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FDA Briefing Document

Advisory Committee Meeting for NDA 21071 Avandia (rosiglitazone maleate) tablet

July 13 and 14, 2010



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To: Advisory Committee Panel Members

Subject: Inter-Office Background Memo and Draft Questions for July 13 and 14, 2010
Advisory Committee Meeting for Avandia® (rosiglitazone)

I. INTRODUCTION

On July 30, 2007, the cardiovascular safety concerns associated with Avandia® (rosiglitazone) were discussed before a joint public advisory committee involving members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Committee (DSARM).¹ The committee was also comprised of experts in cardiovascular disease from the Cardiorenal Drugs Advisory Committee and diabetologists from the National Institutes of Health.

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

1. Do the available data suggest² a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus?

20 voted yes, 3 voted no

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

22 voted yes, 1 voted no

¹ Transcripts for July 30, 2007 advisory committee available at
<http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic>

² 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).

Subsequent to this advisory committee meeting, the agency held several internal meetings leading up to a Center-level decision that rosiglitazone should remain on the market but with labeling changes to reflect current knowledge of CV risk associated with rosiglitazone. In addition, it was determined that a dedicated safety trial, which would include a direct comparison between rosiglitazone and pioglitazone, would be necessary to provide more conclusive data on the CV risks of rosiglitazone.

On November 14, 2007, the FDA approved revised labeling to Avandia and other rosiglitazone-containing drug product labels to include the following language in a boxed warning:

"a meta-analysis of 42 clinical trials (mean duration 6 months; 14,237 patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive."

The WARNINGS and PRECAUTIONS section of labeling was also updated to provide details on selected at-risk patients for myocardial ischemia with use of rosiglitazone followed by revisions to the Medication Guide in February 2008. With these labeling changes, GlaxoSmithKline (GSK) also committed to conduct a randomized, prospective, controlled clinical trial to evaluate CV safety of rosiglitazone. This trial is titled the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial. Under the new authorities granted to the FDA in the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA made this study a required postmarketing trial.

New clinical data have since become available that merit another discussion before a joint advisory committee. These data include the completed results of RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), a postmarketing trial conducted for the European regulatory authorities; a systematic review of published controlled epidemiologic studies of cardiovascular risk in patients taking rosiglitazone or pioglitazone; an observational epidemiological study of the adverse cardiovascular outcomes and mortality in new users of rosiglitazone and pioglitazone using data from the Center for Medicare/Medicaid Services (CMS); and two meta-analyses of clinical trials, one each of rosiglitazone and pioglitazone.

The objectives of this memo are to provide a historical overview of the events triggering the ongoing debate regarding the cardiovascular safety of rosiglitazone and to present an overarching summary of new clinical data now available for review and discussion.

II. CLINICAL DATA AVAILABLE IN JULY 2007

A. The Initial Signal for Avandia's CV Risk - Meta-analysis of Controlled Clinical Trials

The signal for Avandia's CV risk arose from a meta-analysis of 42 controlled clinical trials. Although other meta-analyses of Avandia trials have been published^{3,4}, this document will highlight only the FDA's meta-analysis of 42 clinical trials submitted to the agency in August 2006 because this is the database for which the agency had complete patient-level data.

³ 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.

⁴ Singh S et al. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007;298(10):1189-1195.

The FDA's review of this meta-analysis noted a signal for cardiac ischemic risk associated with rosiglitazone summarized as an odds ratio for non-serious and serious myocardial ischemia of 1.4 (95% CI: 1.1-1.8) with an associated p-value of 0.02.

The strengths of this database included:

1. large number of patients - 14,237 patients (8604 on RSG/RSG-containing regimen vs 5633 non-RSG containing regimen)
2. all the studies were randomized, blinded and controlled studies

The limitations of this database included:

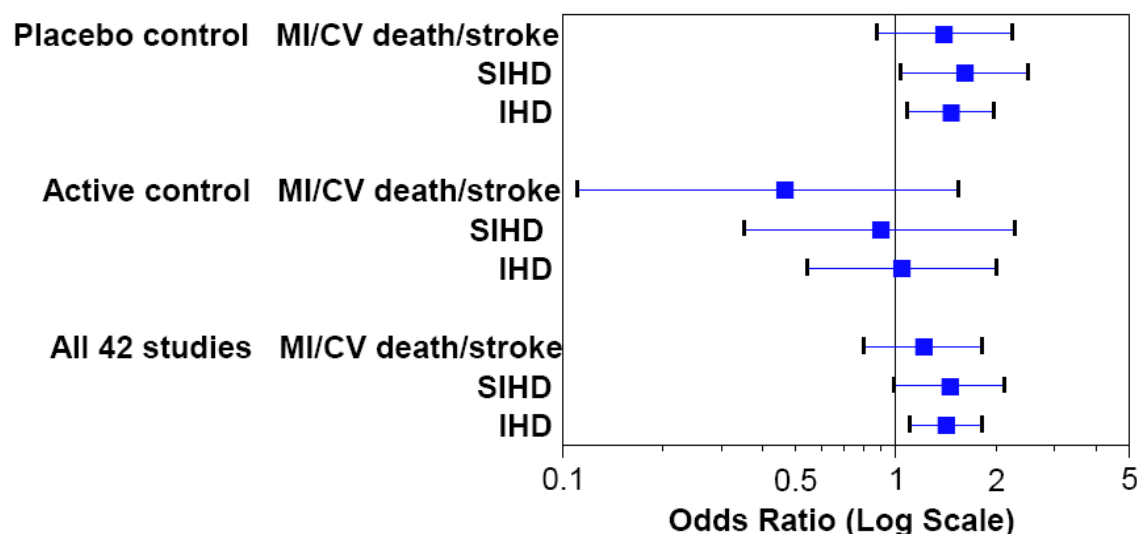
1. majority of trials were of 6 months duration (38 were 6 months or less; 3 were 1 year in duration; one 2-yr trial)
2. studies were not designed to evaluate cardiovascular endpoints; only one study had a blinded adjudication committee for CV endpoints, all other studies had endpoints adjudicated retrospectively
3. heterogeneous population (treatment-naïve, multiple-drug regimen, long-standing vs early diabetes, established heart disease, heart failure)
4. control group varied (placebo, different active controls – sulfonylurea/metformin/insulin)
5. treatment regimen for rosiglitazone varied (monotherapy, combination therapy, add-on)

The impact of these limitations was notable in that the point estimates for myocardial ischemic risk and accompanying 95% CI were affected by certain subgroup analyses. In some cases the risk estimates were no longer significant and even fell below 1.0. In particular, Ms. Joy Mele, the FDA statistician who performed this meta-analysis, found notable differences in the overall risk estimate when she analyzed the data by placebo versus controlled clinical trials, and by baseline nitrate use.

Placebo vs Active Controlled Trials

Approximately 85% of the trials in the meta-analysis were placebo-controlled. When the meta-analysis was performed by placebo- vs active-controlled trials, the increase in ischemic risk was observed in only the placebo-controlled trials. This finding suggests that the risk of myocardial ischemia is similar between rosiglitazone and other oral anti-diabetic agents to which it was compared (metformin and sulfonylureas).

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)



Nitrate Use

There were only 617/14,237 (4.3%) patients in the meta-analysis who were classified as using nitrates at baseline. Despite this small number of patients, analysis by use or non-use of nitrates showed a significant interaction as summarized below. Use of nitrates may represent a higher baseline risk for CVD.

Table 1. Effect of Nitrate Use at Baseline on Risk Estimate in ICT Database

Nitrate Use	N	OR (95% CI)	Exact p-value
Yes	617	2.9 (1.4, 5.9)	0.0012
No	14,179	1.3 (0.9, 1.7)	0.14

Other patient or trial characteristics that affected the overall point estimate included duration of diabetes and co-administration of insulin or metformin. Treatment-naïve patients, who on average had a shorter duration of disease than previously-treated patients, had no evidence of excess ischemic risk with rosiglitazone (OR 0.97; 95% CI 0.5-1.9) compared to previously-treated diabetics who had a significant increase in risk (OR 1.5; 95% CI 1.1-2.1). The highest risk estimates were observed in the insulin (OR 2.1; 95% CI 0.9-5.1) and metformin (OR 3.2; 95% CI 1.2-10) co-administration studies. Although it can be postulated that insulin co-administration correlated with higher baseline risk for CVD due to the longer duration of diabetes in these patients (mean duration of 13 years), it was unclear why the studies of metformin co-administration yielded the highest point estimates.

Given the inconsistent findings by subgroups on the overall risk estimate of marginal statistical significance, the agency looked to three long-term controlled clinical trials involving rosiglitazone.

B. Long-term Controlled Clinical Trials

These trials were:

1. DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) - a large, double-blind, randomized, 2x2 factorial design study in 5269 patients with impaired glucose tolerance or impaired fasting glucose designed to assess the effect of 4 different treatment groups

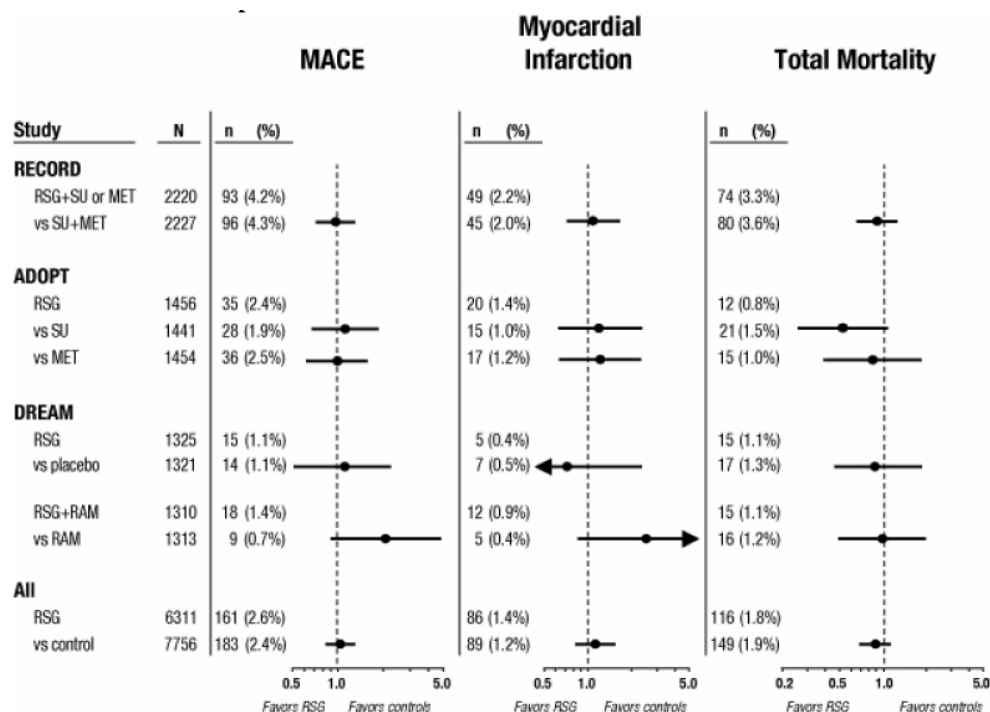
(placebo, rosiglitazone monotherapy, ramipril monotherapy, and rosiglitazone + ramipril) on the composite endpoint of incident diabetes or all-cause mortality.

2. ADOPT (A Diabetes Outcomes Progression Trial) - a randomized, double-blind, parallel group study in 4351 subjects recently diagnosed with T2DM who were previously managed with diet and exercise only. The study evaluated the following treatment groups: rosiglitazone monotherapy, metformin monotherapy, and SU monotherapy. The primary endpoint was time to monotherapy failure defined as having either a FPG > 180 mg/dL on consecutive assessments following at least 6 weeks of therapy at the maximum tolerated dose of study medication or as judged by an independent adjudication committee.
3. RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) - an ongoing, open-label, randomized trial of rosiglitazone as add-on therapy to either metformin or sulfonylurea in comparison to metformin and a sulfonylurea in patients not adequately controlled on their prior therapy. This trial was designed as a non-inferiority trial on the primary endpoint of CV death and CV hospitalization, including CHF. Only the interim analysis was available at this time.

Combined, these three trials contained data in over 14,000 patients with a mean duration of exposure of 41 months. Compared to the meta-analysis, which had approximately 4000 patient-yrs of exposure to rosiglitazone, these three trials had approximately 20,000 patient-yrs of exposure.

The ischemic risk findings from the meta-analysis were not noted in 3 longer-term controlled clinical trials. With exception for heart failure, an established and labeled class effect of these drugs, none of these trials showed a statistically significant increase in other CV adverse events, including myocardial infarction. However, a numerically higher event rate for myocardial infarctions was noted with rosiglitazone treatment in all three trials. Across all three trials, total mortality was lower in the rosiglitazone-treated group compared to controls. The following forest plot was included in the updated labeling in November 2007 to reflect the different findings on CV risks in DREAM, ADOPT, and RECORD.

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

Like the original meta-analysis, the long-term controlled trials did not evaluate rosiglitazone's safety relative to pioglitazone. Except for a 24-week lipid-altering efficacy trial, there are no completed trials directly comparing the safety of these two drugs. The TIDE trial is the only ongoing prospective, cardiovascular outcomes trial designed to assess the CV risks of rosiglitazone compared to pioglitazone.

C. Rosiglitazone Versus Pioglitazone

Actos® (pioglitazone), manufactured by Takeda Pharma, is the only other marketed thiazolidinedione and therefore serves as an alternative to rosiglitazone from the same class for the treatment of type 2 diabetes. As a result, the CV safety of this drug was also considered in July 2007.

The CV effects of pioglitazone were evaluated in the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events), a cardiovascular outcomes trial comparing pioglitazone to placebo (each added on to current anti-diabetic therapies) in patients with T2DM who had significant risk for cardiovascular disease. The primary endpoint was a composite of all-cause mortality, nonfatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, cardiac intervention including coronary artery bypass graft or percutaneous coronary intervention, major leg amputation (above the ankle), or bypass surgery or revascularization in the leg. There was no statistically significant difference between pioglitazone and placebo for this endpoint. A total of 514/2,605 (19.7%) of pioglitazone group patients experienced one or more of these events, compared to 572/2,633 (21.7%) of placebo group patients ($p = 0.0954$). For individual components of the primary endpoint, there was no statistically significant difference between treatment groups for any component; numerically fewer events occurred in the pioglitazone group for all components except major leg amputation and leg revascularization. A late amendment to the protocol designated the composite of CV death, nonfatal MI

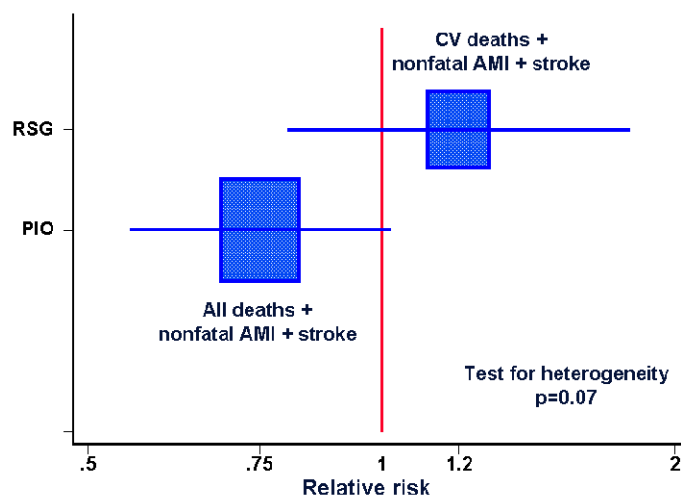
(excluding silent) and stroke as a "main" secondary endpoint for which a significant treatment difference favoring pioglitazone was observed. Upholding the original pre-specified analysis, the main conclusion from this trial is that pioglitazone is not associated with an increased risk of cardiac ischemic events. Such a finding is reassuring, as pioglitazone was associated with a significant increased risk of heart failure similar to other TZDs. The agency approved similar heart failure language in the pioglitazone label in February 2006. There is no implied claim of CV benefit in the label based on the nonsignificant results of the primary composite endpoint.

Despite the absence of a head-to-head comparison of these two drugs on CV outcomes, a comparison between these two drugs has been performed through other means. In July 2007, the FDA did not present any observational studies comparing these two drugs at the advisory committee. However, a few weeks before the meeting, the agency received requests for presentations during the open public hearing from several individuals who had already begun such a comparison of the two drugs utilizing healthclaims databases from TriCare and Wellpoint. These results will not be summarized in this memo. Instead the reader is referred to the meeting transcripts. Overall, data from these two observational studies showed no difference in selected CV events between rosiglitazone and other anti-diabetic medications. However, since July 2007 there have been numerous other observational studies published with contradictory findings to these two studies. These observational studies will be presented during this advisory committee meeting.

In addition to the observational studies, a comparison was made between these two drugs by Dr. David Graham from the FDA's Office of Surveillance of Epidemiology. In October 2006, a meta-analysis of pioglitazone trials was submitted as a major amendment to Takeda's supplement for the PROactive trial to support labeling claims of CV benefit. The FDA did not have access to patient level data for this meta-analysis and did not concur that such a meta-analysis would support an indication or labeling suggestive of CV risk reduction. Using this meta-analysis, Dr. Graham compared its results with the meta-analysis of the rosiglitazone trials performed by Ms. Joy Mele. He presented the following slide which compared total mortality, nonfatal MI and stroke in the pioglitazone meta-analysis with CV mortality, nonfatal MI and stroke in the rosiglitazone meta-analysis

Figure 3. Slide from Dr. David Graham's July 2007 AC Presentation Comparing the Meta-analyses of Rosiglitazone to Pioglitazone

Comparison of CV risk observed in meta-analyses of RSG and PIO



A similar meta-analysis of pioglitazone trials was conducted by Lincoff et al and published in September 2007.⁵ Takeda, who provided funding for statistical analyses of these trials and also collected the data for the trial used in the meta-analysis, provided the FDA with a summary of the 19 studies contributing to this meta-analysis. More than half of these studies (10) were of 1 yr duration or greater with one of these studies being the PROactive study described above. Recall that only 4/42 (9.5%) studies in the rosiglitazone ICT database were of a duration greater than 1 year. The longest rosiglitazone trial was two years. Other notable differences included:

- In the rosiglitazone database, about **85%** of the database is placebo-controlled while in pioglitazone only approximately **18%** are against placebo
- In the rosiglitazone database, about **15%** of the database is head to head against SU while in pioglitazone about **63%** is against SU
- In the rosiglitazone database, about **23%** of the database is add-on to metformin/placebo controlled compared to **6%** in the pioglitazone group
- In the rosiglitazone database, about **26%** of the patients were naïve to therapy compared to **48%** in the pioglitazone database

Given the differences in the databases comprising the meta-analyses of these two drugs as presented above, caution should be applied in making a conclusion that one drug is superior to, or safer than, the other.

Any consideration of regulatory action based on the safety profile of two drugs in the same class must consider the entire safety profile of both. While both agents share increased risk of fractures in women, anemia, weight gain, macular edema, peripheral edema and fluid retention, and exacerbation of heart failure, pioglitazone has an additional risk signal of bladder cancer.

As discussed at the 2007 meeting, bladder tumors have been observed in rats with peroxisome proliferator activated (PPAR) agents that demonstrate dual alpha and gamma activity. Pioglitazone is no exception and these findings were observed at clinically relevant doses. An imbalance of bladder cancer has also been observed in two long-term clinical trials. In PROactive, bladder tumor was reported in 14/2605 (0.5%) of pioglitazone-treated patients compared to 6/2633 (0.2%) in the placebo group. Additionally, in a 36-month liver safety study conducted as a post-marketing commitment to FDA, 3/1051 patients randomized to pioglitazone had bladder tumors reported compared to 0/1046 in the comparator group.

While recognizing that the overall number of cases is small, the bladder cancer imbalance in these two independent 3-year trials alongside a potential signal from nonclinical studies can not be dismissed and FDA has required language in both the package insert and Medication Guide for pioglitazone. It is important to consider this in any regulatory decisions that may channel patients to pioglitazone.

III. New Clinical Data Since July 2007

A. RECORD

On August 25, 2009, the FDA received the completed results of the RECORD trial submitted as a supplement to the NDA with proposed labeling changes. The most notable proposed change to the label was the removal of language to the boxed warning approved in November 2007 based on the findings of the meta-analysis of 42 controlled clinical trials and the 3 long-term controlled clinical trials. The proposed change is shown below:

⁵ Lincoff AM et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298(10):1180-1188.

WARNING: CONGESTIVE HEART FAILURE ~~AND MYOCARDIAL ISCHEMIA~~

See full prescribing information for complete boxed warning.

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.

- AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)

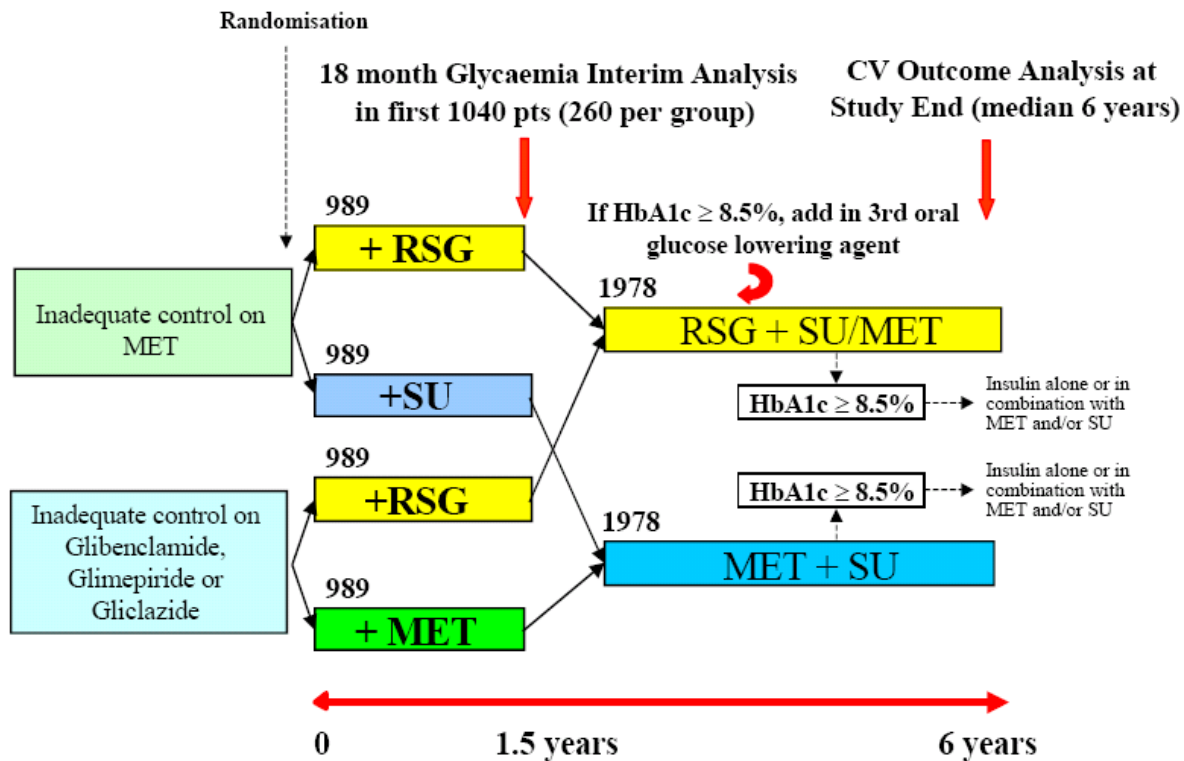
- ~~● A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)~~

The remaining language in the boxed warning is class labeling for both rosiglitazone and pioglitazone. All other sections of the labeling would parallel this change. The submission of this supplement did not alter any plans to conduct the postmarketing required trial, TIDE.

RECORD was not conducted under a U.S. IND; it was designed and conducted to fulfill a post-marketing commitment to the European Regulatory Authorities. It 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 study design and randomization scheme is summarized in the following illustration:

Figure 4. Schematic of RECORD Study Design



At the time of its initiation in 2001, metformin and SU were the primary oral agents relied upon for glycemic control in type 2 diabetes. The approval of the rosiglitazone and pioglitazone in 1999 (troglitazone was withdrawn from the market that year) introduced another class of drugs to consider when patients treated with either metformin or a SU failed to achieve adequate glycemic control. It is important to note that worsening glycemic control over time occurs in the majority of patients with type 2 diabetes. The management of such patients requires the addition of other anti-diabetic agents as switching from one agent to another rarely results in improvement in HbA1c.

The comparison of the following treatment groups:

- rosiglitazone plus metformin versus SU plus metformin
- rosiglitazone plus SU versus metformin plus SU

is relevant to interpretation of the meta-analysis in 2007 that launched the ongoing debate of rosiglitazone's CV safety.

From the applicant's analysis, RECORD met its original objective wherein 321 (14.5%) of rosiglitazone-treated patients compared to 323 (14.5%) of comparators experienced either CV death or CV hospitalization. The hazard ratio was 0.99 with an accompanying 95% CI of 0.85-1.15, the upper bound of this margin below the pre-specified non-inferiority margin of 1.2.

However, in considering whether RECORD supports a conclusion that rosiglitazone has a comparable CV risk profile to metformin or SUs, the review must also address the limitations of the study with respect to its design, conduct, and the presence of confounding variables that might bias the overall findings. The limitations of this trial have been identified by FDA reviewer, Dr. Thomas Marciniak, in his consult to the

review division. In addition, concerns have also been raised by Dr. Steven Nissen in his perspective in JAMA⁶ and his discussions with FDA staff. To the extent possible, review and analyses were performed of the data submitted to explore these limitations and concerns.

The clinical and statistical reviews of RECORD included but were not limited to:

- analyses of the intent-to-treat and per-protocol population to determine the impact of differential glycemic rescue criteria and imbalances in initiation of insulin use
- event rates before and after the interim analysis
- impact of statin use and non-use in the overall findings
- review of secondary endpoints relying on less controversial endpoints such as MACE (CV death, nonfatal MI, and nonfatal stroke) and total mortality
- discussion of overall event rates in RECORD relative to other well-known CV outcomes trials in patients with type 2 diabetes
- discussion of data ascertainment in patients discontinuing from the trial or lost to follow-up

The FDA's Division of Scientific Investigations (DSI) also conducted interviews of study personnel and audits of several clinical study sites and the contract research organization to identify if there were deficiencies in the collection of data and to explore if there was evidence of misconduct.

RECORD did not include pioglitazone as a separate treatment and will not be able to determine whether rosiglitazone carries greater CV risk than pioglitazone. A comparison of the safety of these two drugs was undertaken through observational studies and meta-analyses.

B. Observational data

Since the July 2007 Advisory committee meeting on rosiglitazone, there have been a number of publications of observational studies comparing the cardiovascular side effects of rosiglitazone to those of other antidiabetic agents. These published studies varied from one to the next. Some studies compared rosiglitazone to pioglitazone; others compared rosiglitazone to other antidiabetic agents. In addition, outcome measures varied across these studies. A systematic review of the available controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone was performed by OSE, in collaboration with the Office of Biostatistics. The Newcastle-Ottawa Scale was used as a measure to assess each study's quality. This summary of studies is qualitative and the analysis is qualitative; no quantitative meta-analysis of these studies was done. The results are included in this background package and will be presented at the meeting.

OSE has collaborated with the Center for Medicare and Medicaid Services (CMS) to conduct an observational epidemiological study of the adverse cardiovascular outcomes and mortality in new users of rosiglitazone compared to new users of pioglitazone. OB was consulted on the analyses. Endpoints include hospitalized myocardial infarction, stroke, heart failure, all-cause mortality, and a composite of these endpoints. Data were available on over 220,000 patients receiving either rosiglitazone or pioglitazone. Results of this study are in this background package and will be presented at the meeting.

C. Meta-analyses of Rosiglitazone and Pioglitazone Controlled Clinical Trials

Conclusions on the CV safety of rosiglitazone relative to pioglitazone have been made by some reviewers from the Office of Surveillance and Epidemiology based on meta-analyses of meta-analyses and meta-analyses of observational studies in a review completed in October 2009. In none of these assessments

⁶ Nissen SE. Setting the RECORD Straight. JAMA. 2010;303(12):1194-1195.

did the FDA have access to patient level data for all data sources or details about the individual trials/studies utilized in the meta-analyses.

With its submission of the completed RECORD results, GSK also submitted an update to its original meta-analysis to include 10 additional studies. In preparation for this advisory committee meeting, the Office of Biostatistics has conducted meta-analyses of both rosiglitazone and pioglitazone trials. The objectives 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. Both GSK and Takeda were requested to provide the FDA with patient-level data from trials of their respective drugs that were randomized, double-blind, between 2 months to 2 years in duration, and completed by December 2009. The primary endpoint was MACE (CV death, stroke, or MI) and secondary endpoints of interest included CV death, stroke, MI, total mortality, serious myocardial ischemia, total myocardial ischemia, and CHF. The same statistical analysis plan was applied to both meta-analyses.

The Office of Biostatistics has provided its review of the two meta-analyses in the background package.

D. CV Safety of Rosiglitazone in Other CV Outcomes Trials

The Veterans Affairs Diabetes Trial (VADT) and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) are two large cardiovascular outcomes trial conducted in patients with type 2 diabetes at high risk for a cardiovascular event. Neither of these trials was designed to specifically investigate the cardiovascular risk of rosiglitazone; however, both trials had a high percentage of patients treated with rosiglitazone. As a result of the 2007 meta-analysis, study investigators from both trials conducted analyses to determine the contribution of rosiglitazone to the CV findings in each of these trials. The lead statisticians from both of these trials have been invited to present their findings at this advisory committee meeting.

IV. CV Outcomes Trial – TIDE

The Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial is an ongoing, 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 on the time to first occurrence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke (MACE). Secondary endpoints include total mortality, the individual components of the primary endpoint, and a composite of microvascular outcomes.

The trial has 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 is to demonstrate noninferiority between rosiglitazone and pioglitazone on the primary composite of MACE. This is the only CV outcomes trial including a direct comparison between these two drugs.

The principal investigator for TIDE has also been invited to present the study design and objectives and procedures in obtaining informed consent.

Based on the data presented to the committee members, we will be asking you to address the following questions:

V. DRAFT Discussion Points and Questions to the Panel

1. Please discuss the strengths and weaknesses of the various sources of data available to address the question of an increased risk of ischemic CV events in patients treated with rosiglitazone:

- a) in comparison to other non-TZD anti-diabetic agents (i.e., metformin, sulfonylureas) based on the meta-analysis of rosiglitazone controlled clinical trials, the large outcome trials that included rosiglitazone (i.e., ADOPT, RECORD, VADT, BARI-2D), and the published observational studies.

Please specifically consider and discuss the data addressing the risk of myocardial infarctions in the context of the data addressing the risk of stroke and overall mortality.

- b) in comparison to pioglitazone based on the published observational studies, the observational study in the CMS database, and the separate FDA meta-analyses of rosiglitazone and pioglitazone controlled clinical trials.

Please specifically consider and discuss the following:

- comparability of the patient populations exposed to each of these drugs in the various databases
- completeness of data ascertainment for CV events
- possible impact of publication bias on the availability of data from observational studies
- relevance of different trial designs, comparators, and trial duration between the two meta-analyses

2. Considering all the available data, do you conclude that rosiglitazone increases the risk of ischemic CV events in patients with Type 2 diabetes relative to the comparator agents studied? Please vote yes or no and discuss the rationale for your vote.

3. Based on your assessment of the overall benefit-to-risk profile, do you recommend that rosiglitazone be withdrawn from the U.S. market? Please vote yes or no and discuss the rationale for your vote.

- Please discuss any recommendations for further labeling changes or risk management activities that you recommend FDA pursue regarding rosiglitazone.

4. 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)? Please vote yes or no and discuss the rationale for your vote.

- Please discuss any recommendations for changes to the TIDE protocol or informed consent.

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
06/16/2010

CURTIS J ROSEBRAUGH
06/16/2010

GERALD J DALPAN
06/16/2010



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

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Subject: Cardiovascular events in RECORD, NDA 21-071/S-035

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To: Jena Weber, Project Manager
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This memo responds to your consult to us dated October 27, 2009, requesting our review of cardiovascular (CV) events in the RECORD trial for rosiglitazone (Avandia). You asked four specific questions regarding the CV aspects of the trial. We believe that they can't be answered in isolation but only by a comprehensive review of the trial design; trial conduct; endpoint, adjudication, and analysis issues; and CV results. We provide our detailed evaluation of the CV aspects of these four topics below. Our summary is that RECORD was inadequately designed and conducted to provide any reassurance about the CV safety of rosiglitazone. The results do confirm and extend the recognized concerns regarding increased heart failure (HF) and HF deaths with rosiglitazone. They also suggest that rosiglitazone increases the risk for myocardial infarction (MI), although the confidence intervals for estimated MI hazard ratios are wide and include no risk while biases in the study suggest that the true risk could be higher.

1. Trial Design

RECORD, as you know, was a randomized, open-label, active-controlled trial comparing combined rosiglitazone and metformin or a sulfonylurea to combined metformin and a sulfonylurea. The primary endpoint was a composite of CV death and CV hospitalizations. The design was complex such that we can not summarize the critical aspects succinctly. We have provided detailed comments in Appendix 2. We list in Table 1 the trial design issues that we discuss in Appendix 2 along with our estimates of how they might bias the trial results.

Table 1: Trial Design Issues Detailed in Appendix 2

#	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
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

By “Bias rosiglitazone” in Table 1 we mean that the way the issue was handled in RECORD could potentially lead to results biased in favor of rosiglitazone. All of the issues we count as a bias in favor of rosiglitazone are ones related to the open label conduct of the trial. By “Bias null” we mean that the way the issue was handled in RECORD tends to bias the trial results towards the null, i.e., that rosiglitazone is non-inferior to the active controls regarding CV risk. By “Bias neutral” we mean that the way the issue was handled in RECORD doesn’t directly lead to bias—but how these issues were handled may prevent biases from being detected.

We judge that there are sufficient issues with the study design that introduce biases, particularly towards the null, that we can not rely upon RECORD to provide reassurances regarding the effects of rosiglitazone upon CV risk. Please see the details we provide in Appendix 2 for our justification for this statement. Because of the study design biases and similar biases resulting from study conduct (discussed next), we assert that at best any estimates of rosiglitazone CV risk are lower bounds for the risk rather than valid estimates with reliable statistical confidence intervals.

RECORD was a post-marketing study requested by the European Medicines Agency. We did not review the protocol prior to study implementation. If we had, we would have judged it to be unacceptable for the reasons detailed in Appendix 2.

2. Trial Conduct

These protocol design issues appear to have led to problems with the study conduct that also limit any reassurances that RECORD can provide regarding the CV safety of rosiglitazone. In addition, there are other design limitations not detailed in the protocol that also created problems, and there are study conduct problems independent of design limitations. We discuss all of these

study conduct issues in Appendix 3, relating them to the design limitations when relevant and documenting them with excerpts from the trial documentation and CRFs and analyses of the RECORD data. We list the trial conduct issues we discuss in Appendix 3 in Table 2 below along with our evaluation of how they biased the trial results.

Table 2: Trial Conduct Issues Detailed in Appendix 3

#	Issue	Bias
1	Open label and unblinding	rosiglitazone
	Unacceptable case handling	rosiglitazone
2	Failures to refer events for adjudication	rosiglitazone
3	All hospitalizations not recorded	null
4	Adjudication issues	
	High bar for deaths	null
	Missed endpoints	rosiglitazone
	Insufficient information collected	rosiglitazone
	Adjudication disagreements	rosiglitazone
	Delayed adjudications	null
5	Endpoint definition clarifications	null
6	Errors in end of CV follow-up dates	neutral
7	Limited CV follow-up	null
8	Concomitant medication reporting	null
9	Misunderstandings on SAE handling	neutral
10	Inadequate coding of CV adverse events	null
11	Endpoint CRFs not databased	neutral

The bias column in Table 2 differs from that in Table 1. In Table 1 we judged how the issues might bias the trial results; in Table 2 we based the assignments on our evaluations of the trial data. For example, all 4 cases the handling of which we considered to be unacceptable are rosiglitazone patients as are all 8 failures to refer events for adjudication; 9 of 14 missed endpoint cases are rosiglitazone. While these numbers may seem small compared to the size of the trial, note that about 15 more MIs in the rosiglitazone arms are needed to change the GSK MI results to a relative risk of 1.4 and a p value of 0.042.

