. The results (Graham AC slide 26) were

	Wickelmeyer *n=28,301* *2000-2005*	***Juurlink*** *n=39,736* *2002-2008*	***Graham*** *n=227,571* *2006-2009*
AMI	1.08 (0.93-1.25)	1.05 (0.9-1.23)	1.06 (0.96-1.18)
Stroke	1.07 (0.93-1.23)	------	1.27 (1.12-1.45)
Heart Failure	1.13 (1.01-1.26)	1.30 (1.15-1.45)	1.25 (1.16-1.34)
All Cause Death	1.15 (1.05-1.26)	1.16 (1.02-1.33)	1.14 (1.05-1.24)

Dr. Gelperin described these results (slide 26) as consistent with FDA's meta-analyses of pioglitazone and rosiglitazone, but that does not seem correct. FDA's meta-analysis of rosiglitazone has, as by far its strongest finding, an increase in AMI. But not one of the 3 epidemiologic studies finds a significant excess of AMI for rosiglitazone. That is, to say the least, a failure to support the "going in" hypothesis. The stroke finding, the strongest finding of the Graham study, also does not seem compatible with prior experience, and is not consistently present in the epidemiology studies. Pioglitazone looks good on stroke in its meta-analysis but, as noted above, in PROactive, pioglitazone was not

favored early for stroke. One could say the all cause mortality data for the two meta-analyses are similar to the epi studies but, as noted, the data from RECORD and the other large studies do not show an adverse effect of rosiglitazone on mortality and thus do not suggest that pioglitazone would have an advantage over rosiglitazone for mortality; yet in the Graham and other epi studies they do. This is, I believe, an entirely new observation/hypothesis. For the one endpoint where an advantage for pioglitazone might have been expected based on prior data, NFMI, there is none.

Dr. Graham has suggested that in his trial in the Medicare population, the absence of an effect on AMI can be explained by increased AMI mortality in the elderly Medicare population (average age 74.4) he studied, in effect converting all AMIs to deaths.

This could be examined further, but I looked at rates of fatal and non-fatal MI in 2 studies in elderly populations: STOP (Swedish Trial in Old Patients with Hypertension), with patients aged 70-84 and the Syst-Eur Study of isolated systolic HT in older patients (all > 60, mean age 70). In both studies about 25% of AMI's were fatal.

I. STOP

	Placebo	***Active***
n	*815*	*812*
First Events		
All MI	28	25
Fatal MI	8	6
NFMI	20	19

II. Syst.

	Placebo	***Active***
n	*2397*	*2398*
All MI	45	33
Fatal MI	14	7
NFMI	31	26

Increased AMI mortality in people over 65 thus did not explain the absence of an AMI finding in Dr. Graham's study. It should be noted also that the rate of non-fatal heart attacks increases with age.

B. How credible would an epidemiologic finding be in this case.

Although there is great enthusiasm these days about the possibility that observational data will enable us to gain comparative data rapidly and relatively inexpensively with no real need to do large, costly, and difficult RCTs, it has long been recognized that when epi studies are looking at OR's < 2 (or less than 1.5 if you're very optimistic) they are of uncertain meaning. This recognition is not confined to clinical trialists but is shared by most epidemiologists as well, although there is a persistent hope that better methods will enhance the ability of the studies to defect small effects. At a conference on Comparative Effectiveness Research some months ago at the U of Pa, Dr. Brian Strom, a well-known epidemiologist, suggested that epi findings of odds ratios < 2 were not credible as comparative evidence (that is not to say they could not generate hypotheses).

One surely hopes that better methods will improve on this, but past history is worrisome:

- One of the very best drug epidemiologists, Hershel Jick, found, in three studies, that reserpine increased the risk of breast cancer by > 2-fold (close to 3-fold), a finding that was later discredited.
- Hormone replacement therapy was repeatedly (although not invariably) shown in epidemiologic studies to reduce CV events in post-menopausal women, a plausible outcome that was well- accepted until the Women's Health Initiative (WHI) study found the opposite to be true.
- A series of epidemiologic studies in the mid 1990's found that calcium channel blockers (CCB's) caused heart attacks, death, GI bleeding, all cancer, breast cancer, and suicide. None of these findings is now considered credible but they had a significant effect on published recommendations for blood pressure treatment, which suggested some reservations about early use of CCBs. It is of interest that a recent trial (ACCOMPLISH) comparing amlodipine (a CCB) 5-10 mg with hydrochlorothiazide 12.5-25 mg, an accepted standard if ever there was one, each added to benazapril, found a marked, highly statistically significant advantage for amlodipine on CV events, reducing them by about 20% compared to hydrochlorothiazide. Amlodipine could well be a drug that needs to be used more, and its use was surely limited by the spurious epidemiologic observations on CCBs.

Epidemiologists are appropriately cautious about small OR's. A 2005 study of the risk of AMI and sudden cardiac death in patients treated with NSAIDs found that the only NSAID with a risk of AMI during current use that was lower than the risk during remote NSAID use was celecoxib. Compared to celecoxib, use of ibuprofen, naproxen, and a mix of other NSAIDs had ORs of 1.26 (ibuprofen), 1.36 (naproxen), or 1.35 (other NSAIDs) for AMI, all statistically significant. The paper was by Graham, et al, including Wayne Ray, and I am quite certain it was well done. It was not, however, apparently believed by its author, who, in another published paper, advised anyone needing an NSAID to use naproxen first. There are, of course, other data to consider, but the advice by the author of what seemed to be a highly credible paper was to ignore it, advice that I am not necessarily disputing, but rather noticing.

V. Conclusions:

Since 2007 we have gained a modest amount of additional information to add to the original meta-analysis that raised the issue of rosiglitazone's cardiovascular toxicity. The expanded meta-analysis, which overlaps considerably with the studies in the Nissen meta-analysis, leaves the observed increase in AMI intact; it weakens the observed increase in mortality, but an adverse trend persists. RECORD, as reported, shows a much smaller effect of rosiglitazone on AMI (but this finding needs further assessment), but shows no effect at all on CV or total mortality. Although RECORD needs further evaluation with respect to AMIs, its mortality findings appear solid and, together with ADOPT, DREAM and BARI 2D, it weakens the evidence of increased CV mortality with rosiglitazone to the point where such an effect does not seem at all credible. Again, as noted above, the RECORD on therapy CV deaths total 57, well more than the 32 in small trials in the Nissen analysis. The as treated and ITT analyses have far more. The sum of the RECORD, ADOPT and DREAM on therapy

CV deaths appears to be almost 3 times the number in the Nissen small trials. There has never been any evidence of an increased stroke rate with rosiglitazone.

New pioglitazone data do not suggest any evidence of an adverse effect of that drug on CV outcomes, leaving us with one drug that might have an adverse effect (increased NFMI but no effect on stroke or mortality) and another member of the same pharmacologic class that does not, certainly an issue to be considered.

The epi data, in my view do not help very much. Apart from the skepticism that should attend reports of ORs in the neighborhood of 1.15, neither comparisons with various anti-diabetic drugs nor comparisons with pioglitazone support the one finding in the meta-analysis that remains potentially real, an increased rate of AMIs. Novel findings, such as increased stroke, are not consistently seen. The mortality observation in the epi studies, with RECORD and other large studies having shown no such effect of rosiglitazone, now seems to represent at best a new hypothesis, unsupported by any other data: superiority of pioglitazone to rosiglitazone on CV mortality and heart failure mortality. This is, in effect, a new effectiveness superiority claim, a claim we would never base on an epidemiologic finding, even a replicated one, but one that could very well deserve examination in a well-controlled study, such as TIDE. The impassioned views presented on TIDE, that the study was unethical, arose from the belief that issue was settled, i.e., that it is already known that pioglitazone is superior with respect to critical CV outcomes, notably mortality and stroke, to rosiglitazone. For the reasons given above, I believe we have no basis for such a conclusion. I should emphasize that as suggested by the IOM presentation at the AC meeting, if we did have clear evidence of a mortality (or even stroke) advantage of pioglitazone over rosiglitazone, I would agree that TIDE could not be conducted. But we do not have that evidence.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
09/10/2010

DATE: September 2, 2010

TO: Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

FROM: John K. Jenkins, M.D.
Director
Office of New Drugs

SUBJECT: Recommendations for regulatory actions – rosiglitazone

This memorandum serves to document my evaluation of the available data and recommendations for regulatory actions for all rosiglitazone containing drug products. Please also refer to the separate memoranda from Drs. Parks and Rosebraugh dated August 19 and 23, 2010, respectively, in which they outline their conclusions and recommendations.

Background

The question of whether rosiglitazone increases the risk of ischemic cardiovascular events in patients with Type 2 diabetes mellitus has been the subject of intense review and analysis within and outside FDA since GlaxoSmithKline (GSK), the manufacturer of rosiglitazone, submitted the results of a meta-analysis of controlled clinical trials to the FDA in August 2006. In July 2007 the FDA presented the available data[1] to a joint public meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees.

After hearing multiple presentations from GSK, FDA staff, and the public and considering the available data, the committee members voted 20 "yes" and 3 "no" in response to the question "do the available data *suggest* a conclusion that Avandia increases cardiac ischemic risk in Type 2 diabetes mellitus?"[2] In response to the question "does the overall risk-benefit profile of Avandia support its continued marketing in the United States?" the committee members voted 22 "yes" and 1 "no".

It is important in evaluating these votes, which some inside and outside FDA have suggested are internally inconsistent and illogical, to understand that while nearly all committee members thought the available data raised a concern about an increased risk of

[1] The data presented included the GSK meta-analysis of 42 controlled clinical trials, an FDA meta-analysis of the same 42 controlled clinical trials, a meta-analysis of 42 controlled clinical trials (not the identical trials in the GSK and FDA meta-analysis) conducted by Nissen and Wolski published in the NEJM, the results of several long-term controlled clinical trials of rosiglitazone (DREAM, ADOPT, interim results of RECORD), the results of a long-term controlled clinical trial of pioglitazone (PROactive), and a meta-analysis of 19 controlled clinical trials conducted by Takeda, the manufacturer of pioglitazone.

[2] The question as originally worded by FDA asked the committee to opine on whether "the available data *support* a conclusion that Avandia increases cardiac ischemic risk", however, committee members asked that the wording of the question be changed to substitute "suggest" for "support."

cardiac ischemic events in patients treated with rosiglitazone they did not find the results persuasive enough to offset the demonstrated benefits of rosiglitazone as a treatment for Type 2 diabetes or to recommend that it not be marketed as a prescription drug. The issue of the persuasiveness of the available data suggesting an increased risk of cardiac ischemic events and how those data should influence FDA's regulatory decisions and actions for rosiglitazone remain at the core of our decisions today.

Following the advisory committee meeting there were further discussions within CDER regarding the appropriate interpretation of the data and regulatory actions, the issue was presented for review at a meeting of the CDER Drug Safety Board, staff in OND and OSE reached differing conclusions on the recommended regulatory actions, and, after considering the available data and various staff recommendations, a decision was made by Dr. Woodcock, the Acting Center Director, in October 2007. Dr. Woodcock concluded that:

- rosiglitazone containing products should not be withdrawn from the U.S. market,
- the package insert should be revised to include a boxed warning regarding the cardiac ischemic risk,
- a Medication Guide should be developed to inform patients of the risk, and
- GSK should be required to initiate a controlled clinical trial to compare rosiglitazone to pioglitazone.

CDER implemented these decisions as follows:

- the package insert was updated in November 2007 to include a boxed warning that included the findings from the meta-analysis regarding an increased risk of myocardial ischemic events such as angina and myocardial infarction as well as a statement that three long-term controlled clinical trials (DREAM, ADOPT, and interim results of RECORD) "have not confirmed or excluded this risk." The boxed warning statement concludes that "In their entirety, the available data on the risk of myocardial ischemia are inconclusive."
- the Warnings and Precautions section of the package insert was updated to recommend against co-administration of rosiglitazone with insulin or nitrates based on the subgroup analyses with the highest risk from the FDA meta-analysis.
- in May 2008 GSK was required under FDA's new authorities provided by FDAAA to conduct a long-term controlled clinical trial to assess cardiovascular outcomes of patients treated with rosiglitazone, pioglitazone, and placebo (in addition to other anti-diabetic background treatment). The protocol for this trial (i.e., the TIDE trial) was submitted to FDA in July 2008 and enrollment of patients began in February 2009.

In October 2008 Drs. Graham and Gelperin of OSE completed a review of the available data, including newly published observational trials, and concluded that rosiglitazone should be withdrawn from the market. While awaiting a determination from Dr. Dal Pan, the Director of OSE, on whether this new review included new data or arguments that should lead to a reconsideration of the Dr. Woodcock's October 2007 decision on

rosiglitazone, staff in OND continued to work with the sponsor to ensure timely initiation of the TIDE trial and submission of the final results of the RECORD trial.

In August 2009 GSK submitted the final results of the RECORD trial for FDA review. GSK also submitted an updated meta-analysis that included 10 additional controlled clinical trials that were not included in the original 2006 GSK or 2007 FDA meta-analysis. Based on these new data, GSK requested that the boxed warning for cardiac ischemic risk be removed from the package insert. OND immediately convened a review team to review these new data and initiated plans to convene a public advisory committee to revisit the cardiovascular safety of rosiglitazone in the spring of 2010.

In October 2009 Dr. Dal Pan completed a memorandum in which he concluded, as he did in 2007, that rosiglitazone should be withdrawn from the market. Following internal discussions between Drs. Dal Pan and Woodcock and myself regarding the path forward, in December 2009 Dr. Woodcock determined that OND and OSE should work together with other appropriate offices in CDER (e.g., the Office of Biostatistics) to rapidly evaluate the new data on the cardiovascular safety of rosiglitazone and present this for discussion at another public advisory committee meeting in the spring of 2010. Due to the amount of data that needed to be reviewed and the logistics involved in convening the second advisory committee meeting, the original goal of spring 2010 could not be achieved and a second joint meeting of the EMDAC and DSARM committees was held on July 13 and 14, 2010.

The July 2010 Advisory Committee

The background materials, agenda, questions, and transcripts of the July 2010 AC meeting are available on the FDA website.[3]

The detailed voting results from the second AC meeting are included in Dr. Parks' August 19, 2010, memorandum. The committee's discussion and voting on the proposed FDA questions was notable in that the committee members once again were uncomfortable with the wording of FDA's questions regarding the cardiovascular risk of rosiglitazone. In drafting the questions we intentionally chose to ask the questions about risk in definitive terms; i.e., "do you *find* that rosiglitazone increases the risk….." This was an effort on our part to avoid the ambiguity that arose after the first AC meeting when the committee members changed the wording of the question on risk from *"support"* to *"suggest,"* which has been widely and persistently misstated in the media and scientific journals as a more definitive determination of an increased risk.[4] Despite our encouragement that the committee vote on the questions as originally written, the committee changed the wording to "…these data are *sufficient to raise significant safety concerns* for ischemic CV events…." I interpret this change in wording to once again

[3]http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm

[4] For example, in the slides presented by Dr. Nissen at the July 2010 AC meeting the July 2007 committee's vote on the risk question was misstated as: "Advisory Committee voted 20-3 that rosiglitazone 'increases the risk of myocardial ischemia,' but 22-1 that benefits exceed risks."

reflect the committee members' discomfort with being able to reach definitive conclusions regarding the CV risk of rosiglitazone based on the available data.

In the actual voting, a majority of committee members found that the data were *sufficient* to raise significant safety concerns for ischemic CV events for rosiglitazone relative to non-TZD anti-diabetic agents and to pioglitazone, the other currently marketed thiazolidinedione. The vote was slightly stronger in favor of a *suggestion* of an adverse finding in comparison to pioglitazone than in comparison to non-TZD anti-diabetic agents. It is should be noted that 45% (for the non-TZD anti-diabetic comparison) and 36% (for the pioglitazone comparison) of committee members voted that the data either were not *sufficient* to support an increased CV ischemic risk or they were unable to make a finding based on the available data.

With regard to the question on whether the data were *sufficient* to raise significant safety concerns for mortality, a large majority of the committee voted no with regard to both comparisons. In fact, 97% (for the non-TZD comparison) and 79% (for the pioglitazone comparison) of the committee members voted that the data either were not *sufficient* to support an increased risk of mortality or they were unable to make a finding based on the available data.

When asked to vote on one of five possible regulatory actions they recommended the FDA pursue regarding rosiglitazone, there was no clear majority opinion. No members voted to allow continued marketing and removal of the boxed warning (as had been proposed by GSK in their August 2009 supplemental applications). Essentially equal numbers of committee members voted in favor of options that would allow continued marketing with no changes to the current labeling or changes that might contraindicate use in certain patients or make rosiglitazone "second line", allow continued marketing with additional label warnings and restrictions on use (e.g., restriction to prescribing to certain physicians under a REMS), or market withdrawal. Depending on one's perspective on this issue, the vote could be interpreted as a majority recommending continued marketing (20/33, 61%) or that the single option that received the most votes was market withdrawal (12/33, 36%).

Despite an impassioned presentation by Dr. Graham from OSE regarding his personal view that the TIDE trial was unethical, exploitative of study subjects, and should be stopped, the majority of the committee recommended that the TIDE trial be continued (19 yes, 11 no, 1 abstention, 1 member absent) if rosiglitazone remains on the U.S. market.[5] This suggests that the majority of committee members felt the available data are inconclusive, additional data are needed to evaluate the cardiovascular risk of rosiglitazone as compared to non-TZD anti-diabetic agents and pioglitazone, and that the TIDE trial is ethical.

Data Sources

[5] Note that a majority of committee members voted for a regulatory option that included continued marketing of rosiglitazone.

Data to evaluate the cardiovascular risk of rosiglitazone come from four main sources;

- meta-analyses of rosiglitazone controlled clinical trials,
- large, long-term rosiglitazone controlled clinical trials,
- observational studies of rosiglitazone compared to non-TZD anti-diabetic agents, and
- comparisons between rosiglitazone and pioglitazone from cross-study comparisons of separate meta-analyses, cross-study comparisons of large, long-term controlled trials, and observational studies that have compared the two drugs.

Detailed reviews of each of these data sources have been completed by FDA staff and were part of the background materials made available to the public as part of the recent AC meeting. I will briefly summarize here an overview of these data and their findings.

Meta-analyses of rosiglitazone controlled clinical trials

There have been numerous meta-analyses of rosiglitazone controlled clinical trials; however, I will focus on the updated meta-analysis that was completed by staff in the FDA Office of Biostatics for the 2010 AC meeting. The OB meta-analysis was based on patient level data, used rigorous statistical methodology, and importantly, was conducted by "neutral" parties in this debate, a fact that is not true of some of the other meta-analyses that have been conducted by GSK or vocal public advocates for the withdrawal of rosiglitazone (e.g., Nissen).

As has been true since the initial meta-analysis submitted by GSK to FDA in 2006, the 2010 OB meta-analysis found elevated odds ratios for important cardiovascular endpoints such as MACE, CV death, and MI in addition to the well recognized TZD class adverse effect of worsening CHF. While no statistical corrections were done for multiple comparisons, some of the endpoints achieved nominal statistical significance, and the point estimate for the odds ratio was consistently above 1.0 with the exception of stroke.[6] The OB reviewers also conducted a sensitivity analysis comparing the 2007 42-trial OB meta-analysis to their 2010 52-trial results.[7] The results of the two analyses were generally similar, although for some of the endpoints (e.g., mortality) the findings were less adverse for rosiglitazone in the 2010 analysis. The rosiglitazone meta-analysis findings remain worrisome from a safety perspective if in fact they represent the true risk of rosiglitazone in patients with Type 2 diabetes mellitus.

It is interesting that the results suggesting an increased risk for rosiglitazone were mainly driven by comparisons of rosiglitazone to placebo and were strongest in relatively short-term trials (e.g., $\leq$ 6 months). When analyzed based on trials in which rosiglitazone was compared to active comparators such as metformin or sulfonylurea, the adverse

[6] Refer to slide 26 of Dr. Callaghan's presentation to the July 2010 AC meeting.
[7] Refer to Table 1 in Dr. Rosebraugh's August 23, 2010, memorandum, which shows a comparison of the 2007 42-trial meta-analysis (updated to use the same methods used in 2010) and the 2010 52-trial meta-analysis.

cardiovascular finding was less marked overall, and actually favorable in comparison to metformin.[8] The adverse findings in short-term, placebo-controlled trials remain unexplained. Some have pointed to the fact that rosiglitazone causes an adverse shift in serum lipids (e.g., increases in LDL) to account for this finding. This explanation is not completely satisfactory for two reasons. First, in general, a beneficial effect of treatment with lipid-lowering drugs is not seen in controlled trials as early as the adverse findings seen in the short-term trials in the rosiglitazone meta-analysis.[9] Second, in long-term trials of rosiglitazone significant increases in CV risk have not been seen despite the persistence of an adverse lipid profile in those treated with rosiglitazone.

It is possible that there is some short-term adverse CV effect of rosiglitazone that is no longer active after longer-term use, but a mechanism for such a short-term effect has not been identified to date and it remains unclear why such an effect would not also be observed in comparison to other anti-diabetic agents.[10]

While the meta-analysis findings are worrisome, there are important limitations to the findings that raise doubt about how conclusive they can be considered for regulatory action, particularly a withdrawal recommendation. Some of these limitations have been outlined by other reviewers, including by the OB staff in their review and July 2010 AC presentations. Probably the most concerning in my mind is the relatively small magnitude of the increased risk (e.g., the point estimate for MACE is 1.44), the lack of statistical significance or borderline significance for the various endpoints (with no correction for multiple comparisons), the inconsistent direction of findings for MI and stroke, and the fact that the historical view of meta-analyses has been similar to that for observational studies, i.e., the observed hazard should be large and the p value very small in order to support conclusions, as opposed to hypotheses for further study.

I am not aware of any case in which results of a meta-analysis with results of the magnitude seen for the rosiglitazone controlled clinical trials have supported withdrawal of a drug. The only example I can identify where a meta-analysis of controlled clinical trials provided the data to support marketing withdrawal was Zelnorm (tegaserod). Zelnorm was indicated for the treatment of constipation-predominate irritable bowel

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[8] Refer to slide 28 in Dr. Callaghan's July 2010 AC presentation. Note that these subgroup analyses must be considered with caution, for example, the metformin comparison is based on only 613 patients out of the overall meta-analysis population of 16,995 subjects and the 95% CI are very wide.

[9] Note that most trials in the rosiglitazone meta-analysis were primarily designed as efficacy trials, which generally do not emphasize to the same extent treatment of co-morbid CV risk factors, such as increased lipids and hypertension, as occurs in planned CV outcome trials.

[10] Note that no currently approved drug for the treatment of diabetes has been demonstrated to reduce the risk of cardiovascular disease. In fact, the sulfonylurea class of drugs has long carried a bolded warning regarding a 2.5 fold increased risk of cardiovascular mortality that was seen in patients treated with tolbutamide versus diet alone in the UGDP trial. It is somewhat ironic that despite this finding sulfonylureas (generally newer agents for which we do not have long-term CV outcomes data) continue to be widely used today for the treatment of Type 2 diabetes mellitus and that some individuals who have called for the withdrawal of rosiglitazone have pointed to sulfonylureas as an available alternative. In the OB 2010 meta-analysis the point estimate for the comparison of rosiglitazone to sulfonylurea for MACE was 1.17, however the 95% confidence intervals were very wide and the number of patients in this subset analysis was less than 20% of the total included in the overall meta-analysis.

syndrome and was voluntarily withdrawn by the sponsor (at FDA's request) in 2007. The FDA request for market withdrawal was based on a meta-analysis of controlled clinical trials that showed an increased risk of heart attacks, strokes, and heart-related chest pain.[11] While the numbers of patients who suffered these adverse CV events on Zelnorm was small (0.01%), the rate of events seen in patients on placebo was many fold less (0.001%), depending on the analysis performed. While not directly comparable to the rosiglitazone case in several ways (e.g., indication, seriousness of the disease) this case, and other recent cases of small adverse findings in meta-analyses, point to a general FDA philosophy that views the results of meta-analyses with great caution. FDA often communicates results of meta-analyses to the public in Drug Safety Communications or requires their addition to a package insert to ensure informed decision-making by prescribers and patients, but only in the most extreme cases have meta-analyses supported withdrawal of a drug from the U.S. market.[12]

Large, long-term rosiglitazone controlled clinical trials

Around the same time that GSK submitted their rosiglitazone meta-analysis to FDA in 2006 the results of two large, long-term controlled clinical trials comparing rosiglitazone to placebo in pre-diabetics (DREAM) or to sulfonylurea or metformin (ADOPT) in patients with diabetes became available. Dr. Parks summarized the results of these trials in her AC presentation at the July 2010 meeting and they were discussed in greater detail at the 2007 AC meeting.[13] In short, neither of these studies supported a finding of a significant adverse effect of rosiglitazone on MACE, MI, or mortality.[14] These findings are somewhat reassuring despite the fact that the trials have weaknesses for estimating risk. Specifically, neither trial was designed as a CV outcomes trial and the background risk of CV events for patients enrolled in both trials was low, decreasing the power of the trials to detect differences if they were present.

Shortly before the 2007 AC meeting, an interim analysis of the RECORD trial was published. These data were discussed in detail at the 2007 AC meeting and probably served to reassure some members to the AC regarding the CV safety profile of

[11] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051284.htm

[12] Note that despite the multiple fold increase in risk seen for Zelnorm in the meta-analysis, some have questioned FDA's reliance on such small numbers of events to withdraw the only approved treatment for constipation-predominate irritable bowel syndrome. They note that while this disease is not generally life-threatening, it is very disabling to many patients and that other available (off-label) treatment options do not work for these patients. This highlights the fact that even large potential increases in risk of serious events may be tolerated by physicians and patients depending on their individual risk tolerance, the baseline risk of the patient involved, the absolute magnitude of the risk, the effect of the drug in individual patients, and the benefits and risks of available alternatives.

[13] Refer to slides 8-11 of Dr. Parks' July 2010 AC presentation.

[14] Note that I am focusing on the comparison of rosiglitazone to placebo in DREAM, which is most relevant to the signal seen in the meta-analysis, and not the comparison of rosiglitazone plus ramipril versus placebo plus ramipril where a non-significant increased risk of MACE and MI, but not mortality, was seen. To my knowledge this finding has not been explained and was not confirmed by sub-group analyses of ADOPT and the interim results of RECORD. The data from this comparison are included in the rosiglitazone package insert.

rosiglitazone since RECORD is the only long-term controlled clinical trial that was prospectively designed to assess CV outcomes of rosiglitazone.

RECORD was undertaken by GSK as a postmarketing commitment to the EMEA and FDA was not involved in its design or conduct.[15] The final results of RECORD were submitted to FDA by GSK in August 2009 and have been subjected to extensive review and audit by FDA staff.[16]

Interpretation of the RECORD trial has proven to be quite controversial, both within and outside FDA. The main area of contention relates to the fact that RECORD was an open-label trial and the protocol left considerable discretion to the study investigators in determining which adverse events to refer for adjudication by the blinded central adjudication committee. It should be noted that many CV outcomes trials have by necessity been open-label, so that design feature is not in-and-of itself a fatal flaw. In order to provide reliable results, an open-label trial requires a protocol that is very carefully designed to minimize the potential for bias (intentional and unintentional) and the protocol procedures must be rigorously adhered to by all participants. The concerns related to an open-label trial design are further heightened in the case of a non-inferiority trial, such as RECORD, since "sloppiness" in trial conduct tends to bias toward the null and a finding of non-inferiority. The hypothetical concerns about the reliability of the RECORD results were increased by the findings of Dr. Marciniak from DCRP, who in the course of his audit of the trial found cases that raised legitimate concerns about whether there was a bias favoring rosiglitazone in referral by investigators of adverse events to the adjudication committee.[17]

These legitimate concerns about the RECORD trial make it impossible for FDA to use the results as reported by GSK and the study investigators (and Dr. Marciniak) as a basis for a regulatory decision, with the possible exception of the findings on overall mortality. While I understand Dr. Marciniak's concerns about possible bias and under ascertainment of mortality, I agree with Dr. Unger that the RECORD mortality findings are probably

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[15] There have been many criticisms of the design and conduct of the RECORD trial and suggestion that the design does not meet FDA's current standards. Such statements are factually accurate, but do not outweigh the need to review RECORD carefully to learn what we can from this large trial.