Overall we reviewed the CRFs for 278 rosiglitazone and 271 control patients. Usually we reviewed a CRF because of some potential problem such as initial CEC adjudicators disagreeing, although we also reviewed a random sample of 100 cases stratified by treatment arm to generate statistical estimates. We focused on the endpoints of CV death, MI, and stroke (MACE) but we also recorded other problems when identified. We provide a summary of our findings from our CRF reviews in Table 3.

Table 3: Summary of Reviewed CRFs

	rosiglitazone		control	
	n	%	n	%
randomized & treated - GSK "ITT"	2220	100%	2227	100%
CRFs reviewed (total 549)	278	13%	271	12%
CRFs with problems	45	2.0%	25	1.1%
favoring rosiglitazone	44	2.0%	13	0.6%
favoring control	1	0.05%	12	0.5%
overall which arm is favored	57	10.4% of 549	13	2.4% of 549

The control case problems are evenly distributed between ones favoring rosiglitazone and ones favoring control. The rosiglitazone problem cases almost exclusively favor rosiglitazone and there are more rosiglitazone problem cases than control problem cases. Hence the net favoring of rosiglitazone exceeds 4:1.

In the random sample we identified 9% of cases with endpoint problems, favoring rosiglitazone 2:1. Because the frequency of cases with problems in this random sample was 9%, we probably have not yet identified all cases with problems: We would expect about 283 problem cases from among the patients with routinely submitted CRFs (from which we sampled) while we have only identified 70 problem cases with our completed reviews of CRFs.

Our review of the random sample also identified a significant problem in RECORD not involving endpoint ascertainment: errors in dates of follow-up. We found 7 errors in the end of CV follow-up dates, the censoring dates used for all GSK primary CV event analyses for all patients not having an endpoint for the particular analysis. Four of the errors were substantial: +20, +14, +8 and -24 months. The 95% confidence interval for the frequency of errors in CV follow-up dates is 3 to 14%. GSK has asserted that the errors in CV follow-up date affect the numerical results of their safety analyses slightly. While we agree that that is likely to be true, it is not reassuring at all that both critical values GSK used for its primary CV safety analyses, the endpoint determinations and the censoring date for patients without endpoints, appear to have substantial errors.

Our assignments regarding bias involve varying levels of subjectivity. While we believe we have strong, documented justifications for some assignments, such as our unacceptable handling cases, for other assignments our judgment calls are not unquestionable. For this reason we have provide copies of the relevant case report forms (CRFs—redacted for personal and institutional identifiers) for a selection of problem cases in Appendix 1. We have also provided short summaries of many of the other problem cases in Appendix 3 and short summaries of all cases for which we made a different CV death, MI, or stroke assignment than GSK in Appendices 5-7. We suggest that the best way to familiarize oneself with the RECORD trial conduct is to peruse first Appendix 1 with the copies of actual CRFs and then to read Appendix 3, our comments on study conduct.

Our review of the trial conduct appears to confirm that, as the protocol issues suggest, biases did arise in RECORD. The trial conduct issues reinforce our belief that RECORD can not provide any reassurances regarding rosiglitazone CV safety.

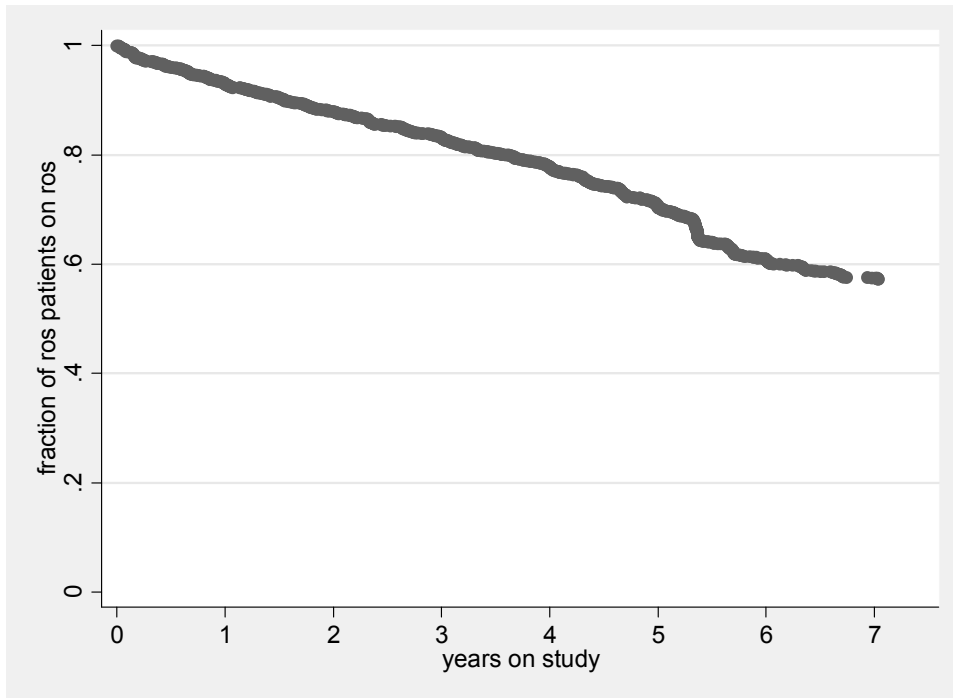
3. Endpoint, adjudication, and analysis issues

Our plan for endpoints, adjudication, and analysis populations differed from GSK's. We pre-specified our adjudication plan (Appendix 4) and our analysis plan (Appendix 8). We summarize the important points here as a prelude to discussing our analyses. The major issues are the following:

- We consider GSK's primary composite endpoint of CV death and CV hospitalization unacceptable for several reasons. CV hospitalization reasons are diverse and include ones that are unlikely to be affected by one drug. There are also ambiguities in the protocol definitions such that, as we have discussed in Appendices 2 and 3, referrals for adjudication and adjudications were erratic. Finally, the suspicion raised by the Nissen meta-analysis is that rosiglitazone increases MI rates while GSK has suggested that rosiglitazone decreases stroke rates. Hence we consider the most appropriate safety endpoints for RECORD to be the major adverse cardiac event (MACE) components analyzed separately, i.e., MI, stroke, CV death (plus the MACE composite as a secondary endpoint), and HF (all events).
- The CEC only adjudicated MIs and strokes involving hospitalizations or deaths. We believe that, in order to increase statistical power and as is usually done, we should include all MIs and strokes in our analyses. Because RECORD did not collect complete documentation for out-of-hospital non-fatal events and out-of-hospital fatal events do not have the biomarkers or neurologic exams needed for strict adjudications, we did not apply strict adjudication criteria for these events and did rely more upon judgment (see Appendix 4).
- GSK specified using an "ITT" (correctly randomized and treated) population including all available follow-up from the start of randomised treatment through study end. Because subjects frequently discontinue randomized treatment prior to study end particularly in long studies, we *a priori* rejected this analysis population for this non-inferiority safety study. To achieve equal durations for endpoints other than all-cause mortality and limit the contributions of patients discontinued from randomized treatment, we prespecified censoring follow-up in all arms at the study day prior to the day on which the percentage of good follow-up falls below 90% provided that the fraction of patients in the rosiglitazone arms still using rosiglitazone is 80% or greater.

Our fears regarding discontinuations of treatment appear to have been justified. We show in Figure 1 the fraction of rosiglitazone patients still taking rosiglitazone by years on-study.

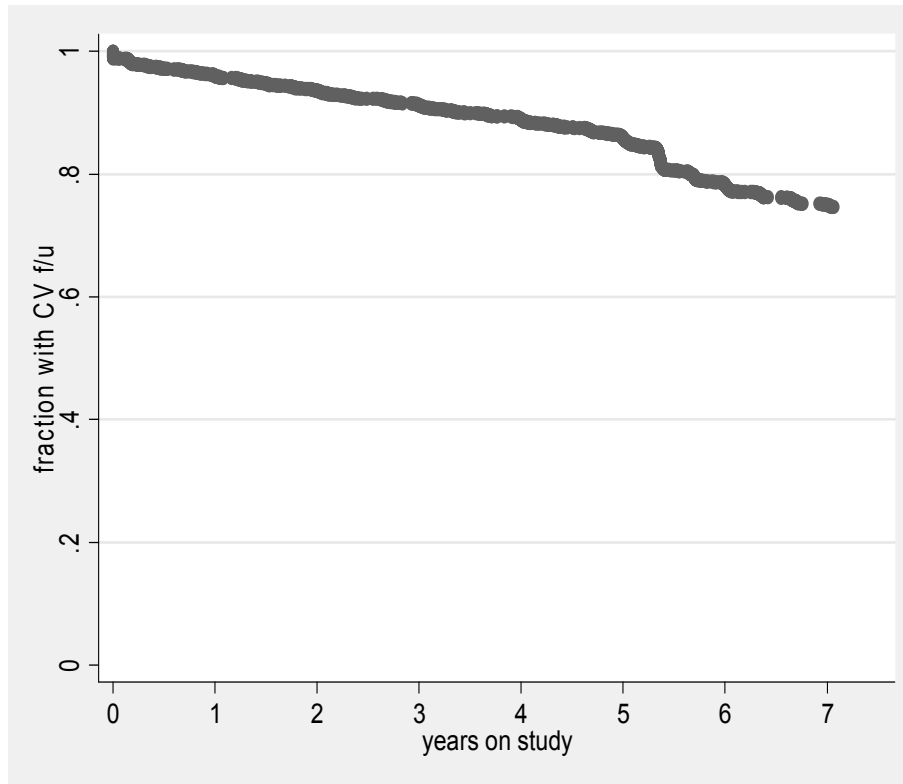
Figure 1: Rosiglitazone Patients Still Taking Rosiglitazone by Years on Study



Note that use of rosiglitazone falls off at a fairly steep, nearly constant rate throughout the entire study. Our pre-specified cut-off criterion of 80% still on rosiglitazone is reached in 3.6 years.

RECORD also suffers from a low rate of good CV follow-up, i.e., patients either dying with an identified cause of death or having a last visit at which SAEs and hospitalizations were solicited on or after the earliest last visit date (08 September 2008). Because of problems with the end of CV follow-up dates that we detail in Appendix 3 Section 3.6, we calculated the rate of CV follow-up using deaths and patient visits to the sites. (The original protocol required all patients to have a final site visit while an amendment left it to investigator discretion to change the type or frequency of visits. The amendment was ambiguous about whether the investigator could convert the final visit to a telephone contact.) We show the fraction of patients with CV follow-up by years on-study in Figure 2.

Figure 2: Patients with CV Follow-up by Years on Study



Note that Figures 1 and 2 are not Kaplan-Meier plots: We considered all rosiglitazone patients in Figure 1 and all patients in Figure 2 to be at risk (counted in the denominator) for the entire study. We counted patients who died with a known cause or who reached the earliest end-of-study visit date of 08 September 2008 as having good follow-up for the entire study. For rosiglitazone use we counted patients who died and had a recorded date of last rosiglitazone use within 30 days (because of uncertainties regarding the last use dates in patients who died) as using rosiglitazone for the entire study. Hence the curves represent the fraction of rosiglitazone patients still using rosiglitazone and the fraction of patients with good CV follow-up; these fractions provide some quantitation of the confidence we should have in any estimates of CV event rates through any duration of years on study.

The minimum potential duration of follow-up was 5.35 years. The discontinuities in both curves at about that time represent patients who had a last follow-up visit 1-2 months prior to the earliest last visit date of 08 September 2008.

CV follow-up drops off at about half the rate of rosiglitazone use but still substantial. Our pre-specified cut-off criterion of 90% good CV follow-up is reached in 3.4 years. Hence per our analysis plan we use follow-up through 3.4 years for calculating confidence intervals for CV event rates.

4. CV Event Results

We present only the results of our CV event analyses. The combined rosiglitazone and control arms were well balanced regarding baseline characteristics and risk factors as documented in the GSK briefing document. There were significant differences between the two strata as we show in Section 4.3. Please note the following about our CV analyses:

- For MACE events we present both our results and GSK's. Because inadequately reported events can be difficult to classify so that adjudication has a subjective element, we have listed in Appendices 5-7 all events for which our classification is different than GSK's along with a brief summary of the most relevant facts regarding the event. Appendix 5 has the CV death disagreements, Appendix 6 the MI disagreements, and Appendix 7 the stroke disagreements.
- Because of the substantial error rate in the GSK end of CV follow-up dates, we did not use them for our analyses, including our analyses of GSK adjudications. We used the validated date for the few cases we manually verified from the CRFs and the date of an adjudicated event or the date of the last visit with vital signs for all other patients (see Appendix 8 for the precise details.) The use of our dates vs. GSK dates should produce minimal differences in any of the time-to-event analyses—the driving force for the differences between our analyses and GSK's is the difference in event ascertainment.
- We use the true ITT population, including the 11 patients randomized but not treated. Because they are censored early and did not have any CV events, including or excluding them makes no appreciable difference in any analysis—but our including them is the reason why our at risk numbers at year 0 are different from those for the GSK event adjudications in the Kaplan-Meier (K-M) plots. We also start counting at the randomization date rather than the date of first treatment, another difference from GSK's that does not appreciably affect the analyses.
- We use the Cox regression analyses, stratified by background metformin or sulfonylurea use, as proposed by GSK. We performed all of our analyses using Stata v11 rather than SAS but have not observed any differences due to the differing statistical packages.
- For our Cox regression analyses we censored patients without the targeted event at the last study day prior to the CV follow-up rate for all patients dropping below 90%. We also present statistics for censoring at the end of CV follow-up (GSK's primary analyses) and for the randomized treatment phase plus 90 days (the latter to avoid missing events due to date errors.) We present K-M plots through seven years, beyond which time there were fewer than 200 patients on-study. We include on the K-M plots a vertical hashed line indicating the time at which CV follow-up for all patients dropped below 90%, our censoring date.
- Our primary comparison is between the combined rosiglitazone arms and the combined control arms, as was GSK's. We do present some comparisons of the two strata analyzed independently for such analyses that we considered revealing.

4.1 Major Adverse Cardiovascular Events (MACE)

We show below in Figures 3 through 10 the K-M plots for time to first MI, stroke, CV death, and any of these “MACE” components for our event ascertainment and for GSK’s.

Figure 3: K-M Plot of Time to First FDA MI

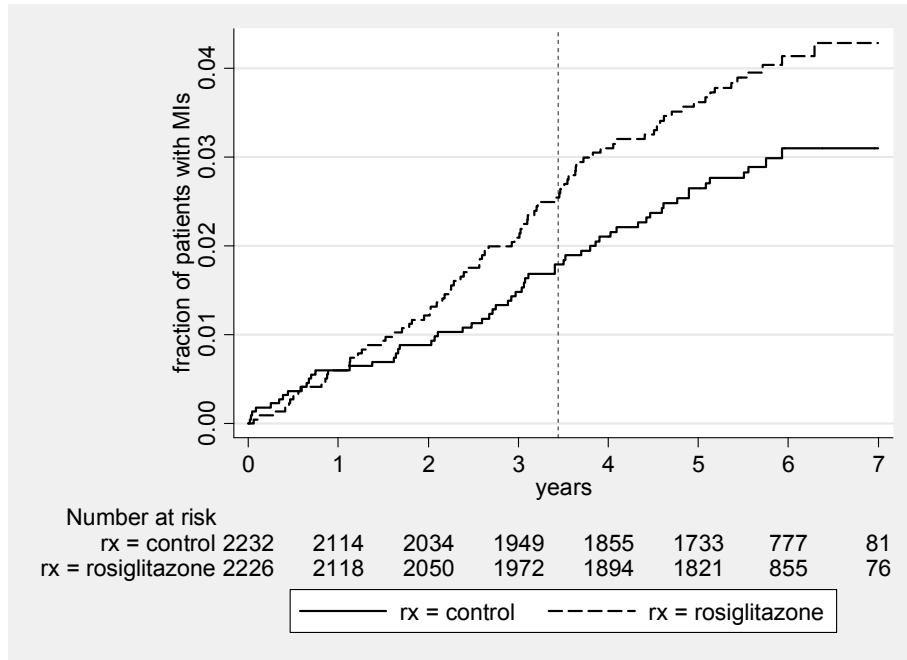


Figure 4: K-M Plot of Time to First GSK MI

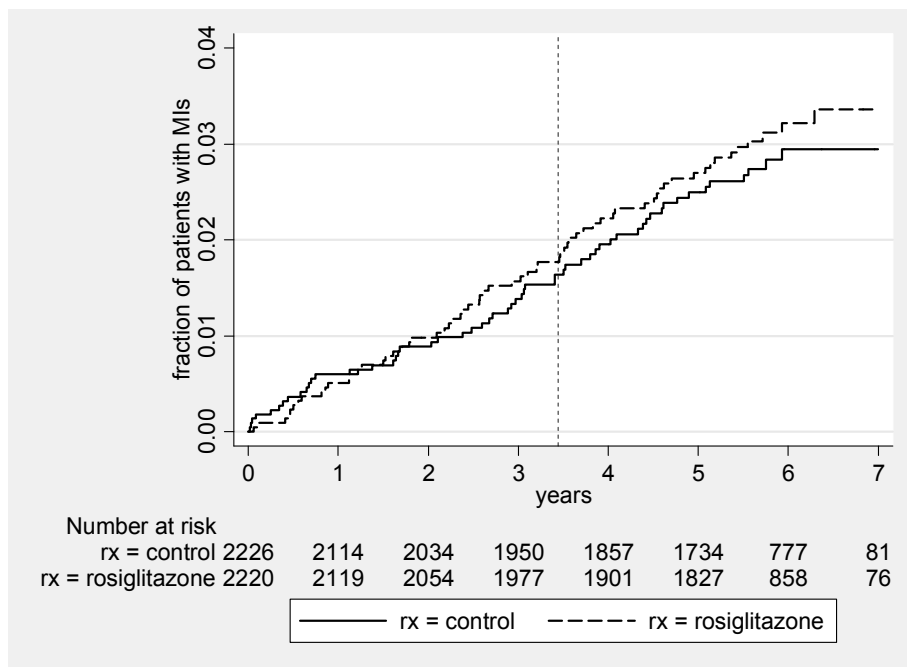


Figure 5: K-M Plot of Time to First FDA Stroke

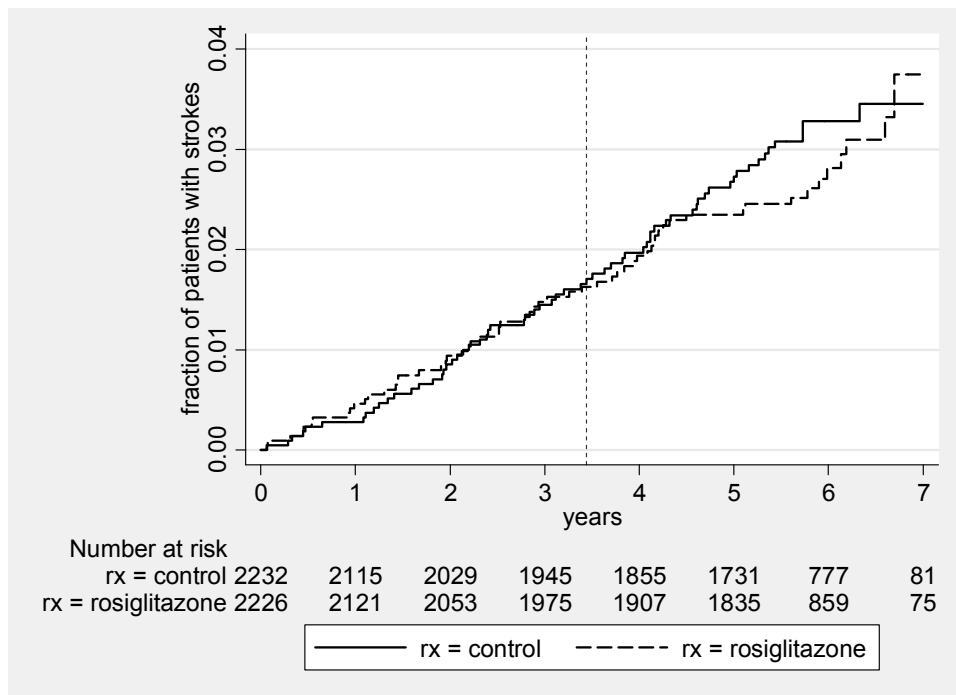


Figure 6: K-M Plot of Time to First GSK Stroke

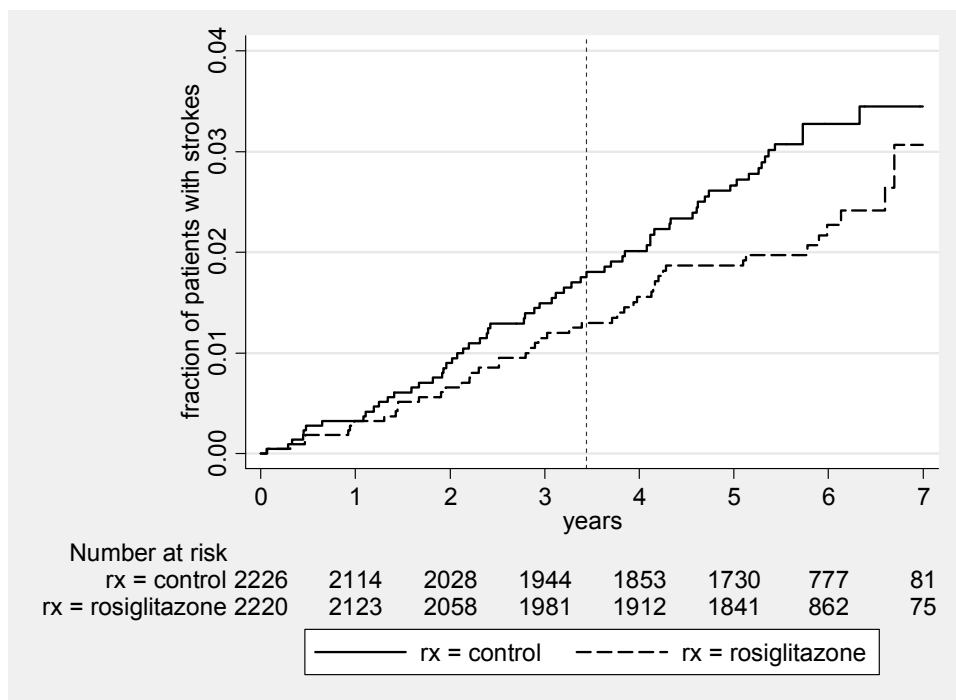


Figure 7: K-M Plot of Time to FDA CV Death

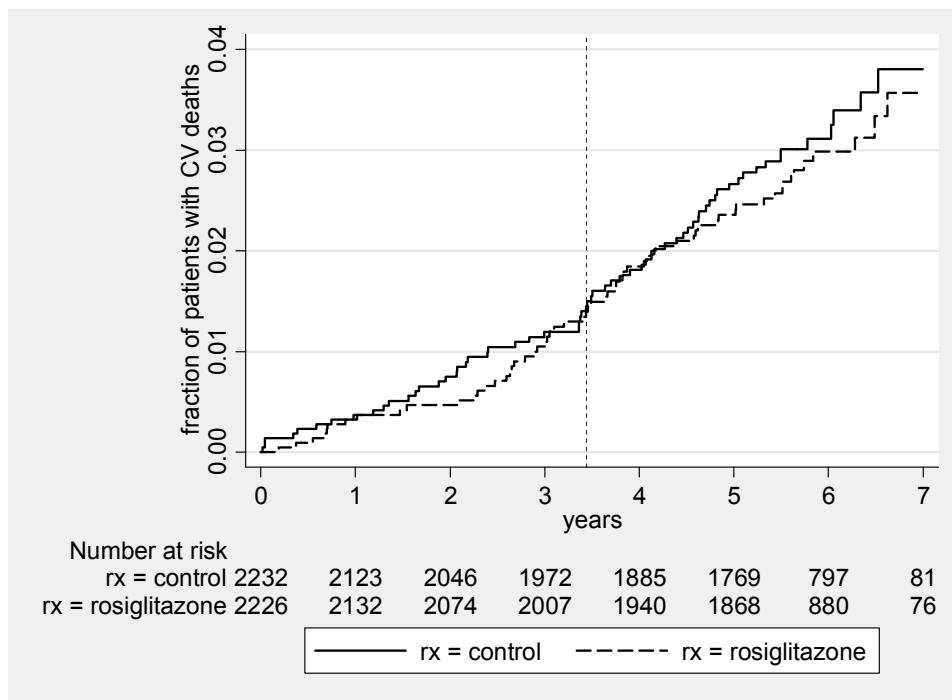


Figure 8: K-M Plot of Time to GSK CV Death

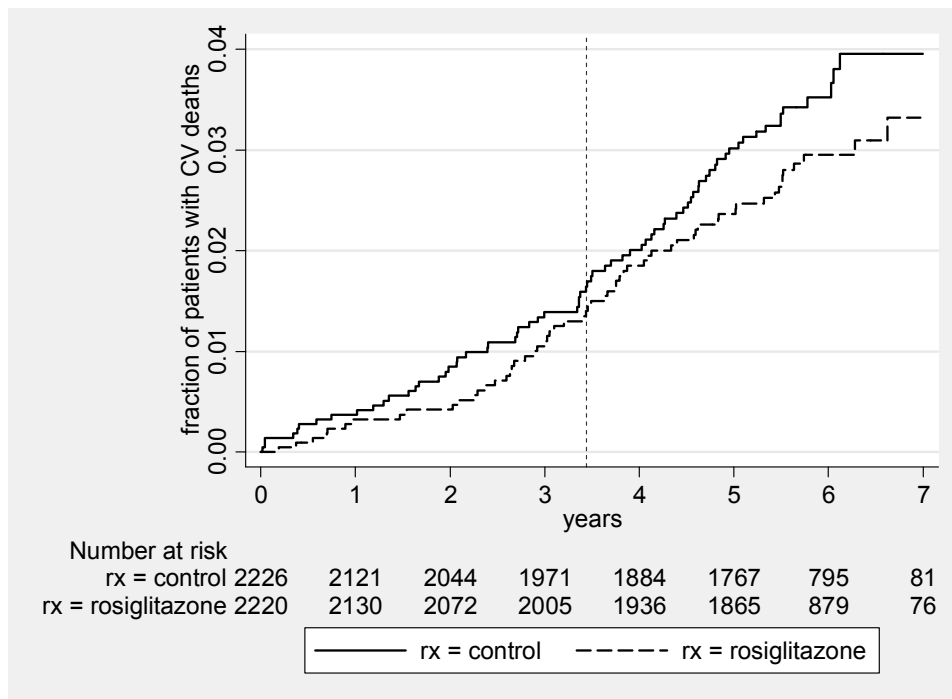


Figure 9: K-M Plot of Time to FDA MACE

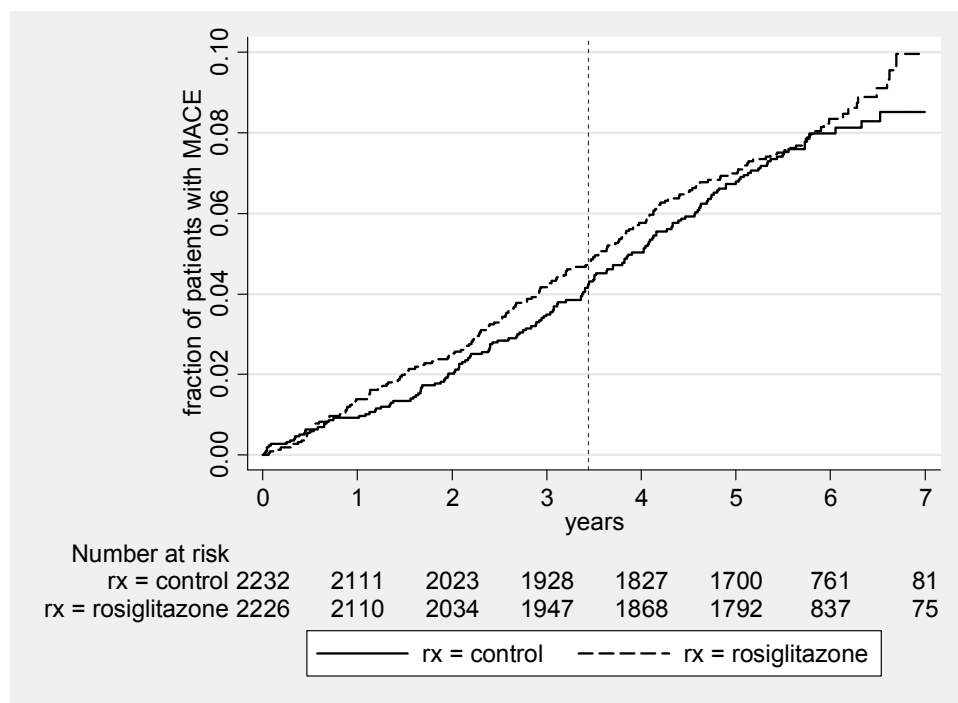
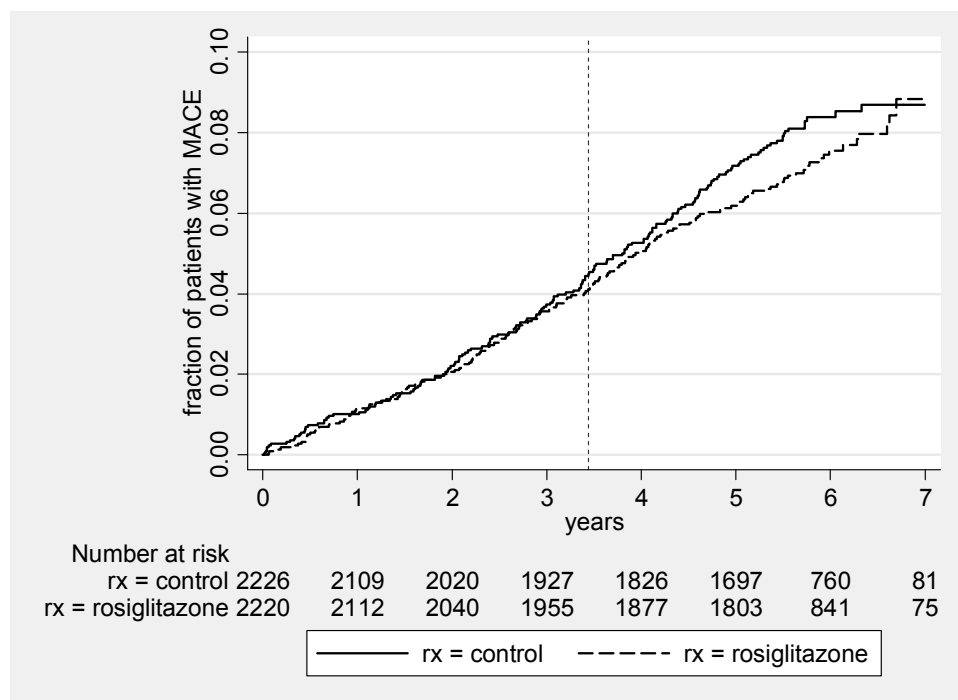


Figure 10: K-M Plot of Time to GSK MACE



Note that our results are less favorable for rosiglitazone than GSK's, particularly for MI and to a lesser degree for stroke. We examined CRFs for about 12% of the patients, so it is possible that with re-examination of all patients' CRFs that the differences would be greater. Furthermore, because of the biases towards the null due to study design limitations and the biases favoring rosiglitazone that we have identified regarding the study conduct, we consider our results to be indicative of lower bounds for rosiglitazone risks rather than validated scientific estimates subject to precise estimates of confidence intervals. We judge GSK's results to be inaccurate.

We show the Cox regression results for MACE and its components in Table 4.

Table 4: Cox Regression Results for MACE and Its Components

	To 90% CV follow-up			Randomized treatment phase			All CV follow-up		
	HR	95% LCL	95% UCL	HR	95% LCL	95% UCL	HR	95% LCL	95% UCL
MI-FDA	1.42	0.93	2.16	1.39	0.97	1.99	1.38	0.99	1.93
MI-GSK							1.12	0.78	1.60
Strokes-FDA	0.96	0.60	1.54	0.79	0.54	1.17	0.89	0.63	1.28
Strokes-GSK							0.71	0.48	1.04
CVD-FDA	0.95	0.57	1.60	0.85	0.55	1.32	0.92	0.65	1.31
CVD-GSK							0.82	0.58	1.15
MACE-FDA	1.13	0.85	1.50	1.04	0.82	1.33	1.07	0.86	1.33
MACE-GSK							0.91	0.73	1.13

HR = hazard ratio; LCL = lower confidence limit; UCL = upper confidence limit

We believe that we can not consider the confidence limits in Table 4 to be precise statistical limits but to be estimates of the variability added by sampling error in addition to the biases from the study design and conduct. Please also note that our results for the GSK events differ slightly from those reported by GSK because we used censoring dates different than GSK's due to substantial errors in the GSK censoring dates.

Note that the point estimates for the hazard ratios (HR) for MIs (1.38-1.42) are remarkably close to the odds ratio reported in the Nissen meta-analysis (1.43). One does not have to be a mathematician or to perform the calculations to estimate that incorporating our RECORD results into a meta-analysis similar to Nissen's will produce a risk for MIs that is highly statistically significant. Because of the substantial amounts of time we needed for verifying the RECORD data we did not complete such a meta-analysis (as well as the other sensitivity analyses described in our Appendix 8 Analysis Plan) prior to filing this consult for pre-meeting review by the FDA advisory committee.

There is additional evidence from RECORD that the MI risk for rosiglitazone is real rather than a random variation:

- We prospectively excluded silent MIs from our primary analysis because we had concerns that silent MIs might represent a different disease mechanism than symptomatic MIs, e.g., could they represent gradual necrosis from diabetic microvascular disease rather than an acute event with coronary thrombosis in an epicardial coronary artery? We did attempt to ascertain silent MIs, i.e., the new appearance of Q waves on ECG without

a history of an MI event. We identified silent MIs in 10 rosiglitazone and 5 control patients, one of whom later had an adjudicated MI event. Because we have not had the time to decide how to and to assign times to these silent MIs, we have not yet combined them with the MI events for a sensitivity analysis.

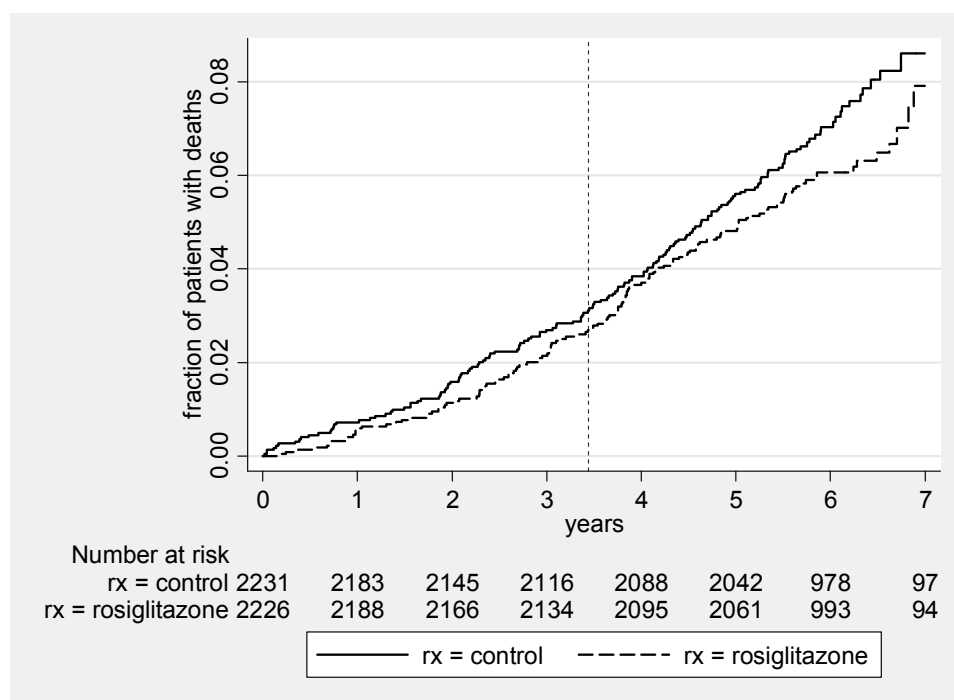
- When we evaluated possible MI events, we classified events as “possible” MIs as well as adjudicated MIs. The possible MI events were typically patients with chest pain and some ischemic changes on ECG with akinesia on ECHO (if done and in the absence of an MI history) but without a positive cardiac biomarker. Note that RECORD investigators usually reported cardiac biomarkers only at a single point in time and that the biomarkers were not infrequently limited to CK and even AST. We classified MI events as possible MIs for 16 rosiglitazone and 6 control patients.