[16] Refer to reviews and slides from the 2010 AC meeting from OND (DCRP, DMEP, ODE I), OB, and DSI staff.

[17] Dr. Marciniak conducted a limited audit of case report forms from the trial and noted 8 patients he considered should have been referred for adjudication, but were not. All 8 were on rosiglitazone. DSI evaluated these 8 cases as part of their audits of the RECORD trial and found that 7 of the 8 were handled according to the study protocol and there was no evidence of investigator misconduct. The DSI findings, do not, however, mean that referral bias was not operational in RECORD or that these cases would not have been referred for adjudication in a well designed trial. Subsequent to the July 2010 AC meeting, Dr. Unger reviewed a limited subset of CRFs from the RECORD trial and noted 3 patients he felt should have been referred for adjudication, but were not. All 3 were on placebo. Note that Dr. Marciniak also conducted a re-adjudication of the RECORD trial results and presented these new analyses in his review and AC presentation. This re-adjudication did not follow well recognized scientific principles for such efforts, and as such, the resulting analyses cannot be viewed as fairly representing the true outcomes of the RECORD trial. FDA would not accept such analyses from a sponsor if conducted in this manner and cannot base our regulatory decisions on Dr. Marciniak's results.

reliable based on the fact that vital status was reported known for approximately 97% of the trial participants and mortality is much less subject to investigator bias than other endpoints, such as MI or stroke. There was no evidence of an adverse effect of rosiglitazone on mortality, in fact, the Kaplan-Meir analysis reported by GSK favored rosiglitazone with a HR of 0.79 (95% CI 0.62 – 1.02).[18]

In my view, the data from RECORD as currently reported by GSK and the study investigators is of limited value in addressing the MI or MACE findings from the meta-analysis, but it provides reasonably strong evidence to address the non-significant, but worrisome, finding on overall mortality seen in the 2010 OB meta-analysis. The lack of an effect on overall mortality in RECORD is an important finding.

I agree with Drs. Parks and Rosebraugh that RECORD should be re-adjudicated in a proper and step-wise fashion to provide reliable data. The re-adjudication should first address overall mortality and if the re-adjudicated results are similar to those reported by GSK and the study investigators, should move to consider other events (e.g., hospitalizations, MACE), which will be more labor intensive and time consuming.

I do not agree with some in CDER who have suggested that a proper re-adjudication of RECORD would not be of value in helping to further address the outstanding questions regarding the safety of rosiglitazone. While the protocol allowed for the introduction of bias in referral of adverse events for adjudication, the underlying records of the study participants can still provide useful information. In addition to confirming (or not) the GSK-reported mortality findings, a properly conducted re-adjudication could require that ALL hospitalizations be referred to a blinded committee, independent of GSK, for adjudication. While a decision to hospitalize a patient is a subjective decision, it is less likely that investigators would have been biased in making a decision on hospitalization, which is a routine part of medical care, as compared to a decision on whether to report the event for adjudication. A re-adjudication of hospitalizations would provide new data on the components of the MACE endpoint, which are the key adverse events in question. It would be a disservice to the subjects who enrolled in the RECORD trial to allow legitimate concerns about investigator bias in adverse event referral to deter us from learning all that is possible from the trial data.

Observational studies of rosiglitazone compared to non-TZD anti-diabetic agents

This section will be limited to observational studies versus non-TZD comparators. Dr. Gelperin from OSE presented a systematic review of published epidemiology studies of cardiovascular risk in patients treated with rosiglitazone at the July 2010 AC meeting. She identified 7 observational studies (4 case control studies and 3 cohort studies) that compared rosiglitazone to other non-TZD anti-diabetic agents. Taken as a whole, these studies failed to demonstrate a signal of concern for acute myocardial infarction and all-cause mortality in rosiglitazone treated patients, while the studies did detect the well recognized increased risk of CHF in rosiglitazone-treated patients.[19] These findings are

[18] Refer to slide 30 from Dr. Unger's 2010 AC presentation.
[19] Refer to slides 8-10 from Dr. Gelperin's July 2010 AC presentation.

consistent with the OB 2010 meta-analysis, which did not identify a signal of concern for the subset of trials where rosiglitazone was compared to an active control, and also consistent with the findings from the large, long-term trials (ADOPT and RECORD) in which rosiglitazone was compared to metformin or sulfonylureas.[20]

Comparisons of rosiglitazone to pioglitazone

A natural question in making regulatory decisions regarding a serious safety concern is how the drug in question compares to the other members of the same class.[21] Unfortunately, as is often the case, there is no adequate head-to-head comparison of rosiglitazone to pioglitazone in a controlled clinical trial. This has led to many cross-study comparisons and observational studies to try to compare the safety risks and benefits of these two drugs. Cross-study comparisons are fraught with hazards and conclusions on their basis should be considered with great caution. In this case, such comparisons do shed light on how the data available for safety of rosiglitazone compares to that available for pioglitazone from the various sources.

Large, long-term controlled clinical trials of pioglitazone
PROactive was a large, long-term cardiovascular outcomes trial that compared pioglitazone to placebo when added to background anti-diabetic therapy. The primary endpoint was a composite of a variety of cardiovascular outcomes that included outcomes not typically included in a CV outcomes trial (e.g., major leg amputations). The primary analysis failed to demonstrate a statistically significant benefit of pioglitazone (HR 0.90, 95% CI 0.80 – 1.02, p=0.0954), but a secondary analysis of the composite of all-cause mortality, MI, and stoke was nominally statistically significant (HR 0.84, 95% CI 0.72 – 0.98, p=0.0277).[22] FDA did not consider this study adequate to support labeling for CV risk reduction with pioglitazone as the sponsor requested, but the results were not suggestive of CV harm in patients treated with pioglitazone.

Meta-analysis of pioglitazone controlled-clinical trials
The FDA Office of Biostatistics conducted a meta-analysis of 29 pioglitazone controlled clinical trials and presented these results at the July 2010 AC meeting. The pioglitazone meta-analysis was conducted using selection criteria and statistical procedures that were the same as those used for the 2010 OB meta-analysis of rosiglitazone controlled clinical trials. This was done to ensure that the meta-analyses were as comparable as possible, however, there were many differences in the types of trials and the patient populations enrolled as outlined by the OB reviewers. The OB reviewers included strong warnings in

[20] For RECORD I'm mainly referring to the mortality findings, which I believe are interpretable. For the other endpoints, such as MACE, the GSK and investigator reported findings cannot support a regulatory action pending confirmation by the suggested re-adjudication.
[21] Comparative assessments of drugs are generally limited to two situations in our regulatory decision-making. First, if one drug in a class appears to cause a serious adverse effect that does not occur, or occurs at a lower frequency or severity, for the other drugs in the class we consider whether the drug in question offers unique benefits to offset the unique risks. Second, if a drug appears to be less effective for an important endpoint such as mortality or irreversible morbidity, we consider whether the drug has other attributes, such as a better safety profile, that might offset the efficacy differences.
[22] Refer to slides 12-13 from Dr. Parks' July 2010 AC presentation.

their review and AC presentations about the appropriateness of cross-study comparisons of the rosiglitazone and pioglitazone meta-analyses, but I believe it is useful to compare the findings in a qualitative manner.

For the primary analysis, the pioglitazone group tended to have odds ratios that were close to or below 1.0 for endpoints such as MACE, CV death, MI, and stoke, and none were nominally statistically significant. There was a statistically significant increase in CHF in the pioglitazone group, a well recognized adverse event associated with TZDs. A sensitivity analysis that included the results of two large, long-term pioglitazone controlled trials (including PROactive) demonstrated very similar point estimates for the OR for all endpoints, tighter 95% CI, and for some endpoints the results were nominally statistically significant.[23] The results for MACE were analyzed by subgroups based on the type of comparator therapy and showed a point estimate for placebo-controlled trials that favored pioglitazone, unlike the finding of increased risk that was seen for the placebo-controlled trial subgroup in the rosiglitazone meta-analysis. For the active controlled trials, the findings for MACE for pioglitazone were essentially neutral and very similar to what was seen in the rosiglitazone meta-analysis.[24] Thus, the main driver of differences between the overall pioglitazone and rosiglitazone meta-analyses was from placebo-controlled trials. As noted in the OB presentations at the July 2010 AC meeting, 81% of the subjects in the rosiglitazone meta-analysis were from placebo-controlled trials, while 39% of the subjects in the pioglitazone meta-analysis were from placebo-controlled trials.

While, in general, the results of the meta-analysis for pioglitazone tended to show neutral or favorable results; the pattern was not true for all endpoints. This contrasts with the general pattern that was seen for rosiglitazone, where most results were neutral to adverse, with a few findings beneficial to rosiglitazone. Again, these general observations must be taken with great caution in making scientific and regulatory inferences since there were significant differences in the sources of data underlying the two meta-analyses with regard to comparators, trial duration, types of patients enrolled, etc.

Observational studies comparing rosiglitazone and pioglitazone

Since the 2007 AC meeting a number of observational studies have been published that have attempted to compare the CV risks of rosiglitazone and pioglitazone. Dr. Gelperin presented a systematic review of these published studies at the July 2010 AC meeting. She identified 4 case-control and 5 cohort studies that provided comparative data.[25] Dr. Gelperin concluded that "overall, comparisons of rosiglitazone and pioglitazone for outcomes including myocardial infarction, congestive heart failure and all cause mortality favor pioglitazone." She further noted that "no studies were identified in this review with results suggesting a protective cardiovascular effect of rosiglitazone compared to pioglitazone."

[23] Refer to slide 13 from Dr. McEvoy's July 2010 AC presentation.
[24] Refer to slide 45 from Dr. McEvoy's July 2010 AC presentation.
[25] Not all studies provided data on all endpoints or comparisons.

The forest plots that Dr. Gelperin showed in her advisory committee presentation would seem to support these conclusions, however, it is important to note that the odds ratios and hazard ratios from these studies were almost all under 2.0, and in the vast majority of the cases were less than 1.5. Due to the fact that observational studies are not prospective randomized comparisons, one must always be cautious in interpreting results with small effect sizes since they could be false positives due to unidentified confounding factors. That is not to dismiss the findings from the observational studies, but rather an attempt to keep them in perspective as they are considered to support scientific and regulatory inferences, particularly inferences that might lead to an action as significant as market withdrawal of a drug. It is also important to keep in mind the possibility of publication bias when considering published observational studies.

More recently, Dr. Graham from OSE and colleagues from CMS reported the results of a very large cohort study that was conducted using data from Medicare claims. The study involved more than 220,000 patients over 65 years of age who were initiated on either rosiglitazone or pioglitazone. This study has much strength, including the fact that even though the groups were not randomized to therapy, their baseline characteristics were very similar. The study found statistically significant increases in adjusted hazard ratios for stroke, heart failure, death, and composites of these three endpoints for patients treated with rosiglitazone, however, there was no significant difference for acute myocardial infarction. This latter finding is of interest since that was one of the "hypotheses" that came from the original rosiglitazone controlled trial meta-analyses.

Dr. Graham and his co-authors postulated that their failure to demonstrate an adverse finding for MI might be due to a higher percentage of acute MIs in older patients resulting in out-of-hospital death, which would not be captured in the medical claims data that were used for this study. They, in effect, concluded that there was in fact a greater risk of MI in the study population, even though such an effect was not actually observed. While an interesting hypothesis, such an explanation is highly speculative and has been met with great skepticism by experts in OND with experience in evaluating CV outcome trials and some experts on the AC.

It is noteworthy that the two other published observational studies included in Dr. Gelperin's review that were conducted in elderly patients also showed a finding of no increased risk of acute MI and significant increases in other CV endpoints. In all three studies the magnitude of increased risk observed was small. In the CMS study the magnitude of the effects seen were generally in the range of HR of 1.15 – 1.25. These are very small effects and their interpretation is the subject of much debate since they are derived from observational studies where patients were not randomized to treatment. For observational studies, hazard ratios under 2.0, even if nominally statistically significant, are generally viewed with great skepticism and caution in making scientific and regulatory inferences both inside and outside FDA. Of course, these effect sizes of increased risk <u>if real</u> would be of significant concern.

During the open public hearing at the July 2010 AC meeting, representatives from Healthcore presented the results of an observational study comparing CV effects of

rosiglitazone and pioglitazone that was conducted using the Wellpoint insurance claims database. A preliminary version of this study was presented at the July 2007 AC meeting and the final report was recently published.[26] The study was a cohort design and used propensity score matching to control for potential confounders. The data were collected prior to the May 2007 publication of the Nissen meta-analysis. The study included over 36,000 total patients, and matched over 29,000 patients for baseline variables. The mean duration of follow up was approximately 19 months and the mean duration of treatment was approximately 14 months for both drugs.

The primary endpoint in the Healthcore study was a composite of acute MI, acute heart failure, or death. There was no significant difference for the primary endpoint between rosiglitazone and pioglitazone-treated patients for either the matched patients (HR 1.03; 95% CI 0.91 – 1.15, p=0.666) or for all patients (HR 1.00; 95% CI 0.90 – 1.11, p=0.981). There was also no significant difference for any of the individual components (AMI, AHD, or death) of the composite endpoint in the matched patients. A subset analysis was conducted in over 5300 patients over 65 years of age and no significant difference was seen for the primary endpoint (HR 0.97, 95% CI 0.83 – 1.12) or any of its individual components. The estimated event rate per 1000 person-years for AMI was 6.18 for rosiglitazone and 6.74 for pioglitazone in the matched patients and 16.45 for rosiglitazone and 15.22 for pioglitazone in the patients over 65 years of age. The estimated event rate per 1000 patient-years for death was 11.44 for rosiglitazone and 11.22 for pioglitazone in the matched patients and 42.9 for rosiglitazone and 44.75 for pioglitazone in patients over 65 years of age.

The results of the Healthcore study are of great interest since the study was conducted by a "neutral" party in the rosiglitazone debate and appears to have well designed and conducted. While the study is much smaller than the CMS study, the authors used propensity score matching of baseline variables to control for confounding and the duration of average study drug treatment was much longer than that reported in the CMS study. The results of this study do not support the findings seen in the CMS study and raise doubts regarding the true comparative CV safety of rosiglitazone and pioglitazone. In order to explore these data further, we have requested that Healthcore submit the underlying study data for further review by FDA. That request is pending.

Discussion

Despite the vast amount of data that have been accumulated and analyzed to address the question of cardiovascular safety of rosiglitazone, the interpretation of these data remains highly controversial among experts both inside and outside FDA. While many have concluded that the available data demonstrate that rosiglitazone definitively increases the risk of ischemic CV events in patients with Type 2 diabetes and have loudly called for market withdrawal, others consider the data inconclusive and believe additional controlled clinical trials are need to more definitively answer the question. Recently, an

[26] Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed care population. Circ Cardiovasc Qual Outcomes. 2010;3:538-545.

expert panel from the American Heart Association and the American College of Cardiology Foundation concluded that the available data were inconclusive and "insufficient…to support the choice of pioglitazone over rosiglitazone."[27] The panel further stated that "More data are urgently needed to clarify the effects of all existing and future glucose-lowering agents, including the thiazolidinediones, on IHD (ischemic heart disease) events," and that "thiazolidinediones should not be used with an expectation of benefit with respect to IHD events."

The rosiglitazone case is an example of the reality that the science (specifically the data) rarely is so definitive that it points to an obvious and widely agreed upon regulatory decision. In the absence of definitive data FDA must still make sound decisions. These are necessarily based on the available data and our understanding of its strengths and weaknesses, but must also consider the law, regulations, precedents for similar cases, the disease treated by the drug, alternative treatment options, patient and physician preferences, "population" benefit-to-risk considerations and even the role of the practice of medicine versus government decision-making and the importance of autonomy of physicians and patients to make decisions about medicines. In the end, all the decisions we make at FDA become a judgment of whether the benefits of the drug outweigh the risks when used as labeled, and these judgments are very much influenced by how one considers all the complex factors that must be considered and weighed.

Unfortunately, in the passion of debate on such critical public health issues some parties lose focus on this reality and begin to demonize those who interpret the data differently and do not agree with their conclusions. Such movement away from healthy debate to name calling and accusations of malfeasance do not serve the public health and can jeopardize the integrity of the FDA decision-making process. As noted by Dr. Rosebraugh in his August 23, 2010, memorandum, the public scrutiny of FDA and its decisions regarding rosiglitazone safety has been unprecedented in its scope and intensity. In making our decisions in such an environment, which is becoming more and more common in today's rapid access to information and increased avenues for voicing one's opinion, we must listen carefully to these voices to understand their underlying assumptions and positions, but also take care to not allow the loudness or intensity of the stated positions to unduly influence our decision making. Our job as regulators and servants of the public health is to reach the best possible decision, not simply one that responds to the loudest voice. It is important to recall that in science, often the loudest voices and conventional wisdom are later proven to be wrong

As I consider the available data, I agree with the majority of the advisory committee members that there continue to be signals of concern regarding the possibility that rosiglitazone is associated with an increased risk of serious ischemic CV adverse events in patients with Type 2 diabetes mellitus. What is less clear is whether the newly

[27] Kaul, S., Bolger, A., Herrington, D., Guigliano, R., Eckel, R. Thiazolidinedione Drugs and Cardiovascular Risks – A Science Advisory From the American Heart Association and the American College of Cardiology Foundation. Journal of the American College of Cardiology 2010;55(17)1885-94. Note that this was published before the July 2010 AC meeting and therefore did not include FDA's review of the RECORD trial or the CMS observational study.

available data that inform this issue are sufficient in their magnitude and consistency to warrant a change from the regulatory action that was taken by CDER in 2007; i.e., including warnings in the package insert and Medication Guide so that physicians and patients can make informed decisions about whether to use rosiglitazone as part of a treatment regimen.

The CDER decision in 2007 to allow continued marketing also included a clear goal to obtain more data to definitively answer the important outstanding questions. That prompted FDA to require GSK to conduct the TIDE trial, which is designed to directly compare rosiglitazone, pioglitazone, and placebo (added to standard of care) in a prospective, randomized trial designed to assess cardiovascular outcomes. Such a trial remains the best option to generate the scientific data needed to more definitively answer the question, but some have raised questions about the ethics of the TIDE trial and have called for it to be halted. In reality, the ethical debate about the TIDE trial comes down to the question of how persuasive one considers the available data regarding ischemic CV risk of rosiglitazone. If one has concluded that the signals of increased risk represent the real effects of the drug and are of a magnitude that warrants withdrawal of the drug or imposition of severe restrictions on its use, then the TIDE trial as currently designed would be unethical. On the other hand, if one considers the available data to be inconclusive, equipoise would still exist and the TIDE trial would be ethical.

In my view the available data for ischemic CV risk of rosiglitazone, while concerning, do not rise to the level that would support a regulatory conclusion that the benefits of the drug as a treatment for Type 2 diabetes no longer outweigh its risks, which is the statutory finding FDA must reach to withdraw approval of a drug. Such decisions as this require a careful balance between placing the threshold for action too high or too low. If the threshold for action is placed too high there is greater protection against actions based on false positive results, but there is also a greater risk that patients will be subjected to undue harm by continued availability of a harmful drug. On the other hand, if the threshold for action is placed too low there is a greater chance of actions based on false positive results with the unintended consequence that physicians and patients do not have access to a safe and effective drug.

In weighing the available data for rosiglitazone the primary signals of concern arise from meta-analyses of controlled clinical trials that were not designed to rigorously collect CV outcome data and observational studies. Data from these sources provided risk estimates of a magnitude that fall well short of what has traditionally been considered a level that would support scientific and regulatory inferences, even in the face of nominal statistical significance. Further, there is considerable inconsistency in the findings across the various sources of data, which calls into question the reliability and robustness of the signals. For example, in the meta-analysis the results for stroke are favorable for rosiglitazone, but in the CMS study they are adverse. Similarly, the signal of increased risk of MI from the meta-analysis, the original signal of concern, was not seen in the CMS study or in some other published observational studies, including the recently published Healthcore study. Also, the adverse findings on mortality suggested by the meta-analyses and seen in the CMS study were not seen in the Healthcore study or in the

long-term controlled trials (i.e., DREAM, ADOPT, and RECORD).[28] While I do not believe the available data are adequate to support a decision to withdraw approval or severely restrict use of rosiglitazone, I do think it is important to ensure that prescribers and patients are aware of the concerns regarding increased risk, and that such information can and should be taken into account in making treatment decisions for individual patients.

Based on my conclusion that the available data are inconclusive in showing an increased risk of ischemic CV risks in patients treated with rosiglitazone, I believe that the TIDE trial is ethical and its conduct remains critical to providing the answers needed to allow the FDA to make an informed regulatory decision regarding the risks and benefits of the TZD class of drugs. I believe that under these assumptions the criteria outlined in the IOM expert committee report letter are met and the trial should continue once the informed consent documents and investigator's brochure are updated to appropriately reflect the currently available data and FDA's decision on the safety of rosiglitazone (i.e., the partial clinical hold imposed on the trial by FDA after the July 2010 AC meeting should be lifted). Just as individual prescribers and patients can consider the available data and make informed individual treatment decisions, I have confidence that local IRBs and ethics committees, investigators, and potential trial subjects can make informed decisions about whether to participate in the trial. Despite the conclusions of others to the contrary, I believe, and the votes and discussion from the July 2010 AC meeting support, that equipoise exists regarding the comparative risks and benefits of rosiglitazone, pioglitazone, and placebo, when added to background standard of care for treatment of Type 2 diabetes mellitus. I believe that a conclusion that pioglitazone is safer than rosiglitazone for CV endpoints remains uncertain and such a critical question warrants a well designed head-to-head comparative trial.

As noted by Dr. Rosebraugh in his August 23, 2010, memorandum, many of the same issues regarding comparative risk/benefit and ethics for rosiglitazone are extant in the ongoing PRECISION trial comparing the CV effects of celecoxib, ibuprofen, and naproxen. Just as that trial is viewed as vital to support valid scientific and regulatory inferences about the NSAID/COX2 class of drugs, where serious concerns have been raised by other controlled trials and observational studies about differential risk/benefit properties of the members of the class, the TIDE trial is vital to address the risk/benefit profile of the TZD class of drugs. The PRECISION trial is just one example of important large, post-marketing safety trials that could be placed in jeopardy if FDA sets the bar too low on the question of when a concern about differential safety between drugs in a class leads to a conclusion that it is unethical to conduct a more definitive trial. That would have a very damaging long-term impact on the ability to actually collect information to

[28] The FDA/CMS partnership provides an exciting new source of data on drug utilization and outcomes in the U.S. elderly population covered by Medicare. I believe it is important for FDA to do further work to explore the sensitivity and specificity of this new tool. Given the large size of the database, we need to better understand how to interpret small, but statistically significant, findings like those seen for the rosiglitazone versus pioglitazone comparison. This could be done by running analyses of variables that are not linked to the outcome of interest to see how often a finding might be reported simply by chance. It is my understanding that OSE staff are working on such analyses. I suggest that these be conducted by experts independent of the recent rosiglitazone study to avoid any perception of intellectual bias.

confirm or refute safety concerns and to provide the evidence needed to support appropriate use of drugs. I believe that trial subjects can be appropriately informed of the potential risks and that their safety can be ensured by employing an independent expert Data Monitoring Committee to oversee the trial in real-time with clear stopping rules should a signal of harm emerge.

I recognize that others may come to different conclusions regarding the appropriate path forward and regulatory actions for rosiglitazone. If the FDA decides to allow continued marketing of rosiglitazone and continuation of the TIDE trial as I recommend, it is safe to assume that the critics of the drug will remain vocal in their opposition and the attendant public attention may jeopardize the ability to complete the trial in a timely manner. A similar situation arose several years ago related to Crestor and the JUPITER trial. Once FDA carefully reviewed and rejected the claims made in a Citizens Petition of increased risk of serious adverse effects, the trial was completed and provided important new information regarding the benefits (an effect on survival in a lower risk population) and risks (the concerns raised in by the Petitioner were not observed) of Crestor. It is my hope that a clear FDA statement that the available data are inconclusive and that the TIDE trial should continue will allow for rapid completion of trial enrollment and timely completion of the trial. Under FDAAA we have clear authority and enforcement tools to ensure that GSK devotes the necessary resources to complete the trial in a timely manner.

There was discussion at the July 2010 AC meeting about whether rosiglitazone should be made "second line" in its labeling as a way to mitigate the concerns about increased CV risk. No clear consensus developed on what was meant by "second line," although some advocated for labeling that would state that rosiglitazone should be reserved for patients who are judged to need a TZD and who have failed to adequately respond to, or cannot tolerate, pioglitazone. As noted above, the data to support such a labeling path are inconclusive and I do not support such language. I agree with Dr. Parks that the labeling for all TZD's should be changed to indicate that they are not for initial use in patients who have failed a trial of diet and exercise and now require pharmacologic intervention to treat their diabetes. This is warranted given the well recognized class effects of TZDs on fluid retention and exacerbation of CHF. I also agree with Dr. Parks that the labeling for rosiglitazone should be amended to state that a signal of increased CV risk has not been seen with pioglitazone, and while this does not clearly support preferential use of pioglitazone in all patients, it should be considered by the prescriber and patient in making decisions about which TZD to initiate and be considered in making decisions about whether to continue a patient on rosiglitazone.

Finally, there was discussion at the July 2010 AC meeting about the possibility of a REMS with restricted distribution if rosiglitazone remains on the market. I do not support imposition a REMS with restricted distribution. First, I believe that the available data to support the concern regarding differential risk of rosiglitazone to non-TZD anti-diabetic agents and pioglitazone remains inconclusive, and thus a REMS is not warranted. Second, the data presented at the AC show that few new patients are initiating use of rosiglitazone since the 2007 publicity about the potential ischemic CV risk and the labeling changes that followed the July 2007 AC meeting. It appears that most of the

patients who are currently taking the drug have been on it for some time, and given the widespread media coverage, it is unlikely that they and their physician have not considered the issues in dispute in making their decision to continue use of the drug. In other words, if the goal of the REMS would be to restrict use, that has already occurred and the usage pattern would likely be maintained if the package insert for rosiglitazone were changed as described above. Third, I do not believe this case meets the criteria we have applied in imposing a restrictive REMS on the healthcare system. We have generally limited the use of restrictive REMS to cases where the drug with a unique safety concern is felt to offer a unique benefit to patients. I agree with others that there are no data to support a conclusion that rosiglitazone is more effective in treating Type 2 diabetes than pioglitazone; however, in making our decisions on benefit and risk of drugs one of the important factors we consider is the availability of a choice of therapies for prescribers and patients. Given that I find the available data on a differential risk between the two TZDs to be inconclusive, I believe that it is important to retain both drugs as choices in patients who are felt to need a TZD to manage their diabetes. I believe that prescribers and patients can make, and have been making, informed decisions in the absence of a restrictive REMS and recommend the labeling changes outlined above instead of a burdensome new REMS.

Recommendations

In summary, I recommend that:

- rosiglitazone continue to be marketed as a prescription drug,
- the package insert and Medication Guide be updated as described above to reflect the newly available information so that physicians and patients can continue to make informed decisions regarding its use,
- the sponsor be required to re-adjudicate the RECORD results,
- the partial clinical hold on the TIDE trial should be lifted once the informed consent and investigator's brochure are updated to reflect the new data and the FDA's decision on the marketing status,
- the sponsor be required to commit the necessary resources to ensure that the TIDE trial is fully enrolled and completed in a timely manner, and
- a truly independent DSB be charged with closely monitoring the TIDE trial so that the trial can be stopped at the earliest sign of a clear adverse safety signal.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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/s/

JOHN K JENKINS
09/02/2010
Recommendations for regulatory actions regarding safety issues.

Memorandum

Date: 12 September 2010

To: Janet Woodcock, MD

From: Gerald J. Dal Pan, MD, MHS

Re: Recommendations for Regulatory Action for Rosiglitazone and Rosiglitazone-containing Products (NDA 21-071, supplement 035, incoming submission dated August 25, 2009)

This memorandum serves as my recommendation to the CDER Center Director for the regulatory actions to be taken regarding rosiglitazone and rosiglitazone-containing products.[1] I have previously documented my review of the available evidence in both October 2007 [2] and October 2009.[3] Thus, in this memo, I will focus only on a brief review of the new evidence and on my recommendations.

Prior Recommendations

In October 2007, and again in October 2009, I wrote memoranda in which I recommended that rosiglitazone be removed from the market. The rationale for that recommendation is stated in those memoranda. In brief, I concluded that the available clinical trial data generated a substantial signal of a serious risk of myocardial ischemia, and that the observational studies strengthened this signal. Though the data did not provide definitive proof of a risk of myocardial ischemia, I argued that the seriousness of the risk and its public health implications outweighed the uncertainty that the risk is not real. I also expressed concern that the RECORD study,[4] whose final results had been published but were still under internal review at FDA, would not provide sufficient evidence to mitigate concerns over the risk of myocardial ischemia.

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[1] Rosiglitazone is a thiazolidinedione oral antidiabetic agent present in three marketed products: Avandia (rosiglitazone maleate), Avandamet (metformin hydrochloride; rosiglitazone maleate), and Avandaryl (glimepiride; rosiglitazone maleate). The conclusions and recommendations in this document apply to all rosiglitazone-containing products.

[2] Dal Pan, G. Office Director Memorandum for Drug Safety Board Meeting. RCM #2006-331; Review date September 27, 2007.

[3] Dal Pan, G. NDA 21-071/S-022; a) Office Director Memorandum b) Response to Request for Consultation from Office of Regulatory Policy Regarding Citizen Petition (Docket FDA 2008-P-0580). Review date October 23, 2009.

[4] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 20; 373(9681):2125-35.

Recent Activities and Review of New Data

Since I wrote the October 2009 memorandum, FDA has engaged in a number of activities to understand further the cardiovascular risks of rosiglitazone, with particular attention to the risk of myocardial ischemia. These include:

a) reviewing the RECORD clinical trial in detail;
b) completing updated, separate meta-analyses of randomized controlled clinical trials of rosiglitazone and pioglitazone;
c) conducting a systematic review of published observational studies of rosiglitazone and pioglitazone that addressed relevant cardiovascular outcomes;
d) performing an observational study using CMS data comparing cardiovascular outcomes in persons age 65 and older taking rosiglitazone to those in persons age 65 and older taking pioglitazone; and
e) examining some *post hoc* analyses examining cardiovascular outcomes in rosiglitazone-treated patients in two clinical trials (BARI-2D and VADT) that were not designed specifically to address these questions.

The RECORD Study

RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) was a multi-center, randomized, open-label study comparing rosiglitazone in combination with either metformin or a sulfonylurea to the combination of metformin and a sulfonylurea in patients with type 2 diabetes. Patients on background metformin who were inadequately treated were randomized to receive, in addition to metformin, rosiglitazone or a sulfonylurea in a 1:1 ratio. Patients on background sulfonylurea who were inadequately treated were randomized to receive, in addition to the sulfonylurea, rosiglitazone or metformin in a 1:1 ratio. The primary objective of RECORD was to compare the time to experiencing the primary combined endpoint of cardiovascular death and/or cardiovascular hospitalization between the rosiglitazone-containing treatment groups and the non-rosiglitazone-containing treatment group. Secondary efficacy endpoints included: all-cause mortality; definite heart failure; microvascular endpoints and combined cardiovascular hospitalizations or cardiovascular death endpoint plus microvascular endpoints. This trial was designed as a non-inferiority study with the objective of showing that rosiglitazone-containing treatment is non-inferior to the non-rosiglitazone treatment if the upper limit of the 95% CI for the hazard ratio was below 1.20. An interim analysis of RECORD was published in 2007,[5] and the final results were published in 2009.[6]

[5] Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones JP, et al, for the RECORD study group. Rosiglitazone Evaluated for Cardiovascular Outcomes - an interim analysis. N Engl J Med 2007; 357(1):28-38.
[6] Home PD, et al for the RECORD Study Team. Lancet. 2009; op.cit.

While results of the RECORD study met the protocol-specified criterion of non-inferiority (HR 0.99, 95% CI 0.85–1.16) for the primary endpoint, the point estimate for myocardial infarction, although not statistically significant, was greater than one (HR 1.14, 95% CI 0.80–1.63). My previous review of rosiglitazone noted several issues with the design of the RECORD clinical trial, including the open-label design, which could compromise objective end-point ascertainment as well as overall adverse event reporting. The Office of New Drugs[7,8,9] (OND) and the Office of Biostatistics[10] have completed several reviews of the RECORD trial. Medical reviewers across OND appear to differ in their interpretation of the RECORD trial. Nonetheless, it appears that many OND staff share the view that certain design and conduct features of RECORD do not render the study adequate to support a conclusion that rosiglitazone does not increase the risk of myocardial ischemia relative to other non-thiazolidinedione oral anti-diabetic treatments. RECORD also found that heart failure occurs more commonly with rosiglitazone than with the other non-thiazolidinedione oral anti-diabetic agents, a finding that is consistent with the known, labeled toxicity of rosiglitazone. (RECORD did not include pioglitazone, which is also associated with heart failure). Because of the concerns I previously raised about the RECORD trial, and based on the OND reviews of the final RECORD data, I conclude that the RECORD study does not provide meaningful information about the risk of myocardial ischemia with rosiglitazone. Thus, the RECORD study does not change my previous view of rosiglitazone.

Meta-analysis of Controlled Clinical Trials

The most recent meta-analyses of controlled clinical trials of rosiglitazone and pioglitazone are those conducted by CDER's Office of Biostatistics and presented at the July 2010 Advisory Committee meeting.[11] Separate meta-analyses of 52 rosiglitazone controlled clinical trials and of 29 pioglitazone controlled clinical trials were performed to examine the association of these medicines with adverse cardiovascular outcomes. These analyses found that rosiglitazone had a higher risk of myocardial infarction than comparator (OR=1.80, 95% CI: 1.03, 3.25) and a nearly statistically significant increase for MACE[12] versus comparator (OR=1.44, 95% CI: 0.95, 2.20). For pioglitazone, the odds ratio for MACE was less than one and not statistically significant (OR=0.83, 95% CI: 0.56, 1.21). In placebo-controlled trials, rosiglitazone had a higher estimated odds ratio for MACE (OR=1.53, 95% CI: 0.94, 2.54) than pioglitazone (OR=0.56, 95% CI: 0.18, 1.67). This difference was attenuated in active-controlled trials, for which the

[7] Marciniak TA. Cardiovascular events in RECORD, NDA 21-021/S-035, June 14, 2010
[8] Unger EF. Memorandum to the file. June 15, 2010.
[9] Mahoney KM. Preliminary Endocrine Medical Officer Review of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) Trial, and Update on Cardiovascular Safety Information from Large Clinical Trials of Rosiglitazone. June 9, 2010.
[10] Hoberman D. Statistical Review and Evaluation.
[11] Briefing Information for the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, available at http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetaboliDrugsAdvisoryCommittee/ucm191113 htm.
[12] MACE refers to "major adverse cardiovascular event", defined as cardiovascular death, stroke, or myocardial infarction.

estimated odds ratios for MACE were 1.05 (95% CI: 0.48, 2.34) for rosiglitazone and 0.88 (95% CI: 0.58, 1.34) for pioglitazone. Both drugs showed an increased risk of heart failure, a known complication of treatment with thiazolidinediones. The biostatisticians who performed these meta-analyses appropriately noted that differences in trial characteristics and study populations between the two meta-analyses limit the ability to make direct cross-drug comparisons. I note, however, that these new meta-analyses, like the multiple meta-analyses that preceded them, continue to provide a strong signal that rosiglitazone, but not pioglitazone, is associated with myocardial ischemia.

In both the rosiglitazone and pioglitazone meta-analyses, the majority of trials were six months or shorter in duration. For rosiglitazone, 70% of rosiglitazone-treated patients in the meta-analysis were in trials of six months duration or less, while in the pioglitazone meta-analysis, 49% of the pioglitazone-treated patents were in trials of six months duration or less. The reason for a clearer signal of the risk of myocardial ischemia for rosiglitazone in studies of six-months duration or less than in long-term studies is not clear. One possibility is that it may relate to individual patient factors, such that individuals who are susceptible to the adverse cardiovascular effects of rosiglitazone experience those effects within six months of treatment initiation, and those who continue in clinical trials for longer than six months are not susceptible and will not experience the adverse cardiovascular effects of the drug. If this is the case, this may explain the stronger signal for myocardial ischemia in short-term (i.e., six-month duration or less) clinical trials.

While some have argued that data from long-term clinical trials are more relevant than data from short-term clinical trials in assessing the cardiovascular risks of anti-diabetic agents, drug utilization patterns suggest that short term data are, in fact, relevant. In my 2009 memorandum, I noted that drug utilization data for rosiglitazone suggest that six months after initiation of treatment, 40% of patients on rosiglitazone monotherapy are no longer taking the drug, 35% of patients on rosiglitazone in combination with either metformin or a sulfonylurea are no longer taking the combination, and 35% of patients on rosiglitazone and insulin are no longer on the combination.[13] Data from the recently conducted observational study[14] using CMS data, which compared the cardiovascular adverse effects of rosiglitazone to pioglitazone, confirm these findings. Six months after initiation of treatment with a thiazolidinedione, 28.5% of rosiglitazone-treated patients are still on the medication and 29.9% of pioglitazone-treated patients are still on the medication. This pattern is similar to that seen with other medications intended for chronic conditions, such as hypertension[15] and hypercholesterolemia,[16] which are often

[13] i3 drug safety. Additional analyses for the study "Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents". July 19, 2007. This analysis was requested by FDA upon its review of the study report "Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents". that GSK submitted to FDA.

[14] Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010 Jul 28;304(4):411-8. Epub 2010 Jun 28.

[15] Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. BMJ. 1995 July;311:293-295.

not taken chronically (i.e., a several year period), but rather are used for less than a year by a substantial proportion of patients. Thus, amongst diabetic patients in the United States prescribed rosiglitazone, a substantial proportion takes the medication for six months or less. For this reason, risks estimated at the six-month time point are important to persons taking rosiglitazone.

The results of the updated meta-analyses of controlled clinical trials continue to provide a signal of increased risk of myocardial ischemia with rosiglitazone, a signal not seen with pioglitazone.

Systematic Review of Observational Studies

A systematic review[17] of published observational studies was performed to assess further the cardiovascular safety signal for rosiglitazone raised by the meta-analysis of clinical trials. This review used formal criteria to select and assess studies. A review of 1226 abstracts yielded 21 published observational studies that met pre-specified inclusion criteria.[18] Seven studies were nested case-control studies, and 14 were retrospective

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[16] Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, and Platt R. Discontinuation of antihyperlipidemic drugs – Do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med 1995 April;332(17):1125-1131.

[17] Gelperin K, Zhou E, Graham DJ. Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. OSE RCM #2010-277. June 15, 2010. Presented at the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Available at: http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetaboliDrugsAdvisoryCommittee/ucm191113 htm.

[18] Since the systematic review of observational studies was complete, FDA is aware of two additional observational studies, each of which compared adverse cardiovascular effects between rosiglitazone and pioglitazone. The first study is a study jointly sponsored and conducted by FDA and CMS, which is described later in this memorandum. The second is a published observational epidemiological study conducted by staff of HealthCore, Inc., which was also presented at the July 2010 Advisory Committee meeting. See Wertz DA, Chang C-L, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circ Cardiovasc Qual Outcomes 2010;3:538-545. The authors used propensity-score matching to construct cohorts of rosiglitazone users and pioglitazone users. The primary outcome measure was time to composite event of acute myocardial infarction, acute heart failure, or death. The authors concluded that no significant differences were found in the risk of the acute myocardial infarction, acute heart failure or death. The Office of Surveillance and Epidemiology has reviewed the publication describing this study and its results, and we have found numerous flaws in this study. First, the outcome measure included not only hospitalized events of acute myocardial infarction and acute heart failure, but also emergency department visits for these two diagnoses. The validity of the emergency department claims in this study is not known, but is felt not to be as strong as that of the inpatient claims. Poor validity of the outcomes measures could bias risk estimates. In addition, it is not clear if the investigators, who describe their access to the HealthCore database, had access to all healthcare claims for persons 65 years of age and over, whose health insurance primary payer is Medicare. As supplemental insurers receive claims only for payment that is not covered by Medicare, the HealthCore researchers may not have had access to all outcomes of interest. Additionally, the exposure definition was defined as the days' supply of the drug, along with an additional 50% of days' supply added, to account for nonadherence to prescribed regimens. This additional time is quite extensive, and could mis-classify non-exposed time as exposed time. Finally, the sample size was relatively small compared to other studies, such as the CMS study. Each of these methodological features

cohort studies. Nine of these 21 studies reported results of direct comparisons of rosiglitazone versus pioglitazone for cardiovascular outcomes of interest including myocardial infarction, heart failure, or stroke.[19,20,21,22,23,24,25,26,27] In addition, three studies were identified which compared rosiglitazone or pioglitazone separately to other antidiabetic agents, but for which unadjusted odds ratios comparing rosiglitazone and pioglitazone to each other could be estimated from data available in the published report.[28,29,30] Results were displayed as point estimates and 95% confidence intervals in a series of forest plots, and were presented at the recent Advisory Committee meeting. No formal quantitative meta-analysis was done.

Of particular note, the forest plot describing acute myocardial infarction risk with rosiglitazone versus pioglitazone showed a strikingly asymmetric distribution, with point estimates greater than one for all comparisons, favoring pioglitazone. (See Figure 1)

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could bias the results toward a finding of no difference between groups, which was, in fact, the actual finding. We conclude that this study does not provide additional useful evidence.

[19] Brownstein, J.S.; Murphy, S.N.; Goldfine, A.B.; Grant, R.W.; Sordo, M.; Gainer, V.; Colecchi, J.A.; Dubey, A.; Nathan, D.M.; Glaser, J.P.; Kohane, I.S. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care, vol 33, no. 3; 2010.

[20] Dormuth, C.R.; Maclure, M.; Carney, G.; Schneeweiss, S.; Bassett, K.; Wright, J. M. Rosiglitazone and myocardial infarction in patients previously prescribed metformin. PLoS One, vol 4(6), e6080; 2009.

[21] Hsiao, F.Y.; Huang, W.F.; Wen, Y.W.; Chen, P.F.; Kuo, K.N.; Tsai, Y.W. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: A retrospective cohort study of over 473,000 patients using the national health insurance database in Taiwan. Drug Safety, 32(8):675-690, 2009.

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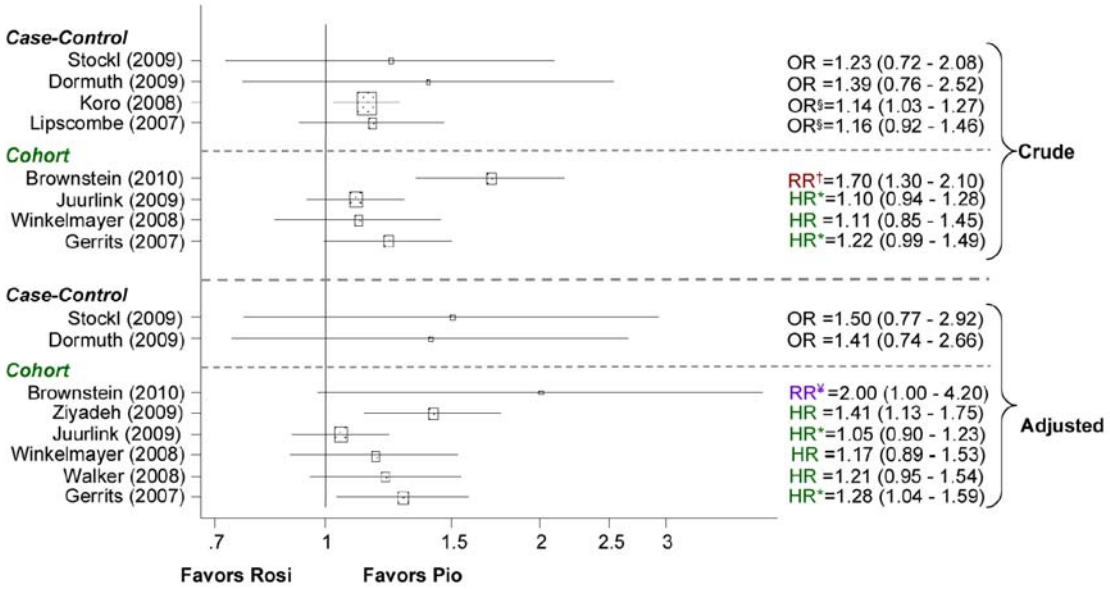
[28] Koro, C.E.; Fu, Q.; Stender, M. An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiol and Drug Safety, 17:989-996; 2008.

[29] Lipscombe, L.L.; Gomes, T.; Levesque, L.E.; Hux, J.E.; Juurlink, D.N.; Alter, D.A. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA, vol 298, no 22; 2007.

[30] Azoulay, L.; Schneider-Lindner, V.; Dell'aniello, S.; Filion, K. B.; Suissa, S. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol and Drug Safety, 2009.

Figure 1: Acute myocardial infarction (comparisons of rosiglitazone vs pioglitazone)[31]



Adjusted point estimates range from 1.05 to 2.00, and are statistically significant in two of the studies, one of which [32] was funded by GSK. The reported crude and adjusted risk estimates from a total of ten different studies are shown on this forest plot. Results are clearly asymmetric, with all point estimates similar in magnitude and direction, and favoring pioglitazone as a safer alternative to rosiglitazone with regard to myocardial infarction risk. In observational studies comparing rosiglitazone to pioglitazone, the risk of heart failure in patients taking rosiglitazone was higher than the risk in patients taking pioglitazone.

When either rosiglitazone or pioglitazone was compared to non-thiazolidinedione anti-diabetic agents, there were no significant differences in the risk of myocardial infarctions. Both agents were numerically associated with higher risk of heart failure than non-thiazolidinedione comparators; statistical significance was reached for rosiglitazone in two of four studies, and in no studies for pioglitazone.

The data from this systematic review strengthen the signal from the meta-analysis of randomized controlled clinical trials, indicating increased risk of myocardial ischemia with rosiglitazone. The magnitude of this risk is similar to what was found in the meta-analysis of randomized controlled clinical trials. These data are also consistent with the observation from randomized clinical trials that such a risk has not been observed with pioglitazone. The general conclusion from this systematic review is that rosiglitazone carries a higher risk of adverse cardiovascular outcomes, including myocardial infarction, compared to pioglitazone.

[31] Figure 9.3.1.1 reproduced from Gelperin K, Zhou E, Graham DJ. Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. OSE RCM #2010-277. June 15, 2010.
[32] Ziyadeh, N.; McAfee, A.T.; Koro, C.; Landon, J.; Chan, K.A. 2009, op.cit.

Observational Study Using CMS Data

The observational study using the CMS data[33] compared the rates of acute myocardial infarction, stroke, hospitalized heart failure, and death in new users of rosiglitazone and pioglitazone. The main findings were that, relative to pioglitazone, rosiglitazone is associated with a higher risk of death, stroke, and hospitalized heart failure, with no statistically significant increase in acute myocardial infarction. Various subgroup and sensitivity analyses confirmed the main study findings. The numerical magnitude of the risk on a relative scale is small (most hazard ratios were in the range of 1.15 to 1.20) and is in the range in which residual confounding might explain the observed results. In these situations, randomized, controlled clinical trials are usually recommended to determine if such findings are not related to residual confounding. However, the results of such a clinical trial are not available at this time, and will likely not be available for several years, if ever. However, certain features of the observational study using CMS data mitigate, at least to some degree, these concerns. First, the rosiglitazone-treated patients and the pioglitazone-related patients were very comparable with respect to multiple baseline cardiac and non-cardiac characteristics, with between-group differences in these measures as small as those seen in large, randomized clinical trials. Second, the adjusted and unadjusted analyses were not substantively different from each other, suggesting that confounding played little role in the overall results. Third, many sensitivity and subgroup analyses yielded the same findings as did the main analysis, suggesting that the findings are robust. Fourth, two other observational studies in the same age group arrived at similar results and conclusions. Given that the rosiglitazone and pioglitazone cohorts are well matched on multiple cardiac and non-cardiac factors, it is difficult to imagine that unmeasured factors are not well matched between the two groups, especially since they correlate with the multiple measured confounders. While this reasoning can not exclude an effect of residual confounding on the observed results, it does underscore the robustness of the findings of the CMS study, which provides an additional signal of risk with rosiglitazone relative to pioglitazone.[34] Even in the absence of a statistically significant difference in acute myocardial infarction rates between the two groups, the data raise significant concerns about stroke, mortality, and heart failure.

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[33] Graham DJ, Ouellet-Hellstrom R, et al. JAMA. 2010 op.cit; full review starts on page 479 of FDA briefing documents for the July 13-14, 2010 Joint Meeting of the EMDAC and DSaRM AC Available at: http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetaboliDrugsAdvisoryCommittee/ucm191113 htm.

[34] To examine the possibility that a very large dataset, such as the CMS dataset used for the TZD analysis, could produce "spurious" results – ie, results that link an outcome to an exposure to which it is clearly known to be not related – the FDA/CMS team analyzed CMS TZD dataset by birth date. Basically, the TZD cohort was divided into those with an even number birth date and those with an odd number birth date. "Even" and "odd" were based on dates in STATA, which uses 01 January 1960 as "Day 0", with dates prior to that assigned a negative number and dates after that assigned a positive number. Each cohort member is assigned a STATA birth data, and the cohort is divided into those with "even" and "odd" number birth dates. When divided into cohorts based on birth date, there were no differences between those with "even" or "odd" number birth dates in terms of baseline characteristics or outcomes, as would be expected. (See Memorandum for David Graham to Gerald Dal Pan. Analysis of Medicare thiazolidinedione study data by date of birth. Review date September 1, 2010.).

Post hoc Analyses of BARI-2D and VADT

The *post hoc* analyses of the BARI-2D[35] and VADT[36] studies, presented at the July 2010 Advisory Committee meeting, do not provide useful information about the cardiovascular safety of rosiglitazone because these trials were not designed to study rosiglitazone. In addition, the *post hoc* analyses designed to study the cardiovascular effects of rosiglitazone did not compare randomized groups.

Advisory Committee Meeting

On 13-14 July 2010, FDA held a joint meeting of the Endocrine and Metabolic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee. [37] GlaxoSmithKline representatives and their consultants presented the company's perspective on rosiglitazone, with a focus on the RECORD trial. FDA staff presented their findings on the RECORD study, the meta-analyses of the rosiglitazone and pioglitazone randomized clinical trials, the systematic review of observational studies, the CMS observational study, and the FDA inspections of the RECORD trial. The committee also heard from several FDA-invited outside speakers, including Dr. Steven Nissen, who presented a critical overview of rosiglitazone; Dr. Maria Mori Brooks, who presented an analysis of rosiglitazone use and cardiovascular outcomes in the BARI-2D trial; Mr. Thomas Moritz, who presented data on the impact of the use of rosiglitazone in the

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[35] According to the study website, BARI 2D, a randomized trial, was designed to determine in patients with Type 2 diabetes and stable heart disease whether: 1) elective coronary revascularization combined with aggressive medical therapy is better for patients compared to aggressive medical therapy with revascularization only if symptoms get worse; and whether 2) providing more insulin (through giving insulin or medication that allows the body to make more insulin), is better for patients than giving medications that increase patients' ability to better use the insulin their bodies already make (reducing insulin resistance) with a target HbA1c level of less than 7.0% for each group. Patient follow-up was completed November 30, 2008. Available at http://www.bari2d.org/public/home html (accessed September 8, 2010).

[36] The Veterans Affairs Diabetes Trial (VADT) randomized 1791 military veterans who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. The primary outcome was the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. The median follow-up was 5.6 years. Results showed that intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria (P = 0.01). The study was sponsored by the Veterans Affairs Cooperative Studies Program. (Reference: Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39. Erratum in: N Engl J Med. 2009 Sep 3;361(10):1028. N Engl J Med. 2009 Sep 3;361(10):1024-5.)

[37] Briefing Information for the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, available at http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetaboliccDrugsAdvisoryCommittee/ucm191113 htm.

Veterans Affairs Diabetes Trial (VADT); Dr. Hertzel Gerstein, who presented an overview of the TIDE Trial; Dr. Dean Follman, who presented an approach to considering the strengths and limitations of various types of clinical research data; and Drs. Ruth Faden and Steven Goodman, who presented the initial letter from the Institute of Medicine on ethical issues in studying the safety of approved drugs.[38]

The committee members were asked to comment on the strengths and weaknesses of the available data. The committee was then asked to vote on a number of questions related to the cardiovascular risks of, and potential for increased mortality with, rosiglitazone, compared separately to non-thiazolidinedione antidiabetic agents and to pioglitazone. The committee was also asked to vote on a regulatory option for rosiglitazone, as well as on a recommendation whether to continue the TIDE trial.

FDA wrote the four voting questions regarding cardiovascular risk and mortality in a way that sought a definitive response – "…do you find that rosiglitazone increases the risk of…?" The committee members re-worded the question to "…do you find that these data are sufficient to raise significant safety concerns…?" This change in wording likely reflects the challenge the committee had in making conclusions with the available data. Using this revised wording, the committee voted as follows:

- Eighteen of 33 members found that the data were sufficient to raise a significant safety concern about an increased risk of ischemic heart disease with rosiglitazone compared to non-thiazolidinedione comparators.
- Twenty-one of 33 members voted that the data were sufficient to raise a significant safety concern about an increased risk of ischemic heart disease with rosiglitazone compared to pioglitazone.
- One of 33 members found that the data were sufficient to raise a significant safety concern about an increased risk of mortality with rosiglitazone compared to non-thiazolidinedione comparators.
- Seven of 33 members voted that the data were sufficient to raise a significant safety concern about an increased risk of mortality with rosiglitazone compared to pioglitazone.

The committee members voted as follows on a regulatory option for rosiglitazone:

- Three voted for continued marketing with no changes to the current label
- Seven voted for continued marketing and revisions to the current labeling to add additional warnings
- Ten voted for continued marketing, revisions to the current label to add additional warnings, and adding additional restrictions on use
- Twelve voted for market withdrawal
- One member abstained

[38] IOM (Institute of Medicine). 2010. *Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report*. Washington,DC: The National Academies Press.

Nineteen of 33 members voted that, if rosiglitazone remains on the market in the US, the TIDE trial should continue. Eleven voted that the TIDE trial should not continue, two abstained, and one had left the meeting before the final vote.

Discussion

Overall Interpretation of the Data

The body of evidence on rosiglitazone is now larger than it was when I wrote my October 2009 memorandum. As before, no single piece of data provides a definitive answer to the question of myocardial risk with rosiglitazone. Interpretation of the data is challenging, as was reflected in the deliberations and recommendations of the advisory committee members.