Note that the curves in Figure 3, time first FDA MI, only diverge after about one year. This pattern suggests that, if rosiglitazone does increase MI risk, the mechanism may not be one related to acute drug levels, such as might be expected from an effect upon platelet aggregation. The mechanism may involve some structural change, such as increased vascular disease or plaque.

4.2 All-cause mortality

We show the K-M plot for all-cause mortality in Figure 11.

Figure 11: K-M Plot for Time to All-Cause Deaths



While it should be reassuring that all cause mortality appears to track lower for rosiglitazone than for control, we are not reassured because of the incomplete follow-up rates. The incomplete follow-up rate for vital status at the end of study is about 12%. We calculated this rate as

follows: We used the GSK-provided dates for the “End of Vital Status Date”, the date GSK has told us that they used for all cause mortality analyses. (Despite the problems we have documented in Appendix 3 Section 3.6 with end of CV follow-up dates, we have not had time to verify end of vital status dates—except see Case T in Appendix 1.) We counted a patient as having good vital sign follow-up either if the investigator reported the patient’s death (with the exception of Case T) or if the end of vital status date (the last contact date regarding vital status) was on or after (b) (6), the earliest last study visit date. The 12% of patients not having good vital status follow-up status by this criterion far exceeds the 1% absolute difference in death rates between rosiglitazone and control.

We document the exception to accepting an investigator report of death as Case T in Appendix 1. Case T illustrates how bad follow-up could be in RECORD.

4.3 Strata

RECORD can be viewed as two studies, i.e., the two strata based on baseline metformin or sulfonylurea use—see Appendix 2 Section 2.2. The baseline characteristics for the two strata are substantially different as shown in Table 5.

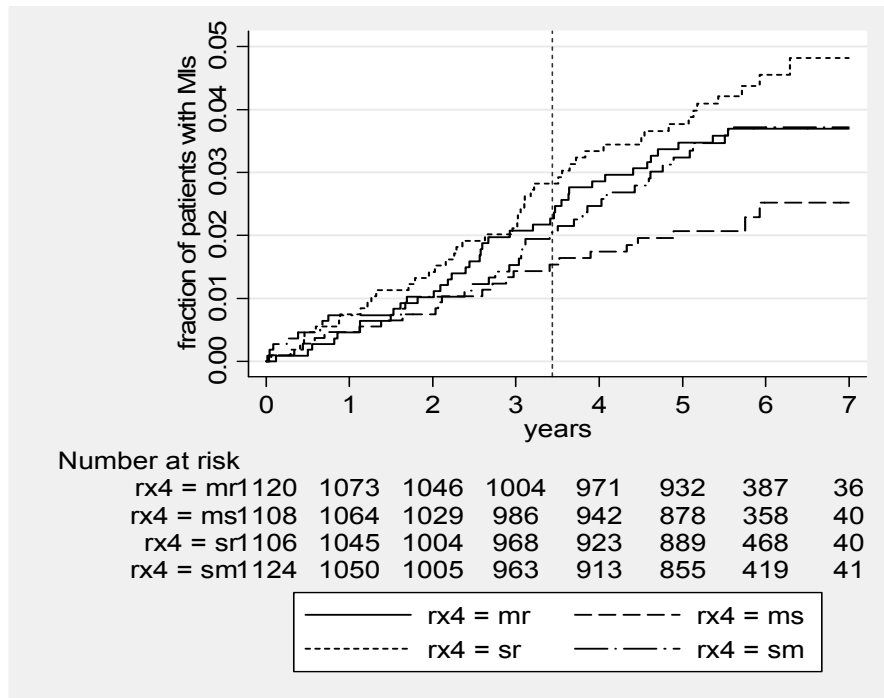
Table 5: Selected Baseline Characteristics by Stratum

	metformin	sulfonylurea	p*
age, mean years	57.1	59.7	<0.001
females, %	47	50	0.021
Australia-NZ, %	3	1	<0.001
E. Europe, %	55	73	
W. Europe, %	42	26	
any smoking, %	46	35	<0.001
ischemic heart disease history, %	15	20	<0.001
duration diabetes, mean years	3.8	5.4	<0.001
statin use at baseline, %	22	15	<0.001

* p value by t-test or ANOVA for continuous variables, Chi-square for categorical variables

Hence it is appropriate to examine results for the two studies separately to determine whether there are any significant differences for or interactions with the strata. We show the time to first FDA MI for all four arms in Figure 12.

Figure 12: K-M Plot of Time to First FDA MI for All 4 Arms

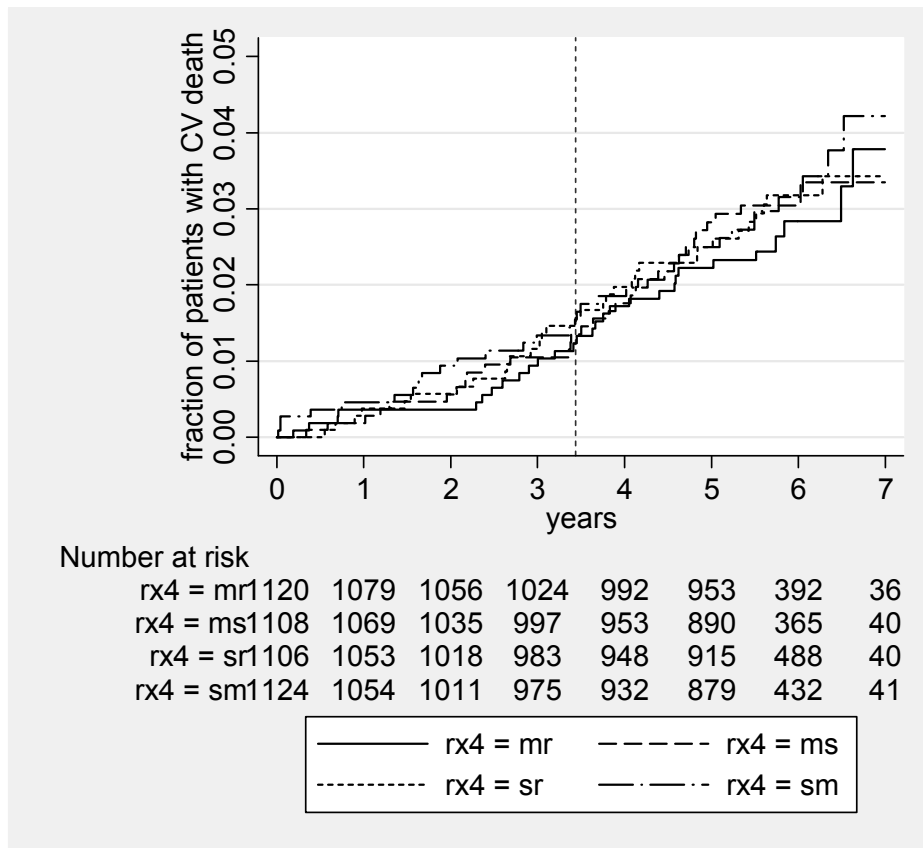


arm abbreviations		
	stratum	randomized
mr	metformin	rosiglitazone
ms		sulfonylurea
sr	sulfonylurea	rosiglitazone
sm		sulfonylurea

Note that the risk for MI is substantially higher in the sulfonylurea stratum than in the metformin stratum independent of rosiglitazone use. The point estimates for the HR from Cox regressions (censoring at 90% good follow-up) are 1.5 for the metformin stratum and 1.4 for the sulfonylurea stratum with wide confidence intervals due to the halved sample sizes. There is no suggestion of a difference in the effect of rosiglitazone on MI risk by stratum.

Strokes and CV deaths show substantial overlap in their curves by the four arms on K-M plots. We show the K-M plot for CV death in Figure 13.

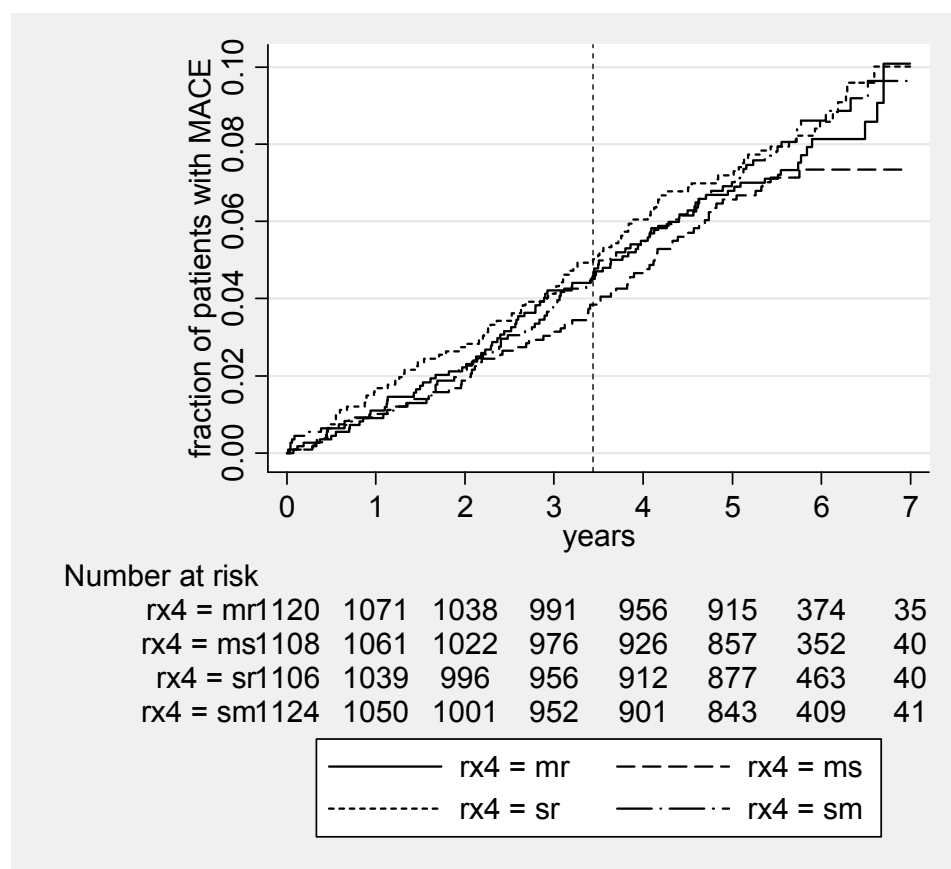
Figure 13: K-M Plot of Time to FDA CV Death for All 4 Arms



The HRs for CV death are 0.91 and 1.0 for the metformin and sulfonylurea strata respectively. Within the limitations of the data quality in RECORD rosiglitazone does not appear to reduce the risk of stroke or CV death.

We show the time to first FDA MACE for all four arms in Figure 14.

Figure 14: K-M Plot of Time to First FDA MACE for All 4 Arms



The curves for MACE are slightly but not statistically significantly differentiated. The HRs for MACE are 1.2 and 1.1 for the metformin and sulfonylurea strata respectively.

The rosiglitazone effects on MACE and its components in each stratum are consistent with those for the combined strata. There do not appear to be substantial differential effects in the two populations.

4.4 Statin use

One of your questions was regarding whether differential use of statins after trial start could have affected the trial results. We believe that this issue will be difficult to resolve given the limitations of the data. Because we spent most of our time on addressing the trial data problems, we did not explore this issue in depth nor did we verify the medication data. We used GSK's values for these analyses. We've summarized statin use throughout the trial in Table 6.

Table 6: Statin Use by Patients Throughout the Study

	mr	ms	sr	sm
none	40%	49%	49%	58%
new	38%	30%	36%	26%
stable	13%	16%	10%	13%
increase	9%	6%	4%	3%

Because drug use was different in the two strata, we have categorized statin use by the four arms. In Table 6 “none” means no statin use either at baseline or during the study. “New” means no statin use at baseline but use at sometime during the study—hence “none” plus “new” is baseline statin use. (Patients with baseline statin use were about a mean 1 year older and 4% absolute more male—except the sm group had reversed gender statistics.) “Stable” means statin use at baseline with the same dosage continued. “Increase” means statin use at baseline with increased dosage post-randomization. (GSK also reported a handful of patients as “added” statin; we have counted them as “increase”.)

Statin use was more frequent in the metformin stratum, an absolute increase of 9%. It was also more frequent in rosiglitazone patients than control, coincidentally also an absolute increase of 9%. It is this latter difference with which you are concerned. We examined CV events rates by statin use throughout the study but found them impossible to interpret. Because statin use was determined post-randomization, we could not draw any inferences from the CV event rates by statin use during the study. We did examine CV event rates by statin use at baseline. We show the rates for patients with new MIs in Table 7 and for CV deaths in Table 8 .

Table 7: Patients with new MIs by Baseline Statin Use

	mr	ms	sr	sm
no	3.2%	2.2%	4.1%	3.2%
yes	4.1%	1.7%	3.8%	3.2%

Table 8: CV Deaths by Baseline Statin Use

	mr	ms	sr	sm
no	2.2%	2.7%	2.6%	3.3%
yes	4.1%	3.3%	4.5%	1.1%

MI rates in Table 7 are consistent in that the rates are always higher in the rosiglitazone arms. Conversely, CV death rates are inconsistent: They are lower in the rosiglitazone arms compared to the control arms for patients not taking a statin at baseline and higher in the rosiglitazone arms compared to the control arms for patients on a statin at baseline. They are similarly inconsistent for the GSK adjudication of CV death and for all-cause mortality. We do not have an obvious explanation for this anomaly, although we have not had time to explore it further.

For additional analyses we would be interested in knowing the cumulative “equivalent” statin dosage through the time of the first event. We suspect the interpretation will difficult. To us the differential statin use represents yet another factor that is biasing the study results towards the null.

4.5 Heart failure

We also examined heart failure (HF) rates. We show K-M plots for various types of HF events in Figures 12 through 15 and the corresponding Cox regression results in Table 9.

Figure 15: K-M Plot of Time to First FDA HF Hospitalization

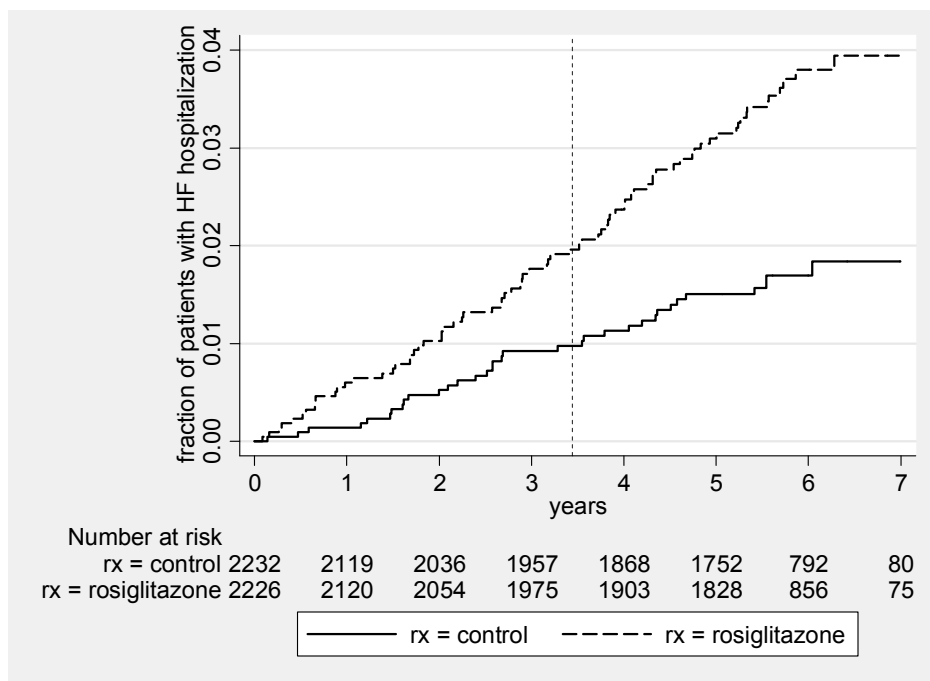


Figure 16: K-M Plot of Time to First GSK HF Hospitalization

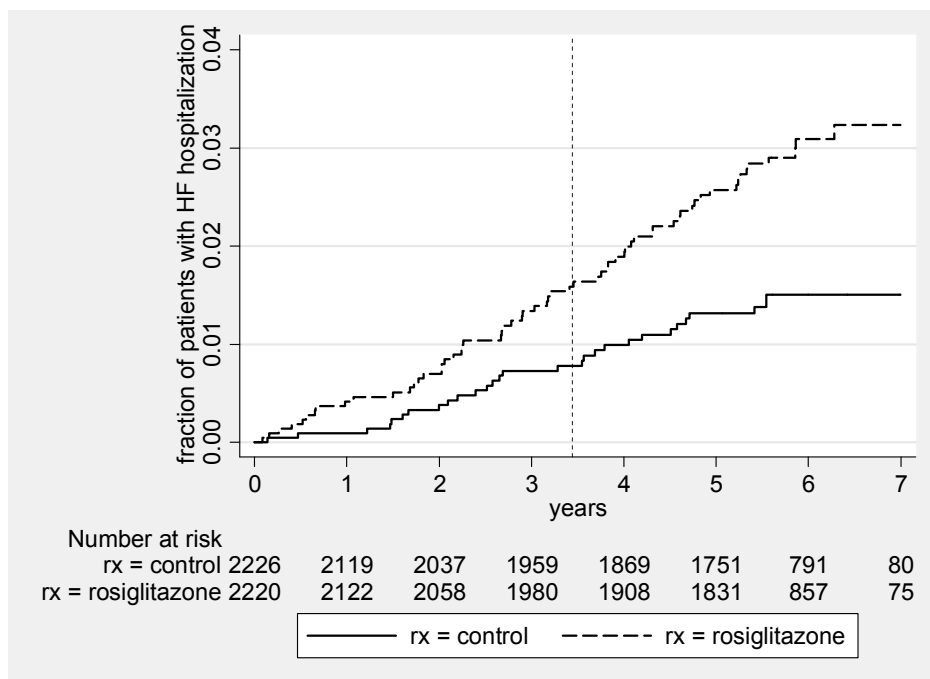


Figure 17: K-M Plot of Time to FDA Any HF

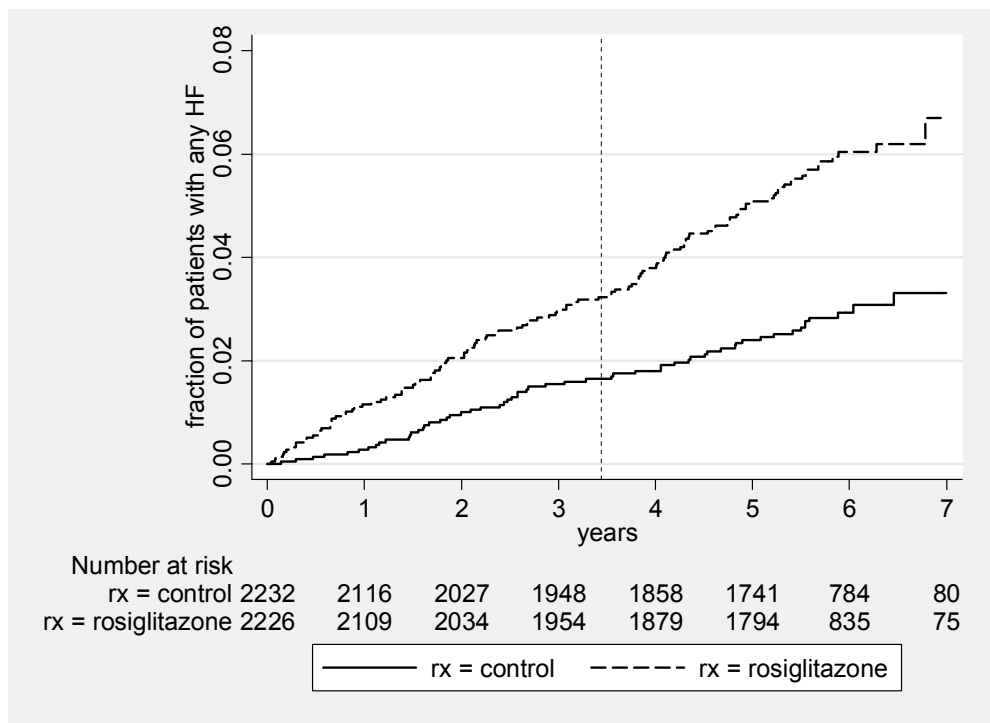


Figure 18: K-M Plot of Time to FDA HF Death

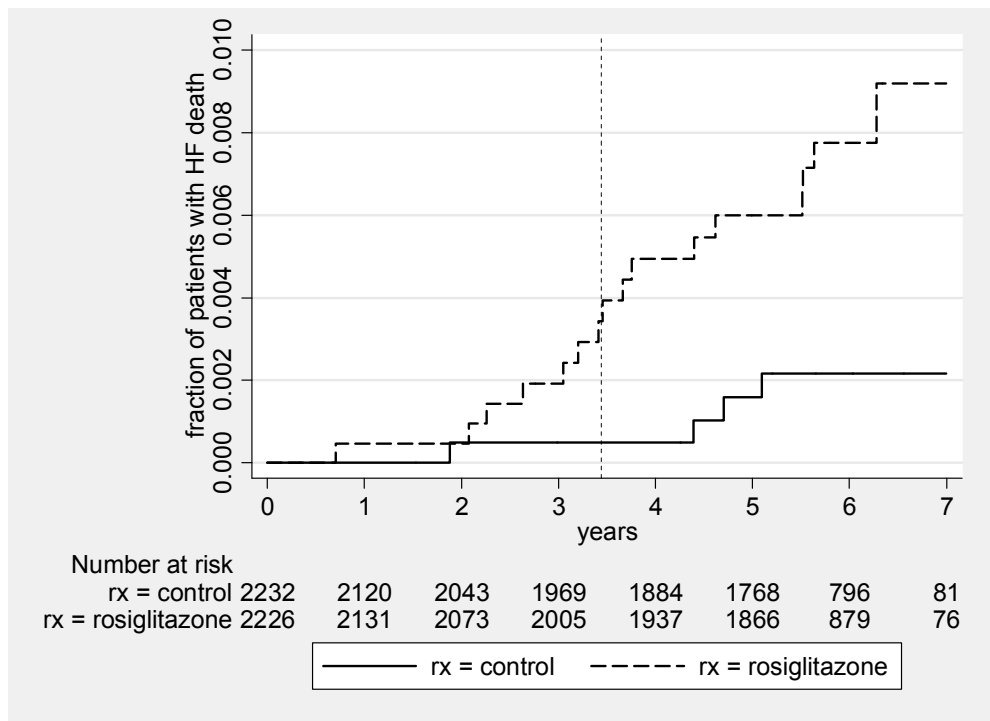


Table 9: Cox Regression Results for Heart Failure (HF)

	To 90% CV follow-up			Randomized treatment phase			All CV follow-up		
	HR	95% LCL	95% UCL	HR	95% LCL	95% UCL	HR	95% LCL	95% UCL
HF hosp.-FDA	2.04	1.19	3.48	2.37	1.52	3.71	2.16	1.44	3.24
HF hosp.-GSK							2.05	1.32	3.2
HF any-FDA	2.00	1.32	3.01	2.18	1.56	3.05	2.05	1.50	2.81
HF death-FDA	6.89	0.85	56	2.45	0.65	9.24	3.82	1.28	11.44

HR = hazard ratio; LCL = lower confidence limit; UCL = upper confidence limit

hosp. = hospitalization

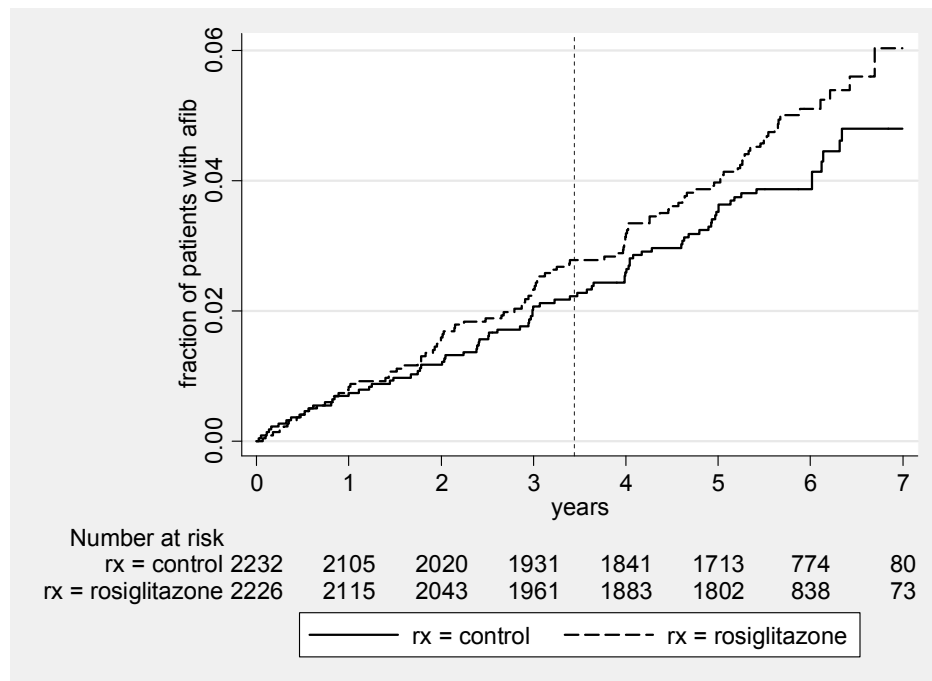
Most of our results for HF are not significantly different those that have been published for RECORD. (Komajda *et al.* (2010). Eur Heart J 31(7): 824-31) HF is substantially increased with rosiglitazone, with the risk of any heart failure event or hospitalization at least doubled.

However, the risk of HF death appears to be even more substantially increased: 2.5-7 fold point estimates by our evaluations and a five-fold increase by Komajda *et al.* We do record higher absolute rates of HF events than GSK or Komajda *et al.*, but this likely reflects our using less strict criteria for HF than the other observers. Regardless, we are concerned that, because of the dramatically higher HF death rates, increased HF rates with rosiglitazone are not simply increased diagnosis rates due to edema but are dangerous. We can not discern from the available data whether the increased HF rates have a different etiology than whatever may be causing the increased MI rates or whether the increased HF deaths reflect only an MI based mechanism.

4.6 Atrial fibrillation

As we discuss in Appendix 3 Section 3.10, GSK coding of CV adverse events was flawed. Because knowing rates of other CV events besides MACE should facilitate understanding the CV risk of rosiglitazone, we preliminarily coded selected other CV events. We then focused on atrial fibrillation (afib) because of its association with HF, a known adverse effect of rosiglitazone, and because we detected errors in its coding. We show the K-M plot for time to first afib event in Figure 19.

Figure 19: K-M Plot of Time to First Atrial Fibrillation Event



Please note that some afib events reported in Figure 19 occurred in patients who had a history of afib at baseline. We found the history of afib at baseline to be unreliable, i.e., we encountered patients with a negative history who had afib on the baseline ECG or who had a long history of afib documented in a hospital discharge summary. The point estimate for the HR is 1.25 with 95% confidence interval 0.85 to 1.8.

Given that rosiglitazone is associated with HF, Figure 19 does not seem surprising: Because afib is associated with HF, we would expect rosiglitazone to have an increased rate of afib. The time course of the afib curves separating is delayed compared to that for HF—compare to Figure 15 for HF hospitalizations. However, what is interesting and revealing is the association of afib and rosiglitazone with the MACE components. We show the rates of afib arm and patients with HF, MIs, strokes, and CV death in Tables 10 to 13.

Table 10: Atrial Fibrillation Rates by Arm and Patients with HF Hospitalizations

HF	Control	Rosiglitazone
no	3%	4%
yes	21%	35%

Table 11: Atrial Fibrillation Rates by Arm and Patients with MIs

MI	Control	Rosiglitazone
no	4%	4%
yes	3%	12%

Table 12: Atrial Fibrillation Rates by Arm and Patients with Stroke

stroke	Control	Rosiglitazone
no	2%	2%
yes	17%	14%

Table 13: Atrial Fibrillation Rates by Arm and CV Death

CV death	Control	Rosiglitazone
no	4%	4%
yes	6%	16%

Note that the rates of afib are substantially higher in the rosiglitazone arm for patients with cardiac conditions. The rate of afib in the rosiglitazone arm in patients with stroke—a cerebrovascular condition—is numerically lower than (but statistically equivalent to) the rate in the control arm. This pattern suggests to us that afib with rosiglitazone is not just the usual complication of HF or an MI. It appears to be another consequence of the same pathological process induced by rosiglitazone that is causing increased rates of HF and likely increased rates of MIs.

4.7 Speculation on Mechanism

Others have speculated that rosiglitazone could increase MI rates through its effects upon lipids or by the same mechanism whereby it increases HF rates. There are no clinical studies establishing these mechanisms. We propose that there is a third mechanism for which there is some evidence from clinical studies. The third possible mechanism is the following: The Avandia label states that “In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.” The published literature suggests that rosiglitazone may also function as an inhibitor of CYP2C8. (Sahi 2003) Allelic variants of the CYP2C9 gene have been associated in epidemiological studies with increased risk of myocardial infarction and atherosclerosis. (Yasar 2003, Kaur-Knudsen 2009) Recently, CYP2C8 variants has also been associated with increased risk of MI. (Rodenburg 2010) CYP2C9 and 2C8 catalyze the metabolism of arachidonic acid to vasoactive substances, providing one potential mechanism for affecting cardiac disease. Interference with cigarette toxin metabolism is another. (Ercan 2008) Rosiglitazone effects upon CYP2C8 and CYP2C9 could be the mechanism for its CV adverse effects. Regardless, there are several possible mechanisms for CV toxicity of rosiglitazone.

References for Speculation on Mechanism

Ercan, B., L. Ayaz, et al. (2008). "Role of CYP2C9 and CYP2C19 polymorphisms in patients with atherosclerosis." *Cell Biochem Funct* 26(3): 309-13.

Kaur-Knudsen, D., S. E. Bojesen, et al. (2009). "Common polymorphisms in CYP2C9, subclinical atherosclerosis and risk of ischemic vascular disease in 52,000 individuals." *Pharmacogenomics J* 9(5): 327-32.

Rodenburg, E. M., L. E. Visser, et al. (2010). "Genetic variance in CYP2C8 and increased risk of myocardial infarction." *Pharmacogenet Genomics*.

Sahi, J., C. B. Black, et al. (2003). "Comparative effects of thiazolidinediones on in vitro P450 enzyme induction and inhibition." *Drug Metab Dispos* 31(4): 439-46.

Yasar, U., A. M. Bennet, et al. (2003). "Allelic variants of cytochromes P450 2C modify the risk for acute myocardial infarction." *Pharmacogenetics* 13(12): 715-20.

Appendices

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Appendix 1: Case Examples with Relevant CRFs

In this appendix we have included examples of problems with the handling of RECORD cases. We selected these examples to illustrate common problems of all types, including referral for adjudication failures, follow-up date errors, inadequate information, etc. We reference these cases in other sections of our consult and provide in the other sections the summary statistics on the problems. We have removed all patient, investigator, GSK and Quintiles staff, and institutional identifiers to preserve privacy and we have also removed treatment assignments so that everyone can review these cases blinded to treatment. For FDA advisory committee reviewers we will provide similar case excerpts for any of the other problem cases that we have identified or complete CRFs for them (but the latter will contain treatment assignments.)

1.1 Extreme mishandling of events (Cases A-D)

These four cases represent what we judge to be the worst mishandling of events in RECORD, mishandlings that we judge should not be found even as single occurrences and that suggest serious flaws with trial conduct. They are four among 70 mishandlings we have documented based on reviews of CRFs for 549 patients. We provide representative examples of the other 66 in Section 1.3.

Case A: This patient had multiple medical problems (e.g., an early adjudicated endpoint of a stroke on (b) (6)) and multiple mishandlings. The most serious one is the deletion of a myocardial infarction SAE and the failure to refer it for adjudication. The investigator recorded the MI with a start date of (b) (6) for this patient on a SAE CRF submitted (b) (6) (A1-A2). The patient died of heart failure on (b) (6) 33 days after the MI. Other SAEs from (b) (6) were submitted (b) (6) and one for a lung embolism dated (b) (6) mentions the MI in the narrative. The MI SAE was deleted on (b) (6) by a data clarification that does not provide any explanation (A3) and after all the '05 endpoints had been sent to the adjudicators on (b) (6).

GSK provided in (b) (6) the following explanation of the deletion: "The SAE of myocardial infarction was deleted at the request of the investigator (Investigator (b) (6)). The subject was hospitalized (b) (6) due to syncope and hypotension caused by CHF. During this hospitalization, the subject had a slightly increased troponin 0.19 (normal range <0.1) but according to the discharge summary the slight elevation in troponin was attributed to renal failure and heart failure rather than MI. In addition, ECG changes were not noted. Since the MI was not confirmed, the investigator requested that the event be deleted." This justification is not consistent with the description of the event in the CRFs, the multiple references to it as an MI, and the subsequent PTCA. Regardless, it does not justify failing to submit the event for adjudication. The whole purpose of the adjudication was to have consistent evaluation of endpoints by experts blinded to the treatment assignment, not erratic decisions by unblinded investigators.

This patient also had several other potential endpoints that were not submitted for adjudication:

- A hospitalization for a suspected stroke on (b) (6)
- The lung embolism from (b) (6)
- The PTCA following the MI on (b) (6)

Additionally, the cause of death on the Form D CRF was changed from heart failure to atrial fibrillation. The CEC adjudicated the cause of death appropriately as heart failure.

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Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
49653/231				Day	Month	Year

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly)		AEGIS Number	
Serious Adverse Experience (Please print clearly)		→ Specify reason(s) for considering this a serious AE. Mark all that apply. [1] <input type="checkbox"/> fatal [2] <input checked="" type="checkbox"/> life threatening [3] <input type="checkbox"/> disabling/incapacitating [4] <input type="checkbox"/> results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] <input checked="" type="checkbox"/> hospitalisation prolonged [6] <input type="checkbox"/> congenital abnormality [7] <input type="checkbox"/> cancer [8] <input type="checkbox"/> overdose [9] <input type="checkbox"/> Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
For SmithKline Beecham			
Onset Date and Time	24 Nov 05 17:15		
End Date and Time (If ongoing please leave blank)			
Outcome If patient died, please complete Form D	[1] <input checked="" type="checkbox"/> Resolved [2] <input type="checkbox"/> Ongoing [3] <input type="checkbox"/> Died		
Experience Course	[1] <input type="checkbox"/> Intermittent No. of episodes [2] <input checked="" type="checkbox"/> Constant		
Intensity (maximum)	[1] <input type="checkbox"/> Mild [2] <input type="checkbox"/> Moderate [3] <input checked="" type="checkbox"/> Severe		
Action Taken with Respect to Investigational Drug	[1] <input checked="" type="checkbox"/> None [2] <input type="checkbox"/> Dose reduced [3] <input type="checkbox"/> Dose increased [4] <input type="checkbox"/> Drug interrupted/restarted [5] <input type="checkbox"/> Drug stopped	Did the SAE abate? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, did SAE recur? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Relationship to Investigational Drug	[1] <input checked="" type="checkbox"/> Not related [2] <input type="checkbox"/> Unlikely [3] <input type="checkbox"/> Suspected (reasonable possibility) [4] <input type="checkbox"/> Probable	Assessment The SAE is probably associated with: <input type="checkbox"/> Protocol design or procedures (but not to study drug) Please specify _____ <input checked="" type="checkbox"/> Another condition (eg, condition under study, intercurrent illness) Please specify <u>Coronary artery disease</u> <input type="checkbox"/> Another drug Please specify _____	
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
Was patient withdrawn due to this specific SAE?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

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Page

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
49653/23				Day	Month	Year

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Test	Date	Value	Units	Normal Range
Troponin	24 NOV 05 Day Month Yr	0.19	20 DEC 06 µg/L	<0.1
	Day Month Yr			
	Day Month Yr			
	Day Month Yr			

Relevant Laboratory Data
Please provide relevant abnormal laboratory data below

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

- During hospital stay myocardial infarction occurred. Initial conservative therapy was done. Because of massive postinfarctional angina patient was transferred to cardiac catheter lab.