The meta-analysis of clinical trials suggests an increased risk of myocardial ischemia, with a point estimate indicating an approximate 46% relative increase in the incidence of serious myocardial ischemic events with rosiglitazone. Larger individual clinical trials appear not to show this signal, though, for the reasons mentioned in my October 2009 memorandum, the lack of this finding does not mitigate the concerns raised by the meta-analyses. Given the multiple problems in its design and execution, the RECORD study does not mitigate this finding. Taken as a whole, the meta-analysis of rosiglitazone controlled clinical trial data do not definitively quantify the risk of myocardial ischemia with rosiglitazone, though they do yield an important finding that can not be ignored. Notably, the meta-analysis of pioglitazone clinical trials does not point to a risk of myocardial ischemia.

The results of the observational studies strengthen the concern over the risks of rosiglitazone, especially when compared to pioglitazone. Observational drug safety studies are often criticized because they lack the experimental design rigor of a controlled clinical trial. Specifically, there is often concern that patients who are prescribed a particular medicine are different from those who are prescribed an alternative treatment, in ways that may be correlated with the outcome of interest. This phenomenon is known as channeling bias, and is often a concern when measures of relative risk are below 2.0, when the effect of unmeasured confounders could account for the observed findings. While this concern is generally valid, it should not be automatically invoked to dismiss the results of observational studies in which the measure of relative risk is below 2.0. Data from the CMS observational study, for example, indicate that rosiglitazone and pioglitazone recipients were similar with regard to multiple cardiac and non-cardiac factors, a finding that suggests minimal channeling bias. Furthermore, the risk estimates from the observational studies are generally similar to those from the meta-analyses of clinical trials. Thus, dismissing the results of the observational studies simply because the observed measures of risk may be due to channeling bias may not be appropriate.

My assessment of the new data, in conjunction with the previously available data, is that they do not change my overall view concerning the cardiovascular risk of rosiglitazone,

including the risk of myocardial ischemia. There is, at a minimum, a persistent, strong and consistent signal of a clinically important risk of myocardial ischemia with rosiglitazone across all sources of data. This signal is more robust when rosiglitazone is compared to placebo than when it is compared to non-thiazolidinedione oral anti-diabetic agents. Importantly, there is a consistent signal when rosiglitazone is compared to pioglitazone. This latter comparison is the relevant comparison, because practitioners need to decide which thiazolidinedione to prescribe when a thiazolidinedione is needed.

My viewpoint is based on synthesizing all the available data, recognizing that each individual piece of data has its strengths and limitations. Ideally, results of a well-designed, rigorously executed, and carefully analyzed clinical trial designed to answer the question at hand would be available. This is not the case here. Nonetheless, based on the totality of the evidence and the consistency of the signal across data sources, I simply can not conclude, for public health and regulatory purposes, that the observed findings are not real.

The public health significance of the observed risk of myocardial ischemia with rosiglitazone – an approximate 40% relative increase compared to treatment without rosiglitazone – if real, is unacceptably high. Though this may seem like a modest signal from an epidemiological point of view, the public health burden of this level of risk elevation is substantial, given the high background rate (about 2-4%/year) of myocardial infarction in diabetics. With this range of background rate of myocardial infarction and observed relative risk, the absolute risk would be in the range of 0.8-1.6% - i.e., 0.8-1.6% of rosiglitazone-treated patients would experience a myocardial infarction due to rosiglitazone treatment. Given the population significance of this risk, I believe that it is neither necessary nor appropriate to demand definitive proof from a clinical trial before taking action, given the data that are already available. In this case, the impact of the harm, if it is real, outweighs the uncertainty that it may not be real.

Any regulatory decision about a medicine must be made in the context of balancing benefits and risks. Rosiglitazone is an effective anti-diabetic agent, though it appears to be no more effective than pioglitazone. I am not aware of any unique advantage of rosiglitazone over pioglitazone.

Because rosiglitazone does not confer any unique efficacy compared to pioglitazone, I continue to conclude that the benefits of rosiglitazone do not outweigh the risks for the treatment of diabetes.

Regulatory Actions

Because I have concluded that the benefits of rosiglitazone do not outweigh its risks, I continue to support market withdrawal as an appropriate regulatory action. This viewpoint is shared by Drs. David Graham and Kate Gelperin in OSE. However, an acceptable alternative approach would be to allow rosiglitazone to be used in very limited, carefully-defined situations on a restricted basis for persons with Type 2 diabetes

for whom other treatment options do not provide satisfactory diabetic control. My rationale is explained below.

The rationale for permitting limited, restricted use of rosiglitazone is that Type 2 diabetes is a progressive disease, and, in some patients, blood glucose is not adequately controlled by one or several anti-diabetic agents. For these patients, achieving adequate blood glucose control is still important. While rosiglitazone does not have any unique efficacy, it is nonetheless an efficacious treatment for Type 2 diabetes mellitus. It is important to note that the available data, upon which I base my conclusion that the benefits of rosiglitazone do not outweigh its risks, do not allow us to identify prospectively, in an evidence-based manner, any subset of patients for whom the risk of myocardial ischemia due to rosiglitazone is not present. Nonetheless, glycemic control is important and I could envision limited availability of rosiglitazone only to patients for whom rosiglitazone is basically the only available agent that allows treatment goals to be met. Patients and prescribers would have to be fully informed about the risks of rosiglitazone and would have to determine that, on an individual basis, the benefits of rosiglitazone exceed its risks. In this situation, the benefit of rosiglitazone is the achievement of adequate glycemic control when other agents have failed to achieve such control. In this setting, it is reasonable to allow physicians and patients to determine, on an individual basis, if this benefit outweighs the risks of rosiglitazone. While I have not fully developed the criteria to be used in selecting patients for rosiglitazone treatment, which would have to be done in conjunction with diabetes experts, I envision the following broad framework for these criteria:

> A) Patients with Type 2 diabetes mellitus whose diabetes has not been adequately controlled with other non-thiazolidinedione anti-diabetic agents despite documented, adequate trials of those agents;
>
> AND
>
> B) Patients for whom a thiazolidinedione is indicated;
>
> AND
>
> C) Patients whose diabetes has not been adequately controlled on, or who are otherwise not candidates for, pioglitazone.
>
> D) For patients who do meet the criteria and who do receive rosiglitazone, there should be a consent process. Patients will also need to be periodically monitored to insure that treatment goals are being met. I have not specified what the treatment goals should be, as this requires input of diabetes experts, and given the progressive nature of diabetes, may not be a specific numerical target based on blood glucose levels or hemoglobin A_{1c} levels.

I do not believe that increasing the warnings on the rosiglitazone label is an adequate option given the available data, since there is no way to identify prospectively, in an evidence-based manner, any subset of patients for whom the risk of myocardial ischemia due to rosiglitazone is not present. I offer the "restricted" plan above as an alternative to market withdrawal, not as an alternative to increasing the warnings on the label.

If the above restricted distribution plan is adopted, the Agency will need to consider the proper regulatory mechanism to implement it. One option is a Treatment Protocol within an IND. This mechanism assures that no product is available outside of the IND. The main disadvantage is that it is a clumsy mechanism to use if many patients are to receive the medication.

An alternative regulatory approach would be to require a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). The REMS would be used to insure that the limited conditions of use under which the benefits of the drug may outweigh the risks, as described above, are met. I believe that only narrow criteria, such as the ones that I have outlined in the restricted proposal above, are appropriate, since there is no other prospective, evidence-based way of determining which patients are not at risk for myocardial ischemia due to rosiglitazone. In this case, a REMS would be developed mainly to insure a) that patients are treated with rosiglitazone if they meet the criteria (which would also be in a revised labeled indication) and b) that patients are monitored appropriately while on rosiglitazone (which would also be in the revised label). Nothing in the REMS would actually mitigate the risks of rosiglitazone. The REMS would thus be used largely to enforce the labeled indication and monitoring.

The above scenario is for patients who are not currently taking rosiglitazone. Currently, there are about 600,000 patients in the US taking rosiglitazone. The path forward for these patients is less clear. I recognize that many of these patients may be doing well on rosiglitazone, and withdrawal of a successful treatment can be disruptive. Nonetheless, I think that these patients need to be informed of the recent findings regarding rosiglitazone, and, like the proposal above for new users, should sign a consent form and be monitored to insure that treatment goals are being met. Enrollment in a REMS, if that path is chosen, would also be a possibility. Whatever the approach, there will have to be a phased implementation to handling the patients currently on rosiglitazone, given the large numbers involved and the need for continuous treatment of diabetes.

My proposals are consistent with the general recommendations of the advisory committee - of the 32 voting members, 22 voted either to restrict the use of rosiglitazone (n=10) or to withdraw it from the market (n=12).

It is unlikely that withdrawal or extensive restriction of rosiglitazone, based on the available data, would lead to a rash of similar regulatory actions on other drug products each time a meta-analysis or epidemiological study is performed. In the case of rosiglitazone, we have looked at data from a wide range of sources, and have tried to synthesize these various pieces of data. The resulting synthesis has been used to re-examine the risk-benefit balance of rosiglitazone. This has been a careful process. Across

the products whose safety we monitor, we deal with data from a multitude of observational epidemiological studies and from an increasing number of meta-analyses, and we do not automatically recommend drug withdrawal when we identify a risk. Rather, we synthesize the available evidence, and re-assess the risk-benefit profile, prior to making regulatory recommendations.

Further Study

I believe that there is limited value to re-adjudicating the cardiovascular events in the RECORD trial, especially if the process of referring events for adjudication in the first place was flawed, as one OND reviewer has noted.[39] While we might learn something about the original adjudication process, a re-adjudication should be undertaken only if we will learn a sufficient amount of useful information about rosiglitazone to change substantively the overall conclusions about the cardiovascular risks of rosiglitazone. I have previously noted several problematic design issues with the RECORD study. The OND reviews that I have read have noted many of the same problematic design issues. Thus, re-adjudication of the cardiovascular events, by itself, is not likely to be helpful. Rather, re-adjudication of cardiovascular events should be undertaken only if other problematic aspects of the study can also be addressed.

I have not previously commented on the TIDE study. Here I will simply note that if the TIDE trial is to continue it will almost certainly require some modifications. One such modification is strengthening the informed consent process. Current and prospective trial participants will need a full, comprehensible, accurate and unbiased disclosure of the potential benefits and potential risks of the study treatments. Given that enrollment into the TIDE trial has been sluggish, I can only imagine that a revised informed consent process will further slow enrollment, to the extent that completion of the trial will not be attainable. Thus, if rosiglitazone remains on the market for unrestricted use (which I do not recommend) and the TIDE trial continues, there is at least a reasonable possibility that the TIDE trial will not be completed in a reasonable amount of time (if ever), and that the answers we need about rosiglitazone will not become available, a situation that is incompatible with the continued availability of rosiglitazone.

Conclusions and Recommendations

1. The benefits of rosiglitazone do not outweigh the risks for the treatment of diabetes.
2. Market withdrawal remains an appropriate regulatory action.
3. An acceptable alternative to market withdrawal would be to allow rosiglitazone to be available on a limited basis, through a restricted distribution program, to patients for whom rosiglitazone is basically the only option that results in achieving adequate glycemic control.
4. If the product remains marketed for general use, even with increased warning, and the TIDE trial continues, changes to the informed consent process will be needed.

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[39] Marciniak TA. Cardiovascular events in RECORD, NDA 21-021/S-035, June 14, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERALD J DALPAN
09/12/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

From: Curtis J. Rosebraugh, M.D., M.P.H.
Director, Office of Drug Evaluation II

To: John Jenkins, M.D.
Director, Office of New Drugs

This memorandum will not be an exhaustive review but is a supplement of certain issues that should be considered in addition to Dr. Parks's review.

My assessment of the most recent rosiglitazone Advisory Committee (AC) meeting held on July 13 and 14, 2010, is that the members voting (exact questions and votes are in Dr. Parks's review) and discussion reflected that:

1. The majority of members felt that there were data to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD agents and relative to pioglitazone. However, the data were not sufficient to raise safety concerns for mortality (or they could not conclude the data were sufficient-a subtle difference) in patients taking rosiglitazone compared to non-TZD agents or to pioglitazone.

2. Panel members were fairly evenly divided between the following regulatory actions for rosiglitazone:

   a) Continued marketing, no change to labeling or changes that could range up to contraindications for certain patient populations, second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents
   b) Continued marketing, revised labeling and restricted use to certain physicians or physician and patient education
   c) Market withdrawal

3. The majority of members felt that if rosiglitazone remained on the U.S. market that the TIDE trial should continue.

I agree with Dr. Parks conclusions which are:

1. Rosiglitazone should not be withdrawn from the market
2. The labeling for rosiglitazone and all rosiglitazone-containing products must be revised to reflect current information on cardiac ischemic risks
3. A postmarketing trial, such as TIDE, should be conducted (continued) to obtain interpretable data on the CV safety of rosiglitazone to inform FDA on an appropriate regulatory action

Based on the distribution and 'spread' of votes above, while it appears that the panel members had concern regarding an ischemic cardiovascular signal with rosiglitazone use, they were not concerned that the signal led to a mortality disadvantage, there was not widespread agreement regarding the strength of

association from the body of evidence for the ischemia signal, and finally, there was not widespread agreement on what regulatory actions should be taken. One could make a compelling argument that this represents equipoise regarding whether there are cardiovascular risk differences between rosiglitazone and other anti-diabetic agents, including pioglitazone, and what regulatory action the agency should take.

There are four issues that I will specifically comment upon:

1. What new information do we have that is different from 2007 that would cause us to alter our thinking from that time and guide us further in determining future action regarding rosiglitazone?
2. What do we need to do, if anything, with the current evidence (i.e. RECORD, CMS) to increase or decrease our reliance on the results?
3. If further evaluation of existing data is warranted, what actions should be taken while it is being conducted?
4. What is the timeline for accomplishing these actions?

The comments that I make regarding rosiglitazone and the associated safety and regulatory issues should be viewed in the context of the extraordinary environment within which we have been conducting our review of these issues, including unprecedented attention and scrutiny specific to rosiglitazone by Congress, the lay press and the scientific community. My hope is that this environment will not have a detrimental influence on our ability to ensure sound, science-based decision making by the Agency. It is essential that we remain attentive to our regulatory framework, standards of evidence under that framework, the needs of patients and their healthcare providers and how these all merge to serve the public health. However, there should be a realistic appreciation of the potential for politics, public opinion, fatigue, and conflict avoidance to influence policy in this environment. We should be vigilant that this does not happen and that science drives the process.

1. What new information do we have that is different from 2007 that would cause us to alter our thinking from that time and guide us further in determining future action regarding rosiglitazone?

There are four major pieces of evidence that are new for 2010 compared to 2007. It should be recognized that these examined the cardiovascular safety of rosiglitazone in several ways, comparing it to agents in different classes (mainly sulfonylureas and metformin), and to the other agent (pioglitazone) within its class. The four sources evidence are:

1) An update of the FDA meta-analysis of rosiglitazone controlled clinical trials that now includes 10 additional trials,
2) A meta-analysis of pioglitazone controlled clinical trials
3) A retrospective cohort study of Medicare claims (CMS study) commissioned by the FDA
4) Review of the data for the final results of the RECORD trial

<u>Updated FDA rosiglitazone meta-analysis</u>
In order to best facilitate comparisons to the pioglitazone meta-analysis, the 2010 rosiglitazone meta-analysis (52 trials=42 original trials from 2007 meta-analysis + 10 new additional) was performed using different methodology than the 2007 meta-analysis (42 trials). However, the Office of Biostatistics (OBS) also performed an analysis of the original 42 trials from the 2007 meta-analysis using the same methodology as that used in the 2010 meta-analysis. The main results are given below.

Table 1: Rosiglitazone, primary and secondary endpoints 42 trials and 52 trials-primary analysis across all trials

Endpoint	Stratified OR (95% CI) 42 Trials	Stratified OR (95% CI) 52 Trials
MACE	1.4 (0.9,2.3)	1.4 (1.0,2.2)
CV Death	2.0 (0.7,6.3)	1.5 (0.6,3.8)
MIF	1.8 (1.0,3.6)	1.8 (1.0,3.3)
Stroke	0.6 (0.3,1.5)	0.9 (0.4,1.8)
All-cause Death	1.9 (0.83,4.7)	1.4 (0.7,2.7)
Serious Myocardial Ischemia	1.8 (1.2,2.7)	1.5 (1.1,2.0)
Total Myocardial Ischemia	1.6 (1.2,2.2)	1.3 (1.1,1.7)
CHF	2.0 (1.3,3.2)	1.9 (1.3,3.0)

From this data, we can see that for the most part, the precision around the point estimate has increased and that most of the point estimates have remained the same, or actually decreased. These new data would not seem to be an important determinant in changing our decisions from that made after the 2007 Advisory Committee meeting. It remains important we be cautious in placing confidence in, or draw final conclusions from, meta-analysis results with small differential estimates that are better used as hypothesis generators.

It should be noted that the above analysis is different from that recently published in the New England Journal of Medicine (NEJM) by one of the panel members, Cliff Rosen, MD.[1] In his perspective piece, Dr. Rosen appears to have used a slide from the FDA OBS presentation that contained the original 2007 analysis of 42 trials (different methodology) and also had the 2010 results of 52 trials. While the presenter explained the differences and that the two different analyses should not be directly compared, Dr. Rosen appears to have done this in his perspective piece. In order to directly compare what effect the addition of 10 trials would have to the original 42 trials, the same method of analysis should be used in both the pool of 42 trials and 52 trials as is presented above.

<u>Pioglitazone meta-analysis</u>

OBS also performed a meta-analysis on pioglitazone data. While they tried to have analyses comparable to that of rosiglitazone such that there could be a comparison of 'apples to apples' between the meta-analyses, they had limited success. The trials within each database were of different designs and patient populations resulting in systematic differences thereby limiting the ability to make direct cross meta-analysis comparisons. Of course, human nature being what it is, different people have done cross meta-analysis comparisons. Our OBS colleagues feel that if one were to do that, the most comparable groups would not be the overall comparison of all trials, but those in which both rosiglitazone and pioglitazone were compared to a common agent. The results from this comparison are below (from page 26 of statistical briefing material for 2010 AC Meeting).

Table 2. Odds ratio estimates for MACE across different trial groups by meta-analysis

		Stratified OR (95% CI)	
Comparator	Meta-analysis	MACE	CHF
Placebo	PIO	0.6 (0.2, 1.7)	1.8 (0.6, 5.8)
	ROSI	1.5 (0.9, 2.5)	2.2 (1,4, 3.5)*
Active	PIO	0.9 (0.6, 1.3)	1.4 (1.0, 2.2)

[1] Rosen CJ. Revisiting the rosiglitazone Story—Lessons Learned. N Engl J Med. 2010 Jul 21. [Epub ahead of print]

	ROSI	1.1 (0.5, 2.3)	1.2 (0.5, 3.3)
Sulfonylurea	PIO	1.2 (0.7, 2.0)	1.6 (1.0, 2.6)
	ROSI	1.2 (0.5, 2.8)	1.2 (0.5, 3.3)
Metformin	PIO	0.6 (0.3, 1.3)	0.9 (0.2, 3.0)
	ROSI	0.4 (0.0, 7.6)	-

*This value is different than the AC briefing document as the briefing document had an erroneous value

From the data above, it would appear that when one looks at MACE, the point estimate for pioglitazone for two groups (placebo, active) is less than for rosiglitazone, while the point estimate for one group (sulfonylurea) is identical and greater for another (metformin). The confidence intervals do not reveal elevated risks as all include unity (1). A similar exercise for CHF reveals that the point estimate for pioglitazone for one group (placebo) is less than rosiglitazone, but is greater for two groups (active, sulfonylurea). This would not support the assertion of some that pioglitazone causes less CHF than rosiglitazone. These results do not seem to warrant a radical change in FDA's regulatory direction with regard to rosiglitazone and actually provide some reassurance that there may not be differences between these two PPAR agents.

Retrospective cohort study of Medicare claims (CMS study)

I agree with Dr. Parks that this study has many strengths and warrants further investigation as a hypothesis generator. I also agree with Dr. Parks that this study has weaknesses, and it is perplexing that the results demonstrate that the original signal that started the rosiglitazone controversy, myocardial infarction, was not demonstrated to be different between rosiglitazone and pioglitazone in this study. Although Dr. Graham explains this by asserting that there were MI cases embedded within the mortality results, this is speculative and fragile at best. The remaining results, hazard ratios of 1.27 for stroke, 1.25 for heart failure, 1.14 for all-cause mortality and 1.15 for acute MI, stroke or death are all less than two and would represent a relatively low magnitude of association.[2] In nonexperimental research, bias can never be entirely eliminated and therefore the association should be large relative to any plausible biases.[1]

In observational studies, there are good reasons why a hazard ratio less than 2 is considered a low magnitude of association and it is worth reviewing the mathematical exercise that Shapiro went through to explain this.[1] In his paper, Shapiro considered a hypothetical exercise from a case-control design study comparing 100 controls to 100 cases and two forms of bias, informational and selection. In the exercise, an information bias of 2 controls and selection bias of 2 exposed cases resulted in a relative risk of 1.14 (similar to some of the point estimate results in the CMS study), demonstrating the fragility of estimates less than 2. Although the CMS PPV% ranged from 85-100% depending on category, this exercise demonstrates that it takes little bias (2% of categorizations-well within the PPV) to account for changes less than 2 and in a very large comparative cohort study like the CMS, modest bias could dominate and account for the observed relative risk of the magnitude observed.

Therefore, reliance on the magnitude of point-estimates demonstrated in the CMS study is problematic and should not be used as a basis for making regulatory decisions. Instead, its utility is in generating hypotheses for further study. Also, this is a very new use of this database and we have not performed any sensitivity analysis to try to determine what level of point estimate may give robust results. In making a regulatory decision such as the one here that could have profound impact on future actions, we should use methods with which we have experience and comfort with the validity of the results.

[2] Shapio S. Bias in the evaluation of low-magnitude associations: An empirical perspective. Am J Epidemiol. 2000 May 15;151(10):939-945

Although I will not discuss it in detail, we are in possession of an abstract of a study by WellPoint that seems to be of the same design as the CMS study that we commissioned. This study compared the risk of myocardial infarction and cardiovascular death among pioglitazone and rosiglitazone-treated patients in a managed care population. The draft manuscript claim that there is not a significant difference between rosiglitazone or pioglitazone treated groups for the risk of acute MI/CV death. This warrants further investigation, particularly in light of the limited magnitude of effect seen in the CMS study. It may also demonstrate that relatively weak association point estimates can easily be biased in either direction.

Review of the RECORD trial

During the 2007 AC, preliminary results of RECORD were presented. The data that formed these results had not been reviewed by the agency at that time, but did offer some reassurance that rosiglitazone did not have increased cardiovascular events compared to agents in different classes (mainly sulfonylureas and metformin) and might actually have a better profile for some individual endpoints. These preliminary data probably gave panel members some reassurance that rosiglitazone, compared to sulfonylurea and metformin, did not have the signal that was seen in the FDA meta-analysis (where the main comparators were also sulfonylurea and metformin), as, despite being open-label, RECORD was a long-term, randomized, controlled trial.

For the 2010 AC, we performed a thorough review of the RECORD data. The review findings and how much reliance can be placed on RECORD have proven to be quite controversial. As part of the review, DMEP placed a consult with the Division of Cardiovascular and Renal Products (DCRP), which was performed by Dr. Marciniak. During his review, Dr. Marciniak originally identified eight cases that he felt represented cases that should have been sent to the independent panel for adjudication and were not. This understandably caused him concern that reporting bias or even manipulation of cases by the sponsor may have occurred. Dr. Marciniak also had several issues with the trial design and endpoints, however, it must be recognized that this trial was designed between the sponsor and the EMEA to answer EMEA specific concerns and not as part of a request by the FDA.

During our preparation for the AC and as part of the review, Dr. Marciniak's eight cases were thoroughly investigated by the Division of Scientific Investigation (DSI) in conjunction with an independent medical reviewer from DRCP. Seven of the eight cases were determined to have had appropriate handling and were in compliance with the protocol. The eighth case was not originally sent for adjudication. Upon review of the SAE by the sponsor, they requested the investigator to submit the case for adjudication. The investigator complied with this request, but apparently filled out the incorrect form, so the case was sent back. Further, careful evaluation by DSI did not reveal any evidence of misconduct.

Dr. Marciniak was not reassured by the findings of DSI for reasons that were unclear and also did not seem to accept their findings regarding these eight cases of concern. His presentation at the 2010 AC meeting focused on his concerns about RECORD's potential bias and probably undermined the panel members' confidence in RECORD thus influencing some of the voting. He also presented his own unblinded readjudication of random cases applying a different set of definitions for cardiovascular events from those stipulated by the RECORD protocol. His review revealed higher rates of cardiovascular events than that reported by the sponsor for rosiglitazone compared to non-rosiglitazone treatment. Finding of important differences for adverse cardiovascular events associated with rosiglitazone use is concerning, and I agree that there are obvious flaws with RECORD (open label being the greatest). There is, however, great concern with a reviewer going into a database that he already believes may have problems, using different definitions of the endpoints for those originally used and in an unblinded fashion searching for further evidence to support their own concerns. This is a practice that we are careful to assure does not occur among investigators or sponsors in analyzing trial data because it is fraught with its own biases.

Dr. Unger, Deputy Director of the Office of Drug Evaluation I, in his review and presentation at the 2010 AC acknowledged concern for potential bias in the open-label nature of RECORD, but also noted the flaws with Dr. Marciniak's approach regarding readjudication. Dr. Unger expressed confidence that the mortality data for the trial are likely secure, as mortality is an objective endpoint less prone to bias by the open-label design.

With the conflicting views of the RECORD database, except (perhaps) for the mortality data (which wasn't concerning and favored rosiglitazone use) without an impartial third party looking at blinded data, it is hard to know what the truth is regarding the data collected for RECORD. However, our review of the data is new since 2007, and the impact of the data integrity controversy in AC panel members thinking was probably great and therefore warranted discussion. Except for the mortality data, at this point RECORD provides limited confidence regarding the results and the controversy surrounding data integrity probably had a greater impact on the voting by panel members for the 2010 AC meeting compared to the 2007 AC meeting.

2. **What do we need to do, if anything, with the current evidence (i.e. RECORD, CMS) to increase or decrease our reliance on the results?**

In order to make a fully informed decision, we need to have a clear picture of what each piece of data adds to the body of evidence. In order to do this, I believe that RECORD should be readjudicated. This could be done in a step-wise fashion, starting first with mortality, then hospitalizations and then the rest of the data. The readjudication should be done by an independent third party in accordance with usual agency procedures. The readjudication should mirror the original intent of the study (although other analyses could be add in for further hypothesis generation), using the definitions for endpoints that were used in the final protocol.

I also believe that we need to perform sensitivity evaluation of the CMS database to understand what level of magnitude correlates with an association. What type of analyses we perform should be undertaken with OBS guidance, but examples are well described in the literature, such as those described by Austin[3], and other exercises such as randomizing the pioglitazone subjects based on even/odd birth date and comparing them to each other to see what level of association may be generated on items that clearly should not have an association. It would also be useful to compare different statin therapies based on the same endpoints to determine if there is a rank ordering as well as perhaps different hypertensive agents or NSAIDS or sulfonylureas. One could wonder if we see rank ordering of these different agents of the magnitude that was demonstrated for the PPARs, if we would take a regulatory action.

Finally, I believe that we should obtain and evaluate the WellPoint database. To make a final decision without this data would be a demonstration of lack of understanding of the nuances of evidence and could be seen as sacrificing scientific process for political expediency.