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number: [REDACTED]

Investigator's Signature: [REDACTED] Date: [REDACTED]
(confirming that the above data are accurate and complete)

Please PRINT Name: [REDACTED]

SB Medical Monitor's Signature: [REDACTED] Date: [REDACTED]
Please PRINT Name: [REDACTED]

Investigator Name:	Site Number:	Protocol Number/Study Identification:
Subject Number:	Subject Initials:	DCF Tracking Number:
Requestor Name:	Requestor Signature:	Date sent to the Site for Resolution:

Subject Visit	CRF Page/ File ID No.	Data Item/Field/ Record No.	Current CRF Entry/Description of Query	Corrected Entry/Resolution	For DM Use Only: Entered (initials/date)
			⇒ Here with I confirm the deletion of SAE page 125-	UD OH 17MAR2007	

Investigator Signature (or approved signatory/authorized designate):
Date Signed:

Distribution: Original - Data Management

Copies - To be filed with all copies of CRFs at site and in the clinical files, as applicable

Case B: This patient had one referred endpoint event, his death on (b) (6) adjudicated as non-CV, pneumonia. While the patient was hospitalized for 46 days starting on (b) (6), 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.

GSK provided in (b) (6) this explanation of the case: “On the SAE page, it is written that the reason for death is pneumonia caused by myelodysplastic syndrome. Pulmonary oedema was not considered as an SAE/AE by the investigator. This hospitalization, including a letter describing pulmonary oedema in the face of a diagnosis of pneumonia, went to the CEC and was adjudicated as non-cardiac in nature. A hospital letter outlining what occurred during the patient’s stay is included in the endpoint package and also a notification of inpatient death to the patient’s GP (attached). The CEC did not request any further information for adjudication of this event. Myelodysplasia was the event leading up to the pneumonia. Relevant information is collected on SAE pages 199-200.”

GSK fails to mention that the patient had also been treated with furosemide for “ankle swelling” since (b) (6). The investigator originally described the “pneumonia” SAE, on (b) (6), as shortness of breath with onset (b) (6) the date of hospitalization and diagnosis of the pulmonary edema. (B2-B3) Note that this was changed to pneumonia on (b) ((b) and faxed on 0 (b) (6)—there were no earlier records of activities between (b) (6) provided. We requested and GSK submitted the “original” and “final” verbatim AE terms provided by the investigators for all patients. For this SAE the original term was “shortness of breath”; the final term was “pneumonia”.

The investigator originally described the “myelodysplasia” SAE as refractory anemia, changed to myelodysplasia at a later date. (B4) Note that on (b) (6) the hemoglobin was 9.0, the WBC 5300 and the platelets were 282,000. WBC counts of 5300 are not typically associated with increased risk of infection so, while a pneumonia possibly was related to the a marrow dysplastic source, the hospital course of 47 days ending in pneumonia should be been explored.

Note that the GSK explanation states “The CEC did not request any further information for adjudication of this event.” Hence this failure to investigate involves failures by the CEC, the investigator, the Quintiles site monitors, and the Quintiles CEC coordinating center.

B1

Royal Hospital



NHS Foundation Trust

Our Ref:

NHS no:

Dr

NORMAL

PHONE DOCTOR

REPEAT TEST

SCRIPT

ATTENTION

10 JUL 2007

Comment

URGENT

LOW-URGENT

Dear Dr

RE: [REDACTED]

PATIENT: [REDACTED]

SITE: [REDACTED]

This lady presented back on the [REDACTED] with shortness of breath. She was treated with Frusemide for pulmonary oedema and her breathing improved. She had a protracted stay in the hospital whilst long term oxygen therapy was established and some of her medications were titrated. Unfortunately on about the 5th June her breathing got worse and she started to retain CO₂. She had a short spell on BIPAP but unfortunately she failed to respond and passed away on the [REDACTED] (b) (6) The cause of death was:

1a) pneumonia

If you have any further queries please do not hesitate to contact us. Many thanks.

Yours sincerely

SB SmithKline Beecham
 Pharmaceuticals

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Protocol 49653/231	Centre Number	Patient Number	SB Receipt Date Day Month Year
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SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly)		AEGIS Number	
Serious Adverse Experience (Please print clearly)		Specify reason(s) for considering this a serious AE. Mark all that apply.	
For SmithKline Beecham		<input checked="" type="checkbox"/> fatal <input type="checkbox"/> life threatening <input type="checkbox"/> disabling/incapacitating <input type="checkbox"/> results in hospitalisation (excluding elective surgery or routine clinical procedures) <input checked="" type="checkbox"/> hospitalisation prolonged <input type="checkbox"/> congenital abnormality <input type="checkbox"/> cancer <input type="checkbox"/> overdose <input type="checkbox"/> Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
Onset Date and Time	Day Month Yr 24hr:min		
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min		
Outcome If patient died, please complete Form D	<input type="checkbox"/> Resolved <input type="checkbox"/> Ongoing <input checked="" type="checkbox"/> Died		
Experience Course	<input checked="" type="checkbox"/> Intermittent No. of episodes <input type="checkbox"/> Constant		
Intensity (maximum)	<input type="checkbox"/> Mild <input checked="" type="checkbox"/> Moderate <input type="checkbox"/> Severe		
Action Taken with Respect to Investigational Drug	<input type="checkbox"/> None <input type="checkbox"/> Dose reduced <input type="checkbox"/> Dose increased <input type="checkbox"/> Drug interrupted restarted <input checked="" type="checkbox"/> Drug stopped	Did the SAE abate? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, did SAE recur? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Relationship to Investigational Drug	<input checked="" type="checkbox"/> Not related <input type="checkbox"/> Unlikely <input type="checkbox"/> Suspected (reasonable possibility) <input type="checkbox"/> Probable	Assessment The SAE is probably associated with: <input type="checkbox"/> Protocol design or procedures (but not to study drug) Please specify _____ <input checked="" type="checkbox"/> Another condition (eg, condition under study, intercurrent illness) Please specify <u>MYELODYSPLASIA</u> <input type="checkbox"/> Another drug Please specify _____	
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
Was patient withdrawn due to this specific SAE?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		

SB **SmithKline Beecham**
 Pharmaceuticals

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Protocol 49653/231	Centre Number [REDACTED]	Patient Number [REDACTED]	SB Receipt Date Day Month Year [REDACTED] [REDACTED] [REDACTED]
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SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below

Test	Date	Value	Units	Normal Range
Now Done	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

ADMITTED WITH SHORTNESS OF BREATH.
 DIAGNOSED WITH PNEUMONIA AND SUBSEQUENT
 DIED.

If applicable, was randomisation code broken at investigational site?

☒ No ☐ Yes

Randomisation / Study Medication Number: [REDACTED]

Investigator's Signature:

(confirming that the above data are accurate and complete)

Please PRINT Name

Date
 Day Month Year
 16 JAN 08

SB Medical Monitor's Signature:

Please PRINT Name

Date
 Day Month Year

Protocol	Centre Number	Patient Number	SB Receipt Date		
49653/231			Day	Month	Year

SERIOUS ADVERSE EXPERIENCE (SAE)

SAE REC

Person Reporting SAE (Please print clearly)		AEGIS Number	
Serious Adverse Experience (Please print clearly) MYELODYSPLASIA REFRAGERY ADENOMA 30/1/06		Specify reason(s) for considering this a serious AE. Mark all that apply. [1] <input type="checkbox"/> fatal [2] <input type="checkbox"/> life threatening [3] <input type="checkbox"/> disabling/incapacitating [4] <input type="checkbox"/> results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] <input type="checkbox"/> hospitalisation prolonged [6] <input type="checkbox"/> congenital abnormality [7] <input checked="" type="checkbox"/> Cancer [8] <input type="checkbox"/> overdose [9] <input type="checkbox"/> Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
For SmithKline Beecham			
Onset Date and Time			
End Date and Time (If ongoing please leave blank)	Day Month Yr 24hr:min		
Outcome If patient died, please complete Form D	[1] <input checked="" type="checkbox"/> Resolved [2] <input checked="" type="checkbox"/> Ongoing [3] <input type="checkbox"/> Died		
Experience Course	[1] <input type="checkbox"/> Intermittent No. of episodes [2] <input checked="" type="checkbox"/> Constant		
Intensity (maximum)	[1] <input type="checkbox"/> Mild [2] <input type="checkbox"/> Moderate [3] <input checked="" type="checkbox"/> Severe		
Action Taken with Respect to Investigational Drug	[1] <input checked="" type="checkbox"/> None [2] <input type="checkbox"/> Dose reduced [3] <input type="checkbox"/> Dose increased [4] <input type="checkbox"/> Drug interrupted/restarted [5] <input type="checkbox"/> Drug stopped		
Relationship to Investigational Drug	[1] <input type="checkbox"/> Not related [2] <input checked="" type="checkbox"/> Unlikely [3] <input type="checkbox"/> Suspected (reasonable possibility) [4] <input type="checkbox"/> Probable		
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
Was patient withdrawn due to this specific SAE?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
		Did the SAE abate? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes, did SAE recur? <input type="checkbox"/> Yes <input type="checkbox"/> No Assessment The SAE is probably associated with: <input type="checkbox"/> Protocol design or procedures (but not to study drug) Please specify _____ <input checked="" type="checkbox"/> Another condition (eg, condition under study, intercurrent illness) Please specify <u>CANCER</u> <input type="checkbox"/> Another drug Please specify _____	

Protocol 49653/231	Centre Number [REDACTED]	Patient Number [REDACTED]	SB Receipt Date Day Month Year [REDACTED] [REDACTED] [REDACTED]
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SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Test	Date	Value	Units	Normal Range
HAEMOGLOBIN	[REDACTED]	9.0	UNITS	11.5-16.5
WHITE CELL COUNT	[REDACTED]	5.3	UNITS	4.0-11.0
PLATELETS	Day Month Yr [REDACTED]	282	UNITS.	135-350

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

LONG HISTORY OF ANAEMIA SINCE 2003. NUMEROUS INVESTIGATIONS PERFORMED TO ASSESS CAUSALITY. REFERRED TO HAEMATOLOGIST. DIAGNOSED WITH MYELODYSPLASIA - REFRACTORY ANAEMIA. BONE MARROW ASPIRATE [REDACTED] SHOWED DYSPLASTIC FEATURES AND PRESENCE OF SOME LEUK. BUT NO EXCESS OF BLAST CELLS. Ferrous Sulphate 600mg daily given. No signs or symptoms were noted prior to the event. (Anaemia was laboratory finding only).

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number [REDACTED]

Investigator's Signature: [REDACTED] Date [REDACTED]

(confirming that the above data are accurate and complete)

Please PRINT Name [REDACTED]

SB Medical Monitor's Signature: [REDACTED] Date [REDACTED]

Please PRINT Name [REDACTED]

Case C: This patient had a seizure and was hospitalized on (b) (6) for 40 days, during which a CT scan showed an intracerebral hematoma in the left temporal region. Both findings were reported on a SAE CRF (C1-C2) but the intracerebral hematoma was deleted on 27oct04. An adjudication dossier was prepared but never sent for adjudication. Note the right-sided focal neurologic findings on neurologic exam and the CT scan results in the excerpt from the hospital discharge summary. (C3) This event should have been adjudicated.

DRQ 572786 AL 07MAR2007

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C1

(b) (6)

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Protocol	Centre Number	Patient Number	SB Receipt Date		
49653/231			Day	Month	Year

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)		AEGIS Number: B0342093A	
Serious Adverse Experience (Please print clearly)		Specify reason(s) for considering this a serious AE. Mark all that apply.	
(b) (6) CEREBRAL HEMATOMA WITH HEMATOMA IN LEFT TEMPORAL REGION		<input type="checkbox"/> fatal <input checked="" type="checkbox"/> life threatening <input type="checkbox"/> disabling/incapacitating <input checked="" type="checkbox"/> results in hospitalisation (excluding elective surgery or routine clinical procedures) <input checked="" type="checkbox"/> hospitalisation prolonged <input type="checkbox"/> congenital abnormality <input type="checkbox"/> cancer <input type="checkbox"/> overdose <input type="checkbox"/> Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
For SmithKline Beecham			
Onset Date and Time			
End Date and Time (If ongoing please leave blank)			
Outcome If patient died, please complete Form D			
Experience Course			
Intensity (maximum)			
Action Taken with Respect to Investigational Drug		Did the SAE abate? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
Relationship to Investigational Drug		If study medication was interrupted, stopped or dose reduced:	
Corrective Therapy If 'Yes', record details in the Concomitant Medication section		Was study medication reintroduced (or dose increased)? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Was patient withdrawn due to this specific SAE?		If yes, did SAE recur? <input type="checkbox"/> Yes <input type="checkbox"/> No	
		Assessment The SAE is probably associated with: <input type="checkbox"/> Protocol design or procedures (but not to study drug) Please specify _____ <input checked="" type="checkbox"/> Another condition (eg, condition under study, intercurrent illness) Please specify NOT KNOWN <input type="checkbox"/> Another drug Please specify _____	

- ③ THE CASE IS STILL UNDER INVESTIGATION DUE TO SUSPECTED BRAIN TUMOR. ACCORDING TO PATIENT, HOSPITALISATION IS PLANNED IN NOVEMBER 2004. FURTHER INFORMATION WILL BE PROVIDED AS SOON AS POSSIBLE.

SB SmithKline Beecham
Pharmaceuticals

C2

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Protocol	Centre Number	Patient Number	SB Receipt Date
49653/231			Day Month Year

SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Test	Date	Value	Units	Normal Range
BLOOD CELL REMENT (SE) (GLUCOSE LEVEL) GUL profil		40	MM Hg	10-12 MM Hg
Triglyceride - total		8-9, 9.5-19	mmol/L	6-7, 7-9
CHOLESTEROL TOTAL		2, 3.4 mmol/L 6.1 mmol/L	mmol/L	ONLY 2, 7.3 mmol/L
		6.1 27.10. 2004 A.S	mmol/L	ONLY 5, 7.4 mmol/L

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

ON [REDACTED] PATIENT WAS HOSPITALISED
DUE TO CEREBRAL HEMANGIOMA AND
SYMPTOMATIC EPILEPSY DUE TO ABOVE REASON.
YOU WILL BE PROVIDED BY RELEVANT MEDICAL
DATA WHEN THE PATIENT BRING IT TO ME.
③ CHANGES WERE DONE ACCORDING WITH DISCHARGE
SUMMARY PROVIDING BY THE PATIENT.

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number: [REDACTED]

Investigator's Signature: [REDACTED] Date: [REDACTED]

(confirming that the above data are accurate and complete)

Please PRINT Name: [REDACTED]

C3

CLINICAL FINDINGS:

Afebrile and eupnoic. No murmur above carotid arteries. Normal breathing sound. Rhythmic pulse, quiet heart sounds, no murmurs. BP 150/90 mmHg, c/p 80/min, abdomen is painless, soft with palpable liver (about 1cm), Spleen is not palpable, normal bowel movements. Extremities are without oedema.

Neurology report : patient is conscious, in contact, oriented. No signs of recent head trauma. Meningeal signs negative. Left eye after surgical treatment- pupil irregular in shape, medium large (3 mm), reactive to light. Mild ptosis of left eyelid (noted earlier). Normal eyeball movements. Discreet horizontal nystagmus. There is no double vision. Discreet ptosis of the mouth angle on the right side. Tongue in medial position. Speech and swallowing normal. Sense of heaviness in the right arm which is placed lower than the left. Both legs in the Mingazzini's position are symmetric with mild oscillations of both. Reflexes on arms symmetrical, on legs weakened but symmetrical. Atypical plantar response on the right side. No sensory loss. Tests for coordination normal. The patient is continent and walks without help.

IMPORTANT PATHOLOGICAL FINDINGS: Laboratory: SE 72 (repeated 40), Hgb 136, Hct 0.408 , WBC 10,3 , cholesterol 6,1, triglycerides 2,34 mmol/l HDL 1.06 mmol/l, LDL 4,0 mmol/l. Blood glucose profile: 8-9.9-5-10,4..

ECG : sinus rhythm (78/min), mild conduction disturbances inferiorly.

EEG: in the left parietooccipital region mild focal changes.

CXR: sclerosis of aorta.

CT brain scan: in the left temporoparietal region ring shaped formation which is filled by contrast. Around formation is the zone of oedema which is compressing trigonum. Chronical vascular lesion in the left region of thalamus.

Case D: This patient was hospitalized for 67 days for a severe stroke starting on (b) (6). 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.)

This case also illustrates the problems with the inconsistencies in the end of CV follow-up dates with the definition for them in the RECORD Reporting and Analysis Plan (RAP). The RAP states for patients like this one who withdraw to survival follow-up that "Subject moves from CV follow-up to survival status updates only . . . use date of CRF visit corresponding to request to withdraw from study procedures." There is a serious problem with this definition because "date of CRF visit" is an ambiguous term and, depending upon how it is applied, may not reflect any confidence in the extent of CV follow-up. For example, if the investigator records in 2006 that the patient withdrew in 2003 but was also lost to follow-up in 2003, is the "date of CRF visit" 2006 or 2003? For validity it should be 2003. For many RECORD patients the date chosen is inappropriate—see Cases E-K below.

The end date for CV follow-up for this patient is 16jul08. On the Study Continuation/Withdrawal CRF (D4) the investigator reported that the date of the last visit before withdrawing was 15May08 (which we confirmed) and that the date of last study med was 16jul08. We believe that the most appropriate date for ending CV follow-up for other CV endpoints for this patient is the last visit date of 15May08. The date 16jul08 is not a visit date and is consistent neither with the RAP nor with the knowledge of CV events for this patient.

Protocol	Centre Number	Patient Number	SB Receipt Date		
49653/231	[REDACTED]	[REDACTED]	Day	Month	Year

SAE REC [REDACTED]

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE [REDACTED] (Please print clearly)		AEGIS Number [REDACTED]	
Serious Adverse Experience (Please print clearly)		CEREBRAL STROKE	
For SmithKline Beecham		→ Specify reason(s) for considering this a serious AE. Mark all that apply.	
Onset Date and Time	[REDACTED]	[1] <input type="checkbox"/> fatal [2] <input type="checkbox"/> life threatening [3] <input type="checkbox"/> disabling/incapacitating [4] <input checked="" type="checkbox"/> results in hospitalisation (excluding elective surgery or routine clinical procedures) [5] <input type="checkbox"/> hospitalisation prolonged [6] <input type="checkbox"/> congenital abnormality [7] <input type="checkbox"/> cancer [8] <input type="checkbox"/> overdose [9] <input type="checkbox"/> Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
End Date and Time (If ongoing please leave blank)	[REDACTED]		
Outcome If patient died, please complete Form D	(1) <input checked="" type="checkbox"/> Resolved (2) <input checked="" type="checkbox"/> Ongoing (3) <input type="checkbox"/> Died		
Experience Course	(1) <input type="checkbox"/> Intermittent No. of episodes [REDACTED] (2) <input checked="" type="checkbox"/> Constant		
Intensity (maximum)	(1) <input type="checkbox"/> Mild (2) <input type="checkbox"/> Moderate (3) <input checked="" type="checkbox"/> Severe		
GR12 [REDACTED]			
Action Taken with Respect to Investigational Drug	(1) <input checked="" type="checkbox"/> None (2) <input type="checkbox"/> Dose reduced (3) <input type="checkbox"/> Dose increased (4) <input type="checkbox"/> Drug interrupted/restarted (5) <input checked="" type="checkbox"/> Drug stopped	Did the SAE abate? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes, did SAE recur? <input type="checkbox"/> Yes <input type="checkbox"/> No	
Relationship to Investigational Drug	(1) <input type="checkbox"/> Not related (2) <input checked="" type="checkbox"/> Unlikely (3) <input type="checkbox"/> Suspected (reasonable possibility) (4) <input type="checkbox"/> Probable	Assessment The SAE is probably associated with: <input type="checkbox"/> Protocol design or procedures (but not to study drug) Please specify _____	
DRQ 803336 [REDACTED] (b) (6)			
Corrective therapy If 'Yes', record details in the Concomitant Medication section	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input checked="" type="checkbox"/> Another condition (eg, condition under study, intercurrent illness) Please specify <u>ATHEROMATOSIS</u> <input type="checkbox"/> Another drug Please specify _____	
Was patient withdrawn due to this specific SAE?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

Protocol 40953/231	Centre Number [REDACTED]	Patient Number [REDACTED]	SB Receipt Date Day Month Year [REDACTED] [REDACTED] [REDACTED]
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SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Relevant Laboratory Data Please provide relevant abnormal laboratory data below				
Test	Date	Value	Units	Normal Range
NA	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
NA	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
NA	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
NA	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			

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.

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number: [REDACTED]

Investigator's Signature: [REDACTED] Date 25 SEP 08
(confirming that the above data are accurate and complete)

Please PRINT Name [REDACTED]

NOTE TO FILE

D3

Protocol Number: 49653/231

Quantum code: [REDACTED]

Site: [REDACTED]

Patient #: [REDACTED]

Endpoint #: [REDACTED]

Re: Hospital Death Summary –Not available

Please note that the Hospital Discharge Summary is not available for this endpoint.

Signed by

[REDACTED]
CEVA coordinator



Protocol 49653/231	Patient Number	Visit 25 Month 76
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STUDY CONTINUATION / WITHDRAWAL

Please mark box A or B below to indicate the patient's status

- A ☐ Patient is **continuing** in the Randomised Treatment phase of the study
- B ☒ Patient is **withdrawing** from the Randomised Treatment phase of the study

Mark below the most appropriate reason for withdrawal from the Randomised Treatment phase

- ☐ Insulin initiated
- ☐ Adverse Experience, including development of any intercurrent condition for which treatment with background or add-on study medication is contraindicated.
- ☐ ALT levels > 3 times the upper limit of reference range on two consecutive assessments
- ☐ Continued participation in the randomised treatment phase of the study presents safety risk due to a medical condition
- ☐ Prohibited glucose lowering medication
- ☐ Patient admitted to long-term healthcare facility
- ☐ Lost to follow-up
- ☒ Other - specify: withdrawal of consent

Date of final visit before leaving Randomised Treatment phase

15 MAR 08
Day Month Year

Date of final dose of add-on study medication before leaving Randomised Treatment phase

16 JUL 08
Day Month Year

If box B is marked, please complete section below

Is the patient entering the CV Outcomes phase of the study (full CVO, modified CVO or survival status)?

X Yes DRQ833708 (b) (6)

☒ No → If 'No' please mark the primary cause of withdrawal (Mark one box only)

- [1] ☐ Adverse Experience
- [4] ☐ Lost to follow-up
- [5] ☒ Patient withdrew at his own request
- [7] ☐ Other - specify: _____

DRQ 793341

Date of final visit or telephone contact

16 JUL 08
Day Month Year

Page Revised - 22 JUL 04, Protocol Amendment 07 - 27 FEB 06

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature

Date

Day Month Year

1.2 CV follow-up date problems (Cases E-K)

Cases E-K are 7 cases for which the reported end of CV follow-up dates are inconsistent with the CRFs or ambiguously reported. We identified all of these 7 cases from a stratified random sample of 100 cases (50 rosiglitazone and 50 control) drawn from the 3,147 CRFs routinely submitted, i.e., deaths and discontinuations (68% of total patients). We do not count them among our 70 problem cases.

We discussed these cases (and one additional) with GSK staff on a phone call on May 26, 2010, and GSK provide further explanations in (b) (6). GSK provided a not previously submitted data query that confirmed the acceptability of the additional case but we judge the 7 cases to be in error as documented in the following CRFs. Hence our estimate of erroneous CV follow-up dates is 7, or 7% of our random sample of 100, with 95% confidence limits of about 3 to 14%. Note that the end of CV follow-up date is used as the censoring date for all patients without an endpoint in the GSK primary CV safety analyses.

For reference, the GSK Reporting and Analysis Plan (RAP) dated 13 March 2009 defines the end of CV follow-up date in Section 9.2.4. as follows:

9.2.4. End of follow-up for Cardiovascular Events

The period from the start of add-on study medication until the date of death, for subjects whose death is eligible for SAE reporting (i.e. subject has not moved to survival-status only follow-up), or the date of ceasing follow-up (see below) for CV events.

Follow-up for CV events will cease at a date dependent on the follow-up path that a subject takes through the study, as follows:

- Subject completely withdraws, does not consent for survival status updates: this constitutes a complete withdrawal event – use date of visit at which complete withdrawal is recorded
- Subject moves from CV follow-up to survival status updates only: at this point the subject is not considered to have withdrawn completely from the study but has withdrawn from CV follow-up – use date of CRF visit corresponding to request to withdraw from study procedures
- Subject completes CV follow-up procedures to final visit (whether via main study or via tracking (CV events) sub-study) – use date of final visit
- Subject dies whilst still eligible for SAE reporting – use date of death

Subjects withdrawn prior to Protocol Amendment 7. The algorithm described above also covers those subjects who withdrew prior to Protocol Amendment 7, and entered the tracking (CV events) sub-study – if subject completes tracking (CV events) follow-up, use final visit date; if subject withdraws from CV event follow-up, use date moved to survival status follow-up or date of complete withdrawal from tracking sub-study, whichever is sooner. If a subject withdrawn prior to Amendment 7 does not enter tracking for further CV event follow-up then use the initial withdrawal date, regardless of any subsequent follow-up for survival status.

Case E: This patient entered the full Tracking Sub-Study on 16nov06 (E1) and then had a last visit with vitals signs, etc., on 24mar08. The Study Conclusions/ Withdrawal CRF (E2) reported the patient as lost with a last contact of 24mar08. The reported end of CV follow-up date is 24mar06. The date consistent with the RAP is 24mar2008.

SB **SmithKline Beecham**
Pharmaceuticals

E1

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Protocol	Centre Number	Patient Number	Visit Date		
49653/231			Day	Month	Year
			16	Nov	06
Cover Page					

CONFIRMATION OF ENTRY INTO TRACKING SUB-STUDY

<p>Confirm with patient:</p> <p>Patient agrees to enter full Tracking Sub-Study</p> <p><input type="checkbox"/> No → Please complete section below</p> <p><input checked="" type="checkbox"/> Yes → Please confirm date of next visit</p> <p>26 Feb 07</p> <p>Day Month Year</p> <p>Patient agrees to enter modified version of Tracking Sub-Study</p> <p><input type="checkbox"/> No → Please complete section below</p> <p><input type="checkbox"/> Yes → Please confirm date of next visit</p> <p>Day Month Year</p>	
<p>If patient only wants survival status updates to be collected, ask them to confirm who can be contacted to obtain future updates on how they are</p> <p><input type="checkbox"/> Patient</p> <p><input type="checkbox"/> Contact #1 on the Consent Form</p> <p><input type="checkbox"/> Contact #2 on the Consent Form</p>	
<p>Patient does not want to enter full or modified Tracking Sub-Study or provide survival status updates</p> <p><input type="checkbox"/> I confirm that the patient does not want to enter the tracking sub-study and does not want either themselves or someone they know to be contacted again about the study in the future</p>	

Protocol	Patient Number	Study Conclusion/Withdrawal
49653/231		

INVESTIGATOR INSTRUCTIONS

Every effort must be made by the investigator to keep patients in the Tracking Sub-Study.

Patients may withdraw completely from the study for the following reasons only

- Adverse Experience only → mark "Adverse Experience box"
- Patient lost to follow-up → mark appropriate box
- Patient withdrew at his/her own request → mark appropriate box
- Termination of the study by the sponsor → mark "Other" box and specify "Termination by sponsor".

Please remember to schedule an early withdrawal ECG assessment.

STUDY CONCLUSION / WITHDRAWAL

Please complete this section only if the patient has completed Visit 27, or if they are withdrawing.

Did the patient complete all the visits of the Tracking Sub-Study?

☐ Yes

☒ No →

If 'No', please mark the **primary** cause of withdrawal. (Mark one box only).

[1] ☐ Adverse experience

[4] ☒ Lost to follow-up

[5] ☐ Patient withdrew at his own request

[7] ☐ Other - specify _____

Date of final clinic or telephone visit

24 MAR 08
Day Month Yr

INVESTIGATOR'S SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____

Date

25 SEP 08
Day Month Yr

Case F: This patient had a visit with vital signs, etc. on 15apr05 and then was reported lost on 20dec06 with a last visit date of 15apr05 (F1), although there is also a crossed out study medication form indicating a last study med date of 30sep05. The reported end of CV follow-up date is 20dec06. The date consistent with the RAP is 15apr05.

SB **SmithKline Beecham**
Pharmaceuticals

F1

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Protocol 49653/231		Patient Number <div style="background-color: yellow; width: 100px; height: 20px;"></div>			20 DEC 06 P.H. B Visit 15-13 Month 36-28
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STUDY CONTINUATION / WITHDRAWAL

Please mark box A or B below to indicate the patient's status

A ☐ Patient is **continuing** in the Randomised Treatment phase of the study

B ☒ Patient is **withdrawing** from the Randomised Treatment phase of the study

Mark below the most appropriate reason for withdrawal from the Randomised Treatment phase

- ☐ Insulin initiated
- ☐ Adverse Experience, including development of any intercurrent condition for which treatment with background or add-on study medication is contraindicated.
- ☐ ALT levels > 3 times the upper limit of reference range on two consecutive assessments
- ☐ Continued participation in the randomised treatment phase of the study presents safety risk due to a medical condition
- ☐ Prohibited glucose lowering medication
- ☐ Patient admitted to long-term healthcare facility
- ☒ Lost to follow-up

L-2:
20 DEC 2006

☒ Other - specify: patient non compliance 20 DEC 2006 L-2.

Date of final visit before leaving Randomised Treatment phase

15 APR 05
Day Month Year

Date of final dose of add-on study medication before leaving Randomised Treatment phase

30 SEP 05
Day Month Year

If box B is marked, please complete section below

Is the patient entering the CV Outcomes phase of the study (full CVO, modified CVO or survival status)?

☐ Yes

☒ No → If 'No' please mark the primary cause of withdrawal (Mark one box only)

- [1] ☐ Adverse Experience
- [4] ☒ Lost to follow-up
- [5] ☐ Patient withdrew at his own request
- [7] ☐ Other - specify: _____

Date of final visit or telephone contact

15 APR 05
D.M. B
20 DEC 06 20 DEC 06
Day Month Year

Revised - 22 JUL 04, Protocol Amendment 07 - 27 FEB 06

VESTIGATOR SIGNATURE

certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____

Date

20 DEC 06
Day Month Year

Case G: This patient has a last visit with vital signs, etc. on 04oct07 and then withdrew completely at his own request with a last visit date before leaving Randomised Treatment of 04oct07, a last contact date of 16nov07, with the investigator signing the CRF on 20jan08. (G1) Other CRFs clearly indicate that there was no visit on 20jan08. (G2) The patient was hospitalized due to an MI from 13oct07 to 05nov07 which was adjudicated by the CEC. The reported date of last CV follow-up is 20jan08. The date consistent with the RAP is 16nov07.

Protocol 49653/231	Patient Number [REDACTED]	Visit 21 Month 60
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STUDY CONTINUATION / WITHDRAWAL

Please mark box A or B below to indicate the patient's status

- A ☐ Patient is **continuing** in the Randomised Treatment phase of the study
 B ☒ Patient is **withdrawing** from the Randomised Treatment phase of the study

Mark below the most appropriate reason for withdrawal from the Randomised Treatment phase

- ☐ Insulin initiated
☐ Adverse Experience, including development of any intercurrent condition for which treatment with background or add-on study medication is contraindicated.
☐ ALT levels > 3 times the upper limit of reference range on two consecutive assessments
☐ Continued participation in the randomised treatment phase of the study presents safety risk due to a medical condition
☐ Prohibited glucose lowering medication
☐ Patient admitted to long-term healthcare facility
☐ Lost to follow-up
☒ Other - specify: **PATIENT WITHDRAWN AT HIS OWN REQUEST**

REF802906

DRQ 802905

Date of final visit before leaving Randomised Treatment phase

04-OCT-07
Day Month Year

Date of final dose of add-on study medication before leaving Randomised Treatment phase

14-OCT-07
Day Month Year

If box B is marked, please complete section below

Is the patient entering the CV Outcomes phase of the study (full CVO, modified CVO or survival status)?

- ☒ Yes
☐ No → If 'No' please mark the primary cause of withdrawal (Mark one box only)

- [1] ☐ Adverse Experience
 [4] ☐ Lost to follow-up
 [5] ☒ Patient withdrew at his own request
 [7] ☐ Other - specify: _____

DRQ 803888

Date of final visit or telephone contact

16-NOV-07
Day Month Year

Revised - 22 JUL 04, Protocol Amendment 07 - 27 FEB 06

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature

Date

20 JAN 08
Day Month Year

Protocol 49653/231	Centre Number [REDACTED]	Patient Number [REDACTED]	Visit Date Day Month Year 20 JAN 08	Visit 21 Month 60
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QUALITY OF LIFE ASSESSMENTS (DIABETES SYMPTOM CHECKLIST)

Please ask the patient to complete a Diabetes Symptom Checklist.

Date completed :

Day	Month	Yr
-----	-------	----

SMOKING STATUS

Does the patient currently smoke ?

☐ No

☐ Yes → If 'Yes' please record the average number of cigarettes per day

--	--

ELECTROCARDIOGRAM

Please perform an ECG after the patient has been in the supine position for 5 minutes and obtain 1 original ECG tracing. Label the tracing clearly with patient initials, patient number, protocol number, centre number and date taken, sign and date, and insert the tracing in the plastic wallet at the end of this section.

Date of ECG :

Day	Month	Yr
-----	-------	----

[1] ☐ Normal / No clinically significant abnormalities

[2] ☐ Clinically significant abnormalities → Please record in the Adverse Experience section.

VITAL SIGNS

Patient may not smoke during the 30 minutes prior to the vital signs measurements.

Sitting Blood Pressure

Prior to any blood pressure measurements being taken, patients should have rested in the clinic for at least five minutes. Blood pressure must be measured in the same non-dominant arm at each visit.

Weight (without shoes) (kg)	Heart Rate (after 5 minutes sitting) (beats/min)	Blood Pressure (after 5 minutes sitting) (mmHg)		Waist Circumference (cm)	Hip Circumference (cm)
		Systolic	Diastolic		
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Record any clinically significant worsenings since the last visit in the Adverse Experience section.

PHYSICAL EXAMINATION

Please perform a physical examination. Any clinically significant abnormalities which represent a worsening since Visit 18 should be reported in the Adverse Experience section.

20 JAN 08

20 JAN 08

Case H: This patient had a last visit with vital signs, etc. on 27oct05 and then was reported lost, CRF signed 15jun06 and referencing the last visit on 27oct05. (H1) There is also a study med CRF from 15jun06 reporting a last study med date of apr06; no other CRFs were completed. The reported end date of CV follow-up is 15jun06. The date consistent with the RAP is 27oct05.

SB **SmithKline Beecham**
Pharmaceuticals

H1

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Protocol 49653/231	Patient Number	Visit 15 Month 36
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STUDY CONTINUATION / WITHDRAWAL

Please mark box A or B below to indicate the patient's status

- A ☐ Patient is **continuing** in the Randomised Treatment phase of the study
 B ☒ Patient is **withdrawing** from the Randomised Treatment phase of the study

Mark below the most appropriate reason for withdrawal from the Randomised Treatment phase

- ☐ Insulin initiated
☐ Adverse Experience, including development of any intercurrent condition for which treatment with background or add-on study medication is contraindicated.
☐ ALT levels > 3 times the upper limit of reference range on two consecutive assessments
☐ Continued participation in the randomised treatment phase of the study presents safety risk due to a medical condition
☐ Prohibited glucose lowering medication
☐ Patient admitted to long-term healthcare facility
☒ Lost to follow-up
☐ Other - specify: _____

Date of final visit before leaving Randomised Treatment phase

27 OCT 05
Day Month Yr

Date of final dose of add-on study medication before leaving Randomised Treatment phase

15 APR 06
Day Month Yr

If box B is marked, please complete section below

Is the patient entering the CV Outcomes phase of the study?

- ☐ Yes
☒ No → If 'No' please mark the primary cause of withdrawal (Mark one box only)

- [1] ☐ Adverse Experience
 [4] ☒ Lost to follow-up
 [5] ☐ Patient withdrew at his own request
 [7] ☐ Other - specify: _____

Date of final visit or telephone contact

27 OCT 05
Day Month Yr

Page Revised - 22 JUL 04

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____

Date

15 JUN 06
Day Month Yr

Case I: This patient had a last visit on 09jul07 and then was reported as completely withdrawn on 06nov07 (I1). The Study Conclusion/Withdrawal CRF, signed 13jan09, reported that the patient was lost to follow-up with a final contact of 06nov07. (I2) The reported end of CV follow-up date is 13jan09. The date consistent with the RAP is 09jul07.

visit not performed

I1

SB SmithKline Beecham Pharmaceuticals		Page 371a	
Protocol 49653/231	Centre Number	Patient Number	Visit Date Day Month Year 06-NOV-07
			Study Continuation/ Withdrawal

DOCUMENTATION OF REQUEST BY PATIENT TO WITHDRAW FROM STUDY

SECTION 1

Patient agrees to stay in CVO.

☒ No → Please complete section below

☐ Yes → Please confirm date of next visit

Day	Month	Year
-----	-------	------

SECTION 2

Patient agrees to enter modified CV Outcomes Phase

☒ No → Please complete section below

☐ Yes → Please confirm date of next visit

Day	Month	Year
-----	-------	------

SECTION 3

If patient only wants survival status updates to be collected, ask them to confirm who can be contacted to obtain future updates on how they are

☐ Patient →

☐ Contact #1 on the Consent Form →

☐ Contact #2 on the Consent Form →

Please confirm with the patient that the contact details provided on the consent form are still correct and that the suggested contacts are still relevant. If they are not, please ask the patient to provide new contact details and inform them that any people that they suggest who are non-healthcare professionals will be sent a letter telling them that they have been nominated as a contact person and giving them the option to refuse the request.

SECTION 4

Patient completely withdraws from study

☒ I confirm that the patient does not want contact made to elicit survival data, wishes to completely withdraw from the study and does not want either themselves or someone they know to be contacted again about the study in the future → Please complete Withdrawal page in main CRF **only** if patient has completely withdrawn from the study.

Date of complete withdrawal from the study

06	NOV	07
Day	Month	Year

Protocol Amendment 07 - 27 Feb 06

Protocol 49653/231	Centre Number <div style="background-color: yellow; width: 50px; height: 20px;"></div>	Patient Number <div style="background-color: yellow; width: 50px; height: 20px;"></div>	Visit Date			Study Conclusion/ Withdrawal
			Day	Month	Year	
			13	Jan	09	

INVESTIGATOR INSTRUCTIONS

Every effort must be made by the investigator to keep patients in the CV Outcomes Phase of the study.

Patients may withdraw completely from the study for the following reasons only

- Adverse Experience only → mark "Adverse Experience box"
- Patient lost to follow-up → mark appropriate box
- Patient withdrew at his/her own request → mark appropriate box
- Termination of the study by the sponsor → mark "Other" box and specify "Termination by sponsor".

Please remember to schedule an early withdrawal ECG assessment.

STUDY CONCLUSION / WITHDRAWAL

Please complete this section only if the patient has completed Visit 27, or if they are withdrawing.

Did the patient complete the CV Outcomes phase of the study ?

☐ Yes

☒ No →

If 'No', please mark the **primary** cause of withdrawal. (Mark one box only).

[1] ☐ Adverse experience

[4] ☒ Lost to follow-up

[5] ☐ Patient withdrew at his own request

[7] ☐ Other - specify _____

Date of final clinic or telephone visit

06 Nov 07
Day Month Yr

INVESTIGATOR'S SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____

Date

13 Jan 09
Day Month Yr

Case J: This patient allegedly withdrew at his own request. The last visit documented in the CRFs is a visit dated 21jun02 at which the last study medication was recorded as 20jun02. However, the Study Continuation/Withdrawal CRF (J1) was signed by the investigator on 20jan06. It has many corrections by data queries. While the investigator reported in data queries that the final visit was 31jul02, there is no confirmation of this in the CRFs. The reported end of CV follow-up date is 30jul02. The date consistent with the RAP is 21jun02.

SB **SmithKline Beecham**
Pharmaceuticals

J1

Page **18**

Protocol		Patient Number		Visit	3
49653/231				Month	2

STUDY CONTINUATION / WITHDRAWAL

Please mark box A or B below to indicate the patient's status

☐ **A** Patient is **continuing** in the Randomised Treatment phase of the study

☒ **B** Patient is **withdrawing** from the Randomised Treatment phase of the study

Mark below the most appropriate reason for withdrawal from the Randomised Treatment phase

DRQ 497405

☐ Insulin initiated

☐ Adverse Experience, including development of any intercurrent condition for which treatment with background or add-on study medication is contraindicated.

☐ ALT levels > 3 times the upper limit of reference range on two consecutive assessments

☐ Continued participation in the randomised treatment phase of the study presents safety risk due to a medical condition

☐ Prohibited glucose lowering medication

☐ Patient admitted to long-term healthcare facility

☐ Lost to follow-up

☒ Other - specify: **PATIENT WITHDREW AT OWN REQUEST**

Date of final visit before leaving Randomised Treatment phase

31-JUL-02
Day Month Yr

Date of final dose of add-on study medication before leaving Randomised Treatment phase

30-JUL-02
Day Month Yr

If box B is marked, please complete section below

Is the patient entering the CV Outcomes phase of the study?

☐ Yes

☒ No → If 'No' please mark the primary cause of withdrawal (Mark one box only)

[1] ☐ Adverse Experience

[4] ☐ Lost to follow-up

[5] ☒ Patient withdrew at his own request

[7] ☐ Other - specify: _____

REF DRQ553366

REF DRQ520668

Date of final visit or telephone contact

21-JUN-02
31-JUL-02
Day Month Yr

Page Revised - 22 JUL 04

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____

Date

20 JAN 06
Day Month Yr

Case K: This patient allegedly withdrew at his own request with a last visit date of 11aug03, a last study med date of 08sep03, and a final contact date of 04nov 05. (K1) He did not enter the CV Outcomes phase. The reported end of CV follow-up date is 08sep03, the date of last study med. The date consistent with the RAP is 11aug03.

SB SmithKline Beecham Pharmaceuticals		K1	RECEIVED 03 FEB 2006	Page 23
Protocol 49653/231	Patient Number [REDACTED]			Visit 12 Month 24

STUDY CONTINUATION / WITHDRAWAL

Please mark box A or B below to indicate the patient's status

A ☐ Patient is **continuing** in the Randomised Treatment phase of the study

B ☒ Patient is **withdrawing** from the Randomised Treatment phase of the study

Mark below the most appropriate reason for withdrawal from the Randomised Treatment phase

- ☐ Insulin initiated
- ☐ Adverse Experience, including development of any intercurrent condition for which treatment with background or add-on study medication is contraindicated.
- ☐ ALT levels > 3 times the upper limit of reference range on two consecutive assessments
- ☐ Continued participation in the randomised treatment phase of the study presents safety risk due to a medical condition
- ☐ Prohibited glucose lowering medication
- ☐ Patient admitted to long-term healthcare facility **DRQ 574967 [REDACTED]**
- ☐ Lost to follow-up

☒ Other - specify: **WITHDRAWING AT HIS OWN REQUEST**

Date of final visit before leaving Randomised Treatment phase

11 AUG 03
Day Month Yr

Date of final dose of add-on study medication before leaving Randomised Treatment phase

08 SEP 03
Day Month Yr

If box B is marked, please complete section below

Is the patient entering the CV Outcomes phase of the study?

☐ Yes

☒ No → If 'No' please mark the primary cause of withdrawal (Mark one box only)

- (1) ☐ Adverse Experience
- (4) ☐ Lost to follow-up
- (5) ☒ Patient withdrew at his own request
- (7) ☐ Other - specify: _____

Date of final visit or telephone contact

04 NOV 05
Day Month Yr

Page Revised - 22 JUL 04

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature _____

Date

5 JUL 04
Day Month Yr

1.3 Other Examples of Case Errors (Case L – S)

We have selected these cases from the 70 problems cases we identified from the 549 CRFs we reviewed. We did not select them randomly but to represent the range of errors we found.

Case L: This patient was hospitalized with several days of intermittent angina, left against medical advice, and returned to hospital because of painful nausea. While the troponin of 0.03 is called positive in one place and doubtful in another, the thrombus on angiography confirms that this case qualifies as an MI rather than unstable angina.

L1

PROGRESS: Despite explanations that were well-understood by the patient and a positive Troponin reading of 0.03, Mr Patient [REDACTED] discharged himself against medical advice (giving the baptism of his grand-daughter on Sunday as an excuse).

Finally, because of painful recurrences of nausea at home, he returned to hospital at 10pm that evening.

Since he is determined to attend the baptism, which is very soon, and because of the positive Troponin reading, we decided with his agreement to perform a coronary angiography on [REDACTED]

CORONARY ANGIOGRAPHY (Dr [REDACTED]): 3-vessel coronary disease in the form of an intermediary tubular instant restenosis of around 60% to the marginal artery, chronic occlusion of the distal CX, which is the dominant artery, and significant stenosis of the proximal right coronary artery, which is a rudimentary artery yet providing revascularization against the flow of the CX run-off vessels. Critical subocclusive stenosis of the LAD at the proximal LAD junction with the median LAD and a thrombus are the reasons for this coronary syndrome.

Simultaneously, we performed an **ANGIOPLASTY** of the critical LAD lesion and implanted an active Sirolimus stent using the direct stenting procedure (Cypher 3.0 stent of 8 mm).

Straightforward results.

Patient [REDACTED] can return home on [REDACTED] with the following **TREATMENT**: KARDEGIC 300 1 sachet daily, PLAVIX 75 2 caps in morning, MOPRAL 20 1 daily, TRIATEC 5 mg 2 x 1 daily, SECTRAL 200 2 x ½ daily, TAHOR 40 1 in evening, CORVASAL 2mg 3 x 1 daily, [REDACTED] daily, LAMICTAL 25 mg 1 daily.

CONCLUSION

Acute coronary syndrome with unstable angina, doubtful Troponin reading with pre-occlusive occlusion of the LAD and of proximal LAD junction with median LAD, endoluminal thrombus.

Angioplasty using direct stenting of the responsible lesion with implant of Sirolimus, Cypher 3.0 stent of 8 mm.


Note the tubular instant restenosis of 60% to the marginal artery.

Rudimentary right coronary artery with stenosis of 80%-90% but providing revascularization against the flow of the circumflex-marginal network.

Patient is a non-insulin dependent diabetic.

Case M: This patient was hospitalized for 10 days because of dyspnea and chest pain. (M1-M2) Blood gases showed a PO2 of 58 with a mild respiratory alkalosis and the ECG showed a sinus tachycardia and a partial RBBB pattern but troponin and d-dimers were reportedly negative. (M3) The patient was treated with IV nitroglycerin and nadroparine. The clinical diagnosis was heart failure. The event was adjudicated as non-CV. While pulmonary embolism appears to be the most likely diagnosis, the precise diagnosis was not clearly established. However, the event is clearly cardiovascular.

EP NO.: [REDACTED]



SmithKline Beecham
 Pharmaceuticals

M1

Page **119**

Protocol	Centre Number	Patient Number	SB Receipt Date
49653/231	[REDACTED]	[REDACTED]	Day: [REDACTED] Month: [REDACTED] Year: [REDACTED]

SAE REC. [REDACTED]

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly) [REDACTED]	AEGIS Number [REDACTED]
Serious Adverse Experience (Please print clearly)	CONGESTIVE HEART FAILURE
For SmithKline Beecham	→ Specify reason(s) for considering this a serious AE. Mark all that apply.
Onset Date and Time	[REDACTED]
End Date and Time (If ongoing please leave blank)	[REDACTED]
Outcome If patient died, please complete Form D	[1] <input checked="" type="checkbox"/> Resolved [2] <input type="checkbox"/> Ongoing [3] <input type="checkbox"/> Died
Experience Course	[1] <input type="checkbox"/> Intermittent No. of episodes [REDACTED] [2] <input checked="" type="checkbox"/> Constant
Intensity (maximum)	[1] <input type="checkbox"/> Mild [2] <input checked="" type="checkbox"/> Moderate [3] <input type="checkbox"/> Severe
Action Taken with Respect to Investigational Drug	[1] <input checked="" type="checkbox"/> None [2] <input type="checkbox"/> Dose reduced [3] <input type="checkbox"/> Dose increased [4] <input type="checkbox"/> Drug interrupted/restarted [5] <input type="checkbox"/> Drug stopped
Relationship to Investigational Drug	[1] <input type="checkbox"/> Not related [2] <input checked="" type="checkbox"/> Unlikely [3] <input type="checkbox"/> Suspected (reasonable possibility) [4] <input type="checkbox"/> Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication section	[1] <input checked="" type="checkbox"/> Yes [2] <input type="checkbox"/> No
Was patient withdrawn due to this specific SAE?	[1] <input type="checkbox"/> Yes [2] <input checked="" type="checkbox"/> No

Did the SAE abate? ☒ Yes ☐ No

If study medication was interrupted, stopped or dose reduced:

Was study medication reintroduced (or dose increased)? ☐ Yes ☐ No

If yes, did SAE recur? ☐ Yes ☐ No

Assessment
 The SAE is probably associated with:
☐ Protocol design or procedures (but not to study drug)
 Please specify _____

☒ Another condition (eg, condition under study, intercurrent illness)
 Please specify _____

☐ Another drug
 Please specify _____

REF DRQ 327252 (b) (6)

Protocol 49653/231	Centre Number [REDACTED]	Patient Number [REDACTED]	SB Receipt Date Day Month Year [REDACTED] [REDACTED] [REDACTED]		
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SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Relevant Laboratory Data Please provide relevant abnormal laboratory data below				
Test	Date	Value	Units	Normal Range
TROPONIN I	18 AUG 03 Day Month Yr	<0.10 µg/L	µg/L	<0.10
CPK	18 AUG 03 Day Month Yr	100	U/L	24-170
CK-MB	18 AUG 03 Day Month Yr	17.6	U/L	< 25
	[REDACTED] Day Month Yr			

Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)

Patient was admitted to hospital [REDACTED] due to episodes of chest pain (within preceding 2 days) and dyspnea. The patient received the following medications: GLYCERYL TRINITRATE IV. from 18.08.2003 16:00 to 19.08.2003 16:00 and NADROPARINE sc. 1x day from 18.08.2003 to 27.08.2003. The patient was discharged from hospital in general good state. After applied treatment - regression of symptoms chest pain, and dyspnea.

If applicable, was randomisation code broken at investigational site? ☒ No ☐ Yes

Randomisation / Study Medication Number: [REDACTED]

Investigator's Signature: [REDACTED] Date: [REDACTED]
(confirming that the above data are accurate and complete)

Please PRINT Name: [REDACTED]

M3

INFORMATION CARD

Name and first name: PATIENT [REDACTED]
 PESEL:
 Residence address:
 Hospitalized since [REDACTED] (b) (6)

DIAGNOSIS

MYOCARDIOPATHIA HYPERTONICA ET ISCHAEMICA CUM RBBB IN STADIO
 INSUFF. CORDIS II PRO NYHA. DIABETES MELLITUS TYP. 2. ADIPOSITAS

TEST RESULTS

SR 39/hr	RR 160/90; 160/95; 150/100
BODY WEIGHT 122-120 kg, BMI 45	HEIGHT

BLOOD COUNT	URINE	ENZYMES (U/L)
Hb (g/dL): 12.6	SG (g/L): 1024	AST: 31.8
Hct (%): 39.7	Protein (mg%): (-)	ALT: 32.1
RBC (m/μL): 4.55	Sugar (g%): (-)	CPK: 100 (N (F): 24-170 U/L)
WBC (K/L): 10.9	Ketones: (-)	CK-MB: 17.6 (N below 25 U/L)
PLT (k/μL): 340	Urobilinogen: 0.2E. U/dL	LIPIDOGRAM (mg/%)
RDW (%): 16.3	Epith. cells: single	Total cholesterol: 130
MCV (f/L): 87.3	Leukocytes (per vf): 2 - 3	LDL cholesterol: 74
Troponine I: I : II < 10 μg/L	Sediment: bacteria and mucus: single	HDL cholesterol: 34
n < 0.1	Multiple crystals of calcium oxalate	TG: 111

myocardial infarction 0.8

GASOMETRY	BIOCHEMISTRY (mg%)
pH: 7.455	Urea 24.6
pCO2 (mmHg): 41.8	Creatinine: 0.63
pO2 (mmHg): 57.7	Uric acid:
HCO3 (mmol/L): 28.1	Glucose: 120-113-111-106
BE (mmol/L): 4.0	CLOTTING SYSTEM
Saturation (%): 91.1	D-dimers: 845.46 ng/mL

ECG: 1. Levogram. Sinus rhythm regular, 90/min rate. Incomplete right bundle branch block.
 2. In control ECG heart rate was reduced to 85/min. Otherwise without changes.

Case N: This patient was hospitalized for 10 days because of a “collapse” attributed to atrial fibrillation. (N1-2) The patient had a history of on-going atrial fibrillation. The investigator determined that this event was not an endpoint. (N3) The event was not adjudicated. This event should have been adjudicated.

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date		
49653/231				Day	Month	Year

SERIOUS ADVERSE EXPERIENCE (SAE)


SAE Rec. [redacted]

Person Reporting SAE (Please print clearly)		AEGIS Number	
Serious Adverse Experience (Please print clearly) SEE DRQ 244766 [redacted]		Specify reason(s) for considering this a serious AE. Mark all that apply. (1) <input type="checkbox"/> fatal (2) <input type="checkbox"/> life threatening (3) <input type="checkbox"/> disabling/incapacitating (4) <input checked="" type="checkbox"/> results in hospitalisation (excluding elective surgery or routine clinical procedures) (5) <input type="checkbox"/> hospitalisation prolonged (6) <input type="checkbox"/> congenital abnormality (7) <input type="checkbox"/> cancer (8) <input type="checkbox"/> overdose (9) <input type="checkbox"/> Investigator considers serious or a significant hazard, contraindication, side effect or precaution	
For SmithKline Beecham Onset Date and Time End Date and Time (If ongoing please leave blank)		COLLAPSE AEMOD: COLLAPSE (NOS) [redacted]	
Outcome If patient died, please complete Form D		(1) <input checked="" type="checkbox"/> Resolved (2) <input checked="" type="checkbox"/> Ongoing (3) <input type="checkbox"/> Died	
Experience Course		(1) <input type="checkbox"/> Intermittent No. of episodes [] (2) <input checked="" type="checkbox"/> Constant	
Intensity (maximum)		(1) <input type="checkbox"/> Mild (2) <input type="checkbox"/> Moderate (3) <input checked="" type="checkbox"/> Severe	
Action Taken with Respect to Investigational Drug DRQ 343390 (b) (6)		(1) <input checked="" type="checkbox"/> None (2) <input type="checkbox"/> Dose reduced (3) <input type="checkbox"/> Dose increased (4) <input type="checkbox"/> Drug interrupted restarted (5) <input checked="" type="checkbox"/> Drug stopped	
Relationship to Investigational Drug		(1) <input type="checkbox"/> Not related (2) <input checked="" type="checkbox"/> Unlikely (3) <input type="checkbox"/> Suspected (reasonable possibility) (4) <input type="checkbox"/> Probable	
Corrective Therapy If 'Yes', record details in the Concomitant Medication section		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
Was patient withdrawn due to this specific SAE?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
		Did the SAE abate? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If study medication was interrupted, stopped or dose reduced: Was study medication reintroduced (or dose increased)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes, did SAE recur? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Assessment The SAE is probably associated with: <input type="checkbox"/> Protocol design or procedures (but not to study drug) Please specify _____ <input checked="" type="checkbox"/> Another condition (eg, condition under study, intercurrent illness) Please specify <u>UNDER INVESTIGATION</u> <input type="checkbox"/> Another drug <u>Atrial Fibrillation</u> Please specify _____	

Protocol 49653/231	Centre Number [REDACTED]	Patient Number [REDACTED]	Patient Initials [REDACTED]	SB Receipt Date Day Month Year [REDACTED] [REDACTED] [REDACTED]
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SERIOUS ADVERSE EXPERIENCE (SAE) (cont)

Relevant Laboratory Data Please provide relevant abnormal laboratory data below				
Test	Date	Value	Units	Normal Range
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
	Day Month Yr [REDACTED] [REDACTED] [REDACTED]			
Remarks (Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary) ECG showed Atrial Fibrillation 1870 Short term memory loss hence probable poor compliance to trial days. A.C.T Scan awaited. Withdrawn from the study because of the above development				
If applicable, was randomisation code broken at investigational site? <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes				
Randomisation / Study Medication Number: [REDACTED]				
Investigator's Signature: [REDACTED]			Date [REDACTED]	
(confirming that the above data are accurate and complete)				
Please PRINT Name [REDACTED]				

From: [REDACTED] on 21/11/2002 10:10
To: [REDACTED] /QDUB/Quintiles@Quintiles
cc: [REDACTED] /QRED/Quintiles@Quintiles
Subject: Re: [REDACTED] endpoint paperwork request 

N3

Dear [REDACTED],

I have just spoken to [REDACTED] who, in turn, has spoken to Dr [REDACTED] at the site and this has been confirmed as NOT being an endpoint but as a SAE.

Do you still require the information listed below, if so please let me know and I shall send it to you. Please also indicate how I should send it to you ie, via fax, post and if so please supply the necessary numbers/address.

Many thanks,
[REDACTED]

Case O: This patient died unwitnessed while swimming at a public beach on (b) (6) An autopsy was performed but the report was stated to be pending and the case was adjudicated as unknown, insufficient information, dated 28jan07. The adjudicator noted from the narrative that an autopsy was performed and that the autopsy report would help. (O1) A data query note from the investigator signed 12.2.2007 (12feb07?) states that drowning was confirmed with only mild generalized atherosclerosis. (O2) Note that hypoglycemia is difficult to diagnose postmortem. The case was not readjudicated.

SB **SmithKline Beecham**
Pharmaceuticals

O1

Protocol	Centre Number	Patient Number	Endpoint Number
49653/231			

ENDPOINT ADJUDICATION FORM

Instructions to CEC: please complete sections in white only.		<input type="checkbox"/> Tick box if re-adjudication										
Please indicate event submitted: <input type="checkbox"/> Hospitalisation <input checked="" type="checkbox"/> Death		Reported on: 08 JUL 2006 Day Month Year										
SUSPECTED ENDPOINT: Cardiovascular Hospitalisation												
Did the event meet the protocol-defined criteria for an endpoint?												
[A] <input type="checkbox"/> Yes If 'Yes', please indicate adjudicated date of event and primary cause for hospitalisation below:												
<table border="0"> <tr> <td>Day</td><td>Month</td><td>Yr</td> </tr> <tr> <td>[]</td><td>[]</td><td>[]</td> </tr> </table>			Day	Month	Yr	[]	[]	[]				
Day	Month	Yr										
[]	[]	[]										
<table border="0"> <tr> <td>[1] <input type="checkbox"/> Acute MI</td> <td>[5] <input type="checkbox"/> TIA</td> </tr> <tr> <td>[2] <input type="checkbox"/> Unstable Angina Pectoris</td> <td>[6] <input type="checkbox"/> Invasive Cardiovascular Procedure</td> </tr> <tr> <td>[3] <input type="checkbox"/> Definite CHF</td> <td>[7] <input type="checkbox"/> Amputation of Extremities</td> </tr> <tr> <td>[4] <input type="checkbox"/> Stroke</td> <td></td> </tr> <tr> <td colspan="2">[8] <input type="checkbox"/> Other Cardiovascular Hospitalisation, please specify: _____</td> </tr> </table>			[1] <input type="checkbox"/> Acute MI	[5] <input type="checkbox"/> TIA	[2] <input type="checkbox"/> Unstable Angina Pectoris	[6] <input type="checkbox"/> Invasive Cardiovascular Procedure	[3] <input type="checkbox"/> Definite CHF	[7] <input type="checkbox"/> Amputation of Extremities	[4] <input type="checkbox"/> Stroke		[8] <input type="checkbox"/> Other Cardiovascular Hospitalisation, please specify: _____	
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[4] <input type="checkbox"/> Stroke												
[8] <input type="checkbox"/> Other Cardiovascular Hospitalisation, please specify: _____												
[B] <input type="checkbox"/> No If 'No', please specify reason:												
<table border="0"> <tr> <td>[1] <input type="checkbox"/> hospitalisation did not involve a change in date (N.B. change in date not required in case of unplanned ambulatory percutaneous cardiovascular intervention)</td> </tr> <tr> <td>[2] <input type="checkbox"/> non-CV hospitalisation</td> </tr> <tr> <td>[3] <input type="checkbox"/> unknown hospitalisation (insufficient data)</td> </tr> <tr> <td>[4] <input type="checkbox"/> non-urgent CV procedure / non-specific symptom</td> </tr> </table>			[1] <input type="checkbox"/> hospitalisation did not involve a change in date (N.B. change in date not required in case of unplanned ambulatory percutaneous cardiovascular intervention)	[2] <input type="checkbox"/> non-CV hospitalisation	[3] <input type="checkbox"/> unknown hospitalisation (insufficient data)	[4] <input type="checkbox"/> non-urgent CV procedure / non-specific symptom						
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[2] <input type="checkbox"/> non-CV hospitalisation												
[3] <input type="checkbox"/> unknown hospitalisation (insufficient data)												
[4] <input type="checkbox"/> non-urgent CV procedure / non-specific symptom												
SUSPECTED ENDPOINT: Death												
Did the event meet the protocol-defined criteria for an endpoint?												
[C] <input type="checkbox"/> Yes If 'Yes', type of death												
<table border="0"> <tr> <td>[1] <input type="checkbox"/> Acute MI</td> </tr> <tr> <td>[2] <input type="checkbox"/> Heart Failure</td> </tr> <tr> <td>[3] <input type="checkbox"/> Sudden</td> </tr> <tr> <td>[4] <input type="checkbox"/> Acute Vascular Event</td> </tr> <tr> <td>[5] <input type="checkbox"/> Other Cardiovascular Death, please specify: _____</td> </tr> </table>			[1] <input type="checkbox"/> Acute MI	[2] <input type="checkbox"/> Heart Failure	[3] <input type="checkbox"/> Sudden	[4] <input type="checkbox"/> Acute Vascular Event	[5] <input type="checkbox"/> Other Cardiovascular Death, please specify: _____					
[1] <input type="checkbox"/> Acute MI												
[2] <input type="checkbox"/> Heart Failure												
[3] <input type="checkbox"/> Sudden												
[4] <input type="checkbox"/> Acute Vascular Event												
[5] <input type="checkbox"/> Other Cardiovascular Death, please specify: _____												
[D] <input checked="" type="checkbox"/> No If 'No', please specify reason:												
<table border="0"> <tr> <td>[1] <input type="checkbox"/> non-CV death</td> <td rowspan="2"><i>from the narrative it looks like there was an autopsy performed → autopsy report would help</i></td> </tr> <tr> <td>[2] <input checked="" type="checkbox"/> unknown death (insufficient data)</td> </tr> </table>			[1] <input type="checkbox"/> non-CV death	<i>from the narrative it looks like there was an autopsy performed → autopsy report would help</i>	[2] <input checked="" type="checkbox"/> unknown death (insufficient data)							
[1] <input type="checkbox"/> non-CV death	<i>from the narrative it looks like there was an autopsy performed → autopsy report would help</i>											
[2] <input checked="" type="checkbox"/> unknown death (insufficient data)												
<div style="background-color: yellow; height: 40px; width: 100%;"></div>												
Adjudication Signature: _____		Adjudication Date: 28 / Jan / 2007										

Amended: 17 Mar 2006

DATA RESOLUTION QUERY

Date: (b) (6)	02	
Patient Number: [REDACTED]	Centre Number: [REDACTED]	Protocol Code: 49653/231

DRQ Number	VISIT	PAGE	QUERY	RESPONSE
549968	End	205	<p>FURTHER TO DRQ 547288, IT IS CONFIRMED THAT 'CAUSE OF DEATH' IS STILL 'PENDING AUTOPSY' BUT THAT CAUSE OF DEATH BASED ON WHAT IS KNOWN NOW IS 'DEATH BY DROWNING'. ONCE AUTOPSY IS PERFORMED, PLEASE RETURN THIS QUERY WITH THE RESPONSES FOR 1) 'CERTIFIED CAUSE OF DEATH', 2) 'WAS A POST MORTEM PERFORMED?' YES/NO AND IF YES, 3) 'SUMMARISE FINDINGS'. THANK YOU.</p> <p><u>WAS MARKED AS CONTRIBUTORY FACTOR; HYPERTENSION IS MENTIONED IN MEDICAL HISTORY. ALL DRUG CONCENTRATIONS WERE WITHIN THERAPEUTIC RANGES. MILD GENERALIZED ATHEROSCLEROSIS WAS SEEN IN CORONARY ARTERIES, AORTA AND CEREBRAL ARTERIES; HYPERCHOLESTEROLEMIA IS MENTIONED IN MEDICAL HISTORY, THESE CHANGES WERE NOT MARKED AS CONTRIBUTORY.</u></p>	<p>1) DEATH BY DROWNING</p> <p>2) YES</p> <p>3) DEATH WAS CAUSED BY DROWNING. HYPERTENSION</p>

I authorise the above changes to be made to the patient record form

Authorised Signature [REDACTED]

Date .. (b) (6)

The Investigator, CEC Reviewer, or other authorised designate should sign and date this DRQ upon completion.

QDUB RECORD Fax Number: + 353 - 1 - 8099523

Case P: This patient had an other CV endpoint for an angina hospitalization in (b) (6) adjudicated as atrial fibrillation (afib). The discharge summary clearly describes the afib starting intermittently in (b) (6) with a stroke occurring during one of the attacks. (P1) It does not describe a neuro exam but does state that exercise testing could not be done due to the post-stroke condition. (P2) The stroke was not pursued or adjudicated.

RECORD 49653/231

124 P.1

P1

Cardiology and Intensive Treatment Clinic

Tel: [REDACTED]

History of Disease No: [REDACTED]

Discharge Survey of

Admitted on: [REDACTED] XXXXXXXXXXXX Age: XX

Discharged on: [REDACTED] UCN: IDN:

Address: City/Village Str.:

Telephone: Personal Doctor:

DIAGNOSIS:

Ischemic Heart Disease. Angina pectoris unstable IIA1. RHYTHM DISTURBANCES – RECURRENT PAROXYSMAL ATRIAL FIBRILLATION – CONDITION AFTER ANOTHER ATTACK. HYPERTONIC HEART DISEASE III GR. HYPERTONIC HEART. METABOLIC SYNDROME – HYPERTRIGLYCERIDEMIA. DIABETES MELLITUS TYPE 2 – IDDM. CEREBROVASCULAR DISEASE. CONDITION AFTER EXPERIENCED ISCHEMIC STROKE IN THE REGION OF LEFT MIDDLE BRAIN ARTERIA.

Dear colleague, the following Discharge Survey is issued to the patient who was treated in the clinic with the following problems.

From the Anamnesis:

The patient is admitted for first time in Cardiology and Intensive Treatment Clinic due to consecutive attack of palpitation on [REDACTED] accompanied with strong breath insufficiency and retrosternal pain. From [REDACTED] the patient is with repeating attacks of atrial fibrillation with spontaneous and medicamentous conversion. During one of the attacks the patient experienced ischemic stroke in the region of left middle brain artery. The patient reports an easy fatigue and shortness of breath at usual physical efforts.

Status:

In good general condition, takes active position in bed. Allo - and autopsychotically oriented. Hypersthenic habitus. Skin and visible mucosa is pale rose. Without cervical venous stagnation. Symmetric chest, Vesicular respiration with single moist wheezes bilaterally basally. Cor – normorhythmic heart activity with rate 100/min. Clear heart tones, protomesosystolic noise 1-2/6 gr. of apex cordis. Arterial blood pressure 160/100 mmHg. Abdomen - soft, painless. Liver and spleen – not increased. Limbs – without swellings, unchanged peripheral arterial pulsations.

21 Sep 2006

P2

Previous diseases: Diabetes mellitus type 2 from 6 years – from one month on [REDACTED] AH – from 5 years – treated with poor control. Cerebrovascular disease. Experienced ischemic stroke in the region of left middle brain artery in [REDACTED]. Chronic calculous pyelonephritis – surgical procedure – 20 years ago.

Family anamnesis: Mother with Diabetes mellitus.

Risk factors: age, sex, metabolic syndrome – weight above the ranges, hypertriglyceridemia, diabetes mellitus, obesity, smoking.

From the tests:

ESR		INR% 89%	aPPT 31"	SGPT 13,6	Protein
Hb 138		Bl. Sugar 13,2	FDP	AP 65,9	Albumin
RBC 4,66		Urea 3,7	CRP 144	γ - GTP	Cholesterol 4,89
Haematocrit 0.38		Creat 86	CRP – MB 21	Na 142	Triglycerides 2,37
WBC 6,7		Ureic acid	Troponin negative	K 3,9	
Plat. count 280		Fibrinogen 3,3	SGOT 15,2	Ca	
Others					

Instrumental tests:

ECG:

ECG – at admission – sinus rhythm. Neutral electrical axis. Insignificant CT-T changes on Anterior wall of LV. Without dynamic in the period during hospitalization and discharge.

Ro:

Echography of abdominal organs:

EchoCG: Ejection Fraction% - 56 Shortening fraction% - 30 Septum - 12 Inferior wall of LV - 10 LA - 42 LV EDD and ESD - 55 38. Diastolic dysfunction. Unchanged kinetics at rest.

Other EchoCG: LV – EDV – 122 ml, LV – ESV – 56 ml, Ejection fraction Simpson – 54%, RA – 34mm, RV – 32mm. Mitral valve – calcinosis of anterior mitral leaflet, regurgitation 0-I gr., Aortic root – intact, Tricuspid valve – intact.

Holter ECG: General sinus rhythm is registered with rate between 48 – 95/min, average – 57/min and single monotopic supraventricular extrasystols. In morning hours in conditions of sinus bradycardia is registered CT depression to 1mm – horizontal type. FA episodes are not registered.

Stress test: It can't be performed due to consequences of cerebrovascular disease.

Consultations: Not performed.

21 Sep 2006

Discharge summary

Translated from Bulgarian into English by [REDACTED] CRA/QSOF on [REDACTED]
Reviewed and corrected by [REDACTED] CRA/QSOF on [REDACTED]

Case Q: This patient was hospitalized for a ventricular arrhythmia and died on (b) (6). However, virtually no other information was collected, the discharge summary and death certificate were not obtained, and the death was adjudicated as unknown. The most detailed explanation of the event was a cryptic, undated note to file stating that the patient had suffered from the ventricular arrhythmia for years. (Q1) This death could have represented an MI and all required documentation for a hospitalization and for an MI should have been obtained. This case illustrates a general problem in RECORD with failure to obtain adequate information.

This case also illustrates the problems with end of CV follow-up dates (see Cases E-L) as well as problems with dates in general. The end of CV follow-up date is reported as (b) (6), the date of death. However, the prior history and circumstances preceding the death were not elucidated and the cause of death was adjudicated as unknown—the date of death in this case is no valid for determining the end of CV follow-up. The investigator signed the Study Conclusion/Withdrawal CRF in (b) (6) and reported a date of final clinic or telephone visit of (b) (6). (Q2) However the last telephone visit CRF has a contact date of (b) (6) (Q3) and the penultimate one has a contact date of (b) (6) (Q4), suggesting that the correct date of end of CV follow-up is (b) (6). The reported end of CV follow-up date is off by about 14 months.

NOTE TO FILE

Q1

Protocol Number: 49653/231
Quantum code: FSKB0565.205
Site: [REDACTED]
Patient #: [REDACTED]
Endpoint #: [REDACTED]

Patients Death

Please note that the patient was hospitalised and died, it states that the patient was hospitalised for ventricular arrhythmia but the patient had suffered from this for years it was not a case that it had worsened.

Signed by

[REDACTED]
Pharmacovigilance Program Manager
Quintiles,
Dublin

Date _____

Protocol 49653/231	Patient Number [REDACTED]	DATE OF VISIT 17-AUG-05	Study Continuation/ Withdrawal
------------------------------	--	--------------------------------	-----------------------------------

SCR12 [REDACTED]

INVESTIGATOR INSTRUCTIONS

Every effort must be made by the Investigator to keep patients in the CV Outcomes Phase of the study.

Patients may withdraw completely from the study for the following reasons only

- Adverse Experience only → mark "Adverse Experience box"
- Patient lost to follow-up → mark appropriate box
- Patient withdrew at his/her own request → mark appropriate box
- Termination of the study by the sponsor → mark "Other" box and specify "Termination by sponsor".

Please remember to schedule an early withdrawal ECG assessment.