3. **If further evaluation of existing data is warranted, what actions should be taken while it is being conducted?**

I believe that it is prudent, due to the uncertainty surrounding the cardiovascular adverse event profile, to fully inform practitioners and patients to the potential risks which should serve to limit the exposure of patients to rosiglitazone to those felt appropriate. I would contend however, that this is probably already happening. Sales for this product are flat, suggesting a great deal of selection in prescribing.

[3] Austin PC, Mamdani MM, Juurlink DN, Hux JE. Testing multiple statistical hypotheses resulted in spurious associations: a study of astrological signs and health. Jo Clin Epidem. 59 (2006) 964-969.

The scientific data do warrant labeling changes for rosiglitazone, including additional information in the box warning, and Warnings and Precautions sections to update the meta-analysis information. I would not include data from the CMS study at this point, because our understanding of the value and dependability of this database is in its infancy, especially for relative risks ratios that are under two. Consideration should be given to whether labeling should indicate that rosiglitazone be used in those who have failed other drugs of the class. We have had other examples where we have employed this mechanism while awaiting additional safety data, such as biologic products for rheumatoid arthritis. However, if labeling of this sort were to occur, I would limit the wording to saying something in regard to a consideration of other agents should be given before starting rosiglitazone due to unresolved cardiovascular safety issues.

It is important to note that that there is not any randomized clinical trial data comparing rosiglitazone to pioglitazone to support specific labeling of using one product over another should we move in this direction. The support would be that trials have not indicated that pioglitazone has evidence of a concern for cardiac ischemia while this issue remains unresolved for rosiglitazone. It should also be kept in the back of our minds that there is an unresolved issue regarding the bladder cancer potential for pioglitazone. So in effect, we could be supporting the channeling of patients (I say supporting because it has already happened without a labeling change) from rosiglitazone to pioglitazone and a potential for increased bladder cancer risk. I also believe we should use the CMS database to compare cancer, and bladder cancer risks between rosiglitazone and pioglitazone.

Finally there is the question of whether we should continue the TIDE, or a similar trial, to make definitive conclusions regarding any cardiovascular adverse event rate. Making appropriate scientific and regulatory decisions in a highly charged environment such as this can be difficult, takes dedication to principles and in most cases, courage, perseverance and thick skin. I have concerns that the degree of negative press surrounding rosiglitazone may make it untenable for local IRBs and other oversight bodies (both domestic and foreign) to continue to support a randomized trial. This may be more indicative of a reluctance to face some of the very vocal critics of rosiglitazone than a true concern about acceptability of such a trial. It is worth noting that up until recently, 39 countries and 816 independent sites had felt that TIDE was an ethical study and were allowing enrollment.[4]

The recent IOM letter report[5] requested by the FDA to examine ethics and scientific issues in studying the safety of approved drugs suggests that a trial such as TIDE can be ethically performed. This report states that the risk-benefit balance should be judged to be acceptable by FDA, participating IRBs, and the DSMB before initiation and throughout the course of the trial. The original decision to begin TIDE fulfilled all these criteria: we required the study, most potential study site IRBs judged it to be ethical, and the DSMB judged it to be ethical. It is now critical to examine what if anything has occurred since initiation (or what new data do we have) that calls its continuation. I believe that we have the same degree of uncertainty and, based on the variety of scientific opinions voiced at the 2010 Advisory Committee Meeting, equipoise as we had in 2007 when we began the process of requiring what ultimately became the TIDE trial.

To further elaborate, the IOM letter report, as part of their conceptual framework, discusses the Public Health Context stating that the "FDA should determine that there is a substantial public health question about the nature or acceptability of the risks, or the risk-benefit profile, of a marketed drug-a question that requires a policy decision from FDA." This is a policy decision of great magnitude in that it is determining the body of evidence necessary to make regulatory safety decisions. It is important to realize

[4] Gerstein H. TIDE presentation, Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. July 14, 2010

[5] Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs. July 9th, 2010

that the 'body of evidence' criteria for a safety decision is not likely to ever be as well-defined as what we have for efficacy evidence (Two or more well-designed randomized trials demonstrating substantial evidence) and is likely to be different to the eye of each beholder. However, like law, regulatory science is built on prior precedents and this decision will be an important, perhaps pivotal, 'case' that will be referenced for future decisions.

The IOM conceptual framework also states under Design Considerations that it is appropriate to require a randomized controlled trial when "uncertainty about the risk-benefit balance is such that a responsible policy decision cannot be made based either on the existing evidence or on evidence from new observational studies." Observational studies in this case have very small effect sizes (odds ratios less than 1.5-2.0, frequently cited as the minimal necessary for an association) that clearly could be influenced by bias. As the IOM conceptual framework states, "If the estimated relative risks are small, selection bias, confounding, and measurement error may be alternative explanations for associations found in an observational study". I submit that we clearly are in an environment of insufficient evidence to make an appropriate policy determination from observational studies. We are also at equipoise, again demonstrated by the voting opinions from the recent Advisory Committee panel members where the majority felt that if rosiglitazone were to stay on the market that the TIDE study should continue. Further evidence of equipoise can be seen by the opposing stances of various professional organizations and societies regarding the marketing and continued study of rosiglitazone. It is important to consider that TIDE has a DSMB so that differences in adverse effects can be closely monitored and, if detected, the trial can be terminated early. It is also interesting to note that the most fervent critics of TIDE seem mute on the PRECISION trial, which is similar in hypothesis and design (i.e. evaluate potential for excess cardiovascular harm from celecoxib compared to naproxen or ibuprofen).

Dr. Parks has observed that TIDE may not be feasible due to recruitment problems and we also heard at the AC that there has been low recruitment. I do not find this unusual given our environment and it is very similar to what occurred at the early stage of the JUPITER trial for rosuvastatin (Crestor). At that time, harsh public criticism and a well publicized Citizen's Petition asking for rosuvastatin's withdrawal from the market due to unsubstantiated safety concerns hampered recruitment. However, once the agency denied the Citizen's Petition, recruitment increased and the trial was able to be performed and completed. It is interesting to note, that JUPITER was performed in subjects that, at the time, were too 'healthy' to qualify for statin therapy so an ethical argument could have been made about exposing such a healthy population to a drug that some felt had greater harm than other available agents. However the final results indicated that rosuvastatin did not have the theoretical adverse events of concern and Jupiter has been considered by some a revolutionary study, expanding the patient population that may receive benefit from statin therapy. It is concerning that studies like JUPITER that have clearly advanced public health may not conducted should there be widespread adoption of the viewpoint of what constitutes an ethical study that some have advanced during this debate.

Finally, despite the unprecedented negative publicity that has surrounded rosiglitazone, the sponsor has determined that approximately 550,000 patients still use this medication. It is important that we do know if there is a cardiovascular risk for this population.

4. What sort of timeline should we do this under?

We can take fairly quick action in implementing the labeling changes recommended in Dr. Parks and my review. However, it will take some time to resolve other issues such as re-adjudication of RECORD and sensitivity analysis of the CMS database. The FDA Office of the Commissioner has set a goal for resolving rosiglitazone by the end of August. If by resolve it is meant that a path forward is charted, that can be accomplished. I am not confident that a definitive conclusion about the drug's risk and a decision that it should be removed from the market is possible in that time frame simply because the data remain incomplete and inconclusive needing further refinement as described above.

Our action on this drug must take into account the precedence of the decision and how factors such as the enormous publicity, often devoid of balance, might weigh in on the process. We must consider unintended consequences of whatever action is taken and how they may affect the next drug with an inconclusive safety signal, and there are many inconclusive safety signals for many drugs. We must ensure that FDA's decision rests on scientific underpinnings, something that is difficult to do in the environment we find ourselves in with rosiglitazone. To do otherwise risks undermining our statutory responsibility and our scientific and regulatory objectivity.

CONCLUSIONS AND RECOMMENDATIONS

There is evidence, mostly through meta-analyses and observational studies, of a higher risk for some ischemic cardiovascular events of rosiglitazone, but not others, compared to other diabetic agents in different classes. There is not evidence of increased mortality of rosiglitazone compared to different classes of diabetic agents (and perhaps there is an advantage). This creates cognitive dissonance for understanding what the true effect may be as one would expect these two outcomes to track together. This is the hallmark of equipoise: we simply do not have robust, confidence-inspiring data that informs us as to whether there is a true risk.

Some have concluded that the data suggesting a potentially increased risk for ischemic events with rosiglitazone along with the absence of such evidence for pioglitazone, should lead FDA to withdraw rosiglitazone from the market. Understanding how drugs compare to one another is always desirable, but employing this type of logic along with the scientific treachery of cross study comparison is extremely problematic. Taking action on the basis of such a strategy would set a precedent that 'suspicion' should translate into immediate regulatory action. It is a narrow perspective that does not give full consideration to quality of data and risks erroneous conclusions, as history has already shown us. Dr. Gerstein, the lead investigator for the TIDE trial was correct to point out at the 2010 AC meeting that if we were to apply this paradigm (acting on 'suspicion' generated by meta-analysis or observational studies and not looking for more definitive evidence), we would still be routinely using hormone replacement therapy for cardiovascular benefit, a myth propagated by observational studies but dispelled by the Women's Health Initiative randomized trial[6] (WHI). The WHI trial is an example of how incorrect observational studies and biological plausibility can be as there was a large body of observational studies showing cardiovascular benefit and there was biological plausibility support as hormone replacement has a positive effect on lipid profiles. Yet, the WHI randomize trial demonstrated that all this was incorrect and there was actually cardiovascular harm from hormone replacement therapy. We should also realize that the WHI was delayed many years as the proponents of observational studies felt it was unethical to place women on placebo, denying them what they felt was clear evidence of cardiovascular benefit from hormonal therapy.

The WHI is not an isolated example. We would also still be suppressing ventricular pre-mature beats after myocardial infarction as the evidence from observational studies indicated this improved mortality, but was ultimately soundly refuted with randomized trials. For both of these examples, if we were to allow the concept that observational or meta-analysis revealed 'truth' that would make any control trial impossible due to ethical reasons associated with placebo exposure. While these two examples were of using randomize trials to further define 'benefit' of therapy, there are examples where randomized trials have been used to explore whether there is possible 'harm' from drug use. Meta-analysis or observational studies (and theories of 'biologic plausibility') demonstrated cardiovascular harm with the use of digoxin, calcium channel blockers and tiotropium. All of these examples were proven to be quite wrong when adequately design randomized trials were performed. There have been, and will continue to be false

[6] Rossouw JE et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002 jul 17;288(3):321-33.

‘dogmas’ that arise from meta-analysis and epidemiologic data with small magnitude of effects and we should always explore these with more definitive data. It is also important to keep in mind that pioglitazone itself may have a cancer adverse effect not seen with rosiglitazone which needs to be further explored and weighed in any decision.

The evidence that we have regarding the potential for rosiglitazone to cause ischemic events is concerning but tenuous and does not support removal at this point. I recommend continued marketing, the labeling changes outlined by Dr. Parks, and continuation of the TIDE trial and further analysis of existing data as outlined above.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	ORIG-1	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
08/23/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

DATE: August 19, 2010

FROM: Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products

TO: Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation 2

John K. Jenkins, M.D.
Director
Office of New Drugs

SUBJECT: Recommendations on marketing status of Avandia® (rosiglitazone maleate) and the required post-marketing trial, Thiazolidinedione Intervention and Vitamin D Evaluation (TIDE) following the July 13 and 14, 2010 public advisory committee meeting

I. INTRODUCTION

On July 13 and 14, 2010, the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) held a second advisory committee meeting involving members of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC), the Drug Safety and Risk Management (DSARM) Committee, and invited experts in biostatistics, epidemiology, endocrinology, and ethics to discuss cardiovascular safety concerns involving Avandia®, hereafter referred to as rosiglitazone. This memo serves as the final recommendations from the Division of Metabolism and Endocrinology Products (DMEP) regarding the marketing status of rosiglitazone and the status of the required postmarketing trial, Thiazolidinedione Intervention and Vitamin D Evaluation, hereafter referred to as the TIDE trial.

On the second day of the meeting, panel members were asked six voting questions. These questions were preceded by requests for discussion. Prior to the formal discussion session, a majority of the panel members voted to revise four of the six voting questions (Questions 2, 3, 5, and 6 were revised). I have summarized below all voting questions posed to the panel members, including the revisions made, and the final votes. The results of the votes and the explanations for each member's vote, along with the discussions from the meeting, were considered in the Division's decision. Please see the transcripts from the two-day advisory committee meeting for a detailed account of all presentations, discussions, and recommendations available at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm

VOTING QUESTIONS (ORIGINAL AND REVISE) AND FINAL VOTING RESULTS

2. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
C. I am not able to make a finding A or B.

REVISED QUESTION #2
Considering the available data, do you find that, for rosiglitazone (choose 1):

A. These data are sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
B. These data are not sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
C. I am not able to make a finding A or B.

VOTING RESULTS:
A. 18
B. 6
C. 9

3. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

REVISED QUESTION #3
Considering the available data, do you find that, for rosiglitazone (choose 1)

A. These data are sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
B. These data are not sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 21
B. 3
C. 9

5. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
B. Does not increase the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
C. I am not able to make a finding A or B

REVISED QUESTION #5
Considering the available data, do you find that, for rosiglitazone:

A. These data are sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
B. These data are not sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 1
B. 20
C. 12

6. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of mortality in patients with Type 2 diabetes relative to pioglitazone
B. Does not increase the risk for mortality in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

REVISED QUESTION #6
Considering the available data, do you find that, for rosiglitazone (choose 1):

A. These data are sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to pioglitazone
B. These data are not sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 7
B. 12
C. 14

8. Based on the available data, which of the following regulatory actions do you recommend FDA pursue regarding rosiglitazone? Please select only one option or if you wish to abstain, do not vote. (These options are listed from most favorable to rosiglitazone to least favorable to rosiglitazone and do not reflect any prejudgment on the part of FDA.)

A. Allow continued marketing and revise the current label to remove the boxed warning and other warnings regarding an increased risk of ischemic CV events, or
B. Allow continued marketing and make no changes to the current label, or

C. Allow continued marketing and revise the current label to add additional warnings (e.g., contraindications for certain patient populations, recommendation for second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents); or
D. Allow continued marketing, revise the current label to add additional warnings, and add additional restrictions on use (such as restricting prescribing to certain physicians or requiring special physician and patient education)
E. Withdrawal from the U.S. market

VOTING RESULTS:

A. 0
B. 3
C. 7
D. 10
E. 12
Abstain: 1

9. If rosiglitazone remains on the U.S. market, do you recommend that the TIDE trial be continued in order to provide further data on the comparative CV safety of rosiglitazone, pioglitazone, and standard-of-care management of type 2 diabetes (placebo add-on)?

Vote Yes/No/Abstain

VOTING RESULTS:

YES: 19
NO: 11
ABSTAIN: 2
NON-VOTING: 1 (member departed before meeting adjourned)

In reviewing the data presented and the advisory panel recommendations I have concluded the following:

1. Rosiglitazone should not be withdrawn from the market
2. The labeling for rosiglitazone and all rosiglitazone-containing products must be revised to reflect current information on cardiac ischemic risks
3. A postmarketing trial, such as TIDE, should be conducted to obtain interpretable data on the CV safety of rosiglitazone to inform FDA on an appropriate regulatory action.

In the remainder of this memo I will outline the reasons for my recommendations and action items for each of these recommendations.

II. RECOMMENDATION #1: Rosiglitazone should not be withdrawn from the market

I am making this recommendation because I do not believe there is sufficient evidence from available data to conclude that rosiglitazone is associated with significant cardiovascular risks to outweigh its benefits as an effective glucose-lowering agent. We also do not have adequate and well-controlled data comparing rosiglitazone to pioglitazone to conclude that pioglitazone is a safer alternative and should be the only marketed thiazolidinedione available to patients.

The clinical evidence put forward to conclude rosiglitazone has cardiovascular risks has come from:

A. Meta-analyses of controlled clinical trials of rosiglitazone
B. RECORD trial
C. Indirect comparisons of rosiglitazone to pioglitazone from observational studies of health claims database
    1) Published observational studies
    2) Retrospective cohort study of Medicare claims
D. Separate meta-analyses of controlled clinical trials of rosiglitazone and pioglitazone

As there are well over 1000 pages recently prepared by the FDA on these four sources of clinical data, I will only highlight the key findings from and the characteristics of these data which have swayed me in the direction of recommending the continued availability of rosiglitazone in the U.S. In this memo, I will only discuss the new information presented by FDA at the July 13 and 14, 2010 advisory committee meeting.

A. Meta-analyses (MA) of Randomized Controlled Clinical Trials of Rosiglitazone

There were multiple meta-analyses performed of randomized controlled clinical trials of rosiglitazone, all suggesting a risk for cardiovascular harm associated with rosiglitazone use. Although the large sample size of these databases (data from 16,995 patients in FDA's 2010 MA and 35,531 patients in Nissen's 2010 MA) and the inclusion of only randomized, controlled trials are strengths of these databases, the limitations were numerous and outweighed these strengths. Unlike rare drug-related safety concerns such as Stevens-Johnsons syndrome, agranulocytosis, or rhabdomyolysis, which are more easily identified and attributed to drug exposure, CV events are common in the diabetes patient population and require more precision in their ascertainment and adjudication. Reliance on meta-analyses, particularly the ones considered for rosiglitazone, is problematic for the following reasons:

- The MAs were comprised of studies that were not prospectively designed to evaluate cardiovascular risk in patients with type 2 diabetes. These studies, like all other clinical trials for anti-diabetic therapies approved at that time, were designed to assess glycemic control effectiveness. As a result, CV events were not prospectively adjudicated in a blinded fashion but relied on investigator reporting of adverse events in the clinical trial which has the potential for biased ascertainment and misclassification contributing to an imprecision in assessing CV risk.
- The overall event rates were too low to allow a meaningful assessment on a common condition. In the FDA's 2010 MA, the overall incidence of MACE was 0.6%. In order to accurately determine whether a drug is associated with an excess CV risk, a sufficient number of events is needed to determine if different event rates between treatment groups reflect true risk differences and not chance finding.
- The majority of these trials were < 1 yr duration. In the FDA 2010 MA, 45/52 (86%) of the trials were < 1 yr duration. Trials of short duration may not be adequate to assess long-term CV risks and benefits. To highlight this point the following table shows the risk estimates in the FDA's 2010 MA broken down by duration of trials for MACE, CV death, MI, stroke, and all-cause death where a trend of decreasing risk is noted with longer duration of evaluation on all events except stroke.

Table 1. FDA's Meta-analysis of Rosiglitazone Trials Subgrouped by Trial Duration

Outcome	Trials < 6 mos (21 trials)			Trials ≥ 6 mos to < 1 yr (24 trials)			Trials ≥ 1 yr to ≤ 2yrs (7 trials)		
	RSG N=2942	Control N=2258	OR (95% CI)	RSG N=5729	Control N=3504	OR (95% CI)	RSG N=1368	Control N=1194	OR (95% CI)
MACE	12	2	4 5(0.97,4.2)	36	19	1.3(0.73,2.5)	22	18	1.19 (0.6,2.38)
CV death	2	0	Inf (0.09,inf)	12	3	2.8(0.73,15.6)	3	6	0.5(0.08,2.37)
MI	10	0	Inf (1.75,inf)	22	10	1.57(0.7,3.78)	13	10	1.21(0.49,3.13)
Stroke	2	2	0.6(0.04,9.04)	10	9	0.74(0.26,2.12)	6	5	1.23(0.3,5.1)
All-cause death	5	1	3.78(0.4,183.4)	15	5	2.02(0.68,7.22)	9	11	0.83(0.30,2.22)

Similarly, in the long-term CV outcomes trial with pioglitazone (PROactive), assessment of CV risk at 6 months in this 3-yr trial showed an unfavorable trend for this drug compared to placebo for nonfatal MI, stroke, acute coronary syndrome, major leg amputation, coronary intervention, and leg revascularization procedures (Table 2 below).

Table 2 Results for Predefined Secondary Endpoints for PROactive (Measured at 6 Months)

Endpoint	Pio N=2605 n (%)	Pbo N=2633 N (%)	HR[1]
Cardiovascular mortality	20 (0.8)	27 (1.0)	0.8
All-cause mortality	25 (1.0)	30 (1.1)	0.9
Nonfatal myocardial infarction	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	1.3
Acute coronary syndrome	14 (0.5)	8 (0.3)	1.7
Major leg amputation	4 (0.2)	2 (0.1)	2.0
Coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention)	33 (1.3)	32 (1.2)	1.1
Leg revascularization	18 (0.7)	9 (0.3)	2.3

Source: Tables 1-12, Table 2.1, Table 2.2, provided by Takeda by email 13 May 07
1 Pio rate/ pbo rate; confidence intervals for the 6-month hazard ratios not provided

If assessment for CV risk of pioglitazone was limited to just 6 mos or < 1 yr, a similar conclusion of CV harm might have been made for this drug.

- Choice of studies to include in a MA can have a marked effect on the risk estimate. This was noted in Nissen's 2010 MA when he presented data including and excluding the RECORD trial. The point estimate shifted by 10% and 37% for MI and CV death, respectively. In both analyses, exclusion of the long-term trial resulted in a higher risk estimate.
- There was no prospective analysis plan that would correct for multiple comparisons. Many CV events were analyzed in these MAs and no correction for multiplicity was applied. Disparate findings (e.g., increase risk of MI, decreased risk of stroke) may be weighted differently depending on what position one holds in this debate.

Overall, the meta-analyses of rosiglitazone trials suggest a signal of CV risk; however, the limitations of such a database in assessing this risk, the inconsistent findings between the MA and long-term controlled trials on stroke and mortality, and the non-robust increase with marginal statistical significance all require

the FDA to apply a more rigorous scientific standard beyond reliance on these MAs alone to withdraw rosiglitazone from the U.S. market.

B. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Trial

RECORD was an open-label trial comparing the addition of rosiglitazone to metformin when either one was added on to background sulfonylurea and the addition of rosiglitazone to sulfonylurea when either one was added on to background metformin. The primary objective was to show non-inferiority, defined as the demonstration that the upper bound of a two-sided 95% CI for the hazard ratio would be below 1.2, between rosiglitazone combined with either metformin or sulfonylurea to the combination of metformin and sulfonylurea on the primary composite endpoint of CV death and CV hospitalizations. The published results and data presented by GlaxoSmithKline (GSK) supported the company's conclusion that the primary objective was met and that rosiglitazone had no significant CV risk over two commonly prescribed anti-diabetic agents. In an efficacy supplement, GSK is proposing removal of language on increased risk of myocardial ischemia from the boxed warning and elsewhere in the product label based on the findings from RECORD.

Dr. Tom Marciniak from the FDA's Division of Cardiovascular and Renal Drug Products (DCRP) identified deficiencies in events reported to the adjudication committee and undertook a re-adjudication of a random sample of case report forms (CRFs) from the rosiglitazone and control groups. He identified 8 adverse events which should have been sent for adjudication by the investigator and all cases were in the rosiglitazone group. All 8 cases were reviewed by the Division of Scientific Investigations and an FDA medical officer from DCRP who participated in the inspection of several clinical sites. Only one of the 8 cases was identified as inappropriately dismissed by the investigator as a possible endpoint that should have been sent to the adjudication committee.

In his readjudication of events, Dr. Marciniak recalculated hazard ratios based on his assessment of which events should have been counted as MI, stroke, CV death, or MACE. His analyses yielded higher risk estimates for MI and MACE, not favoring rosiglitazone. Although his findings are concerning, I can not conclude that his numbers reflect the true event rates in this trial because an unblinded readjudication by one individual applying a more current definition for some of these events which occurred out to 10 years ago may also introduce its own bias. Furthermore, even though his re-analysis of CV death and all-cause death showed less of a risk reduction for rosiglitazone, the overall finding still favored rosiglitazone. I also agree with Dr. Ellis Unger, who wrote a secondary review accompanying Dr. Marciniak's review, that the mortality findings, which are less subject to biased adjudication and consistently show a lower risk for rosiglitazone in both the ITT and per-protocol analyses, provide me with reassurance that the RECORD trial may provide relevant long-term CV safety data for rosiglitazone since it has been argued that the majority of deaths in the diabetes population is CV-related.

Regardless of the differences in opinion, I agree with the important points made by both Drs. Marciniak and Unger, that the open-label design and the allowance for investigators to determine whether an event should be submitted for adjudication by the blinded endpoint committee diminishes the strength of this randomized, controlled trial. However, since RECORD remains the ONLY large, completed, prospectively-designed, controlled trial that might immediately address the concerns raised from the meta-analyses, I believe the FDA should require GSK to re-adjudicate events in this trial by an independent committee (no GSK representation) with clearly defined procedures for identifying events vetted by a team of cardiologists and neurologists. Because this will be a significant undertaking, I would propose a re-adjudication of mortality findings be performed initially. If significant problems are identified with completeness of vital status and causality of death, I would conclude that RECORD can not be relied upon and no further efforts should be placed into complete adjudication of this trial. If this initial re-adjudication yields similar findings to what the applicant reported in its efficacy supplement, a complete re-adjudication should then be undertaken for MI, stroke, and CV death, the components of

MACE, and the composite endpoint that is more widely accepted in intervention trials assessing CV risks and benefits.

I would note that Drs. Teerlink and Geller both recommended re-adjudication of RECORD in their responses to voting questions 2 and 3 and Dr. Flegal also raised concerns about Dr. Marciniak's "revisiting" events in RECORD without having his findings adjudicated.

C.1. Published Observational Studies

At the July 2010 advisory committee meeting, Dr. Kate Gelperin presented her review of published controlled epidemiologic studies of rosiglitazone and pioglitazone. The methodology for selecting published studies has been described in her review. She identified 21 studies: 7 nested case-control and 14 cohort, all retrospective in design. Events of interest included acute MI, stroke, mortality, coronary artery disease, heart failure, angina pectoris, transient ischemic attack, cerebrovascular accidents, coronary heart disease, coronary revascularization, unstable angina, cardiac death, and coronary artery procedures. Many of these outcomes were identified through ICD-9 or -10 codes but some studies relied on other identifiers unique to the healthcare database upon which the studies were based. Some of the studies identified the outcome of interest based on the primary reason for hospitalization. It should be noted that this endpoint was a component of the primary endpoint in RECORD and was criticized by Dr. Tom Marciniak as follows:"*CV hospitalization reasons are diverse and include ones that are unlikely to be affected by one drug."* And as noted by Dr. Gelperin, collection of only hospitalized events would miss events not requiring hospitalization. Consequently, complete ascertainment and appropriate adjudication of events are some of the limitations of this database.

Another concern about the observational studies is the contribution of publication bias to the availability of data. Since studies published after 2007 may be affected by the Nissen meta-analysis either as publication bias or biased reporting of events, it is important to note the year of publication for all 21 studies. Of the 21 studies, only two were published before 2007 (Karter and Rajagopalan) and both of these involved the comparison of pioglitazone to another anti-diabetic agent (SU or insulin). Therefore, we have no published observational studies evaluating rosiglitazone specifically prior to 2007. Of the remaining 19, 3 were published in 2007, 4 in 2008, 10 in 2009, and 2 in 2010.

The review was a qualitative evaluation of cardiovascular safety between rosiglitazone and other anti-diabetic agents, pioglitazone and other anti-diabetic agents, and rosiglitazone and pioglitazone. The FDA's Office of Biostatistics was consulted but as noted in their conclusions and recommendations, no quantitative analysis was performed due to dissimilarities across the 21 studies. They further noted that "interpretation of results from graphical displays (e.g., forest plots) that include different measures of effect (e.g., odds ratio vs. hazard ratio, adjusted vs crude) or different study designs (e.g., case-control vs cohort) should be done with caution."