STUDY CONCLUSION / WITHDRAWAL

Please complete this section only if the patient has completed Visit 27, or if they are withdrawing.

Did the patient complete the CV Outcomes phase of the study (full CVO, modified CVO or survival status)?

☐ Yes

☒ No →

If 'No', please mark the **primary** cause of withdrawal. (Mark one box only).

[1] ☒ Adverse experience

SCR 13 [REDACTED]

[4] ☐ Lost to follow-up

[5] ☐ Patient withdrew at his own request

[7] ☒ Other - specify Pearl

Date of final clinic or telephone visit

Day Month Year

INVESTIGATOR'S SIGNATURE

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator's Signature

Date

Day Month Year

22448

SB **SmithKline Beecham**
 Pharmaceuticals
Q3

Page		326	
Protocol	Centre Number	Patient Number	Patient Initials
49653/231			
Contact Date			Visit 14
Day Month Year			Month 32
17 AUG 04			(Telephone Visit)

TELEPHONE VISIT

22448

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Q4

Page		324	
Protocol	Centre Number	Patient Number	Patient Initials
49653/231			
Contact Date			Visit 13
Day Month Year			Month 28
20 APR 04			(Telephone Visit)

Case R: This patient was adjudicated as having an MI during a (b) (6) hospitalization for pneumonia based on elevated CK and troponin. However, the discharge summary is from a later rehabilitation hospitalization. (R1) The MI endpoint form provides the CK and troponin values without normal limits and reports that there were no typical ischemic symptoms and no other diagnostic tests. (R2) No ECGs (other than baseline) or ECG reports were submitted for this event. The correct discharge summary should have been obtained as well as ECGs. Furthermore, by the CEC Charter MI definition either ischemic symptoms or ECG changes are needed along with the biomarker elevation for adjudication of an MI. Please note that pneumonia alone has been reported to be associated with troponin elevations. This patient also had renal failure, another condition associated with troponin increases.

PRIVATE AND CONFIDENTIAL

R1

Primary Care Trust



Our ref:
NHS No:

Dear Dr:

Re:

Date of discharge:

Discharge medication:

Clopidogrel 75mg OD
Simvastatin 40mg nocte
Aspirin 75mg OD
Glibenclamide 5mg at midday meal
Glibenclamide 10mg at breakfast

Furosemide 40mg OD
Nicorandil 20mg OD
Isosorbide Mononitrate 20mg BD
Bisoprolol 5mg OD
Carbamazepine syrup 100mg TDS
Sytro Elixir 10mls (Ferrous Fumarate) OD
Temazepam 5mg PRN to aid sleep at night
Anusol HC PRN up to TDS for haemorrhoids - 7 day course

SITE:

PATIENT:

Mr [REDACTED] is a 74 year old gentleman who fell at home on 5 April 2007 due to a mechanical overbalance whilst trying to mobilise; he had only been recently discharged from hospital on (b) (6). Due to his poor mobility he was transferred for rehabilitation to a therapy bed on (b) (6).

[REDACTED] recent spate of falling has made him quite concerned about his ability to cope at home, even though his previous falls were attributed to heart block requiring a permanent pacemaker fitted in (b) (6). This was followed by heart failure plus an MI and renal failure in (b) (6) and during that admission [REDACTED] had a bout of Clostridium difficile. His general recovery has been slow and marked with various illnesses so he and the family made a decision that he would be better in permanent residential care following discharge from rehabilitation.

Protocol 49653/231	Centre Number	Patient Number	Endpoint Number E	Myocardial Infarction/ Unstable Angina Endpoint Form
-----------------------	------------------	-------------------	-------------------------	---

MYOCARDIAL INFARCTION / UNSTABLE ANGINA ENDPOINT FORM

Date of onset of event

Day Month Year

Where there any typical ischaemic symptoms ?

- ☒ No
☐ Yes

Cardiac Biomarkers

Were any cardiac biomarkers assessed

- ☐ No
☒ Yes → If 'Yes' please complete the following table.

Date Captured Day Month Year	Creatine Phosphokinase (CK)			CK-MB Isoenzyme			Troponin I			Troponin T		
	Value	Units	ULN	Value	Units	ULN	Value	Units	ULN	Value	Units	ULN
	916	u/L								2.25	µg/L	

Where any other diagnostic procedures performed ?

- ☒ No
☐ Yes → Please specify below :

Case S: This patient was hospitalized for a lung infection and died. The hospitalization form (S1-S2) and the death form (S3-S4) as well as the SAE form (not included below) consistently report lung infection as the reason for hospitalization and death and do not mention any other conditions. The death apparently occurred at a hospital other than the investigator's. The investigator reported that no additional information was available (S4) and a note to file (not included below) states that the wife did not provide any additional information. The CEC adjudicated the death as unknown, hence CV. We do not consider this adjudication completely unreasonable, but please compare the handling of this case to that for Case B. We included this case as an example of a suspect but not clearly wrong handling (12 of our 70 problem cases.)

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S1

Protocol	Centre Number	Patient Number		Endpoint Number	Hospitalisation / A&E Visit Endpoint Form
49653/231	[REDACTED]	[REDACTED]		E [REDACTED]	

Page HAE01

HOSPITALISATION OR ACCIDENT AND EMERGENCY DEPARTMENT VISIT ENDPOINT FORM

This form should be completed for all patients who were hospitalised or attended an Accident and Emergency Department during the course of the study. Please complete an SAE form ensuring details remain consistent. (Please note : the admission date must be different from the discharge date, except for unplanned ambulatory percutaneous intervention). Please enter details below :

Accident and Emergency visit only

☒ No
☐ Yes

Hospitalisation

☐ No
☒ Yes

Date of admission to hospital:

Date of discharge from hospital:

12.1.06

PRIMARY REASON FOR VISIT

Was the patient hospitalised or visited an Accident and Emergency Department for a : (mark one only)

☐ Cardiovascular reason →

Classification of CV reason (please mark one reason only)
Please complete the appropriate endpoint form

- ☐ Acute Myocardial Infarction
- ☐ Unstable angina pectoris
- ☐ CHF
- ☐ Stroke/TIA
- ☐ Invasive Cardiovascular procedure or amputation of extremities
- ☐ Other or suspected CV reason, (e.g. ambulatory invasive procedure)

specify:

☒ Non-cardiovascular reason →

Please specify: Lung Infection

- ☐ End-stage renal disease
- ☐ Laser coagulation
- ☐ Cataract extraction
- ☐ New pedal ulcer

Please complete an Adverse Experience form.

Protocol 49653/231	Patient Number	Endpoint Number	Hospitalisation / A&E Visit Endpoint Form
		E	

OTHER MAJOR EVENTS OCCURRING DURING HOSPITALISATION AFTER ADMISSION

Did any other major events occur during the hospitalisation after admission ?

☒ No

☒ Yes → Please mark all that apply :

- 13.1.05
JP
- ☐ Acute Myocardial Infarction
 - ☐ Unstable angina pectoris
 - ☐ CHF
 - ☐ Stroke/TIA
 - ☐ Invasive Cardiovascular procedure or amputation of extremities
 - ☐ Other or suspected CV reason, specify: _____

Please complete
the appropriate
endpoint form

☒ Non-cardiovascular reason → Please specify: Lung Infection

- ☐ End-stage renal disease
- ☐ Laser coagulation
- ☐ Cataract extraction
- ☐ New pedal ulcer

Please complete an Adverse
Experience form.

Did the patient die during this hospitalisation ?

☐ No

☒ Yes → Please complete a Death Endpoint Form. Please complete an SAE form ensuring all details remain consistent.

Investigator name (please print) : _____

Investigator Signature : _____

Date

Day Month Year

Please courier/fax this form and copies of source documentation to Quintiles

SB SmithKline Beecham
 Pharmaceuticals

S3

					Page	DEATH1
Protocol	Centre Number	Patient Number	Patient Initials	Endpoint Number	Death Endpoint Form	
49653/231				E		

DEATH ENDPOINT FORM

Please ensure that a hospitalisation endpoint form has been completed for all cardiovascular hospitalisations which occurred prior to the death of the patient.

Date of death

Did death occur during a hospital admission?

☐ No

☒ Yes → *Please complete a hospitalisation endpoint form.*

Primary cause of death - Please mark one box below as appropriate :

☐ Cardiovascular cause - (please mark one box only) :

☐ Death following heart failure

☐ Death following acute myocardial infarction

☐ Sudden death

☐ Death following acute vascular event - Please specify which event :

☐ Aortic dissection

☐ Aortic aneurysm

☐ Pulmonary embolism

☐ Stroke

☐ Other vascular event, please specify : _____

☐ Other cardiovascular cause, please specify : _____

☐ End-stage renal disease

☒ Non-cardiovascular cause, please specify : *lung infection*

☐ Unknown cause

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 Pharmaceuticals

S4

Page **DEATH2**

Protocol	Patient Number	Patient Initials	Endpoint Number	Death Endpoint Form
49653/231				

DEATH ENDPOINT FORM - Continued

Source documentation

Please enclose copies of the following documents (where available) and mark one box per item below :

	Enclosed	Requested	Not Done
Death Certificate	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Hospital Death summary	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Autopsy / Post-mortem report	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Police Records	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other, please detail : _____	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other, please detail : _____	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Other, please detail : _____	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Please record below any other relevant information pertaining to the terminal event. If the patient died outside hospital, please make every effort to obtain as much information as possible on the event from the patient's family practitioner and / or a close relative of the patient.

(b) (6)

No further information available

Investigator name (please print) : _____

Investigator Signature : _____ Date / /

Please courier/fax this form and copies of source documentation to Quintiles

1.4 Bad Vital Status Tracking (Case T)

Please note all of the problems with last contacts that we discuss regarding CV follow-up in Appendix 3 Section 3.6. We did not scrutinize vital status follow-up because, even by GSK's reported dates of last vital status contact, it was poor: About 12% of patients presumably alive at the end of the study did not have a vital status contact date on or after 08 September 2008, the earliest last study visit date. For us this poor rate makes total mortality estimates in the trial unreliable. We did chance across one case that illustrates one of the extreme of problems in capturing vital status. We did not count this case among our 70 bad cases, i.e., the ones related to endpoints.

Case T: This patient was withdrawn from the study after about 8 months because of poor compliance. Reportedly he then died, with the only information about the death submitted contained on a tracking form. (T1) No queries or other follow-up on this death were submitted.

SB	SmithKline Beecham Pharmaceuticals	T1	Page 498
Centre Number	Patient Number	Investigator	Tracking Form for Completely Withdrawn Patients

TRACKING FORM FOR COMPLETELY WITHDRAWN PATIENTS (Pre-Protocol Amendment 7) *Note: Do not include patients who were dead at the time of complete withdrawal.*

SECTION 1

Will site attempt to contact patient to ask them to enter tracking sub-study?

☒ No → Complete Section 2

☐ Yes → Complete Section 3

SECTION 2

If site is not going to attempt to contact patient, provide reason below

☐ PWCS (In investigator's opinion, patient has withdrawn consent from further participation in study and should not be contacted again)

☐ PKLFU (Investigator knows patient is lost to follow-up and is not contactable)

☒ PD (Investigator knows patient has died since they withdrew from study (Provide date of death if available))

Cause of death (if available) NOT AVAILABLE

11

11

11

Day

Month

Year

CAUSE

SECTION 3

If site agrees to attempt to contact patient, indicate below if successful contact has been made

☐ No

☐ Yes

☐ D → If patient has died, provide date of death (if available)

Cause of death (if available) _____

Day

Month

Year

A Tracking Sub-study CRF should be completed for all patients successfully contacted

Appendix 2: Protocol Comments

RECORD was a post-marketing safety study performed at the request of the European Medicines Agency. We did not review the protocol prior to study implementation. Our comments below include ones that we would have provided to GSK if we had been consulted in advance. (We could not have commented in advance on protocol changes effected after study start or provided references to Appendix 3 Study Conduct and to the other Appendices describing our plans for our review.)

The sponsor's brief description of RECORD is the following: "This was a multi-centre, randomized, open-label, cardiovascular outcomes study. Subjects with type 2 diabetes inadequately controlled on either metformin (MET) or sulfonylurea (SU) were randomised to the addition of either rosiglitazone (RSG, n=2220) or SU (for subjects on background MET) or MET (for subjects on background SU) (MET/SU, the active control group, n=2227). The primary endpoint was the time to the first occurrence of (adjudicated) cardiovascular (CV) hospitalization or CV death, with a pre-specified hazard ratio (HR) non-inferiority margin of 1.20." RECORD had a very complex study design. This brief description necessarily omits some other trial design features that are important for understanding the limitations of this trial regarding establishing CV safety for rosiglitazone. We summarize the important design limitations below, including issues with the protocol, the CRFs, and the CEC charter:

2.1 Open label

One major limitation is that RECORD was open label. While some may believe that open label is not a major limitation provided that the adjudication of events is blinded as it allegedly was in RECORD, the problems with the conduct of RECORD that we discuss in Appendix 3 illustrate that open label studies may have substantial problems limiting their value for evaluation of CV safety—or for other safety or efficacy concerns. Our short explanation of this limitation is that, even with blinded adjudication, biased referral for adjudication of cases and data by unblinded investigators and site monitors may lead to biases in event rates. We document the biases that appear to have occurred in RECORD in Appendix 3 Study Conduct.

2.2 Two studies

RECORD was not a simple study comparing rosiglitazone to placebo. As noted in the sponsor's summary, if the patient was inadequately controlled on metformin, then the active control was a sulfonylurea (glibenclamide, gliclazide, or glimepiride.) If the patient was inadequately controlled on a sulfonylurea, then the active control was metformin. While RECORD did enroll approximately equal numbers of baseline metformin and sulfonylurea patients, in essence RECORD was two studies done in parallel: one comparing initial add-on therapy with rosiglitazone to initial add-on sulfonylurea in the baseline metformin patients and the other comparing initial add-on therapy with rosiglitazone to initial add-on metformin in the baseline sulfonylurea patients. That the two studies are not strictly comparable is shown by the differences in baseline characteristics summarized in Table 5 in Section 4 of the main body of this consult. This dual study design has implications for analysis that we discuss in Appendix 8 Analysis Plan.

2.3 Active controls

The use of active controls introduces additional complications. There are inadequate data on whether either metformin or sulfonylureas increase CV risk—and data are inadequate for other diabetic drugs as well. There have been studies suggesting that some diabetic drugs, such as some sulfonylureas, increase CV risk. Hence RECORD at best can provide reassurance that rosiglitazone is not much worse than other oral antidiabetic drugs regarding affecting CV risk. While the use of a multidrug approach to controlling hyperglycemia in type 2 diabetics is routine clinical practice such that some may argue that a simple placebo control is infeasible, we believe that RECORD could and should have been conducted as blinded addition of rosiglitazone to other standard therapy.

2.4 Complex design with post-randomization determination of treatment phases

The RECORD trial design was very complex as shown in Figure 1.

Figure 1 RECORD Study Design

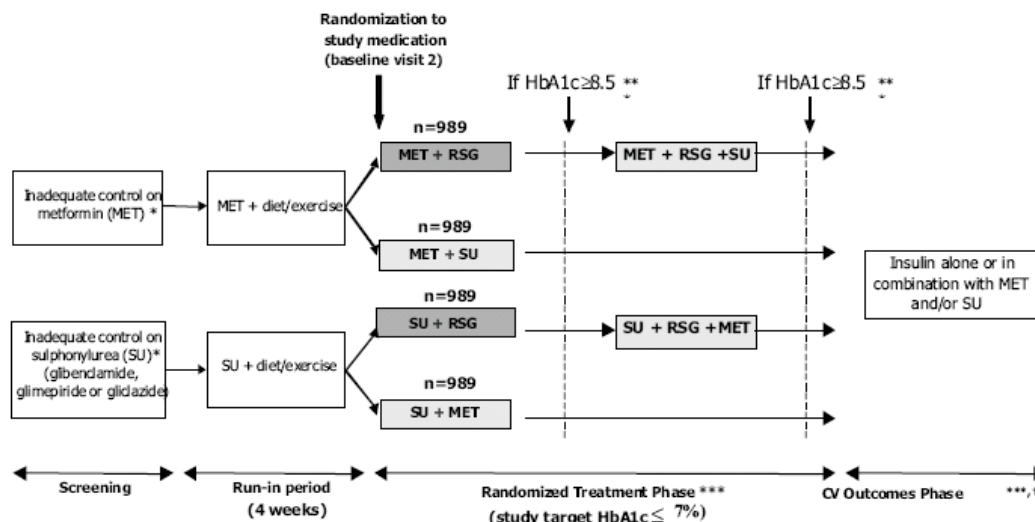


Figure 1- RECORD Study Design. *Subjects must be taking the following doses of background medication upon entry into the study: Metformin 1.7 g/day; Glimepiride 15 mg/day (10.5 mg/day micronised form); Glizalide 240 mg/day; Glimepiride 4 mg/day. The dose of background medication must remain unchanged throughout study unless subject experiences recurrent hypoglycaemia. **Treatment with third oral agent (subjects taking RSG only) or insulin (+/- oral agent) should only be initiated after two consecutive values (at least one month apart) of HbA_{1c} ≥ 8.5% and at least 8 weeks of treatment with maximum dose of add-on study medication. *** Add on study medication can be titrated to the following maximum doses: RSG 8mg/day, Metformin 2.55 g/day; Glimepiride 15 mg/day (10.5 mg/day micronised form); Glizalide 240 mg/day; Glimepiride 4 mg/day. Initiations and dose adjustments of add-on study medication and insulin should be implemented according to clinical practice and tablet strengths available. † RSG is withdrawn (where applicable) and subjects are switched from randomised treatment to insulin +/- oral agent and assessed for CV Outcomes, liver function and glycaemia only.

Note that none of the phases are of a fixed duration. Investigator decisions determined when a phase transition occurred and patient decisions (which could be influenced by investigator advice) determined to what outcome phases patients transitioned. The phases were different for the rosiglitazone and control arms. Rosiglitazone patients were to transition from dual to triple randomized treatment while control patients transitioned from dual treatment to insulin treatment. It is impossible with this study design to do a true ITT analysis with evaluation of all randomized patients for the same duration or at a fixed time post randomization and with the study treatment remaining randomized until the ITT evaluation time. Because the transitions depend upon patient characteristics, e.g., patients with many comorbidities are likely to have poor control, and outcome events, e.g., patients in the rosiglitazone arms should have transitioned after developing heart failure, treated or per protocol analyses are also biased in uncertain ways.

2.5 Treatment crossovers

The protocol prohibited use of non-study PPAR- γ agonists by statements such as “To avoid confounding the primary analysis, the use of other agents, including acarbose and PPAR- γ agonists such as pioglitazone, is prohibited up to the point of study conclusion” and, for the CV outcomes assessment phase, “There are no restrictions on medical care or glucose-lowering therapy during this part of the study, **except** that treatment with a PPAR γ -agonist such as pioglitazone (this also includes participation in blinded studies involving investigation of PPAR γ -agonists) is not permitted up to the point of study conclusion.” It would have been preferable for the CV outcomes assessment phase to mention both pioglitazone and rosiglitazone. As the first protocol statement above notes, crossovers confound the primary analysis—in fact all analyses. We discuss in Appendix 3 the data available regarding crossovers and the limitations of the data collection.

2.6 Investigator determination of visit frequencies and types

The protocol specifies visits every two months through 12 months, then every three months through 24 months, and then every four months during the randomized treatment phase. During the CV outcomes phase, the protocol specifies annual visits with interim telephone calls every 4 months. All patients were to have a study completion visit. However, to “encourage retention” Protocol Amendment 7, dated 27 February 2006, relaxed visit requirements: “For example, the annual clinic visit could be optional and the patient contacted only by telephone (ideally every 4 months, but this is flexible and the frequency of contact can be increased or decreased to fit in with the patient).” The protocol does not address whether the final study visit is to be considered an annual visit and could be converted to a phone contact.

This change had a detrimental interaction with visit CRFs. The visit CRFs were pre-printed with the visit number, visit month, and (only for CRFs for the CVO phase) type of visit (i.e., telephone or clinic visit). They lacked a field for the site to indicate the type of visit. This limitation is reflected in the study data sets. It is impossible for many visits to determine the type of visit. (As we discuss in Appendix 3 Section 3.6 it is impossible sometimes to determine from a CRF whether a visit, particularly a phone contact, even occurred.)

We consider the original protocol specification of a minimum of annual visits, a study completion visit, and quarterly phone contacts to be reasonable. However, we also believe that the changes specified by Protocol Amendment 7 introduced problems, one of which we have described above. We consider telephone calls to be adequate for determining survival but far from optimal for eliciting medication changes—and note that medication changes can involve confounding crossovers. We also have reservations about investigators determining visit frequencies for individual patients in this open label study. We discuss in Appendix 3 Study Conduct, Section 3.6 how the investigator discretion regarding phone contacts may have affected the reliability of follow-up date reporting.

2.7 Lower CV risk population

The inclusion and exclusion criteria appear reasonable and define a typical, inadequately controlled (i.e., HgbA1c 7.1-9%), type 2 diabetic population except that CV risk was likely lower than typical for the general population of diabetics because of the following exclusions: “Hospitalisation for a major cardiovascular event in the last 3 months, scheduled major cardiovascular intervention (e.g., cardiac surgery or angiography plus stenting), or presence of gangrene” and heart failure (HF), including patients receiving HF medications other than diuretics and other than other indications such as hypertension. The protocol also specifies the typical exclusion criterion for any condition or abnormality in the judgment of the investigator precluding safe participation. While we judge these exclusion criteria to be acceptable, we also believe that they may have contributed to the low CV event rates that concerned the RECORD Steering Committee and that external critics of RECORD have noted.

2.8 CV hospitalizations in primary endpoint

The primary endpoint for RECORD was time to first event of CV hospitalization or CV death. We have many concerns about this endpoint and how the sponsor defined it for RECORD.

We advise against using all CV hospitalization as part of a primary endpoint for three reasons:

1. All CV hospitalizations include a wide range of disorders, e.g., valvular heart disease, many of which are unlikely to be affected by one drug. Even if a drug has strong effects upon some CV disorders, including hospitalizations due to the other disorders will introduce noise. This noise will bias towards the null—highly undesirable for a noninferiority study.
2. Adjudicating CV hospitalizations is problematic. Patients frequently don’t present cleanly with one clear cause for admission. Should any contributing factor be adjudicated or just the primary? What about other events occurring during the hospitalization—what are the criteria for judging that they prolonged hospitalization or should be adjudicated separately? What about conditions that are CV but that can be caused by other disorders, e.g., pulmonary hypertension caused by lung disease?

The original protocol discussed these categories for CV hospitalizations:

- Hospitalisation for Myocardial Infarction
- Hospitalisation for Definite Congestive Heart Failure
- Hospitalisation for Stroke
- Hospitalisation for Unstable Angina Pectoris
- Hospitalisation for Transient Ischaemic Attack
- Hospitalisation for an Unscheduled (emergency) Arterial Revascularisation or Amputation of Extremities*
- Hospitalisation for an undefined CV reason (i.e. possible any of the above)

The protocol and the CEC Charter provide definitions or qualifications for the first six categories above. They do not explain further the seventh category, later changed (in Protocol Amendment 1 in 2001) to “Hospitalisation for other CV or undefined CV reasons”. We discuss in Appendix 3 Study Conduct observed problems particularly with

the CV procedure (also discussed next) and undefined categories. We also observed problems with missed adjudications when multiple events occurred during the same hospitalization and we present examples in Appendix 3.

3. Hospitalizations for CV procedures are particularly problematic. Rates of CV procedures such as angioplasties may be influenced as much by physician factors, the availability of facilities, and economics as by patient or disease conditions. Restricting to urgent CV procedures, as was attempted in RECORD, may reduce the contribution of physician factors but it also introduces another complication: determining “urgent”. We present in Appendix 3 Section 3.5 examples of problems in adjudicating urgency.

2.9 Ambiguities regarding the endpoint definition of amputations

The GSK primary endpoint includes amputation of extremities. The protocol qualifies amputation as follows: “Amputation of extremities due to macrovascular peripheral vascular disease related to diabetes. Amputation of an extremity due to clear trauma will be excluded.” They are ambiguities both with how this definition was presented to investigators and with its interpretation. For example, a presentation slide for 2001 states that amputation “will be endpoint only if no other cause than diabetic vascular complication” as shown in Figure 2—does infection complicating a severely ischemic foot constitute another cause?

Another slide, Figure 3, states that “Planned surgery for a pre-existing condition does not constitute an SAE.” The original protocol contributed to this ambiguity for amputations with its heading “10.5.6 Hospitalisation for Unscheduled (emergency) Arterial Revascularisation or Amputation of Extremities.” Does the “Unscheduled” modify “Amputation”? While this latter ambiguity was corrected in later versions of the protocol, we are concerned that this dichotomous treatment of amputations (needn’t be urgent) vs. other CV procedures (must be urgent). Amputations are frequently planned and they are for a pre-existing condition, i.e., peripheral ischemia that is longstanding and commonly slowly progressive. Because all endpoints were supposed to be SAEs, Figure 3 may have discouraged investigators from reporting planned amputations.

Figure 2: Confusing Slide on Amputations

Clinical Endpoint Definitions (6)

- Peripheral vascular disease
 - new symptoms of claudication (AE, no endpoint)
 - worsening of symptoms / pain (AE, no endpoint)
 - revascularisation (part of composite 1ry endpoint)
 - amputation (part of composite 1ry endpoint)#
#capture primary cause of the amputation, will be endpoint only if no other cause than diabetic vascular complication

QUINTILES

gsk GlaxoSmithKline

Figure 3: Planned Surgery Not an SAE

SAEs

Hospitalisation (continued):

- Hospitalisation for insurance, social or convenience purposes **does not** constitute hospitalisation.
- Planned surgery for a pre-existing condition **does not** constitute an SAE.

QUINTILES

gsk GlaxoSmithKline

In particular we believe that the question of how amputations for extremities complicated by infection, e.g., gangrene or osteomyelitis, was not addressed clearly. We queried GSK and received a response in (b) (6) as follows:

“b. How were amputations adjudicated? Would an amputation for osteomyelitis be an endpoint? For osteomyelitis in an ischemic foot? For an extremely ischemic foot upon which a pot was dropped?”

Response: According to the protocol amputation of extremities due to macrovascular peripheral vascular disease related to diabetes constituted a cardiovascular endpoint. Amputation of extremities due to clear trauma was not an endpoint. It was the responsibility of the CEC to make a judgement on which amputations met these criteria.”

However, investigators—not the CEC—made the initial decision about whether an amputation was to be considered an endpoint and referred for adjudication to the CEC. If GSK can not tell us now how amputations were handled, how could they have informed investigators about which cases to refer for adjudication? We do not have confidence that sites appropriately referred amputations. Also, lacking information in the CRFs about reasons for hospitalizations and no requirement for investigators to record the procedures unless he or she judged it to be an endpoint, we have no way of verifying whether amputations were handled correctly. We have no confidence that amputations were referred and adjudicated consistently.

2.10 Strict MI definition

The CEC Charter states that “Acute Myocardial Infarction will be adjudicated according to the definition in the document: ‘Myocardial Infarction redefined- A consensus documents of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. EHJ 2000 vol. 21; 1502-1513’”. However, the CEC Charter then describes criteria of hospitalization PLUS biomarker elevations PLUS one of the following: typical symptoms of cardiac ischemia or new ECG findings. These restrictive criteria exclude MIs for which biomarkers were either not obtained because of death prior to drawing or for which biomarkers were obtained at the hospital but the results never forwarded to the CEC. They ignore out-of-hospital MI deaths as MIs (but the deaths are captured as CV deaths.) They also ignore MIs confirmed on autopsy whether the patient was hospitalized or not. We used the updated version of the international definition of MI, the “universal” definition from 2007, and adjudicated MIs in all settings and by all criteria—see Appendix 4 Adjudication Comments.

2.11 Primary endpoint not reflecting suspected problems

Because CV effects of non-CV drugs (like most adverse effects) are not predictable in advance, we do not consider safety studies to follow rigidly the efficacy paradigm, i.e., a well pre-specified primary endpoint with absolute conservation of alpha. We may judge safety findings to be clinically relevant even if they were not pre-specified and even if they are not strictly statistically significant. However, for purposes of introducing some statistical rigor, we do favor pre-specifying some safety endpoints. For drugs about which the CV effects are unclear, we favor the standard CV death, MI, stroke (MACE) endpoint as discussed in the 2008 FDA Guidance *Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. We favor MACE because it captures the most significant events for the leading causes of CV morbidity and mortality in the US particularly for diabetics; because the mechanism for MI, stroke, and most CV deaths are similar; and because its components are “hard” events that are well defined and more reliably ascertained than CV hospitalizations. (Note, however that if the mechanism for a drug adverse effect is not related to atherosclerotic CV disease, then MACE is not appropriate, e.g., the HF effects of rosiglitazone, QT prolongation, etc.)

For rosiglitazone we do have some prior evidence regarding CV effects: The Nissen meta-analysis raised the question of whether rosiglitazone increases MI rates. (Nissen, S. E. and K. Wolski (2007). *N Engl J Med* 356(24): 2457-71.) Conversely, GSK has alleged that the drug may lower blood pressure and decrease stroke rates—typically we do not include components in a composite endpoint that go in different directions. Finally, HF is a known adverse effect of PPAR- γ agonists but relative risk and effects upon HF mortality could be defined better. Hence we consider the most appropriate safety endpoints for RECORD to be the MACE components analyzed separately, i.e., MI, stroke, CV death (plus the MACE composite as a secondary endpoint), and HF, including separate analyses for all HF events, for HF hospitalizations, and for HF deaths.

2.12 Endpoint date definition

The protocol and the CEC Charter do not discuss how the CEC will adjudicate endpoint dates. At a CEC meeting on December 10, 2003, the CEC stated that they would adjudicate endpoint events as follows: “The date of onset was discussed, as there have been discrepancies between the SAE onset date, endpoint onset date and admission date. It was agreed that in case of hospitalisation, the date of admission to the hospital will always be taken as the date of the endpoint. So if for example a patient reported chest pain for 3 days at admission to the hospital and that is adjudicated as Unstable Angina, the endpoint date is the hospitalization and not the onset of symptoms. The previous agreement regarding consecutive events (February 2001 minutes) will remain the same. ‘In case of consecutive events it was decided that death is always the primary endpoint. So for example if a patient has an MI, Heart Failure, Stroke, Death, the time to death will be captured. In case of consecutive events, where the patient survives, the time to first event will be captured.’ For consecutive events where there is no death the situation is as follows: The date of onset of the endpoint leading to hospitalisation will be the date of hospitalization. For any subsequent events that occur during the same hospitalisation the date of onset of each subsequent event will be the date of onset of the event, as reported by the investigator.”

We consider these endpoint date adjudication rules to be unacceptable. For example, consider two patients who suffer a MI on the same date, one of whom survives and the other of whom dies 15 days later. By the CEC rules the patient who survives will have an endpoint 15 days earlier than the patient with the more severe endpoint—death! While we would not expect these differences in dates to affect greatly the time-to-first-event analyses, we believe we should use the more appropriate analysis. Furthermore, depending upon censoring rules for events occurring after discontinuation of treatment, these rules could greatly affect results.

2.13 Minimal documentation on rationale for adjudication of cases

We judge the Endpoint Adjudication Form used by the CEC to be inadequate because it only provides checkboxes for adjudicated endpoints and non-endpoint but does not provide space or fields for the adjudicator to document why he or she selected the endpoint or non-endpoint and whether the source documentation provided was adequate. This lack of document is inconsistent with the protocol that states “All decisions and deliberations by the CEC will be fully documented and archived by GSK in accordance with GCP guidelines.” Having this documentation is useful to us for understanding how the CEC made its decisions and whether the adjudication is appropriate. We also recommend including on the adjudication form an explicit space for the adjudicator to note that another event, detected in the source documents submitted for adjudication, should also be adjudicated.

2.14 Analysis populations

We have concerns regarding the proposed analysis populations for the CV endpoints. While the original protocol defined the primary study population as “All Randomized Patients”, an early amendment changed it to “All Randomized and Treated Patients”. A secondary analysis was to be done using the “Per Protocol Population”. The protocol does not define these populations further. The Report Analysis Plan dated March 13, 2009 (the only version submitted initially) refers to “All Randomized and Treated Patients” as the “Intent-to-treat population” and clarifies that “all available follow-up from start of randomised treatment through to study end” will be used, including post-dual therapy follow-up. It clarifies the “per protocol” analysis as “on-randomised-dual-combination treatment” and excluding “triple therapy for subjects in the RSG arm.” It also provides for “A supplementary on-randomised-treatment analysis of the primary endpoint will also include all events/follow-up up to 30 days after last dose of randomised treatment (dual therapy) for those subjects who have discontinued dual therapy and continued follow-up for CV events.”

While we usually accept an “All Randomized and Treated Patients” for efficacy analyses and some experts prefer it to true ITT for safety analyses, we prefer to reference this population as the “full analysis set”—it is not true ITT. We accept randomized and treated as appropriately randomized because we assume that dropouts between randomization and start of treatment are random. However, for open label studies we should not make this assumption. Investigators could randomize older patients with incipient HF (overt HF was excluded), obtain a rosiglitazone assignment, and then decide (or the patient could decide) not to treat with rosiglitazone. (In RECORD dropouts prior to treatment were low: 6 rosiglitazone, 5 control. So, while the mean age of the rosiglitazone dropouts was 4 years older than the control dropouts, dropouts prior to treatment are not a significant problem.)

As we mentioned previously, the treatment plan was complex and exposure to rosiglitazone potentially could be very short for some patients. These factors and the noninferiority comparison suggest that a traditional ITT approach including all follow-up may not be most appropriate for this study. Furthermore, treating the RSG arms and the control arms differently is not appropriate. In fact, the treatment phases as defined in the protocol are problematic for this reason and because their durations are defined post-randomization. How long a patient remained in the initial randomized dual treatment phase was likely dependent upon the patient’s comorbid conditions, including CV conditions: Clinically comorbid conditions contribute to poor

diabetic control so patients with CV conditions such as worsening heart failure or angina may be more likely to progress from dual treatment to triple treatment or insulin therapy.

When to stop counting events, e.g., at discontinuation of treatment or some arbitrary time thereafter, is not clear. For another CV outcome study (the LIFE study comparing losartan to atenolol in patients with hypertension and LVH), event rates did not stabilize until 90 days after discontinuation of study drug. Whether this delayed stabilization reflects a prolonged biologic effect or uncertainly in date collections or a combination of these two factors we can only speculate. Unless analysis of event rates post discontinuation in RECORD suggest otherwise, we will use 90 days after drug discontinuation for on-treatment analyses.

Finally, good follow-up for CV events, i.e., by face-to-face patient-investigator exchanges during a physical visit by the patient to the site, typically become sparser as long term trials proceed. We discuss how RECORD fared in this regard in Appendix 3 Section 3.6.

In summary, we believe that the analysis approach must take into account four factors: (1) the duration of rosiglitazone treatment; (2) the post-randomization nature of the protocol treatment phases; (3) the imprecision of dates; and (4) the nature of the follow-up. We address all of these factors in Appendix 8 Analysis Plan.

2.15 Endpoint reporting

The protocol is sparse on the details of endpoint reporting. It states the following regarding protocol defined clinical endpoints: “SAEs which may constitute protocol defined CV hospitalisation and CV death endpoints (refer to Section 10 for definitions) will also be collected from the time of randomisation, and throughout both the Randomised Treatment and the CV Outcomes Assessment (Post-Randomised Treatment) Phases of the study, in endpoint forms. [Note: will not be collected for patients who are only being followed up for survival status data].” Regarding reporting of study endpoints, it states that “All potential CV hospitalisation (with the exception of hospitalisation for invasive CV procedures or amputation of extremities – see paragraph below) and CV death endpoints occurring during the study will be reported to GSK as SAEs, and in the appropriate endpoint form in the CRF. Wherever possible, all supporting documentation should be provided to the CEC to aid their assessment of each endpoint. [paragraph below] Hospitalisation for invasive CV procedure or amputation of extremities (see Section 10.5.6) will be reported as a study endpoint but will not be reported as an SAE.”

The protocol does not address how sites should report hospitalizations for endpoint reporting. The Hospitalization and Accident and Emergency Department Visit Form (HAE01) states that “This form should be completed for all patients who were hospitalised or attended an Accident and Emergency Department during the course of the study. Please complete an SAE form ensuring details remain consistent.” This statement implies that the sites should complete HAE01 forms for all hospitalizations. However, the presentations to investigators define hospitalization as “Further defined as hospitalization for cardiac and/or macrovascular causes excluding routine or planned visits not associated with a worsening of the disease conditions of the patient.” The presentations specify completing the SAE form and the event report fax coversheet before completing the hospitalization (or death) form.