One of the panel members, Dr. Sanjay Kaul, called attention to the reluctance of the biostatisticians to make inferences from these data and also questioned whether there was any pre-specified hypothesis in these studies that was justified by the findings (question not answered by FDA at meeting) and whether the analyses corrected for multiple comparisons. FDA statistician, Dr. LaRee Tracy responded that perhaps one or two adjudicated for multiplicity. In the FDA statistical review, Dr. John Yap stated under his Summary and Conclusions that "*many of the studies showed multiple comparisons for various anti-diabetic agents or assessed multiple outcomes. However, these studies did not provide any adjustment for multiplicity which could result in inflated type 1 errors.*"

Notwithstanding the limitations already outlined by FDA biostatisticians, I would again emphasize that these observational studies are retrospective analyses of non-randomized comparisons between drugs on unadjudicated outcome measures whose data are subject to biased reporting and decisions by medical journals to accept for publication. Differences in patient demographics, risk factors, concomitant medical

conditions and medications and other factors and their impact on the results, are largely unknown. At best, I view these data as hypothesis-generating and insufficient evidence to support regulatory action to withdraw rosiglitazone from the market.

C.2. Retrospective cohort study of Medicare claims

This study represented the most comprehensive effort of the agency to obtain comparative safety data between rosiglitazone and pioglitazone. It remains a retrospective and non-randomized comparison of the two drugs but its strengths, as listed below, should not be dismissed.

- Largest patient database comparing these two drugs
- Baseline characteristics and risk factors between the two drugs were comparable at T0 (time of initiation of each TZD)
- CV endpoints of acute MI, stroke, heart failure, and all-cause mortality were appropriate. Of note, the selection of only events coded by ICD-9 codes in only the 1st or 2nd position may reduce the potential for selecting non-specific events or remote events which might not be associated with drug use
- Patient population (≥ 65 years) is a relevant subset of patients with T2DM who are at greater CV risk than younger cohorts. Although clinical trials do not exclude patients ≥ 65 years of age, the percentage of such patients often make up a minority of those enrolled in prospective clinical trials.
- Information on concomitant anti-diabetes medication revealed that the majority of these patients received either pioglitazone or rosiglitazone as add-on therapy to metformin or sulfonylurea which may reflect the more appropriate use of the products
- The *post-hoc* analyses performed to assess the affect of the Nissen meta-analysis on different patients entering the study provided reassurance that the findings did not reflect differences in patients *enrolling* in the program

I believe this is a higher quality epidemiologic study with efforts to control many of the confounders often precluding definitive conclusions made from these types of data. However, I do not believe the results from this observational study support a regulatory decision for drug withdrawal for the following reasons:

- The signal of CV risk for rosiglitazone identified in the original and subsequent meta-analysis and observed in other databases has been increased myocardial infarction. The inability to demonstrate a significant difference in MI risk between rosiglitazone and pioglitazone in a database of this magnitude is perplexing. The explanation given by Dr. Graham that these older patients are manifesting their cardiavascular disease differently and are presenting with sudden cardiac death is speculative although means of obtaining cause of death in the 2562 fatalities should be explored.
- The mean and median durations of follow-up (162 and 105 days, respectively) represent a very short timeframe of assessment for the overall cohort. Similar to concerns raised about the short-duration of treatment exposure in the meta-analysis limiting ability to adequately evaluate CV risk for both these drugs apply in this study.
- After the Nissen MA in May 2007 there was a sharp decline in patient entry for the rosiglitazone cohort. Dr. Graham looked at the characteristics of patients in both treatment groups before and after May 2007 and did not identify any significant differences in the patients entering the two treatment groups before and after this time point. However, from Figure 8 in Dr. Graham's review, only 22.2% of this cohort were initiated on rosiglitazone for the remainder of the study whereas 63.5% of the pioglitazone were new initiators after this timepoint. So while there were no differences between the two cohort for new initiators (tended to be younger post May 2007), the rosiglitazone cohort after this time point had a higher percentage of patients who were not new initiators. As described by Dr. Mahoney in her presentation, the pioglitazone cohort after May 2007 was continually being refreshed with new initiators whereas the rosiglitazone cohort

after May 2007 had a greater percentage of patients who were initiated before this timepoint remaining in the trial. This imbalance in the two cohorts and what impact it had on the event rates for the remaining 25 months of the study is not known.

- The risk estimates are concerning but for an observational study, adjusted hazard ratios of 1.27 for stroke, 1.25 for heart failure, 1.14 for all-cause mortality, 1.11 for acute MI or death, 1.15 for acute MI, stroke, or death, and 1.18 for all four combined, are modest increases that we can not entirely dismiss the effect of unmeasured biases on these findings. This was also noted by voting DSARM member, Dr. Morrato, as she explained her votes on Questions 5 and 6. At a minimum, additional sensitivity analyses should be performed on this database to determine whether such modest findings are more likely due to the large sample size of the database.

In conclusion, I do not believe the Medicare study provides sufficient evidence for a regulatory decision on *both* the marketing status and labeling changes for rosiglitazone. As noted above, I believe there are strengths in this study and the FDA should carefully review it further as it was only recently completed.

There would also be value in querying the database for other differences between these two drugs. In particular, FDA should determine if there are differences between these two drugs for cancer risk. As pointed out in the FDA background package, pioglitazone and many other dual PPAR-alpha and -gamma agonists have nonclinical cancer findings. For pioglitazone, a finding of excess bladder tumors in male rats at clinically relevant exposures can not be dismissed given the imbalance in the rate of bladder cancer not favoring pioglitazone observed in two 3-year clinical trials. For the past three years, the primary focus has been on cardiovascular safety of rosiglitazone and whether it should remain on the market. Yet do we know enough about the safety of the remaining thiazolidinedione to confidently make it the sole TZD for patients? The uncertainty in risk of cancer with pioglitazone was raised in 2007 by one member (Dr. David Schade) and again in 2010 by two members (Dr. Weide and Dr. Henderson).

D. Separate meta-analyses of controlled clinical trials of rosiglitazone and pioglitazone

The last new piece of information presented at the July 13 and 14, 2010 advisory committee was the FDA's updated meta-analysis of rosiglitazone trials and its meta-analysis of pioglitazone trials. In 2007, FDA did not conduct a meta-analysis of pioglitazone trials, citing differences between the two clinical development programs and the lack of patient-level data for the pioglitazone trials that would not enable construction of a comparable set of databases for purposes of making definitive conclusions on CV safety between these two drugs. Despite these concerns, these comparisons were done both internal and external to FDA and have formed the basis for some to conclude that pioglitazone is a safer alternative to rosiglitazone to support withdrawal of this drug from the market.

To determine whether such comparisons or conclusions were scientifically justifiable, FDA biostatisticians performed a meta-analysis of trials of each of these two drugs. The rationale for study selection and methodology has been described in their reviews but to reiterate, the objectives of the meta-analyses were to assess the CV risks of each of these drugs individually, to assess the differences between the clinical trials available for the two drugs, and to the extent possible, to make qualitative comparisons between the safety profiles of the two drugs. The same endpoints and statistical analytical approaches were applied to both meta-analyses. Despite these efforts to achieve parity between these two databases, the two FDA biostatisticians, Drs. Callaghan and McEvoy, noted the obvious differences between the two development programs. And on multiple occasions, Drs. Callaghan and McEvoy, emphasized the limitations of comparing these meta-analyses to each other through the following points made in each of their presentations:

- most trials were not prospectively designed to evaluate cardiovascular endpoints
- results of trials were known before statistical analysis plan was developed
- statistical significance was not adjusted for multiple testing
- comparisons between the two meta-analyses are subject to the deficiencies of cross-trial comparisons

The overall findings for these meta-analyses were that pioglitazone tended to have less risk compared to controls whereas rosiglitazone tended to have higher risk compared to controls for the MACE endpoint (Figure 1). None of the findings reached statistical significance. For CHF, both drugs tended to have greater risk compared to controls (Figure 2).

Figure 1. Overall Results of Meta-analyses for Pioglitazone and Rosiglitazone on MACE Endpoints (Forest Plot created by Dr. Bradley McEvoy and presented at July 13 and 14, 2010 advisory committee meeting)

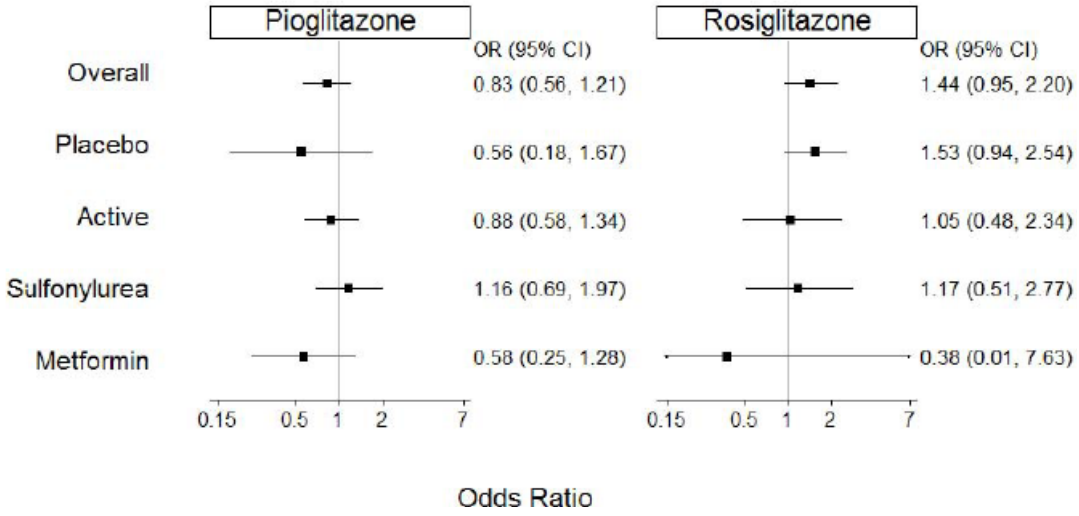
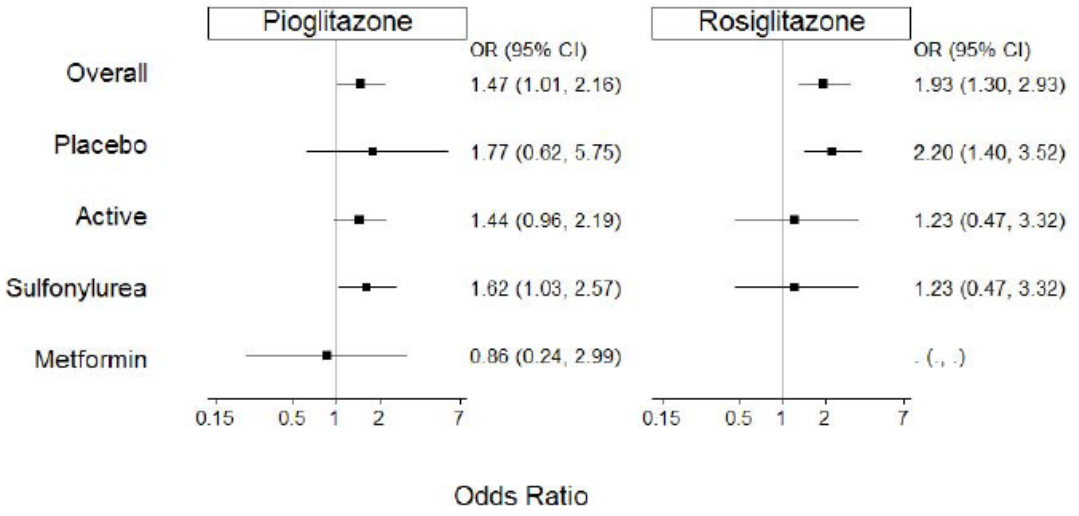


Figure 2. Overall Results of Meta-analyses for Pioglitazone and Rosiglitazone on CHF Endpoint (Forest Plot created by Dr. Bradley McEvoy and presented at July 13 and 14, 2010 advisory committee meeting)



In looking at these side-by-side forest plots, I would concur with many others that a concerning signal of increased risk for CV ischemic events defined as MACE (CV death, MI, and stroke) is present with rosiglitazone relative to comparators but not evident in the pioglitazone trials. For CHF, both drugs show

a greater risk than their comparators, which is consistent with the known class effect of these drugs. In both meta-analyses, comparators were primarily metformin and sulfonylureas. Except for one 24-week study to compare lipid effects of rosiglitazone and pioglitazone, none of the trials included in these meta-analyses compared rosiglitazone to pioglitazone. Hence, the FDA has no direct, randomized comparison of these two drugs in order to make accurate CV safety comparisons.

The limitations of these meta-analyses for evaluating CV risk of these drugs have already been outlined in earlier sections of this memo. Given these limitations and the magnitude of these risk estimates, I am concluding that neither of the meta-analyses represents adequate and well-controlled studies to support any definitive conclusion on the risks and benefits of pioglitazone or rosiglitazone individually. At best, these data should be viewed as signals requiring further investigation. By extension, if these meta-analyses are not sufficient for a definitive conclusion on risks and benefits of the individual drugs, it would be inappropriate to make comparative safety claims between the two products by taking each meta-analysis with its inherent limitations and compare it to the other because we lack a direct head-to-head study of the two drugs. Consequently, I have concluded that the individual meta-analyses provide insufficient evidence to recommend withdrawal of rosiglitazone by way of citing a safer alternative with pioglitazone.

III. RECOMMENDATION #2: The labeling for rosiglitazone and all rosiglitazone-containing products must be revised to reflect current information on cardiac ischemic risks

Although I have argued under Section II that each of the data sources does not provide sufficient evidence for me to conclude risks outweighing benefits for rosiglitazone to recommend its withdrawal, I believe the data sources meet the regulatory requirements to modify safety labeling for this drug. Sections of the package insert (or professional labeling) pertaining to safety that should be updated for rosiglitazone include its Contraindications, Warnings and Precautions, and Boxed Warning. Any changes to these sections of the package insert should then be reflected in the Medication Guide and other communication plans to the public.

In this section of my memo, I base much of my recommendations on the requirements for labeling cited under 21CFR201.57 and the Guidance for Industry titled, *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products*. The changes to the Contraindications and Warnings and Precautions sections of the rosiglitazone label should be reflected in its Boxed Warning.

Contraindications

In addition to the current contraindication for use in patients with NYHA Class III or IV heart failure, rosiglitazone should be contraindicated in:

- Patients currently receiving insulin

  The basis for this recommendation comes from the consistent observation of an increased OR of approximately 2.0 for CV ischemia in the MAs involving the insulin trials. There may be a reasonable explanation for this observation as all of these trials involved patients who were already receiving insulin and had a long duration of diabetes that would make them more sensitive to the fluid-retaining effects of rosiglitazone. Patients currently receiving insulin can achieve adequate glycemic control through appropriate dosing and titration of their insulin making the addition of rosiglitazone to insulin non-essential.

- Patients at high risk for a CV ischemic event as defined by recent acute coronary syndrome or who are symptomatic requiring use of anti-anginal therapies

  The basis for this recommendation comes from a concern that the fluid-retaining effects of rosiglitazone may be poorly tolerated in this vulnerable patient population limiting any benefit of glycemic control.

Warnings and Precautions

I believe the updated meta-analysis of rosiglitazone clinical trials performed by the FDA reflects continued concern about cardiovascular ischemic risk with this drug's use. Although the limitations of the meta-analysis preclude a definitive conclusion about this risk, the addition of 10 new studies has not weakened this signal but has rather shown a shift for myocardial infarction from slightly non-significant to slightly significant. Consequently, the labeling should be changed to discuss risk of myocardial infarction not myocardial ischemia, as observed in the updated meta-analysis. This recommendation will affect Section 5.2 of the currently approved label and the accompanying text in the boxed warning.

Twenty members of the advisory committee panel did not vote to remove rosiglitazone from the market. Three of these members did not recommend any changes to the current label while 17 voted for options which recommended revisions to the labeling, including 10 who voted for the addition of restrictions on use. However, in reading the explanations given by these 17 members, there was no clear universal recommendation on what to revise or add to the label. Recommendations broadly covered restricted use with a registry to no specific recommendation other than its availability would signify choices to prescribers. Several members made note that the market already shows preferential use of the alternative

drugs over rosiglitazone. In and among the pages of transcribed discussion was the suggestion that rosiglitazone be reserved for second-line use.

Second-line use was referred to in a variety of ways by panel members. Some suggested that rosiglitazone be second-line therapy only after pioglitazone while others suggested it be second-line after metformin. One member specifically suggested second line therapy for the class of TZDs. I highlight only a few direct quotes below to make these points.

- Dr. Hammerschmidt: "…I'm concerned that there might be a small group of people out there who don't do well on pioglitazone for whom this might be a good salvage drug."
- Dr. Kaul: "Make sure that this is available as a second line, not as a first line, especially if metformin cannot be used in the patients…."
- Dr. Vaida: "…I actually like the recommendation for second-line use. And I'd like to put the qualifier on second-line for thiazolidinediones so rather than just any agent."

My recommendation here is to label <u>against</u> use of rosiglitazone or any rosiglitazone-containing product (Avandamet or Avandaryl) as a first-line agent after the patient has failed to achieve adequate glycemic control on diet and exercise alone. I do not recommend that the label specifically advise physicians to select pioglitazone before rosiglitazone because the evidence upon which to base such a recommendation is not from adequate and well-controlled studies but from observational studies or comparisons of meta-analyses of two different clinical development programs. I am concerned about the precedent that would be set in which the quality of evidence from meta-analyses and observational data and there non-robust signal of excess risk will be relied upon to recommend use of one drug over another within and across a broad class of drugs. If the FDA makes such a labeling change with rosiglitazone, will it then entertain meta-analyses of other anti-diabetics, lipid-altering drugs, anti-hypertensives, or osteoporosis drugs and label a hierarchy for use which will circumscribe prescribing practices? How will FDA deal with a supplement containing a meta-analysis or observational study performed by a drug company to show that its drug has equal efficacy but a lower rate of a singled-out safety concern relative to its comparator supporting labeling changes for preferential use of its drug over the comparator?

Labeling against first-line use can be similar to what was done with the recent approval of the anti-diabetic agent, Victoza (liraglutide), in which the following statements were made under Indications and Usage, Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (under Highlights section)
- Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise (under the Full Prescribing Information section of labeling).

In this setting, another drug is not identified as preferred over Victoza. Instead, prescribers are cautioned against using Victoza first.

For rosiglitazone, the Full Prescribing Information section might state the following:

Indications and Usage
Important Limitations of Use

- *A meta-analysis of 52 randomized controlled trials demonstrated an increased risk for major cardiovascular events (MACE) comprised of CV death, MI, and stroke associated with AVANDIA relative to comparators (metformin and sulfonylureas). Although the trials comprising the meta-analysis were not designed to investigate CV risk, there has not been sufficient evidence from large long-term trials to dismiss this finding of increase CV risk. Therefore, AVANDIA is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise or who are at increased risk for a heart attack such as those with prior heart disease or the elderly (see Warnings and Precautions).*

Although specific text for a revised label should involve others on the FDA review team, I would propose the following text for consideration under the Boxed Warning to replace the current language on CV ischemic risk. The class labeling for congestive heart failure will remain the same for both rosiglitazone and pioglitazone.

- *A meta-analysis of 52 randomized controlled trials demonstrated an increased risk for major cardiovascular events (MACE) comprised of CV death, MI, and stroke associated with AVANDIA relative to comparators (metformin and sulfonylureas). Although the trials comprising the meta-analysis were not designed to investigate CV risk, there has not been sufficient evidence from large long-term trials to dismiss this finding of increase CV risk (see Warnings and Precautions)*

- *No adequate and well-designed head-to-head studies have been conducted between rosiglitazone and another member of the thiazolidinedione class to assess CV risks. However, a similar finding of excess CV risk has not been identified with another drug in the TZD class. Consequently, this information should be considered in any clinical decision to initiate therapy with rosiglitazone, especially in patients with established heart disease or the elderly.*

- *Avandia is contraindicated in the following:*
  -Patients with NYHA Class III or IV heart failure
  -Patients currently receiving insulin
  -Patients with symptomatic heart disease (e.g., current use of nitrates) or with a recent acute coronary events (e.g., past 6 months)

I am proposing that a statement clearly describe the current situation in which there are no direct head-to-head comparisons between rosiglitazone and pioglitazone. I am also willing to describe the absence of an CV ischemic risk finding observed with pioglitazone so that a prescriber can be informed enough to decide what drug is appropriate for his/her patient.

IV. RECOMMENDATION #3: A POSTMARKETING TRIAL, SUCH AS TIDE, SHOULD BE CONDUCTED TO OBTAIN INTERPRETABLE DATA ON THE CV SAFETY OF ROSIGLITAZONE TO INFORM FDA ON AN APPROPRIATE REGULATORY ACTION

My recommendation to allow the continuation of TIDE stems from the arguments I have laid out under Sections II and III. Since I do not believe there is sufficient evidence to conclude that rosiglitazone has greater cardiovascular risk than other anti-diabetic agents and pioglitazone, I believe that each of the treatment arms proposed in TIDE is appropriate. Similarly, the two co-primary research questions in TIDE are appropriate as discussed below:

1. Does adding a TZD (either rosiglitazone or pioglitazone) reduce MI, stroke, or CV death vs placebo (N.B. this is standard diabetes care not NO treatment)?

This research question is not describing a non-inferiority trial design but a question of whether TZDs will result in CV benefit over current diabetes care. To date, this question has not been answered, including for pioglitazone in its PROactive trial. Safety concerns of weight gain, fluid retention, and heart failure associated with the TZDs are countered by beliefs that improved insulin sensitivity, durable glycemic control, and lower risk for hypoglycemia are characteristics of these drugs which will result in long-term benefits, including the prevention of diabetes. Absent data from adequate and well-designed trials, practice guidelines have not endorsed the use of these drugs as first-line therapy. TIDE would be able to test whether there is long-term clinical benefit of this class of drugs to better inform its use in the chronic management of Type 2 diabetes.

The fact that all FDA-approved labels for anti-diabetic agents carry the statement that "there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Drug X* or any other oral antidiabetic drug" is indicative that even this regulatory agency has not concluded CV benefit of one drug over another to oppose this research question from the TIDE trial.

2. Is rosiglitazone non-inferior to placebo with respect to the composite of MI, stroke, or CV death?

This is similar to what the FDA is requiring of all new anti-diabetic agents under its recent Guidance for Industry titled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes"[1]. New anti-diabetic therapies need to show that they do not result in an unacceptable increase in CV risk by way of establishing non-inferiority to placebo add-on to standard-of-care diabetes therapies.

Both Drs. Graham and Gelperin from the FDA have been opposed to the conduct of TIDE. In Dr. Graham's presentation he stated in Slide 4 that the primary analysis will compare rosiglitazone vs non-TZD, not rosiglitazone vs pioglitazone, the more clinically relevant comparison. It should be noted that they have each already concluded that pioglitazone is a safer drug than rosiglitazone in their 2008 memo, so to modify the protocol to address this criticism would also contradict their position that such a comparison is unethical.

Nonetheless, the TIDE trial, as originally designed, included secondary analyses to determine if one TZD was superior to the other. Based on estimated event rates and proposed sample size, the trial had over 90% power to demonstrate a 25% relative risk reduction between these two drugs over a period of 5.5 years follow-up.

To help committee members determine whether it was ethical to conduct the TIDE trial, FDA invited Drs. Ruth Faden and Steven Goodman, co-chairs from the Institute of Medicine's Committee on Ethical and

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Scientific Issues in Studying the Safety of Approved Drugs to present on Day 2 of the meeting. Due to the timing of this advisory committee meeting, FDA requested a letter report of the committee to address the following question: "What are the ethical and informed consent issues that must be considered when designing randomized clinical trials to evaluate potential safety risks?" This letter report was also provided in the FDA background materials and provided a conceptual framework for which the advisory committee members (and FDA) can apply in its decision regarding the conduct of TIDE.

In this section of my memo I will present my arguments for why TIDE should be conducted using this conceptual framework as guiding principles.

The Public Health Context of Drug Safety

The FDA should determine that there is a substantial public health question about the nature or acceptability of the risks, or the risk-benefit profile, of a marketed drug-a question that requires a policy decision from FDA

The policy decision facing FDA is whether there is sufficient evidence regarding CV risk of rosiglitazone to warrant its removal from the U.S. markets. In the absence of sufficient evidence, the next policy decision facing FDA is whether a post-marketing trial should be required to gain important public health information.

I have already argued under previous sections of this memo that all available data *suggest* an increase in CV risk with rosiglitazone but that such data are fraught with limitations due to, but not limited to, their design, objectives, data collection, and duration, such that a reasonable conclusion can not be made that rosiglitazone causes myocardial infarction, strokes, or death at rates greater than other available anti-diabetic therapies.

Diabetes mellitus is a disease of chronic hyperglycemia that has well-known complications that one can not ignore poor glycemic control. Patients now have 11 different classes of anti-diabetic agents to choose from and given the chronic nature of type 2 diabetes, the majority of patients will require several drugs and many will eventually require insulin. All of these therapies have shown effectiveness at lowering blood glucose levels, an important clinical endpoint not a surrogate, as some have argued. But while we continue to develop and approve drugs based on their ability to treat hyperglycemia, we do not know whether they have an impact, negative or positive, on cardiovascular disease, a major long-term complication of diabetes. The TIDE trial, as currently designed is intended to provide us with knowledge on the long-term benefits and risks of rosiglitazone, pioglitazone, and other therapies currently approved for diabetes, a condition affecting over 20 million individuals in the United States. To that end, I believe TIDE will not only provide clarity on the debate about rosiglitazone but it will answer broader important public health questions.

Regulatory Science and Public Accountability

FDA should use regulatory-science principles and practices that include processes of public accountability and transparency to determine the need for a policy decision, the need for new knowledge to support a policy decision, and the policy decision based on the new knowledge.

On this issue, Dr. Faden remarked that the 2-day advisory committee represents the FDA's willingness to publicly disclose all available information and internal opinions voiced in this regulatory decision. In keeping with this principle, I would advocate that when the final decision is made for rosiglitazone and the TIDE trial, all FDA documents in this decision-making process be made available to the public.

Design Considerations

It is appropriate for FDA to require that a randomized controlled trial be conducted to provide additional evidence about an approved drug's efficacy and safety only when (i) uncertainty about the risk-benefit

balance is such that a responsible policy decision cannot be made based on the existing evidence or on evidence from new observational studies, and (ii) the trial is properly designed and implemented to reduce uncertainty about the risk-benefit balance sufficiently for a responsible policy decision to be made.

I have already presented my reasons for why current evidence, including observational studies, has not provided clarity on the CV risk of rosiglitazone relative to other anti-diabetic therapies, including pioglitazone. A majority of committee panel members (19/33) voted in favor of continuing the TIDE trial should rosiglitazone remain on the market. Eleven voted against its continuation, 2 abstained, and one member forfeited his vote as he left the meeting early. However, I find it intriguing that many members, even those who stated they were voting in a hypothetical sense because they had already voted for withdrawal of the drug, viewed such a trial as the only means of resolving a debate that has twice gone before an advisory committee. In my mind, such a view undermines the position that the trial is unethical. More importantly, I believe their votes and explanations are aligned with what Dr. Goodman said in the IOM presentation,

"……a precondition for the choice to require a randomized controlled trial by the FDA must be the determination that the current evidence base is insufficient, and that no other research or information-gathering effort, including new observational study, can reduce the uncertainty about the drug's risk-benefit profile sufficiently to support a responsible policy decision."