However, the net result appears to be that sites made the initial decisions regarding whether to consider hospitalizations to be potential endpoints and to refer them for adjudication. We discuss these issues further in Appendix 3 Study Conduct.

2.16 SAE reporting

Every contact was supposed to include a “Serious Adverse Experience Check”. However, there was no CRF that could be checked “If no adverse experiences occurred since the previous visit, please mark this box” as was done for non-serious adverse events. Hence we have no confirmation that at a visit or phone contact the investigator queried the patient about SAEs. In addition, there appear to be problems with investigators understanding what constitutes an SAE that we discuss in Appendix 3 Section 3.8.

2.17 Concomitant medication reporting

Collecting concomitant medications is critical for RECORD because of the issue of crossovers confounding the analyses (see Section 2.5). The protocol text and Table 1 Outline of Study Procedures specify checking concomitant medications at all visits. However, during the CV outcomes phase Table 2 Outline of Study Procedures During CV Outcomes Assessment Phase does not specify check concomitant medications while the text has this statement: “Changes in the use of glucose lowering oral agents, insulin, and other prescription concomitant medications should be recorded on the appropriate page of the CRF.” The first item on the first page of the telephone visit CRFs for the CVO phase direct the investigator to “If information is available, please complete the Concomitant Medication section for prescription only medication to date.” The Concomitant Medication section was not part of the packet of forms for the visit but a separate sheet at the end of the CVO phase book for the entire year. We believe that it is difficult to collect concomitant medications accurately over the phone. For research, as for practice, it is desirable to have the patient bring in all of the medications that he or she is taking. We address the frequencies of concomitant med recording in Appendix 3 Section 3.8.

2.18 Handling of withdrawals

The CEC Charter states that “Patients that are discovered to have died between the date of their complete withdrawal from the study and the attempt by the site to contact them about the tracking sub-study should not be reported as endpoints to the CEC (as patient is officially withdrawn from RECORD). . . Patients that are re-contacted after completely withdrawing from RECORD that agree to only provide survival status data [and do not enter sub-study] should not be reported as endpoints to the CEC as we are not collecting dossiers on these patients.” We disagree with these statements and believe that it is ethical and critical for interpretation of the study to maximize follow-up. These statements allow the possibility of informative censoring, in this open label study, by unblinded investigators declaring sick Avandia patients to be completely withdrawn, making death—typically viewed as the “hardest” endpoint—subject to bias. We also judge these statements to contradict the protocol statements that “**Every effort should be made to follow up patients who withdraw completely from the study**” (bolding in original) and “At the end of the study, and if possible, the investigator will review public records (e.g., the National Death Registry) to ascertain if the patient is alive or dead. Survival status on as many patients as possible is considered crucial information for the success of this study” (underlining in original.)

Appendix 3: Study Conduct

The RECORD study had many design limitations—please see Appendix 2 Protocol Comments for our discussion of them. These protocol design limitations led to problems with the study conduct that limit any reassurances that RECORD can provide regarding the CV safety of rosiglitazone. In addition, there are other design limitations not detailed in the protocol that also created problems, and there are study conduct problems independent of design limitations. We discuss all of these study conduct issues here, relating them to the design limitations when relevant and documenting them with excerpts from the trial documentation and CRFs and analyses of the RECORD data.

3.1 Open Label and Unblinding

One major limitation is that RECORD was open label. The one aspect that was blinded was the provision of endpoint (EP) adjudication dossiers to the Clinical Endpoint Committee (CEC). While we have documented rare errors in redacting study drug identities from the EP dossiers, overall the blinding of the EP dossiers appears to be good. However, the redacting of EP dossiers appears to be the only aspect of blinding that was good.

The extent of the unblinded nature of RECORD is documented by this statement from the Final Draft Minutes 8th Steering Committee Meeting – September 03: “The Steering committee members were informed of the unrestricted availability of unblinded treatment code within Quintiles and GSK : no concerns raised.” Pertinent excerpts from the sponsor’s explanation of this note are as follows: “This excerpt from the minutes of the Steering Committee meeting of September 2003 is not worded clearly and more specific wording could have been used. The excerpt relates to a discussion of planning for the glycaemic sub-study analysis and how blinding could be managed for a subsequent submission to CPMP. . . Quintiles staff involved in data-processing were by necessity unblinded at the individual patient level as they were responsible for data entering, querying and validating add-on dosing/titration data from the CRFs. . . Access to unblinded patient-level data was provided for the GSK Pharmacovigilance group on an as-needed basis for the purpose of documenting and acting on reports of serious adverse events in accordance with sponsor reporting obligations.” The described access by the pharmacovigilance group and Quintile staff involved in data-processing does not match the phrase “unrestricted availability.” The explanation is inconsistent with the Steering Committee Meeting minutes.

We have another piece of evidence that suggests that the firewalls between Quintiles and GSK regarding study information and the ability to influence study conduct and results were not impermeable. A patient died with a clinical picture of pulmonary embolism but a fresh MI was also reported on autopsy. The note to file shown in Figure 1 was included with the patient’s CRFs.

Figure 1: Note to File Regarding GSK Requesting CEC Coordinating Center to Split SAE

NOTE TO FILE

Protocol Number: 49653/231
Quantum code: FSKB0565.205
Site: [REDACTED]
Patient #: [REDACTED]
Endpoint #: [REDACTED]

Re: Suspected Myocardial infarction

Please see note from the Investigator and CRA in relation to a reported SAE of Myocardial infarction. The original SAE was reported as Haemoptysis. Following review of the autopsy report GSK requested that the SAE be split to include a myocardial infarction. However the Investigator has stated that there was no MI. Therefore an endpoint of Myocardial infarction has not been reported.

Signed by

[REDACTED]
Manager, Clinical Event Validation
& Adjudication Services (CEVA)
CEC co-ordinating centre, Quintiles,
Dublin

10 FEB 2005

Date

As Figure 1 documents, GSK requested that the Quintiles CEC Coordinating Center include an SAE of MI. This patient was a control patient so adding an MI to the control arms would reduce the relative risk of rosiglitazone regarding MI. The CEC Co-ordinating Center rejected this request on 10feb05 while the adjudication for this death was not completed until 30jan07. This event should not have been adjudicated as an MI anyway because the CEC Charter MI definition does not include MIs diagnosed only by pathological findings. (We did pre-specify in our Adjudication Comments in Appendix 4 that we would count MIs diagnosed only by pathological findings so we have counted this event as an MI.)

We judge that it was highly inappropriate for GSK to have attempted to influence the work of the CEC Coordinating Center in this way. We have no mechanism for verifying whether such influences were common or rare.

Regardless of whether many GSK, Quintiles, and other contractors may have had unrestricted access to unblinded treatment code or whether GSK attempted to influence CEC referrals, some facts are irrefutable: (1) the investigators knew the treatment assignments; and (2) the CRFs, other source documents, and communications included drug identities such that anyone handling them (in particular Quintiles staff and site monitors) had access to treatment assignments for individual patients. These staff determined which cases were referred to the CEC Coordinating Center and to the CEC and what information was included in the EP dossiers. Conscious or subconscious biases could have influenced the adjudication referrals.

Several pieces of evidence suggest that there were such biases. We began our review by browsing the CRFs for deaths to familiarize ourselves with the submission. We quickly encountered a case the handling of which we judged to be unacceptable: A myocardial infarction SAE was deleted about 18 months after its occurrence (Case A in Appendix 1). Because of the extremely poor handling of this case, we expanded and documented our review of CRFs. We targeted cases for which the CRF information contained in the submitted SAS datasets suggested the possibility of problems regarding the ascertainment of MIs, strokes, or CV deaths; other cases for which a CV event was deleted or changed; endpoints regarding which the initial two adjudicators disagreed; multiple episodes of unstable angina without any MI; TIA hospitalizations; acute heart failure hospitalizations without an MI; and late adjudicated cases. Because we continued to find problems of varying levels of concern, we ultimately checked CRFs for 549 cases (278 rosiglitazone, 271 control). The results of our review suggest a bias based on the following observations:

1. We identified four cases whose handling we consider to be completely unacceptable. All four of these cases are rosiglitazone cases; the mishandlings of all four favor rosiglitazone. We have provided the relevant CRFs for these cases in Appendix 1, Cases A-D. We briefly summarize the mishandlings below:
 - A. An MI SAE was deleted 16 months later and never referred for adjudication; four other events were also not referred for adjudication
 - B. A non-CV death was adjudicated that terminated a 46-day hospitalization with admission for pulmonary edema documented only in a short, one page letter—from a UK hospital; the hospitalization for pulmonary edema was not adjudicated
 - C. An intracerebral hematoma was deleted from an SAE initially reported as epilepsy and intracerebral hematoma; an adjudication dossier was prepared but not submitted despite that fact that the neurologic exam documented focal neurologic signs and the intracerebral hemorrhage was documented on CT scan
 - D. No information was obtained regarding a 67-day hospitalization for a severe stroke; the stroke was adjudicated as non-CV

We have attempted to classify the nature of the mishandlings. For cases A through C the major failures were failure to refer events for adjudication; case B also exhibited a failure to collect sufficient information as did case D as the primary failure. Both types of failures were due to study personnel who were aware of the treatment assignments.

2. We identified other problem cases among all of the 549 CRFs that we reviewed. We summarize the numbers of cases with problems in Table 1.

Table 1: Summary of CRF Reviews

	rosiglitazone		control	
	n	%	n	%
randomized & treated - GSK "ITT"	2220	100%	2227	100%
CRFs reviewed (total 549)	278	13%	271	12%
CRFs with problems	45	2.0%	25	1.1%
favoring rosiglitazone	44	2.0%	13	0.6%
favoring control	1	0.05%	12	0.5%
overall which arm is favored	57	10.4% of 549	13	2.4% of 549

The control case problems are evenly distributed between ones favoring rosiglitazone and ones favoring control. The rosiglitazone problem cases almost exclusively favor rosiglitazone and there are more rosiglitazone problem cases than control problem cases. Hence the net favoring of rosiglitazone exceeds 4:1. Note, however, that our overall CRF sampling was not random—see subsection 3 below for results of a random sampling.

We tried to characterize the nature of the problem cases. While for at least 8 of the cases we judged that several factors contributed to the nature of the problems or that there were multiple problems for a single patient, we selected what we judged to be the most contributory single factor. We show these primary factors in Table 2.

Table 2: Primary Factors for Problem Cases

	favors:	
	rosiglitazone	control
adjudication issue	22	4
insufficient information	18	4
missed event	9	5
not referred for adjudication	8	0

Adjudication issue, insufficient information, and not referred for adjudication are self-explanatory except for this comment: Adjudication issues may be related to insufficient information or the “high bar” that the CEC appears to have used that we discuss below. “Missed event” refers to a CV event that we noted in a discharge summary or other non-CRF document and that was not documented in the CRFs and not referred for adjudication—the event may have occurred in the past or during the same hospitalization.

All factors were more frequent for cases favoring rosiglitazone. The lowest ratio favoring rosiglitazone was for missed events while, at the other extreme, failures to refer for adjudication occurred only in the rosiglitazone arms.

While the absolute numbers of patients with problems appears small compared to the total number of patients in the GSK “ITT” population (4,447), the better comparison is to the number of events needed to change the significance of MI results. We count 120 adjudicated MIs (64 rosiglitazone, 56 control) in the GSK “ITT” population for a relative risk of about 1.14 and a p value by chi square of >0.2 . Only about 15 more MIs in the rosiglitazone arms are needed to change the results to a relative risk of 1.4 and a p value of 0.042. We count 25 patients with a potential MI and questionable handling favoring rosiglitazone.

3. To check for problems other than CV events and to provide statistical estimates of the extent of problems, we reviewed a stratified random sample of 100 CRFs (50 rosiglitazone, 50 control) from the CRFs routinely submitted, i.e., deaths and discontinuations (71% of patients). We show the results of our review in Table 3.

Table 3: Summary of Random Sample CRF Review

	rosiglitazone		control	
	n	%	n	%
routinely submitted CRFs	1561	100%	1586	100%
CRFs reviewed	50	2%	50	2%
CRFs with problems	4	0.2%	5	0.2%
favoring rosiglitazone	4	0.2%	2	0.1%
favoring control	0	0.0%	3	0.1%
overall which arm is favored	6	6% of 100	3	3% of 100

Please note that these CRFs reviewed and problems are also included in subsection 2 above. We had already reviewed some of the randomly sampled CRFs by the time we performed the random sample.

For this random sample the numbers of CRFs with problems were relatively evenly distributed between rosiglitazone and control. However, similar to the results of our reviews based on potential for problems, the control case problems were neutral with regard to favoring rosiglitazone while the problems with the rosiglitazone cases all favored rosiglitazone.

The ratio of problems favoring rosiglitazone to those favoring control for the random sample is 2:1 compared to about 4:1 for all CRFs reviewed. This may reflect random variations in small numbers or that our targeted CRF selections did identify bad cases more frequently in the rosiglitazone arms. The problem cases identified in this random sample appear to be less serious than those from our targeted samples. We classified the problem cases into more serious and less serious. For the targeted samples excluding the random sample about 18% of the cases were less serious, while for the random sample 40% of the cases were less serious. Note that, because of the small size of our random sample, all of the estimates from the random sample have wide confidence intervals.

Because the frequency of cases with problems in this random sample was 9%, we probably have not identified all cases with problems: We would expect about 283 problem cases from among the patients with routinely submitted CRFs (deaths and discontinuations) while we have only identified 70 problem cases with our completed reviews of CRFs.

From our random sample we identified another major problem not related to endpoint determination: ascertaining the end date of CV follow-up. We discuss follow-up date issues in Section 3.6.

The open label issues are ones related to how the unblinded study participants handled individual patients. A set of related issues is the unblinding, and timing thereof, of the sponsor regarding interim study results. The press has published summaries of the unblinding issues prior to the interim publication and a Senate report presents the details. Because we can only speculate how any such potential unblinding may have affected the trial conduct, we do not discuss it in this review.

3.2 Failures to refer events for adjudication

Because RECORD was open label, the threshold for the unblinded investigators and the unblinded monitors to refer cases to the blinded CEC should have been very low. Hence in our reviews of CRFs for deaths, strokes, heart failure, and MIs we scrutinized the CRFs for failures of the site or the monitor to refer possible events for adjudication. We identified the failures to refer events listed in Table 4.

Table 4: Failures to Refer Events for Adjudication

#	Description
1	MI SAE deleted 16 months later not adjudicated; four other events, including also not adjudicated; see Appendix 1 Case A
2	hospitalized for pulmonary edema 46d not adjudicated; death from pneumonia terminating hospitalization adjudicated not CV; see Appendix 1 Case B
3	intracerebral hematoma deleted from SAE & reported as epilepsy alone & not adjudicated despite hospitalized 40d with focal signs on neuro exam and hemorrhage on scan; see Appendix 1 Case C
4	hospitalized 10d for HF with edema, EF 45% & hypokinesis on echo, new rx torsemide, study drug discontinued
5	hospitalized 13d for MI starting 21apr05 not adjudicated because confused with 8d hospitalization for HF 16-23may05 adjudicated not CV because insufficient information
6	hospitalized 18d for "collapse" attributed to afib not adjudicated; chronic afib on warfarin but hospital discharge summary, INR not provided; see Appendix 1 Case N
7	hospitalized 5d for digit amputation and 9d for peripheral artery disease '03 not adjudicated; died postop sudden onset heart failure '05 adjudicated not CV
8	hospitalized 5d for facial paralysis with cat scan done to detect stroke not adjudicated

While eight cases of failure to refer for adjudication may not seem to be a large number, please note the following:

- All of these failures were in the rosiglitazone arms.
- The number of additional MIs needed to change the relative risk of MI for rosiglitazone vs. control to clinically significant is about 15. This one problem potentially provides 4 of those MIs (cases #1, 2, 4, and 5)—and the post-op death for #7, adjudicated but adjudicated non-CV, is a potential 5th. Three cases (#3, 6, and 8) are relevant to stroke comparisons.
- Both investigators and monitors appeared to be comfortable with making endpoint determinations on complex and confusing cases. The data query (CRF N3 in Appendix 1) for case #6 in **Table** documents this problem. In an email exchange between monitors one closes out the case with this statement: “I have just spoken to [redacted] who, in turn, has spoken to Dr. [redacted] at the site and this has been confirmed as NOT being an

endpoint but a SAE.” Investigators should not have confirmed potential endpoints as not endpoints and monitors should have recognized investigators’ uncertainties and referred for adjudication all uncertain but potential CV events.

The following GSK response in (b) (6) to one of our questions documents how convoluted the decision not to refer obvious events for adjudication could be:

“FDA Request 6: Patient [redacted]: This patient had an adjudicated endpoint for a right carotid endarterectomy on (b) (6)

a. This patient had an AE of stroke, which the site changed to left hemiparesis, on (b) (6). The discharge summary mentions this stroke as well as a TIA in (b) (6), while the site reported transitory brain ischemia on (b) (6). Why was the stroke not pursued as an SAE?

Response: For this case, the Quintiles monitor brought a potential un-reported endpoint to the investigator’s attention. Please see the attached Site Monitoring Visit report fo 25-26 Dec2007 in the supporting documentation for patient [redacted], which states:

“Patient [redacted] has left hemiparesis due to vasoconstriction since 02Nov2007 and investigators are going to refer him to vascular department for hospitalization; CRA instructed site to follow this patient for possible Endpoint.” Please also see the next Site Monitoring Visit report for 29 Feb 2008 (also attached in the supporting documentation for patient [redacted]), which states:’ - [redacted] – SAE and Endpoint reported according to requirements on 01Feb2008 to CRA, GCSP, CEC and GSK. “

From review of the chronology of events, the investigator classification of the event evolved from an initial identification of an AE of TIA to a more precise diagnosis of an AE of left hemiparesis following medical assessments and then later to an even more precise diagnosis as an SAE of right internal carotid stenosis (which is a single event that was assessed at different timepoints). Therefore, the site eventually reported the event as an SAE, under the verbatim of “right internal carotid stenosis.” (SAE pages in the supporting documentation for patient [redacted]). The event was adjudicated as an invasive CV procedure. The discharge summary was available to the Clinical Endpoint Committee when they adjudicated this event.”

- If the investigator decided that a hospitalization was not an endpoint, the site would collect and record little information on the hospitalization, i.e., only the dates of hospitalization and the relationship to diabetes on the Medical Care Utilisation CRFs. If an adverse event prompted the hospitalization then the investigator should also have recorded an SAE. For MIs and strokes SAEs should have been reported routinely but the same was not true for CV procedures—for the last two years of the trial CV procedures were officially not reported as SAEs per Protocol Amendment 7 dated 27 February 2006.
- Note that among the 8 cases in **Table** that we selected based on death, MI, stroke, or HF events, one of the cases (#7) has two CV procedure events not adjudicated. Failure to refer is likely more problematic for potential CV procedure events than for MIs, strokes, and deaths. However, we did not audit CV procedures systematically because, being problematic for many reasons, we did not include them in our primary endpoint. Furthermore, because of protocol and MedDRA SAE reporting issues for procedures, we

Failure to refer events for adjudication has the potential for affecting MI and stroke rates to a non-ignorable level. Its detrimental impact upon complete ascertainment is likely worse for the GSK primary endpoint including CV procedure hospitalizations than it is for MACE as discussed above. We do not understand why GSK appears to have been reluctant to encourage a low threshold for referring potential events for adjudication and instead relied upon an initial adjudication by unblinded investigators and monitors: The CEC Charter states in Section 3.1 that “The total number of expected cases to be reviewed is approximately 5000.” The CEC ultimately adjudicated 1643 events.

3.3 All hospitalizations not recorded and characterized

Given a primary endpoint including CV hospitalizations, we would consider it highly desirable to record the dates and reasons for all hospitalizations and the occurrences of any CV complications during the hospitalizations. Such a record would provide a valuable means of checking whether the referrals for adjudication of CV hospitalizations were complete both by the study monitors and by us.

The protocol does not mention a hospitalization CRF just as it does not mention other forms not routinely completed at one or more types of visits, i.e., CRFs that are event dependent rather than routine. It does not specifically address collecting hospitalizations with the following exceptions:


- Collecting cardiovascular hospitalizations, one component of the primary endpoint, during the entire study is mentioned in many sections throughout the protocol.
- Collecting dates of hospitalizations is required by the protocol specification of completing medical care or healthcare utilization assessments or questions at all visits. All of the Medical Care Utilisation CRFs have fields for dates of admission and discharge and for relationship to diabetes. (The CV outcomes phase CRFs have a field for reason for hospitalization in the BLANKCRF.PDF file originally submitted but GSK confirmed that the CRFS with reason for hospitalization were not used.)
- Protocol Section 3.2.2. Patients who Withdraw from the Randomised Treatment Phase of the Study has the following specification in all versions: “Between annual visits a telephone visit will replace all other clinic visits. During the telephone visit, the investigator will ask the patient about the incidence of hospitalisation for a cardiovascular event, and a number of Healthcare utilization and Indirect Economic Costs Assessments.” There is no similar specification regarding annual visits.

The hospitalization CRF itself states that the investigator was to complete the form for all hospitalizations and emergency department visits as shown in Figure 2.

Figure 2: Hospitalization CRF

Information on this page was not databased

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SmithKline Beecham
 Pharmaceuticals

Page HAE01

Protocol	Centre Number	Patient Number	Patient Initials	Endpoint Number	Hospitalisation / A&E Visit Endpoint Form
49653/231	<div style="display: flex; justify-content: space-around; width: 100px;"><div></div><div></div><div></div></div>	<div style="display: flex; justify-content: space-around; width: 100px;"><div>0</div><div>0</div><div>0</div><div>0</div><div>0</div></div>	<div style="display: flex; justify-content: space-around; width: 100px;"><div></div><div></div><div></div></div>	<div style="display: flex; justify-content: space-around; width: 100px;"><div>E</div><div></div><div></div><div></div><div></div></div>	

HOSPITALISATION OR ACCIDENT AND EMERGENCY DEPARTMENT VISIT ENDPOINT FORM

This form should be completed for all patients who were hospitalised or attended an Accident and Emergency Department during the course of the study. Please complete an SAE form ensuring details remain consistent. (Please note : the admission date must be different from the discharge date, except for unplanned ambulatory percutaneous intervention). Please enter details below :

When queried about when hospitalization CRFs were to be completed, GSK responded in (b) (6) as follows: “According to the protocol and the procedures agreed with the CEC, the HAE1-2 forms were only mandatory for CV hospitalizations or hospitalizations resulting in deaths. The HAE pages were designed to facilitate endpoint adjudication and therefore only reported for hospitalizations that could constitute an endpoint.” The GSK explanation does not appear to be consistent with the hospitalization form, while the protocol is ambiguous as we described above. However, GSK’s response does appear to correspond to what was submitted for the study. In the submitted CRFs we found hospitalization CRFs only for hospitalizations submitted for adjudication or planned to be submitted.

The one cross-check we are able to do is comparing the adjudication dates to the hospitalization dates from the Medical Care Utilisation forms. During the randomized treatment phase, we could not match about 4% of the endpoints to hospitalizations, virtually identical in the pooled rosiglitazone and control arms. During the CVO/TSS phase we could not match about 7% in the rosiglitazone arms and 9% in the control arms. (The CVO/TSS phase was the phase following the randomized treatment phase during which SAEs but no AEs were collected and patients were followed for endpoints. CVO references patients who were directly entered into this CV follow-up while TSS references patients who had discontinued early but were later entered into the Tracking Substudy.)

Conversely, about 28% of the hospitalizations had matching adjudicated events and this rate varied little by treatment phase or arm. Hospitalizations/100PEY were slightly higher during the CVO/TSS phase and in the rosiglitazone group (20.6 vs. 18.5) than during the randomized treatment phase (14.3 vs. 15.2). Adjudicated CV hospitalizations/100PEY were similarly higher in the CVO/TSS phase than in the randomized treatment phase (5.9 vs. 3.7) but were not differentiated by treatment arm. Note that entry into the CVO/TSS was not randomized so any statistics regarding it are difficult to interpret.

Of these statistics we have minor concerns that 9% of the control endpoints can’t be matched to a hospitalization and that the overall hospitalization rate may be slightly higher for the rosiglitazone patients in the CVO/TSS phase. However, our major concern is that we are unable

to verify that referrals of possible CV hospitalizations were complete based on comparison to a complete and accurate collection of hospitalization dates and reasons.

3.4 Adjudication issues

For adjudications we are primarily concerned with adjudications for CV death, MI, stroke, and heart failure. We believe that the GSK primary endpoint including CV hospitalizations is undesirable for reasons we discuss in Appendix 2 and not susceptible to verification and likely invalid as we discuss elsewhere in this Appendix.

We discuss several general issues with adjudication in Appendix 4 Adjudication Comments. Here we discuss adjudication issues that we have identified from reviewing the data. For discussion we have grouped the adjudication issues into five categories: (1) “high bar” for deaths; (2) missed endpoints; (3) insufficient information; (4) adjudication disagreements; and (5) delayed adjudications.

1. “High bar” for deaths. The endpoint definitions in the protocol and in the CEC Charter are not unreasonable (except for some issues we have identified in Appendix 1.) However, while they are largely reasonable they are not operational definitions that can be applied objectively. The lack of objectivity is easiest to illustrate by the protocol definition of unknown death: “Deaths which are due to unknown causes (and therefore cannot be categorised 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.” So, how much information is needed to categorize a death as something rather than unknown? Three “unknown” deaths illustrate how high an undefined bar the CEC set for some cases. We summarize these deaths briefly in Table 5.

Table 5: Drowning and Accidental Fall Deaths Adjudicated as Unknown

#	Description
1	died unwitnessed while swimming at a public beach adjudicated unknown; drowning confirmed on autopsy with mild generalized atherosclerosis seen in coronaries, aorta, and cerebral arteries, drug concentrations within therapeutic ranges but autopsy results obtained late and not provided to CEC; see Appendix 1 Case O
2	died from fall from roof while painting; SAE term was "accidental fall" & narrative states "call today from daughter saying pt died from an accident"; the initial two adjudicators disagreed and the full committee adjudicated unknown
3	drowned while swimming; taken to the local hospital where the clinical and autopsy-verified cause of death was drowning; full committee adjudicated unknown

Note that the two drowning deaths were confirmed on autopsy. The accidental fall death is referenced consistently as an accident and occurred in a setting (painting on a roof) where accidents are not rare. GSK counted all unknown deaths, including these, as CV. We judge the deaths in Table 5 to be non-CV. We observe that all three of these deaths were in control patients.

For deaths the “high bar” for causality and the stipulation that all unknown deaths are CV deaths led to more deaths—and even non-CV deaths—being classified as CV. For a superiority study we would accept this as reasonable and, while perhaps introducing noise, closer to our preferred superiority endpoint: all cause mortality. For a non-inferiority study we consider the added noise to be undesirable and biasing towards the null, i.e., non-inferiority. For MIs and strokes the CEC also appears to have applied a “higher bar” than we did—see Appendices 6 and 7. Hence this reduced the relative contribution of the “harder” MI and stroke events to the GSK composite endpoint compared to the “softer” CV hospitalization events. We estimate that this also biased towards the null.

There is another implication of setting a “high bar” for death that also applies to the MI definition: Adjudications are more likely to be biased due to the lack of availability of data provided to the CEC (see case #1 in **Table**) for “high bar” interpretations than for “lower bar.” The CEC charter definition required hospitalization PLUS elevated biomarkers PLUS ischemic chest pain or ECG changes. Hence having or not having biomarkers usually determined the adjudication decision. We usually found biomarker measurements at a single undefined point in time. Troponins are not available in many cases and biomarkers for chest pain admissions are frequently absent. CEC MI adjudication may have been more dependent upon the reporting of biomarkers than the clinical presentation. The use of biomarkers appears to be one clinical practice at the RECORD sites that differs dramatically from US practice; unfortunately it is one that is critical for the accurate diagnosis of MIs.

2. Missed endpoints. By missed endpoints we mean additional findings described on any acquired clinical document, typically a hospital discharge summary, that are potential endpoints not specifically reported as such by the site. There appears to have been inadequate follow-up on such findings by the monitors or by the CEC. We have included below, from (b) (6), responses by GSK regarding two cases of missed potential endpoints:

“FDA Request 11: Patient [redacted]: This patient had an 18d hospitalization for acute heart failure on (b) (6) following two shocks for vtach. The discharge summary lists a suspected MI.

a. Why was this hospitalization also not submitted for adjudication as a MI?

Response: Two endpoints have been reported and adjudicated for this hospitalization – Congestive heart failure (E[redacted]) – adjudicated as a CHF, and death (E[redacted]) – adjudicated as a Death - Cardiovascular - Death following heart failure. It is the Investigator’s clinical decision to report suspected MI or not. The discharge summary of the hospitalization, including the description of shocks for Vtach prior to hospitalization as well as EKG and CPK-MB results and the listing of the suspected MI, were available for CEC review during their adjudication of this hospitalisation. . .

FDA Request 14: Patient [Appendix 1 Case P]: This patient had an other CV endpoint for an angina hospitalization in (b) (6) adjudicated as atrial fibrillation.

a. The discharge summary clearly describes the afib starting intermittently in (b) (6) with a stroke occurring during one of the attacks. It does not describe a neuro exam but does

state that exercise testing could not be done due to the post-stroke condition. Why were details on the stroke not sought?

Response: The investigator did not report the stroke as an adverse event or an end point. A full data package including the discharge summary, was sent to the CEC paired reviewers for adjudication, resulting in a consensus of OTHER CV event. The CEC paired reviewers did not request additional information or query additional endpoints.

b. Only one hospitalization is reported. Why was a query regarding a stroke hospitalization not done?

Response: A full data package including the discharge summary, was sent to the CEC paired reviewers for adjudication, resulting in a consensus of OTHER CV event. However, the CEC paired reviewers did not request additional information or query additional endpoints.”

Note that in the GSK response to the FDA Request 11 above, GSK relied upon the decision of the unblinded investigator regarding whether a suspected MI should be reported. While relying upon the unblinded sites for many trial activities is unavoidable in an open label study, we believe that GSK should have stressed that investigators, and all other unblinded staff, should apply very low thresholds for referring events to the CEC. Furthermore, all staff involved in the study and reviewing or checking clinical documents should have checked for potential missed events.

For both cases GSK also depended primarily upon the CEC to identify additional events to be adjudicated. Because the CEC adjudicated events with frequent long delays after their occurrence and with dispersed submission dates for some temporally close events in the same patient, we believe that the CEC was not the best mechanism for catching missed endpoints. The two cases above and the other missed endpoints we have identified are confirmatory that the GSK processes for capturing potential endpoints were less than optimal.

We identified 14 patients (9 rosiglitazone and 5 control) with missed endpoints. We scrutinized the records for these patients and assigned endpoints when we judged the information available to be supporting. Because study personnel had not solicited the required information for these potential endpoints, we did not follow rigidly the CEC Charter definitions. See also our Adjudication Comments in Appendix 4.

We do not summarize all of the missed endpoint cases in this section. What we have done instead is summarize in separate appendices the cases of CV death, MI, and stroke endpoints that we adjudicated differently than the CEC. We summarize CV death endpoint differences in Appendix 5, MI differences in Appendix 6, and stroke differences in Appendix 7. This approach applies to all of the subsections of this Section 3.

3. Insufficient information. We have already presented one example of extremely insufficient information: Case D from Appendix 1 referenced in Section 3.1 of this Appendix. The short summary of Case D is as follows: No information was obtained regarding a 67-day hospitalization for a severe stroke; the stroke was adjudicated as non-CV. Missing or insufficient information is common in clinical practice and, for complex

adjudications, in clinical trials. We focused on identifying blatant examples of missing information, such as Case D, and cases for which the missing information was supposed to have been submitted and the lack of the information was critical for MACE endpoint adjudication. We summarize two additional examples below and provide the relevant CRFs for them in Appendix 1:

- Case Q: This patient was hospitalized for a ventricular arrhythmia and died on (b) (6). However, virtually no other information was collected, the discharge summary and death certificate were not obtained, and the death was adjudicated as unknown. The most detailed explanation of the event was a cryptic, undated note to file stating that the patient had suffered from the ventricular arrhythmia for years. (Q1) This death could have represented an MI and all required documentation for a hospitalization and for an MI should have been obtained. (This case also illustrates the problems with end of CV follow-up dates—see Section 3.6.)
- Case R: This patient was adjudicated as having an MI during a (b) (6) hospitalization for pneumonia based on elevated CK and troponin. However, the discharge summary is from a later rehabilitation hospitalization. (R1) The MI endpoint form provides the CK and troponin values without normal limits and reports that there were no typical ischemic symptoms and no other diagnostic tests (R2) No ECGs (other than baseline) or ECG reports were obtained. The correct discharge summary should have been obtained.

In the CRFs we reviewed we identified 22 cases (16 rosiglitazone and 6 control) for which inadequate information affected the adjudication. Of these, the bias favored rosiglitazone in 18. Inadequate information, like failure to refer, appears to be a mechanism biasing endpoints in favor of rosiglitazone.

4. Adjudication disagreements. Adjudication of CV events is an art based on evaluating inadequate information. We expect some disagreements even between unbiased reviewers, whether the CEC and us or one initial CEC adjudicator and the other. In fact, GSK tracked the disagreement rate between the initial CEC reviewers and provided a flag for reviewer disagreement in the adjudication data set. Per GSK records the initial reviewers disagreed for about 41% of potential endpoints adjudicated. Note that this percentage reflects disagreements on the CV endpoint categories, not on whether an event was CV or not.

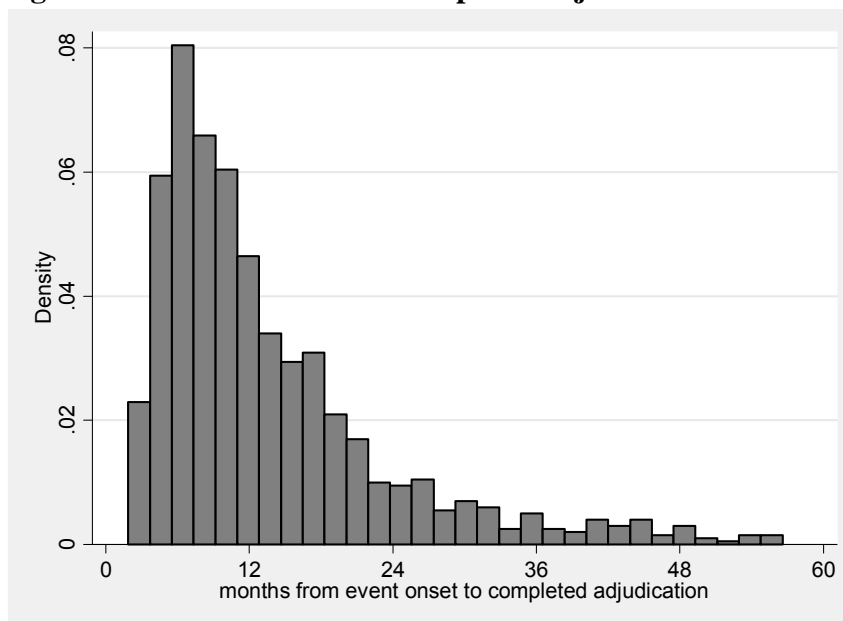
We have already presented several of the cases for which we disagree with the CEC adjudication. The two drownings and one accidental fall are deaths that the CEC adjudicated unknown but that we adjudicate non-CV (see subsection 1 above.) The other highly relevant case is Case R presented in Section 3 regarding insufficient information. We adjudicate the event as not an MI because biomarker elevations alone do not justify an acute MI diagnosis by the CEC Charter definition based on the 2000 international standard or by the 2007 universal definition that we use. The CEC Charter MI definition explicitly requires either ischemic symptoms or ECG changes in addition to the

biomarker elevation. The alternative expressed in the international and universal definitions is to have an appropriate pattern of biomarkers rising and falling. Please note, however, that pneumonia alone (as this patient had) has been reported to be associated with troponin elevations. This patient also had renal failure, another condition associated with troponin increases. We do not deny that this patient may have suffered an MI as his health care providers diagnosed. Regardless, by either the CEC Charter or the universal MI definition the event should not be adjudicated as an MI.