Additional Ethical Obligations to Trial Participants

FDA should ensure that the trial will answer the public health question with a design that minimizes the risks to trial participants and involves ongoing monitoring of risks. The risks should be judged to be acceptable by appropriate oversight bodies before and during the trial and by trial participants at enrollment and as appropriate during the trial. Specifically, FDA and appropriate oversight bodies should ensure that the trial includes a comprehensive and meaningful informed consent process that continues during the trial and that takes into account any substantial changes in clinical practice and professional standards and any new research findings relevant to a participant's willingness to accept the risks associated with the trial. The FDA and appropriate oversight bodies should ensure that those conducting the trial convey such changes to participants in a timely and understandable fashion.

I have already concluded that the TIDE trial objectives are appropriate and the research questions can be answered by its design. Unlike the criticism of RECORD, this is a double-blinded, placebo- and active-controlled trial with blinded adjudication by an independent endpoints committee. Its primary endpoint is also the more widely accepted composite of CV death, stroke and MI. However, from the discussions at this advisory committee I believe the protocol should be revisited to make certain inclusion and exclusion criteria reflect enrollment of patients for whom available data have not identified clear hazard from exposure to rosiglitazone. The protocol should also be reviewed with respect to duration and type of monitoring throughout the trial, stopping rules, and updates to the oversight bodies and participants. If necessary, participants might need to be consented annually to make certain they understand what the trial objectives are and the risk-benefits of all treatments studied. If rosiglitazone will remain on the market, its labeling will undoubtedly be modified. The informed consent will have to be updated to reflect accurately any new information. The informed consent should also be reviewed routinely by oversight bodies to provide updates on new knowledge about risks and benefits of any treatments in the trial.

V. CONCLUSIONS

In conclusion, I believe that there are clinical data suggestive of CV risks associated with rosiglitazone. However, the sources of data from which this signal arises have serious limitations upon which a regulatory decision for drug withdrawal should not be based. Despite this, the data suggesting increased CV risk can still be communicated to prescribers and patients to allow informed medical decisions and prescribing practices for rosiglitazone, including the decision to never use rosiglitazone or to select rosiglitazone only after failing other anti-diabetic therapies. Some might ask why I don't just recommend the drug's withdrawal given that the safety signal is sufficient enough to justify its relegation to second-line or even last-option therapy. After all, withdrawal would effectively eliminate any chances for the drug to continue to do harm. While I cannot dispute that fact, I believe withdrawal of rosiglitazone in the setting of scientific uncertainty is an inappropriate display of FDA's authority to make a decision for all healthcare providers because of concern that these trained professionals can not reasonably decide on or take responsibility for the use of this drug. I am also concerned that such an action would set an unsettling precedent for future regulatory decisions or may be referenced in legal challenges to the FDA to withdraw other drugs based on meta-analyses and observational studies of similar uncertainty for drug risk.

In making my 3 recommendations to CDER senior officials, I am heeding the advice of Commissioner Hamburg in her opening statement "to follow the science where it leads and the rest will fall into place". I have argued my position based on my interpretation of scientific evidence available which, in turn, has formed the basis for my recommended regulatory actions. In doing so, I am also cognizant that some of my labeling recommendations and the actions of others outside the agency may impact the ability of the company in conducting a required postmarketing trial to better inform us in our regulatory decision. If my three recommendations are adopted, FDA should monitor the progress of this postmarketing trial and the efforts of the company and investigators in conducting it in a timely fashion. If the impact from labeling changes or the negative publicity given to this matter from the media, members of Congress, or other individuals make this an unfeasible clinical trial, FDA should release GSK from this FDAAA-mandated required trial. If this should happen, I would support more restrictive use of rosiglitazone since the uncertainty of its CV safety will never been resolved without this required postmarketing trial.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	ORIG-1	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
08/19/2010

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Consultation for NDA 021071 SDN1652

DATE: Consult requested: 12/20/2011
Date of reassignment: 01/24/2012
Desired completion date: 04/30/2012
Date of review: 04/28/2012
Date of revision 05/07/2012

FROM: Preston M. Dunnmon, M.D., Clinical Reviewer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Jena M. Weber
Regulatory Project Manager
Director, Division of Metabolism and Endocrinology Products

SUBJECT: DCRP consult to review and to comment on both all-cause and CV deaths from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia and Diabetes trial (RECORD, BRL-049653/231), according to the Phase-I re-adjudication of the trial's mortality outcomes by the Duke Clinical Research Institute (DCRI)

This memo responds to your consult to us requesting review of DCRI's re-adjudication of the mortality results from RECORD (NDA 021071 SDN1652), which compared cardiovascular (CV) outcomes between rosiglitazone (RSG) therapy in combination with metformin (MET) or a sulfonylurea (SU) to CV outcomes with the MET/SU combination. DCRP reviewed the following material:

- Prior DCRP consult (June 14, 2010)
- FDA Briefing Document Advisory Committee Meeting for NDA 21071 (July 13 and 14, 2010)
- RECORD final study report (FSR)
- Original RECORD CEC charter
- DCRI Re-adjudication Protocol AVD115170 for RECORD, Report of the First Phase: Blinded Re-adjudication of All-cause Mortality and Cardiovascular Mortality
- DCRI re-adjudication mortality dataset

Regulatory Background

The cardiovascular safety of AVANDIA® (rosiglitazone) has been the subject of two recent public proceedings:

- July 30, 2007 - joint public advisory committee concluded that AVANDIA® increases cardiac ischemic risk in type 2 diabetes mellitus based on then available data but that the overall risk-benefit profile of AVANDIA® supported its continued marketing in the US

- July 13-14, 2010 – advisory committee meeting for AVANDIA® (NDA 021071, rosiglitazone maleate) considered data from three newly available long-term outcome studies (RECORD, ADOPT, and DREAM) in a discussion regarding whether rosiglitazone should continue to be marketed in the United States.

As part of the 2010 advisory committee briefing document, the weaknesses of RECORD's open label non-inferiority design, as well as the consequent opportunities for ascertainment biases, were very thoroughly vetted. At the completion of the July 2010 adviory committee, FDA decided that rosiglitazone could remain on the market in the US if:

1. GSK undertook a restricted access program under a REMS with ETASU

2. GSK commissioned an independent re-adjudication of the RECORD study outcomes. If the mortality finding were found to be valid on the first phase of re-adjudication, then a second phase re-adjudication of other MACE elements would be performed (nonfatal MI, nonfatal CVA, and CV Death).

3. The TIDE trial was placed on full clinical hold.

GSK agreed to the above conditions for continued marketing of rosiglitazone in the US, and commissioned the DCRI to perform a full and independent re-adjudication of the RECORD study's cardiovascular outcomes as delineated by FDA. Accordingly, the phase-I mortality re-adjudication has now been completed. The purpose of this document is to review the findings of the phase-I (mortality) re-adjudication.

During this re-evaluation period, the labeled indication for rosiglitazone has read as follows:

> *After consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of AVANDIA®, this drug is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are already taking AVANDIA®, or not already taking AVANDIA® and are unable to achieve adequate glycemic control on other*

diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone (ACTOS®) for medical reasons.

Background – RECORD Study design

RECORD was a post-marketing commitment to the European Medicines Agency. Its design was reviewed and approved by the Committee for Proprietary Medicinal Products (now known as the Committee for Medicinal Products for Human Use). RECORD was not conducted under a U.S. IND.

RECORD was a randomized, multicenter, open-label, parallel group trial of 4447 subjects with type 2 diabetes, comparing cardiovascular outcomes in subjects randomized to rosiglitazone in combination with metformin or a sulfonylurea to the combination of metformin plus a sulfonylurea. A four-week run-in period was followed by a proposed median of 6 years of treatment with study medication, in addition to continuation of background glucose-lowering therapy. Patients on background metformin (MET) were randomized to receive, in addition to continued metformin, either rosiglitazone or a sulfonylurea (glibenclamide, gliclazide or glimepiride), in a ratio of 1:1. Patients inadequately controlled on background SU were randomized to receive, in addition to continued sulfonylurea (SU), either RSG or MET, in a ratio of 1:1. Equal numbers of patients on background MET and SU were to be randomized.

Throughout study, target hemoglobin A1c (HbA1c) was to be ≤7%. After 8 weeks of treatment, if a patient's HbA1c was >7%, the investigator was to increase the dose of study medication. If tolerated, RSG was to be titrated to a dose of 8 mg/day, administered as 4 mg BID, in order to achieve an HbA1c of 7%. Doses of MET and SU were to be titrated to the maximum allowable dose approved by the regulatory authority of the country in which the study site was located, also to achieve an HbA1c of 7%.

If a patient's HbA1c remained ≥8.5% after at least 8 weeks on the maximum permitted or tolerated dose of add-on study medication, a confirmatory HbA1c was to be performed at least 1 month later. If the HbA1c was still ≥8.5%, another agent was added. For patients in the RSG + MET group, SU was added. For patients in the RSG + SU group, MET was added. For patients in the MET + SU group, insulin was added; with or without continuation of MET and/or SU, "according to local clinical practice".

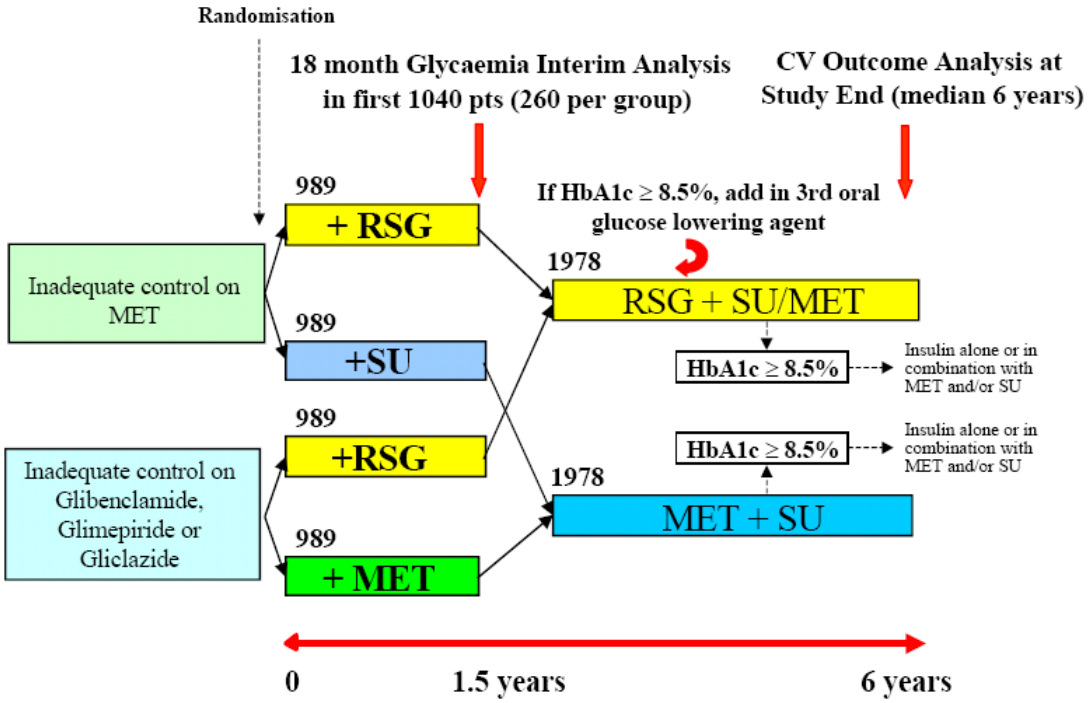
For patients in the RSG groups who had progressed to triple oral therapy, had remained on the maximum permitted or tolerated dose of the triple therapy for at least 8 weeks, and still had a HbA1c ≥8.5%, insulin was added and rosiglitazone was discontinued. The combination of RSG and insulin was not approved in Europe at the time the study was initiated. For these patients, MET and/or SU might or might not be continued, again according to local clinical practice.

The primary endpoint/analysis of RECORD was an ITT analysis of the time to first adjudicated CV hospitalization or CV death (any death for which an unequivocal non-CV cause count not be established (acute MI, heart failure, sudden death, acute vascular

events, other CV mortality, unknown causes), over the full duration of the study. To reiterate, deaths of unknown cause were counted as CV deaths.

The objective of the study was to rule out a 20% increase in the relative hazard of RSG combination compared to the combined control groups (MET/SU). Formal non-inferiority was to be achieved, according to protocol definition, if the upper limit of the 95% confidence interval for the hazard ratio of RSG versus MET/SU at study end was less than 1.2.

The following figure illustrates the study phases from randomization through initiation of insulin in both treatment groups:



DCRI Methodology

Overview

Re-adjudication and analysis of mortality for the RECORD study was performed in accordance with the following documents:

- Re-adjudication Protocol for RECORD, Version 1, 28 January 2011
- Re-adjudication Protocol for RECORD, Amendment Version 2, 24 June 2011
- Statistical Analysis Plan: First Phase (Mortality), 13 July 2011

DCRI-CEC processes for the re-adjudication of RECORD mortality were described in the DCRI CDC Charter for Re-adjudication of RECORD (Effective Date: 02 May 2011). Subsequently, DCRI developed a comprehensive trigger process of automated and manual procedures to systematically identify all suspected endpoint events from all potential data sources in which deaths may have been reported by the site investigators (RECORD Re-Adjudication Trigger Specifications, August 4, 2011). Data sources for re-adjudication included:

- The original RECORD dataset
- Original RECORD paper case report forms
- Original RECORD SAE reports
- Event packets used in the original adjudication (and the source documents they contained)
- Site queries for additional information and query responses
- All information collected by GSK between November 2010 and March 2011 regarding patients whose last contact was made during the survival status follow-up phase as recorded in the CRF
- Third party search for end-of-study documentation – MediciGlobal, an independent third party vendor (King of Prussia, Pennsylvania), was employed to search for additional vital status information on patients that DCRI identified as missing vital status information at the end of the study
- GSK retrieved available source documents from the Investigators' Archive so that these would be available to DCRI during the re-adjudication of RECORD
- Quintiles sent a letter to each site explaining the request for source data; a copy of the letter was to be submitted to each site's ethics committee for notification. A remote call was placed to each site to further explain the requirements and to understand the site's ability to provide the requested source data.

Triggers for Identification of Suspected Events and DCRI CEC Review

DCRI employed a comprehensive combination of both automated program triggers and manual trigger procedures to identified suspected mortality events for review by their CEC, described as follows:

- Automated trigger program – computer trigger program that included:
  - Screening of all Adverse Experience (AE) and Serious Adverse Experience (SAE) forms from the CRF data fields in the GSK RECORD datasets
  - Pre-specified MedDRA coded terms. The coded preferred terms were reviewed by Clinical, CEC and Safety experts to identify terms that would potentially be indicative of an endpoint with a low threshold. A similar approach has been used in previous re-adjudication efforts
  - Death Form (Form D) when present in the database.

- Manual trigger procedures – RECORD CEC Coordinators performed manual review of paper documents as well as reviewing the output from the automated trigger program. All were experienced in cardiology event

reporting and CEC methodologies. Paper sources that the CEC Coordinators reviewed to identify potential endpoints included:

- The unscheduled visit form
- Source documents used as part of the original RECORD CEC adjudication process and any additional source documents collected as part of the re-adjudication activities (discharge summaries, progress notes, pertinent lab values, and physician narratives)
- Investigator verbatim
- All SAE and AE forms - SAEs and AEs that were deleted by RECORD investigators were identified from the audit trail of the study's electronic datasets, which GSK provided to DCRI. The electronic data sets were sent to the DCRI prior to the event packet files which included data from the CRF and source documents.
- All cases that were sent to the original RECORD CEC; this would include endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator
- All Death Endpoint Forms
- All Myocardial Infarction/Unstable Angina Endpoint Forms
- All Stroke/TIA Endpoint Forms
- All Hospitalizations
- All Survival Status Forms
- All Documentation of Third Party Survival Data Forms
- All Tracking Forms for Completely Withdraw Patients
- All Study Completion Forms

Patient Dispositions – Incomplete Follow-up

One objective of the re-adjudication of mortality in RECORD was to define independently the study follow-up phases and derive dates last observed without an event (i.e., date last known surviving) for patients who were not reported to have died, because precise determination of end-of-study dates could not be done for all patients based on the SAS datasets alone. For each patient who did not have a last face-to-face visit well-documented in the SAS datasets, additional efforts were made to determine the patient's vital status at the study end.

Patients were considered to have completed follow-up if the patient died, had a face-to-face visit with vital signs recorded on or after 24 August 2008, or had a face-to-face visit in 2008 and a phone visit (no vital signs recorded) after 24 August 2008. On this basis:

- 3,843 patients were designated as having completed follow-up
- 604 patients were deemed incomplete (included the 127 patients who were reported in the original RECORD trial to have unknown vital status at study end).

For the 604 patients deemed incomplete due to unknown vital status at the end of the study, the following was done:

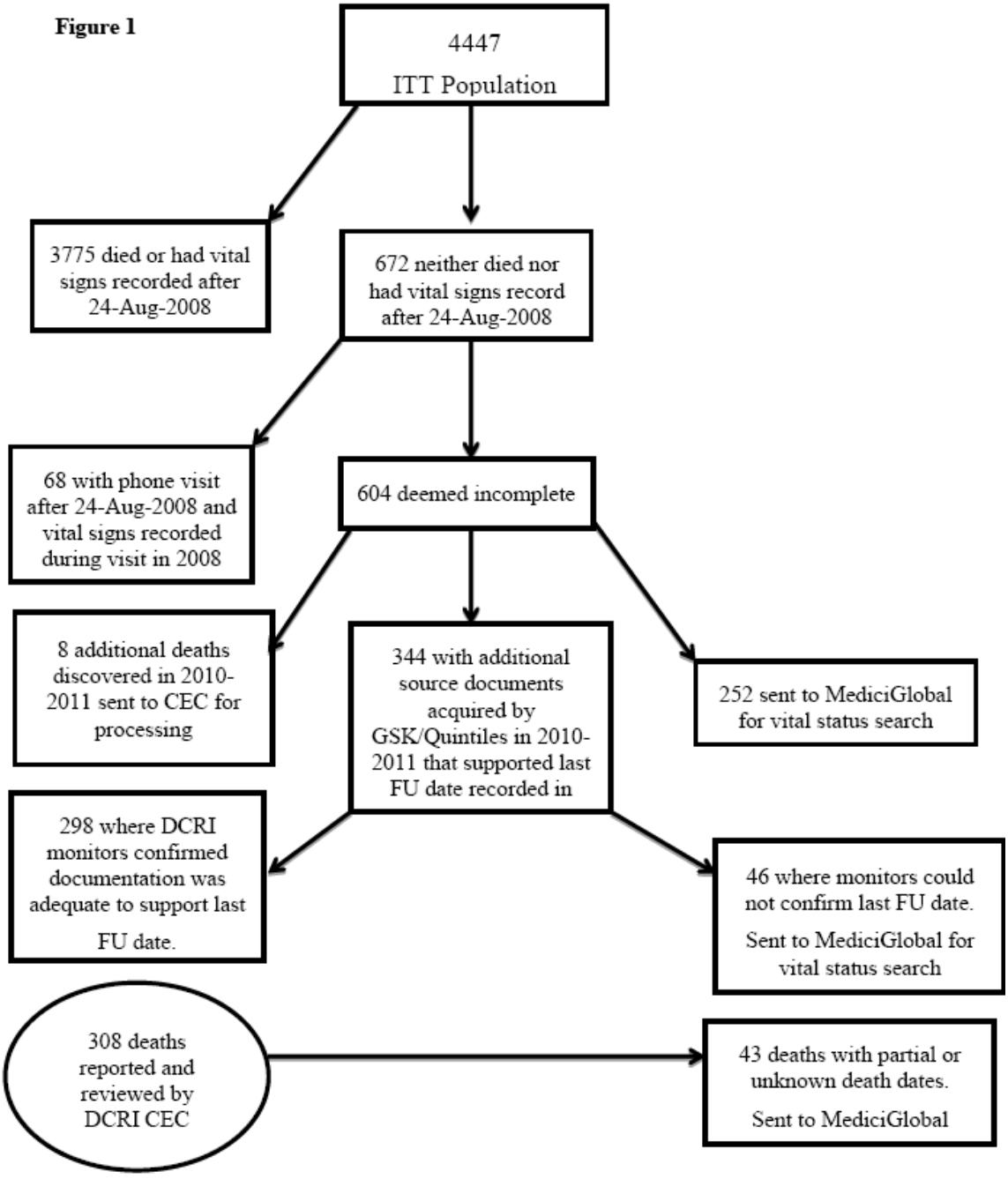
- For 298 patients, additional source documentation was obtained by GSK/Quintiles in the 2010-2011 post-study time frame that confirmed a last follow-up date
- For another 298 patients, additional source documents were either not available, or additional source documents could not confirm a last follow-up date, and so these cases were sent to MediciGlobal for vital status search
- 8 additional deaths were discovered in the 2010-2011 time frame that were sent to the DCRI CEC for processing.

In addition, 308 known deaths were reported to and reviewed by the DCRI CEC, of which 43 had partial or unknown death dates and were referred to MediciGlobal for vital status search.

See the figure below for a diagrammatic representation of the disposition of patients with incomplete follow-up (from DCRI phase I report, Figure 1; "ITT" population excludes 11 randomized patients who never took study drug):

12.1.1 Patients with Incomplete Follow-up

Figure 1



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DCRI CEC Query of Suspected Events

The DCRI CEC issued 127 queries for additional information to follow up on death events classified as "unknown" and "insufficient information". Response to these queries approximately two to three years after the study was completed was predictably poor:

- 43 queries were closed with no response from the site
- 61 queries were closed with a response from the site that no additional data is available
- 23 queries were closed with additional data received from the site. Of these 23 queries,
    - 16 events were re-reviewed with no change to the adjudication result
    - 7 events were re-reviewed with a change to the adjudication result from "unknown" to a known cause of death.

Disposition of Events Triggered for Re-adjudication: All-Cause Mortality

A total of 419 triggers for all-cause mortality were identified representing 9.4% of the 4447 patients included in the ITT Population in the original RECORD report. Of the 419 patients who triggered, 396 (94.5%) were identified from the automatic trigger program and 23 (5.5%) were identified manually. Adverse event forms, death forms, and study continuation/withdraw forms accounted for the large majority of triggers identified programmatically. All triggers identified manually were found in source documents.

Of the 419 potential deaths triggered, 102 death triggers were set to a status of "No action needed" and not adjudicated because the source documentation present indicated that the subject was still alive. The remaining 316 death triggers were adjudicated.

Between all patients treated with RSG (N=2220) and all treated with MET/SU (N=2227), DCRI reported that the proportional distribution of patients by triggering method and by sources of triggers appeared to be similar with no evidence of clinically important differences between the treatment groups.

All of the 316 death triggers referred for re-adjudication were reviewed by DCRI's CEC Phase 1 re-adjudication committee. Because of disagreement between CEC Phase-1 reviewers regarding death classification and/or death sub-classification, 86 death triggers were also reviewed by the CEC Phase-2 committee; that is, a full Adjudication Committee comprising at least 3 faculty physicians.

> *Reviewer Comment: I would inquire of DCRI the breakdown of new deaths and deaths with incomplete vital status by study arm. There were 604 DCRI-identified patients with incomplete vital status information/dates versus 127 for GSK/Quintiles – a substantial difference. How many ended up having vital status/censoring dates changed that were part of the original 127 versus the remaining 477? There were 127 DCRI CEC generated queries for vital status. Were these the same 127 patients identified by GSK as having unknown vital status at the end of the study?*

New Death Events Found on RE-adjudication

In accord with DCRI's prospective statistical analysis plan (SAP) for the re-adjudication, all deaths occurring on or before 31 December 2008 were included in the primary re-analyses of all-cause mortality, CV mortality, and non-CV mortality. In the original RECORD trial, the date of last follow up was the latest date the subject was known alive on or before 31 December 2008.

Twenty-three (23) death events, in addition to those identified in the original RECORD data set, were discovered after DCRI re-adjudication efforts began, as follows:

- Eight (8) newly discovered events occurred before 31 December 2008: 3 deaths were found by the GSK/Quintiles search effort, 3 deaths were found from the AVANDIA® IND annual reporting of the ongoing RECORD observational follow-up substudy, and 2 deaths were found by the MediciGlobal effort.
- Eleven (11) newly discovered deaths occurred after 31 December 2008: 5 deaths were found by the GSK/Quintiles search effort, 1 death was found from the IND annual reporting, and 5 deaths were found from the MediciGlobal effort.
- The remaining 4 deaths occurred on an unknown date, 2 identified from the Quintiles tracking database and 2 from the MediciGlobal effort.

  Reviewer's comment: I would inquire of DCRI how the 4 deaths of unknown date were handled in the data re-adjudication.

Alternative Derivations of End of Follow-up

Final follow-up dates were derived by four different sets of rules, outlined in the DCRI stat plan, as follows:

1. Parsimonious approach: defined the last known alive date as the last date of a documented face-to-face visit at which one or more vital signs were recorded on the VITALS module of the CRF. Patients with a last known alive date after 24 August 2008 were considered to have completed survival follow-up.
2. Primary analysis: for patients who, based on the parsimonious approach, had not completed survival follow-up, the primary approach (used for the primary analysis) added follow-up information for 1) patients with a vital sign face-to-face visit in 2008 and phone visit after 24 August 2008; 2) patients with an updated last known alive date based on independent third party search; and 3) patients with an updated last known alive date based on DCRI review of CRFs or associated documents.
3. Primary analysis + tests and events: using dates for electrocardiogram assessments, laboratory tests, microvascular (diabetes-related) endpoints, adverse events, and fractures reported in the electronic data base, survival follow-up was updated for patients whose vital status was unknown after 24 August 2008 with the primary approach.
4. Primary analysis + tests and events + survival status: for patients whose vital status after 24 August 2008 could not be determined by the rules described in the first 3

approaches, vital status was updated from Survival Status follow-up and third party search conducted as part of the RECORD study.

To assess the possible impact of censoring / follow-up end-date derivation methodology, analyses for overall mortality and CV mortality were repeated using the three approaches other than the primary analysis survival follow-up for deriving study phase end dates. For analyses of mortality by these alternative rules, follow-up for patients was started at randomization and censored on date last know alive on or before 31 December 2008.

Quality Control

Twenty-five adjudicated death events were randomly selected for QC review by the lead (blinded) statistician and "QC re-adjudicated" by the DCRI RECORD CEC Committee. Of the 25 QC events, the following was determined:

- For 14 QC events, the QC result matched the original DCRI RECORD CEC re-adjudication result on all variables
- For 11 QC events, the QC result did not match the original DCRI RECORD CEC re-adjudication result on all variables.

OF the 11 QC events that did not match the original re-adjudication on all variables, six (6) events had a minor discrepancy between the QC re-adjudication and the original DCRI re-adjudication result regarding event date/time. No further action was taken for these events. The original adjudication result remained unchanged in the database. Three (3) events had a minor discrepancy between the QC re-adjudication and the original DCRI re-adjudication result regarding death sub-classification. These 3 events were re-reviewed and reconciled by the DCRI RECORD. The adjudication result was updated in the database as necessary. Two (2) events had a major discrepancy between the QC re-adjudication and the original DCRI re-adjudication result regarding the death classification. These 2 events were re-reviewed and reconciled by the DCRI RECORD CEC Committee. The re-adjudication result was updated in the database as necessary.

Re-adjudication Results – All cause Mortality

A total of 313 deaths were identified by the re-adjudication process, 299 before and 14 after the 31 December 2008 last RECORD follow-up date. Of these 313 deaths, there was insufficient evidence to determine cause of death (cardiovascular vs. non-cardiovascular) in 120 cases (38% of all deaths). The distribution of cause of death (cardiovascular, non-cardiovascular or unknown) was identical by the original RECORD and new FDA definitions. Follow-up for patients who did not die was censored on the date they were last known to be alive on or before 31 December 2008.

Based on the survival primary analysis (DCRI Table 3.1 below), all-cause mortality occurred in 139 of 2220 patients (6.3%) in the RSG group at a rate of 1.07 events per 100 patient years (95% CI: 0.89, 1.26). All-cause mortality occurred in 160 of 2227 patients (7.2%) in the MET/SU group at a rate of 1.25 events per 100 patient years (95% CI: 1.05,

1.45). The hazard ratio (95% CI) for RSG vs. MET/SU was 0.86 (0.68, 1.08); there was no evidence of a treatment effect (DCRI Table 3.1 and Figure 3.1 below), no interaction observed between treatment and background therapy, and no treatment-by-subgroup interaction for characteristics tested.

RECORD Trial: DCRI Independent Review

Table 3.1 (page 1 of 1)
All-Cause Mortality: Summary by Treatment Arm
Based on Survival Follow-up for Primary Analysis*

		Treatment	
	Total (N=4447 PY=25768.6)	Combined RSG (N=2220 PY=12953.6)	Combined MET/SU (N=2227 PY=12815.0)
Number of patients with an event	299 / 4447 (6.7%)	139 / 2220 (6.3%)	160 / 2227 (7.2%)
Rate per 100 patient years (95% CI)	1.16 (1.02, 1.30)	1.07 (0.89, 1.26)	1.25 (1.05, 1.45)
Hazard Ratio** (95% CI)		0.86 (0.68, 1.08)	
Absolute rate difference per 100 patient years (95% CI)		-0.18 (-0.44, 0.09)	

* Follow-up for patients who did not die is censored on date last known alive on or before 31-Dec-2008.
** Hazard ratio from a Cox proportional hazards model stratified by background therapy. A hazard ratio < 1 favors RSG.
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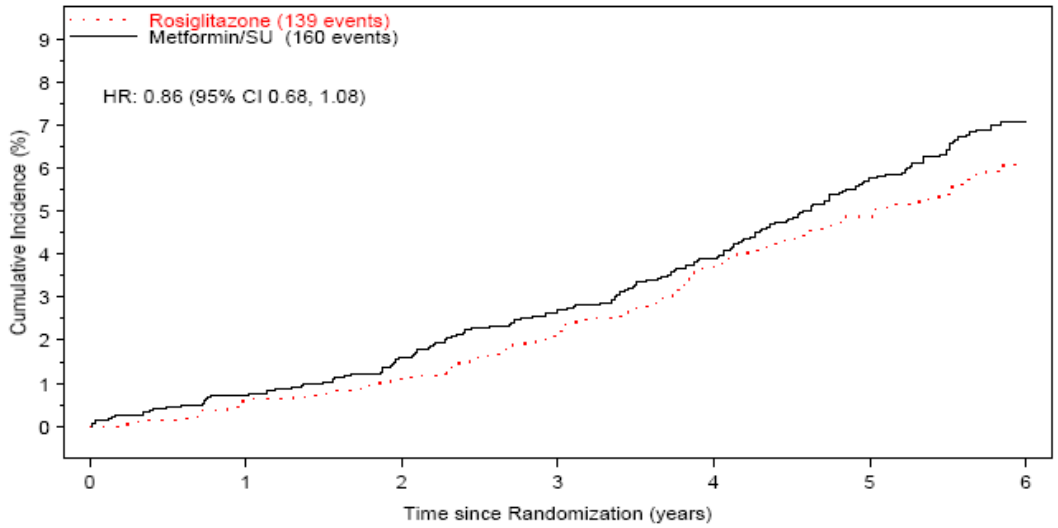
RECORD Trial: DCRI Independent Review

Figure 3.1
All-Cause Mortality - Time to Death
Kaplan-Meier Estimates and Hazard Ratio with 95% Confidence Interval for RSG vs. Met/SU
Based on Survival Follow-up for Primary Analysis



Rosaglitazone							
Events	0	13	24	46	81	106	129
At Risk	2220	2190	2165	2130	2087	2048	988
Metformin/SU							
Events	0	16	35	59	85	125	150
At Risk	2227	2181	2140	2110	2079	2019	953

Generated from ct/record/graphs/a_allcause_outcome.sas on 30NOV2011 at 17:31

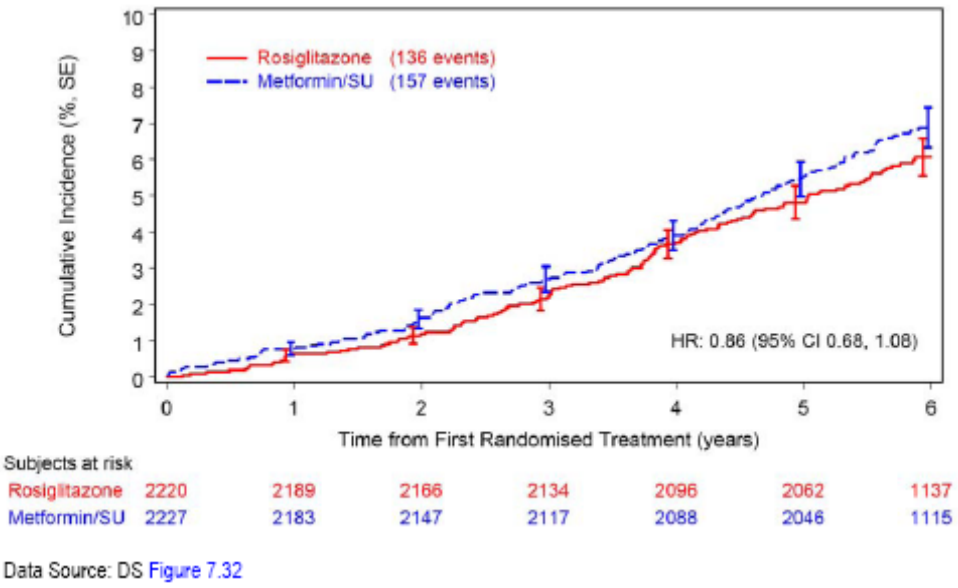
From the original RECORD study analysis, the "death from any cause, ITT population, vital status follow-up" is the counterpart to the DCRI all-cause mortality analysis above. Overall, there were six fewer all-cause deaths in the RECORD analysis, but the deficiency was evenly split, with 3 fewer deaths in both the RSG and the SU/MET arms (table 81 below, from the original RECORD FSR), and the Kaplan Meir appearance virtually identical to the DCRI re-analysis of all-cause mortality (Figure 22 below, from the original RECORD FSR):

Table 81 Death from Any Cause Including Survival Status Updates (ITT population)

All-Cause Death (including survival status update)	Treatment Group: Combined RSG (N=2220)	Treatment Group: MET/SU (N=2227)
No. subjects (%) who died (all-cause) during the study including survival status updates	136 (6.1)	157 (7.0)
Incidence: rate/100 PY[1] (95% CI)	1.05 (0.88, 1.24)	1.22 (1.04, 1.43)
Hazard ratio[2], (95% CI); p-value	0.86 (0.68, 1.08); p=0.1934	
Absolute rate difference/100PY[1]	-0.17 (-0.43, 0.09)	

Data Source: DS Table 7.114 and DS Table 7.115

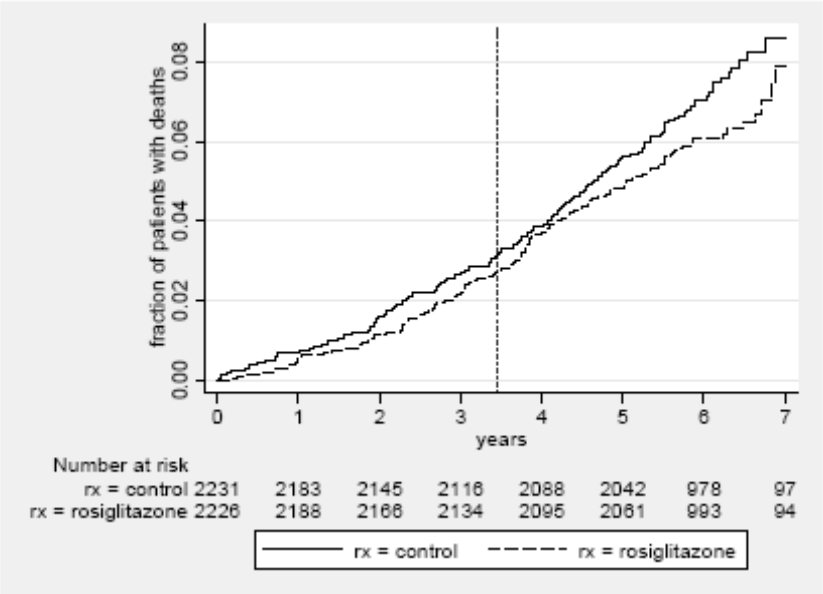
1. Person-years up to first event/censoring.
2. Based on Stratified (by background stratum) Cox's Proportional Hazards Model: Time = Treatment. HR is relative to MET/SU.



Data Source: DS Figure 7.32

The FDA plot of time to all-cause death, produced for the July 2010 Advisory committee, demonstrates essentially the same K-M morphology as well (Figure 11 below, Marciniak, June 2010):

Figure 11: K-M Plot for Time to All-Cause Deaths



Re-adjudication Results – CV and Unknown Mortality

Reviewer Comment: The RECORD trial included deaths of unknown cause in its definition of CV death. Therefore, CV death in RECORD is equivalent to CV+unknown cause death in the DCRI re-adjudication.

Based on the survival primary analysis, CV and unknown cause mortality as per the new FDA definitions occurred in 88 of 2220 patients (4.0%) in the RSG group at a rate of 0.68 events per 100 patient years (95% CI: 0.53, 0.83). Cardiovascular and unknown cause mortality occurred in 96 of 2227 patients (4.3%) in the MET/SU group at a rate of 0.75 events per 100 patient years (95% CI: 0.59, 0.90). The hazard ratio (95% CI) for RSG vs. MET/SU treatment was 0.90 (0.68, 1.21).

For CV and unknown cause deaths, primary survival analysis based on the original RECORD CEC definitions and the new FDA definitions produced identical results, including number of patients with an event, event rates, hazard ratios (RSG vs. MET/SU) by treatment and background therapy, and subgroup interaction results. There was no evidence of a treatment effect (DCRI Table 5.1 and Figure 5.1 below):

RECORD Trial: DCRI Independent Review

Table 5.1 (page 1 of 1)
CV and Unk. Cause Mortality (Original Def.): Summary by Treatment Arm
Based on Survival Follow-up for Primary Analysis*

		Treatment	
	Total (N=4447 PY=25768.6)	Combined RSG (N=2220 PY=12953.6)	Combined MET/SU (N=2227 PY=12815.0)
Number of patients with an event	184 / 4447 (4.1%)	88 / 2220 (4.0%)	96 / 2227 (4.3%)
Rate per 100 patient years (95% CI)	0.71 (0.61, 0.82)	0.68 (0.53, 0.83)	0.75 (0.59, 0.90)
Hazard Ratio** (95% CI)		0.90 (0.68, 1.21)	
Absolute rate difference per 100 patient years (95% CI)		-0.07 (-0.28, 0.14)	

* Follow-up for patients not reaching endpoint is censored on date last known alive on or before 31-Dec-2008.
** Hazard ratio from a Cox proportional hazards model stratified by background therapy. A hazard ratio < 1 favors RSG.
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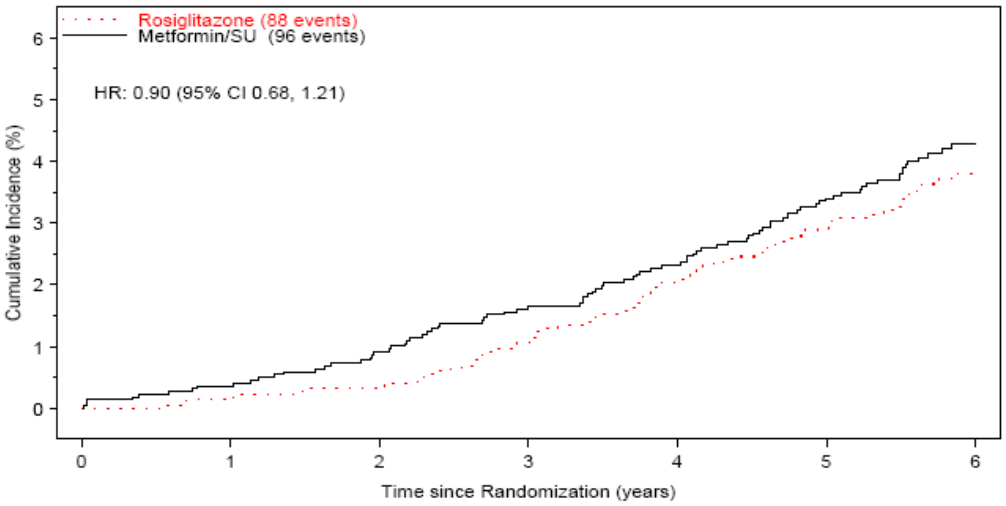
RECORD Trial: DCRI Independent Review

Figure 5.1

CV and Unk. Cause Mortality (Original Def.) - Time to Endpoint
Kaplan-Meier Estimates and Hazard Ratio with 95% Confidence Interval for RSG vs. Met/SU
Based on Survival Follow-up for Primary Analysis



Rosaglitazone							
Events	0	4	7	23	45	62	79
At Risk	2220	2190	2165	2130	2087	2048	988
Metformin/SU							
Events	0	8	20	36	50	73	89
At Risk	2227	2181	2140	2110	2079	2019	953

Generated from ct/record/graphs/a_allcause_outcome.sas on 30NOV2011 at 17:31

There was some evidence of treatment-by-subgroup interaction for duration of diabetes < 6 years or ≥ 6 years (p=0.069). The hazard ratio (95% CI) was 1.24 (0.80, 1.94) for the subgroup with diabetes < 6 years and 0.72 (0.49, 1.06) for the subgroup with diabetes ≥ 6 years. No other demographic or disease characteristic showed evidence of treatment interaction.

There was some evidence of treatment-by-baseline therapy (MET or SU) interaction (p=0.093). There was also evidence of interaction by baseline use of statins or not (p=0.003). Among patients using statins at baseline, the hazard ratio (95% CI) was 2.29 (1.16, 4.54) favoring MET/SU. Among patients *not* using statins at baseline, the hazard ratio (95%) was 0.72 (0.52, 1.00) favoring RSG.

From the original RECORD analysis, the definition of CV death included deaths of unknown cause. As opposed to a total of 184 CV + Unknown-cause deaths in the DCRI re-adjudication, there were only 131 total CV + Unknown-cause deaths in the original RECORD report (53 additional deaths of this classification in the DCRI re-adjudication). From the original RECORD analysis, there was no evidence of treatment effect on CV + Unknown-cause mortality (RECORD Table 76 and Figure 20 below):

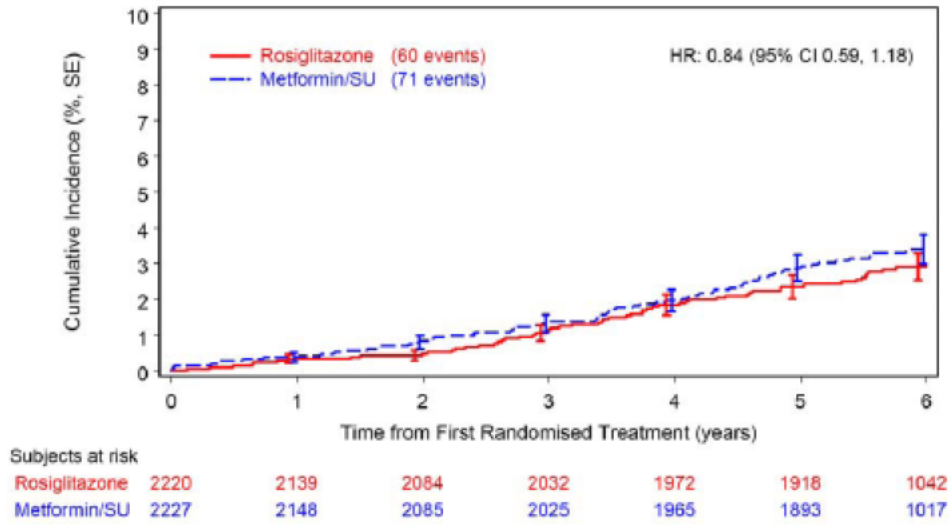
Table 76 Occurrence of Death from CV Causes (ITT population)

Time to CV Death	Treatment Group: Combined RSG (N=2220)	Treatment Group: MET/SU (N=2227)
No. (%) subjects who died from CV causes	60 (2.7)	71 (3.2)
Incidence: rate/100 PY[1] (95% CI)	0.49 (0.37, 0.63)	0.58 (0.45, 0.73)
Hazard ratio[2], (95% CI); p-value	0.84 (0.59, 1.18); p=0.3158	
Absolute rate difference/100PY[1]	-0.09 (-0.27, 0.09)	

Data Source: DS Table 7.102 and DS Table 7.103

1. Person-years up to first event/censoring.
2. Based on Stratified (by background stratum) Cox's Proportional Hazards Model: Time = Treatment. HR is relative to MET/SU.

Figure 20 Cumulative Incidence of Time to Death from CV Causes (ITT population)



Data Source: DS Figure 7.28

As shown in the table below, of the 53 additional deaths included in the DCRI analysis of CV + Unknown deaths, 46 were additional "unknown cause" deaths – only seven were additional CV deaths. Both the RECORD original analysis and the DCRI re-analysis demonstrate numerically higher CV deaths from the MET/SU arm than from the combined RSG arm:

Adjudicated Death Events	RSG (N=2200)		MET/SU (N=2227)	
	RECORD	DCRI	RECORD	DCRI
CV+Unk	60	88	71	96
Unk	28	53	33	54
CV	32	35	38	42

To further characterize re-adjudicated "unknown-cause" deaths from the DCRI CEC as compared to the original RECORD CEC, an assessment was made of how these two patient groups overlapped, and what their outcomes were (Mahoney, 2012). 61 deaths were adjudicated to be of unknown-cause in the original RECORD FSR. These were not a perfect subset of the 120 deaths re-adjudicated to be of unknown-cause by the DCRI:

- Of the 120 deaths due to unknown-cause in the DCRI re-adjudication, 82 had not been adjudicated as due to unknown cause in the original RECORD adjudication. These 82 deaths were evenly distributed between the RSG group and the MET/SU comparator group (41 deaths each).

- Of the 61 deaths originally adjudicated as due to an unknown-cause, 23 of these were not re-adjudicated by the DCRI as being due to an unknown cause. Among these 23 cases, 9 were in the RSG group, and 14 were in the comparator group. OF the 9 deaths in the RSG group, DCRI re-adjudicated 4 as CV deaths, and 5 as non-CV deaths. OF the 14 deaths in the MET/SU comparator group, DCRI adjudicated 8 as CV and 6 as non-CV deaths.

Re-adjudication Results – CV Mortality

An analysis of CV mortality without "unknown-cause" death was not performed in the original RECORD analysis, though a breakdown of the total numbers of the CV versus unknown-cause events are shown in the CV + Unknown-cause mortality section above.

DCRI analyzed CV deaths (without deaths of unknown-cause), using both the original RECORD definitions for CV death, as well as the new draft FDA definitions for CV death. In this analysis, 76 CV deaths were confirmed by re-adjudication representing 1.7% of the total ITT population (N=4447) (See DCRI Table 1.5 below). All confirmed CV deaths occurred on or before 31 December 2008; no CV deaths occurring after the RECORD end of follow-up date were identified. Cardiovascular death events occurred in 34 of 2220 patients (1.5%) in the combined RSG treatment group and 42 of 2227 (1.9%) in the combined MET/SU treatment group.

Of note, deaths due to CHF were strikingly more frequent in the RSG group as opposed to the MET/SU comparator group, both by the original definition (9/34 (26.5%) vs. 1/42 (2.4%), respectively) and by the new definition (8/34 (23.5%) vs. 1/42 (2.4%), respectively). On the other hand, acute vascular events were more common in the MET/SU group by the original definition (and stroke + other CV deaths more common in the MET/SU group by the new definition).

RECORD Trial: DCRI Independent Review

Table 1.5 (page 1 of 1)
Cardiovascular Mortality by Time Period

	Deaths Occurring On or Before 31-Dec-2008			Deaths Occurring After 31-Dec-2008		
		Treatment			Treatment	
	Total (N=4447)	Combined RSG (N=2220)	Combined MET/SU (N=2227)	Total (N=4447)	Combined RSG (N=2220)	Combined MET/SU (N=2227)
Original Definition						
Total Cardiovascular Deaths	76 / 4447 (1.7%)	34 / 2220 (1.5%)	42 / 2227 (1.9%)	0 / 4447	0 / 2220	0 / 2227
Cause of Death						
Heart Failure or Cardiogenic Shock	10 / 76 (13.2%)	9 / 34 (26.5%)	1 / 42 (2.4%)	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction	20 / 76 (26.3%)	8 / 34 (23.5%)	12 / 42 (28.6%)	0 / 0	0 / 0	0 / 0
Sudden Cardiac	29 / 76 (38.2%)	14 / 34 (41.2%)	15 / 42 (35.7%)	0 / 0	0 / 0	0 / 0
Acute Vascular Event	13 / 76 (17.1%)	1 / 34 (2.9%)	12 / 42 (28.6%)	0 / 0	0 / 0	0 / 0
Other Cardiovascular Cause	4 / 76 (5.3%)	2 / 34 (5.9%)	2 / 42 (4.8%)	0 / 0	0 / 0	0 / 0
New Definition*						
Total Cardiovascular Deaths	76 / 4447 (1.7%)	34 / 2220 (1.5%)	42 / 2227 (1.9%)	0 / 4447	0 / 2220	0 / 2227
Cause of Death						
Heart Failure or Cardiogenic Shock	9 / 76 (11.8%)	8 / 34 (23.5%)	1 / 42 (2.4%)	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction	21 / 76 (27.6%)	8 / 34 (23.5%)	13 / 42 (31.0%)	0 / 0	0 / 0	0 / 0
Sudden Cardiac	29 / 76 (38.2%)	14 / 34 (41.2%)	15 / 42 (35.7%)	0 / 0	0 / 0	0 / 0
Stroke	6 / 76 (7.9%)	0 / 34	6 / 42 (14.3%)	0 / 0	0 / 0	0 / 0
Other Cardiovascular Cause	11 / 76 (14.5%)	4 / 34 (11.8%)	7 / 42 (16.7%)	0 / 0	0 / 0	0 / 0

* Contemporary definitions under development by FDA through the Standardized Data Collection for Cardiovascular Trials Initiative.
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Re-adjudication Results – All-cause Mortality on Treatment LDRT + 30 days

No treatment effect or background therapy effect was demonstrated.

Re-adjudication Results – CV + Unknown-cause Mortality on Treatment LDRT + 30 days

No treatment effect or background therapy effect was demonstrated. Primary survival analysis based on the original RECORD CEC definitions and the new FDA definitions produced identical results, including number of patients with an event, event rates, hazard ratios (RSG vs. MET/SU) by treatment and background therapy, and subgroup interaction results.

Re-adjudication Results – All-cause Mortality on Treatment LDRT + 60 days

No treatment effect or background therapy effect was demonstrated.

Re-adjudication Results – CV + Unknown-cause Mortality on Treatment LDRT + 60 days

No treatment effect or background therapy effect was demonstrated. Primary survival analysis based on the original RECORD CEC definitions and the new FDA definitions

produced similar results, including number of patients with an event, event rates, hazard ratios (RSG vs. MET/SU) by treatment and background therapy, and subgroup interaction results.

Re-adjudication Results – Sensitivity Analyses

- CV mortality using original and new FDA definitions – no evidence of treatment effect
- Impact of Amendment 7 (tracking study to collect endpoint data from withdrawn patients) on all-cause mortality – no evidence of treatment effect and no interaction with background therapy
- Landmark analysis, Amendment 7 to 31 December 2008, all-cause mortality – no evidence of treatment effect and no interaction with background therapy
- CV + Unknown-cause mortality prior to Amendment 7 – no evidence of treatment effect and no interaction with background therapy
- Landmark analysis, Amendment 7 to 31 December 2008, CV + Unknown-cause mortality – no evidence of treatment effect and no interaction with background therapy
- All-cause mortality prior to published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- All-cause mortality following published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- CV + Unknown cause mortality (new definition) prior to published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- CV + Unknown cause mortality (new definition) following published interim report (05 June 2007) - no evidence of treatment effect and no interaction with background therapy
- All-cause mortality by alternative rules for derivation of end of follow-up – the three alternative approaches (parsimonious, primary analysis + tests and events, primary analysis + tests and events + survival status) demonstrated no evidence of treatment effect and no interaction with background therapy
- CV + Unknown-cause mortality by alternative rules for derivation of end of follow-up – the three alternative approaches (parsimonious, primary analysis + tests and events, primary analysis + tests and events + survival status) demonstrated no evidence of treatment effect and no interaction with background therapy
- Impact of censoring at earliest study completion date (24 August 2008 instead of 31 December 2008) on all-cause mortality – no evidence of treatment effect (no test for background therapy interaction)
- Impact of censoring at earliest study completion date (24 August 2008 instead of 31 December 2008) on CV + Unknown-cause mortality (new definition) – no evidence of treatment effect (no test for background therapy interaction)

Assessment

This well-conceived and comprehensive re-adjudication of the RECORD trial mortality experience demonstrated no evidence of a difference in all-cause mortality, cardiovascular plus unknown-cause mortality or non-cardiovascular mortality between the RSG and MET/SU treatment arms of RECORD. This was true regardless of whether the original RECORD definitions or new/draft FDA definitions of mortality endpoints was utilized. Hazard ratios for RSG vs MET/SU for all-cause mortality, CV+Unknown-cause mortality, and non-CV mortality were all less than 1.0 in the DCRI re-adjudication of the mITT results of RECORD. None of the many sensitivity analyses demonstrated a treatment effect. Accordingly, the findings of this phase-I mortality re-analysis corroborate the mortality findings of the original RECORD analysis.

The degree to which no stone was left unturned in this re-analysis is highlighted by the number of patients who ultimately required imputed end-dates for study events. Recall, 604 patients were deemed by DCRI to have incomplete follow-up. By the end of the investigations and record reviews by DCRI and MediciGlobal, only 21 patients required imputation of death dates. Of these 21 patients, a year of death was documented for all. For 11 of the 21 patients, documentation for a month and year were found, requiring imputation only for the day of the month of death.

To be sure, the critic would point out that of the 127 queries for information that went out to sites, only 23 of the 127 generated additional data (response rate 18%), and only 7 of these resulted in a change to the adjudication (action rate 6%). Yet we would point out that these queries went out to sites after the study had been closed for approximately 2-3 years. Furthermore, considering staffing limitations (and sometimes closure of practices), this response rate should have surprised no one, as most investigators simply do not have the capacity to open up large paper data files to look for details on a study that has long since been shut down.

Though we commend the DCRI for an impressive re-analysis effort, it must be recognized that what comes out of an analysis directly depends on what goes in. There is no amount of analytical rigor that can compensate for a weak trial design that is exacerbated by elements of poor execution, both of which afflicted RECORD. Its open-label non-inferiority design was simply problematic, especially for ascertainment of non-mortality MACE during trial execution. Of the 313 deaths that DCRI identified and re-adjudicated, there was insufficient evidence to determine cause of death (cardiovascular vs. non-cardiovascular) in 120 cases (38% of all deaths).

Thus, while we agree with the analytical findings of the DCRI mortality re-analysis, we would emphasize that RECORD's design irreparably hampers its ability to characterize definitively the CV risk of rosiglitazone.

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/s/

PRESTON M DUNNMON
05/13/2012

STEPHEN M GRANT
05/14/2012

NORMAN L STOCKBRIDGE
05/14/2012