Case R illustrates the difficulty of adjudicating cases particularly when critical information is not collected. However, Case R is actually the only MI endpoint that the CEC adjudicated positive and that we adjudicate negative. The rest of our MI disagreements are events that the CEC either called negative or did not adjudicate. As we stated earlier, we tabulate our MI adjudication disagreements in Appendix 6, our CV death disagreements (such as the drownings and the accidental fall) in Appendix 5, and our stroke disagreements in Appendix 7. Our adjudication disagreement cases are relatively evenly distributed between rosiglitazone and control (12 vs. 14) but the CEC adjudications heavily favor rosiglitazone compared to ours (22 vs. 4).

5. Delayed adjudications. Potential endpoint events were not always referred to the CEC promptly and the CEC did not always adjudicated events promptly. For events adjudicated as CV—the ones for which we have an adjudicated onset date for the event—the median time to completed adjudication was about 11 months with a distribution as shown in Figure 3.

Figure 3: Distribution of CV Endpoint Adjudication Times*



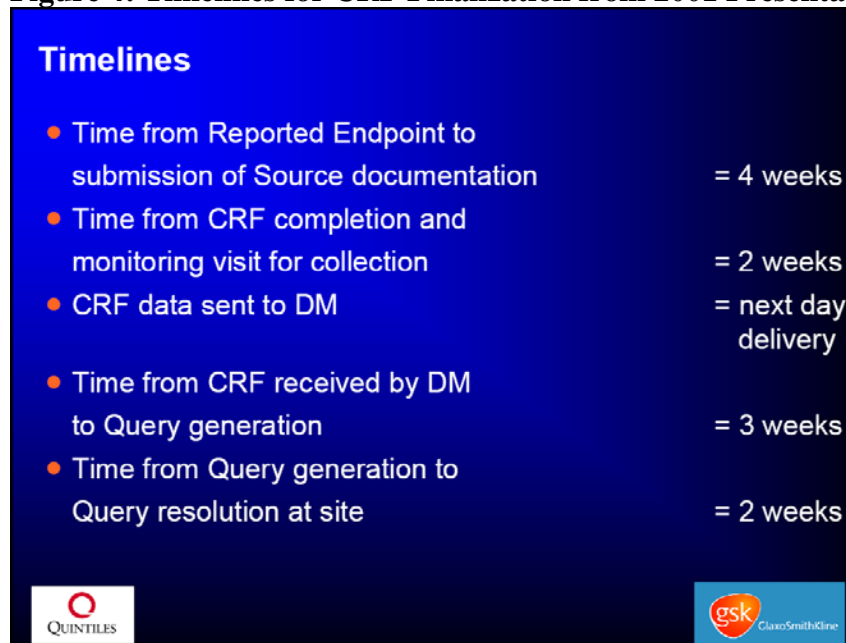
*Excluding 32 cases exceeding 60 months to adjudicate

We could not find anything in the study documentation regarding goals for completing adjudications, although we did find several statements in the Steering Committee Minutes

regarding delays in adjudication. The following ones from the minutes dated 23 November 2006 are representative: “The letter also informed PH that the DSMB considered that the length of time to final adjudication of the clinical endpoints is unacceptably long” and “The number of events adjudicated since last meeting has increased, and there has been a good reduction in the endpoint dossier preparation time [backlog in dossier preparation reduced to approx. 5 months by end of 2006]”.

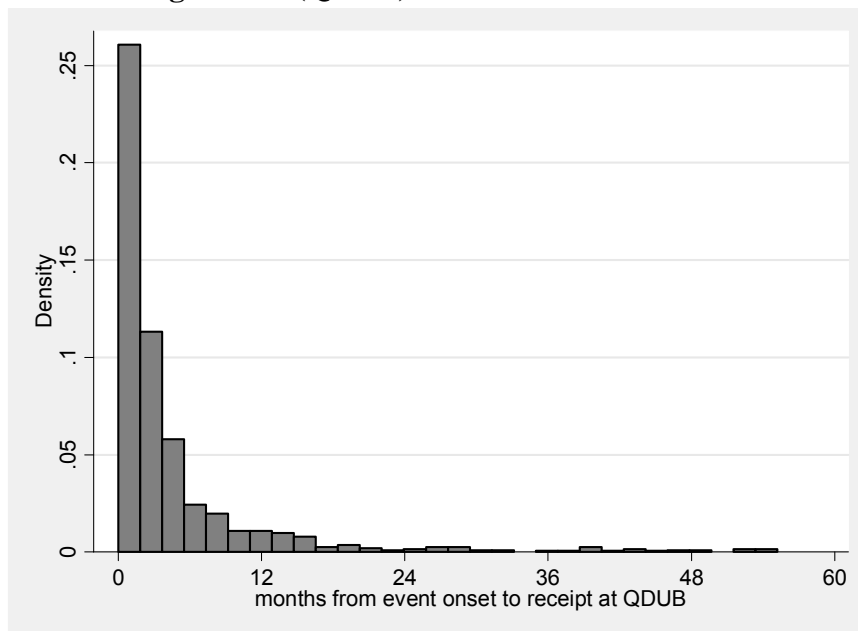
The protocol and other investigator materials had ambitious goals for the speed with which sites were to report events. Per the protocol sites were to report serious adverse events (SAEs) within 24 hours. Per the Clinical Endpoint Manual “Endpoint forms and source documentation associated with the forms must be sent by the investigator to the Quintiles CEC Co-ordinating Centre or to the Site Monitor within a maximum of 2 weeks from the point that the investigator reports the SAE.” The sites were to complete all CRFs per these protocol specifications: “When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days.” The 2001 presentation to investigators specified the timelines shown in Figure 4.

Figure 4: Timelines for CRF Finalization from 2001 Presentation to Investigators



The goals for completion of CRFs were ambitious. We do not have data on all of the steps listed in Figure 4. We do have data on the lags from CV endpoint event onset to receipt at QDUB, the CEC Coordinating Center. We show the distribution of these lag times in Figure 5.

Figure 5: Distribution of CV Endpoint Event Receipt Times at the CEC Coordinating Center (QDUB)



*Excluding 7 cases exceeding 60 months to receipt at QDUB

The median time for receipt of a CV endpoint event at QDUB was about 2 months while the 90th percentile was about 1 year, i.e., about 10% of the events were received at QDUB a year or more after the event occurred. The time distribution in Figure 5 is better than that in Figure 4. However, the two figures suggest that there were problems with delays in handling cases both at the sites and at the QDUB.

Besides providing evidence that the study was not conducted well, delayed adjudication is undesirable because it can contribute to inaccurate adjudication if the adjudication package is incomplete. It decreases the probability of success for obtaining useful responses to queries about the events being adjudicated and for getting complete information on events missed by the sites. Insufficient information for adjudication and missed endpoints are problems that we have observed in RECORD and documented above.

3.5 Endpoint definition clarifications

The CEC clarified or analyzed several endpoint definition issues during the course of the trial. We discuss some of them, such as the definition of endpoint dates, in Appendix 2 Protocol Comments. We believe that three of the issues are worth examining with regard to the trial results. These three endpoint issues are the following:

1. Unknown deaths counted as CV deaths. The original protocol dated 7 February 2001 had this statement: “Deaths which are due to unknown causes (and therefore cannot be categorised into the categories listed below), but which have a high probability of being related to a cardiac/vascular event, will also constitute cardiovascular deaths.” At the recommendation of the CEC Protocol Amendment 1 dated 3 October 2001 changed this

statement to “Deaths which are due to unknown causes (and therefore cannot be categorised into the categories listed below), will be classified as 'unknown deaths'. The CEC cannot adjudicate the deaths for unknown causes as being cardiovascular as this is basically a statistical exercise.” Protocol Amendment 7 dated 27 February 2006 changed the statement further: “Deaths which are due to unknown causes (and therefore cannot be categorised 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.”

Hence the documentation of the decision to count unknown deaths as CV deaths was done after all enrollment was done and substantial follow-up was completed. As we discuss in Appendix 4 Adjudication Comments, we believe that we should count unknown deaths as CV only if they are sudden unknown deaths. We also applied a “lower bar” (see Section 1) than the CEC did for assigning a cause of death. We classified 15 cases adjudicated as unknown deaths by the CEC as non-CV deaths. Five of the 15 cases were rosiglitazone and 10 were control, a 2:1 ratio favoring rosiglitazone based on the late clarification classifying all unknown deaths as CV deaths.

2. No adjudication for non-urgent procedures and non-specific symptoms. CEC Charter Amendment 1 dated November 4, 2003, clarified that two categories would not in the future be adjudicated as endpoints:
 - “non-urgent/routine cardiovascular investigations and procedures not driven by emergency situations, new onset or aggravation of symptoms (e.g., coronary angiography even when followed by angioplasty, PM implant, peripheral angiograph or plasty, ICD implantation, carotid angiography).”
 - “non-specific symptoms without definite cardiovascular origin such as e.g., atypical chest pain without ECG or enzyme change, rise in blood pressure without any sign of hypertensive emergency, dyspnea of unknown origin, fainting episodes or bradycardia without any further documentation.”

We believe this change exacerbated two problems. They are the following:


- While the CEC Charter statement tries to provide some guidance regarding what constitutes “non-urgent”, the decision regarding urgency remains very subjective. The subjectivity and variability are illustrated by the accidental duplicate adjudication of two events by the CEC: A hospitalization in 2006 for a history of angina culminating with a PTCA was adjudicated as non-CV in 2006. It was resubmitted in 2008 and adjudicated as a CV procedure. A different patient had bilateral carotid stenting at two different hospitalizations. The left carotid stenting was adjudicated in 2006 as a CV procedure and in 2008 as non-CV. Interpretation of non-specific can also be difficult.
- The initial decision about what was “non-urgent” and “non-specific” was made by the unblinded investigator. If the investigator decided that one of these terms applied, then the hospitalization would not be referred for adjudication and little information would be captured. This problem was not limited to the non-urgent and non-specific category but include any CV hospitalizations that fell into the “other” category. For example, one investigator asserted that pulmonary embolism was not a CV endpoint—see Figure 6.

Figure 6: Note to Record That Pulmonary Embolism is Not a CV Endpoint

The PI confirmed that the primary reason related to this death is non cardiovascular and is Steady-state disorder related to aggravation of ongoing multiple sclerosis disease

The PI confirmed again that SAE Bilateral Pulmonary embolism is not a cardiovascular endpoint but a vascular event, that the SAE Bronchial infection with hyperthermia is not a cardiovascular endpoint but a pulmonary event.

Signed by


Senior CEVA Co-Ordinator
Clinical Event Validation
& Adjudication Services (CEVA)
CEC co-ordinating centre, Quintiles,
Dublin

18/22/2005
Date

The Senior CEVA Co-ordinator appears to accept this error, although the CEC ultimately adjudicated the event as other cardiovascular, pulmonary embolism.

The difficulty of adjudicating non-urgent, non-specific, and other CV events and the reliance upon unblinded investigators to make the initial determination reinforces our belief that the GSK primary endpoint including CV hospitalizations is less desirable than the MACE endpoints.

3. Silent MIs. The Steering Committee (SC) discussed the issue of including silent MIs in the MI endpoint definition as follows as documented in the SC Meeting Minutes:
 - a. 11 August 2000: The consensus was to record them as adverse events and analyze them as part of a secondary endpoint of all fatal and non fatal MI.
 - b. 21 February 2003: The SC discussed that silent MIs were being reported as an ECG abnormality on the yearly ECG but they were not being captured as endpoints.
 - c. 20 October 04: The SC agreed that a pilot study by GSK/Quintiles for reviewing ECGs (baseline vs. year 2) for the first 1,000 patients enrolled should go ahead.
 - d. 3 November 2005: The pilot study results were presented. 2 new MIs were identified from 640 analyzable ECG pairs.
 - e. 9 May 2006: The SC discussed a draft manuscript on the sMI results.
 - f. 23 November 2006 – 22 April 2008: The SC periodically discussed a draft paper that was scaled back to a letter.

The SC Meeting Minutes do not record any discussion about silent MIs as endpoints after 20 October 04. We proposed not counting silent MIs as MIs for the primary endpoint in our Review Plan. We will follow the recommendation of the SC and include them in secondary analyses.

We did try to capture all silent MIs reported as AEs or noted in hospital discharge summaries. We identified 15 silent MIs, 14 in patients who did not have a symptomatic

MI reported. Nine of the silent MIs were in the rosiglitazone arms and 5 in the control arms.

3.6 Errors in end of CV follow-up dates

For performing survival analyses such as those GSK uses for its primary endpoint analyses one needs only two post-randomization pieces of information for each patient: (1) whether the patient experienced the endpoint; and (2) the censoring date. For patients not experiencing the endpoint—usually the vast majority of patients—the censoring date for the GSK primary analyses is the end of CV follow-up date. We examined problems with the endpoint determination in the previous sections in this Appendix. We describe below substantial problems in RECORD with errors in the end of CV follow-up dates.

The original protocol specified that sites do quarterly patient visits while the patient was in the randomized treatment phase and then annual patient visits interspersed with quarterly phone contacts while the patient was in CV follow-up. All patients (except those in survival follow-up only) were to have study completion patient visits. However, Amendment 7, dated 27 February 2006, Section 3.4.1 relaxed the frequency of patients visits: “If it will help to retain a patient in the study, the investigator can modify the frequency and schedule of assessments in the CV Outcomes phase (Post-Randomised Treatment Phase) to a ‘modified schedule’ agreeable to the patient. For example, the annual clinic visit could be optional and the patient contacted only by telephone (ideally every 4 months, but this is flexible and the frequency of contact can be increased or decreased to fit in with the patient).” The unblinded investigator could decide the frequency and types of visits.

This amendment, the designs of some CRFs, and date recording and data extraction errors caused problems with the ascertainment of the end of CV follow-up dates.

- The Study Continuation (Conclusion)/Withdrawal CRFs had fields for “Date of final clinic or telephone visit”. However, they had no fields to identify the type of last contact or whether the patient had been willing to provide detailed information about possible endpoints and medications.
- The routine CRFs for visits were pre-printed with the type of visit, i.e., clinic or phone contact, based on the protocol visit schedule. If the investigator changed the nature of the visit, the CRFs did not have field to indicate the type of visit.
- Investigators did not complete all visit CRF sections at all contacts. Sometimes they marked the sections “not done” but such annotations were not routine and not captured in the SAS data sets. Some “visits” appear to correspond to these “not done” CRFs.
- Investigators not infrequently discovered or documented a withdrawal months after its occurrence. Errors in recording last visit dates were not uncommon. The problem of date errors and the uncertainties regarding visits appears to have led to data extraction errors.

One net effect of the above flaws is that it is impossible to determine from the SAS data sets what were the dates of the last visits or contacts for CV follow-up for all patients and whether the contacts were site visits or phone contacts. We did not conclude this because of the theoretical problems itemized above but because of our experiences with our random sample of CRFs. We have provided copies of the pertinent CRFs for cases with end of CV follow-up date errors in Appendix 1, Cases E-K. We also provide there the definition of the end of CV follow-up date from the GSK Reporting and Analysis Plan. We summarize these problem cases below:

- E. This patient entered the full Tracking Sub-Study on 16nov06 (E1) and then had a last visit with vitals signs, etc., on 24mar08. The Study Conclusions/ Withdrawal CRF (E2) reported the patient as lost with a last contact of 24mar08. The reported end of CV follow-up date is 24mar06 rather than the correct 24mar08—*2 years off*.
- F. This patient had a visit with vital signs, etc. on 15apr05 and then was reported lost on 20dec06 with a last visit date of 15apr05 (F1), although there is also a crossed out study medication form indicating a last study med date of 30sep05. The reported end of CV follow-up date is 20dec06 rather than the correct 15apr05—*15 months off*.
- G. This patient has a last visit with vital signs, etc. on 04oct07 and then withdrew completely at his own request with a last visit date before leaving Randomised Treatment of 04oct07, a last contact date of 16nov07, with the investigator signing the CRF on 20jan08. (G1) Other CRFs clearly indicate that there was no visit on 20jan08. (G2) The reported date of last CV follow-up is 20jan08 rather than 16nov07—*2 mos off*.
- H. This patient had a last visit with vital signs, etc. on 27oct05 and then was reported lost, CRF signed 15jun06 and referencing the last visit on 27oct05. (H1) There is also a study med CRF from 15jun06 reporting a last study med date of apr06; no other CRFs were completed. The reported end date of CV follow-up is 15jun06 rather than 27oct05—*6 mos off*.
- I. This patient had a last visit on 09jul07 and then was reported as completely withdrawn on 06nov07 (I1). The Study Conclusion/Withdrawal CRF, signed 13jan09, reported that the patient was lost to follow-up with a final contact of 06nov07. (I2) The reported end of CV follow-up date is 13jan09 rather than the correct 06nov07—*14 mos off*.
- J. This patient allegedly withdrew at his own request. The last visit documented in the CRFs is a visit dated 21jun02 at which the last study medication was recorded as 20jun02. However, the Study Continuation/Withdrawal CRF (J1) was signed by the investigator on 20jan06. It has many corrections by data queries. While the investigator reported in data queries that the final visit was 31jul02, there is no confirmation of this in the CRFs. The reported end of CV follow-up date is 31jul02 rather than the correct 21jun02—*1 month off*.
- K. This patient allegedly withdrew at his own request with a last visit date of 11aug03, a last study med date of 08sep03, and a final contact date of 04nov 05. (L1) He did not enter the CV Outcomes phase. The reported end of CV follow-up date is 08sep03 rather than the correct 11aug03—*1 month off*.

For all but one of these 7 cases the reported follow-up was longer than documented in the CRFs by a median of about 6 months. The discrepancies are evenly split between favoring rosiglitazone and favoring control. So, while the median changes favor rosiglitazone slightly, we

believe that these discrepancies are due to the CRF flaws and data extraction errors rather than bias.

These discrepancies in 7 per cent of the cases, 95% confidence interval 3% - 14%, in our random sample have major implications:

- The end of CV follow-up dates are used for all patients in the GSK primary analyses of CV events not having a CV event targeted by the analysis. All of the GSK CV analyses (and the publications?) must be at least slightly wrong. As GSK asserted at a teleconference, the statistical significance of the survival analyses are far more dependent upon the endpoint occurrences and endpoint dates than the censoring dates for patients without endpoints. Fortunately our proposed primary analyses (see Appendix 8) are even less dependent than GSK's "ITT" primary analysis upon these censoring dates. However, we will use for our analyses censoring dates based on deaths and clinic visits (see next section.)
- We are concerned by this high error rate for one of the two critical values for the primary CV analyses. One would think that GSK should have placed special emphasis on assuring the accuracy of the critical values. The other critical value—endpoint ascertainment—has a similar or higher error rate as we discuss in the previous sections of this Appendix.
- The extent of good follow-up in RECORD appears to be overstated. Without good follow-up we can not be confident that the supposedly reassuring findings, such as a lower point estimate for CV mortality, are real.

3.7 Limited CV follow-up

The errors in CV follow-up dates listed above are ones that we could detect only by a manual review of the CRFs. We had neither the time nor the resources to complete such a review of all CRFs prior to the Advisory Committee Meeting. Hence we could not compute a study completion rate for RECORD based on true CV follow-up dates—at least ones including final phone contacts. However, as we discussed in Appendix 2 Protocol Comments, we believe that it would have been preferable to have a final face-to-face patient-site visit rather than a final phone contact. The recording of vital signs is a reasonable surrogate for the occurrence of a face-to-face patient-site visit. Because of the unreliability of the GSK-provided end of CV follow-up dates, we used the last of the date of the last visit as evidenced by vital signs recording, the date of the last adjudicated hospitalization not adjudicated as insufficient information, or the date of an adjudicated death not adjudicated as unknown as our measure of the end of CV follow-up.

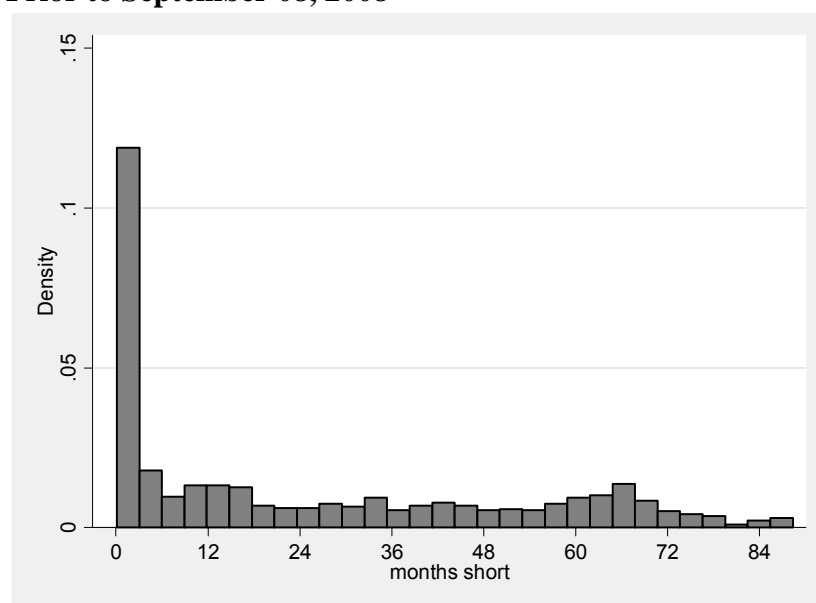
To estimate the extent of good follow-up one needs to know the study close-out date. (b) (6) provides this explanation: "At the Steering Committee meeting held on 3 May 2007, the Steering Committee were asked for endorsement of a proposed 'last patient last visit date'. GSK proposed that patients had their last visits over a 4 month period (the scheduled visit interval) around Nov 08 (from Sept 08 to Jan 09). The SC recommended that the last visit date should be 24 December 2008. The actual last patient last visit was 26 Dec 08 as one subject came for their last visit after

the planned study end.” Hence we use a last visit date on or after September 08, 2008, as the criterion for good follow-up.

The summary of CV follow-up from Section 6.1.2.1 of the study report is as follows: “The proportion of subjects who completed CV follow-up to the final visit (approximately 82%) and who completed follow-up for the primary endpoint (approximately 89%) was comparable between the combined RSG and MET/SU groups. Approximately 11% of subjects were lost to CV follow-up without having a primary event and 2.9% had unconfirmed vital status at study end, and these were comparable between treatment groups.” By the criterion of the end of CV follow-up date on or after September 08, 2008 there is good follow-up in about 80% by GSK dates and 76% by our dates. The numbers of patients with inadequate follow-up exceeds 20%, or about 1,000 patients.

The average number of months of missing follow-up was substantial, with a median of 13.9 and a mean of 24.9 months. We show the distribution in Figure 7.

Figure 7: Distribution of Missing Follow-up for Patients with End of CV Follow-up Dates Prior to September 08, 2008



The distributions were similar between rosiglitazone and control. The durations were longer in the sulfonylurea stratum (median 17.5 months) than in the metformin stratum (median 10.9 months). Likely most of the patients with last CV follow-up visits shortly (i.e, within a month, the bulk of the first bar height in Figure 7) before the earliest study end date of September 8, 2008, represent lax enforcement of study procedures rather than lost or biased follow-up. Counting them as good follow-up still leaves about 700 (16%) of study patients with inadequate CV follow-up, a number far greater than the differences of any of the CV endpoints between treatment arms.

We did not find any obvious variations in baseline characteristics by quintiles of missing follow-up and rosiglitazone arm and compared to the patients with good follow-up. We did find that

patients with longer durations of missing follow-up had higher rates of SAEs per 100 person-exposure years (PEYs) than those with shorter durations. For the GSK primary endpoint (PEP) there were no differences between the rosiglitazone and control arms, although the gradient varied from 6.6 PEPs/100PEY in the quintile with longest missing follow-up to about 2.5 PEPs/100PEY in the two shortest duration quintiles and in the patients with good follow-up. For this analysis we used only the first reported PEP so the gradient may be due to the longer follow-up durations in the better follow-up groups. However, because numbers of PEPs are arbitrary and dependent upon the investigators' decisions (e.g., an admission for atrial fibrillation and heart failure could be submitted as one endpoint or two), we did not analyze all PEPs.

We did find variations in heart failure (HF), atrial fibrillation (afib), and MI first event rates—the stroke rates were erratic by quintile without an obvious difference between treatment groups. For HF and afib we would argue that the first event is the event of concern since both are chronic or recurrent. For MI, while repeat MIs are of great concern, they were uncommon in RECORD. We show the variations for HF, afib, and MI in Table 6.

Table 6: Rates of Selected CV Events by Quintile of Duration of Missing Follow-up

	Mean mos missing	PEYs		Atrial fibrillation		Heart failure		MIs	
		Ctrl	Ros	Ctrl	Ros	Ctrl	Ros	Ctrl	Ros
Good f/u	0.0	9969	10139	0.1	0.3	0.5	1.0	0.5	0.7
Quintile 1	0.2	619	632	0.2	0.3	0.3	0.5	0.5	0.6
Quintile 2	1.7	594	594	0.3	0.3	0.3	0.7	0.7	0.2
Quintile 3	14.7	531	470	0.6	0.6	0.6	1.5	0.6	0.9
Quintile 4	40.4	291	253	0.0	1.2	1.4	2.8	0.3	2.0
Quintile 5	67.9	61	74	0.0	1.3	0.0	2.7	0.0	2.7

We would expect that HF SAEs should be associated with discontinuation of rosiglitazone; it is less clear that they should be associated with discontinuation from follow-up. Because afib is associated with HF, the gradient for afib in Table 6 may reflect this association. Possibly the same is true for MI. One limitation is that the exposures in quintiles 4 and 5 are low. Table 6 does suggest that sicker rosiglitazone patients may have withdrawn earlier than control patients. It also suggests that rates of MIs may be differentiated between rosiglitazone and control.

3.8 Concomitant medication reporting

We discussed in Appendix 2 Section 2.17 our concerns regarding the capturing of concomitant medications. Because we have no absolutely fool-proof way of detecting concomitant medications not reported: There would be no CRF filled out and hence no record. As a surrogate measure we calculated the number of medication changes per person exposure year (PEY) in the randomized treatment phase (RTP) and the CV outcomes phase (CVO) for patients who had both phases. We counted medication changes in the RTP phase if the medication change was post-randomization and the start date was within the RTP phase dates or the stop date was less than or equal to the RTP phase end date. Otherwise we counted the medication change in the CVO phase. We believe this algorithm overestimates the medication changes in the CVO phase for this reason: Patients not uncommonly exited the RTP phase immediately preceding a hospitalization. If the hospital medications were captured, then our algorithm counts them in the CVO phase. We show the reported medication changes per PEY for both phases in Table 7.

Table 7: Reported Medication Changes per PEY by Study Phase for Patients Having Both Phases

	rosiglitazone	control
Randomized treatment phase	6.2	5.3
CV outcome phase	4.0	4.1

Note that reported medication changes per PEY did decrease from the RTP to the CVO phase despite our algorithm’s likely overestimate of the CVO phase. It is also interesting that medication changes were more frequent with rosiglitazone than control during the RTP phase—perhaps diuretic use? We have no easy way of ascertaining the reason. These reported medication change rates do suggest that medication changes may have been underreported during the CVO phase. Because medication changes can include new rosiglitazone or pioglitazone use, crossovers may have been missed. Medication use is also helpful for confirming diagnoses such as heart failure, angina, and atrial fibrillation. However, we judge that this problem does not appear to be one of the major problems with the study.

3.9 Misunderstandings on the handling of SAEs

While the misunderstandings on the handling of SAEs we describe below do not impact directly endpoint determinations, they are another example of the lack of rigor in implementing the protocol specifications—Section 3.2 errors in end of CV follow-up dates and Section 2.3 the completion of hospitalization CRFs are others. These misunderstandings do raise questions about any SAE statistics reported from RECORD and the training and research competencies of some investigators and monitors.

The protocol in Section 8.12 had the usual regulatory definition of a SAE (fatal, life-threatening, disabling, resulting in or prolonging a hospitalization, or a congenital abnormality) plus investigator-determined, cancer, overdose, and pregnancy. In Section 8.3 it specified the usual expedited reporting required by regulatory authorities. The reporting of AEs during the CV outcomes phase was relaxed in Amendment 1 from both AEs and SAEs to SAEs only as described in Section 3.2.2. Patients who Withdraw from the Randomised Treatment Phase of the Study: “SAEs will be collected during the CV Outcomes assessment part (Post-Randomised Treatment Phase) of the study for those patients for whom CV outcomes data are being collected. SAEs will not be collected for those patients that are only being contacted to provide survival status data [Section 3.4.1 and Section 3.4.2].” There is no statement in the protocol that SAEs were not to be collected other than for the survival status only patients.

Because endpoints had to involve a death or an overnight hospital stay, investigators appear to have been confused that SAEs also had similar requirements. Because strokes are arguably always serious, we checked for stroke AEs. We found three cases for which the investigators classified strokes as AEs rather than SAEs. For two the cases the monitor queried the investigators that the strokes should be SAEs but the investigators insisted they were AEs because the patients were not hospitalized. We show the query responses in Figure 8.

Figure 8: Examples of Investigator Misunderstandings about SAEs

The reported event "ischemic stroke" May 2003 did not lead to hospitalization and is therefore considered to be a non-serious adverse experience, not an endpoint according to the study protocol.

*Patient was not
hospitalized for
the AE hemiparesis
left arm, so no
SAE to be reported*

We found no record that the monitors corrected the misunderstandings of the investigators; both events were submitted as AEs. In the third case, the investigator reported a stroke as an AE and then changed it to left hemiparesis. Despite the patient being hospitalized for carotid endarterectomy the stroke was not reported as an SAE or adjudicated.

We analyzed strokes because they are arguably always SAEs while other events may be AEs or SAEs depending upon their severity. Because the protocol did not require the reporting of AEs during the CVO/TSS phase, we do not know how many other SAEs were missed then. We also have no way of determining whether other SAEs not involving hospitalizations, e.g., angioedema or other severe allergic reactions, were not reported as SAEs throughout the entire study. While these SAE misunderstandings do not impact the endpoint determinations, they do reduce our confidence that RECORD was conducted well.

We analyze SAEs/100PEYs by treatment phase and treatment arm. The SAE rates were higher during the CVO/TSS phase and higher for rosiglitazone than control (27 vs. 22) than during the randomized treatment phase (both 16). Because the CVO/TSS phase was not randomized we can not make any strict interpretation of these results but they are suggestive of more problems in the rosiglitazone arms late.

3.10 Inadequate coding of CV adverse events

During our review of CV AEs we noted that sites were reporting "arrhythmia" (single word) without any qualifiers. From the CRFs we determined that these events were atrial fibrillation (afib) and that "arrhythmia" was atrial fibrillation for these European investigators. However, in the AE data sets GSK had coded these "arrhythmia" events to the non-specific MedDRA preferred term "arrhythmia" and had not sought clarification. GSK did code terms reported as arrhythmia absolute, absolute arrhythmia, and variations as atrial fibrillation.

Because RECORD is a CV outcomes trial we believe that it is critical to code CV AEs as specifically as possible. Hence we scrutinized all of the non-specific arrhythmia AEs and attempted from the CRFs, related AEs for the same patient, and concomitant medications for the same patient to classify all arrhythmias more specifically. We also recorded afib events not reported as separate AEs that we discovered in hospital discharge summaries if the afib was described as causing clinical complications or required new treatment. We believe that accurate

collection and coding of CV AEs is important for understanding better rosiglitazone's adverse effect on heart failure as well as rosiglitazone's potential for other CV adverse effects.

We show the rates of patients with afib by GSK's and our codings (all phases) in Table 8.

Table 8: Rates of Patients with Atrial Fibrillation by Different Codings

	Control	Rosiglitazone	RR*
GSK atrial fibrillation AE MedDRA preferred term	3.2%	3.6%	1.14
FDA atrial fibrillation AE MedDRA preferred term	3.5%	4.2%	1.21
FDA afib AEs + afib events not reported as AEs	3.7%	4.7%	1.29

*relative risk = (rosiglitazone rate)/(control rate)

Note that the GSK coding missed about 13% of the rosiglitazone patients with any afib AE based on the AE event reports alone and at least 23% of the patients with any afib event if descriptions of afib events in any part of the CRF are counted. The rates in the last row in

Table are low estimates because we did not review CRFs for all patients and sites did not even report AEs during the CVO/TSS phase.

Note also that the relative risk of having at least one afib event increases from 1.14 by GSK coding to 1.29 by the most comprehensive coding. We explore in more detail the possible clinical implications of afib rates in the body of this consult.

We queried GSK regarding the failure to obtain more information on a cardiac rhythm disturbance for one patient. GSK responded in (b) (6) as follows:

“FDA Request 2: Patient [redacted]: This patient had a 5 day hospitalization for cardiac rhythm disturbance for suspected CAD in 9/03 during which a PTCA was done. The SAE was initially reported as PTCA and adjudicated as non-urgent and therefore non- CV. In 2008 a new PI at the site resubmitted this case for re-adjudication, noting that the hospitalization was for “coronary heart disease with cardiac rhythm disturbance” and that a PTCA was also done during the hospitalization.

a. Why was the nature of the cardiac rhythm disturbance never documented?

Response: It is not routine procedure for Quintiles Clinical, Data Management or CEVA to clarify/establish nature of SAE terms unless it is necessary for coding purposes. GCSP would only request clarification of the SAE term if it did not autoencode. Since this event autoencoded no query was issued. This hospitalization was sent for adjudication; no queries were raised by the CEC around the rhythm disturbance.”

We believe that getting a match on an autoencoder to a non-specific term is not adequate coding for CV events. The problem with non-specific AE terms is not limited to atrial fibrillation. We note the following non-specific and overlapping AE terms (cardiac SOC) in Table 8.7, Summary of Adverse Experiences by System Organ Class and Preferred Term - Randomised Treatment Phase, of the study report: cardiovascular disorder, arteriosclerosis coronary artery, coronary artery disease, coronary artery insufficiency, myocardial ischemia, cardiomyopathy, cardiomegaly, cardiac hypertrophy, dilatation ventricular, ventricular hypertrophy, left atrial hypertrophy, left atrial dilatation, dilatation atrial, right atrial dilatation, tachycardia, tachyarrhythmia, bradycardia, bradyarrhythmia, cardiac fibrillation, and cardiac flutter.

One peculiarity of MedDRA coding likely contributed to the ambiguity of the CV terms: Capturing the clinical relevance of CV procedures with MedDRA coding is frequently problematic because the ICH guidance *MedDRA Term Selection: Points to Consider* advises that “The use of the SOC Surgical and medical procedures is generally not appropriate for ADR/AEs” and “it is considered sufficient to select a term for the diagnosis alone.” While this MedDRA guidance is appropriate for many non-CV procedures, e.g., “colon cancer” is more informative than “colectomy”, it is inadequate for most CV procedures, e.g., “coronary artery disease” or even “coronary stenosis” is less informative than “PTCA” or “CABG”. MedDRA does recommend coding the diagnosis and the procedure. However, the “diagnosis” capturing the findings of the procedure does not capture the clinical circumstances necessitating that the procedure be performed, e.g., whether the procedure was done for symptomatic stable angina, ischemia detected on a screening treadmill test, or an emergency visit for chest pain. Investigators do not consistently report the clinical event leading to the procedure. Hence we are left not infrequently with a single, nondescript term like “coronary artery disease”. This reporting and MedDRA coding issue is not unique to RECORD—we have observed it particularly in CV outcome meta-analyses of non-CV trials.

We found it difficult to interpret what many GSK CV codings represent regarding clinical events. We can not combine and analyze them in meaningful ways to understand what cardiac adverse events RECORD patients suffered. We performed our own codings from the investigator verbatim terms for all of our analyses.

3.11 Endpoint CRFs not databased

In Figure 2 above (the header for the hospitalization CRF) note that GSK annotated that “Information on this page was not databased”. GSK included identical disclaimers all endpoint forms—for CV procedure/amputation, MI/unstable angina, TIA/stroke, death, and other. GSK has never provided data sets with the information on these most critical forms for CV event determination. In fact, for the initial NDA submission on August 25, 2009, GSK omitted providing copies of these forms in the CRFs for patients with deaths and discontinuations for AEs as required by 21 CFR 314.50. GSK submitted copies of endpoint forms for patients selected by us on January 21, 2010, and complete CRFs (with all CRFs in one PDF file per patient) for the selected patients starting on March 23, 2010. The complete CRFs, including data queries, notes to file, available source documents, and redundant copies of some adjudication package materials, are voluminous: One patient’s CRF file has 1,700 pages and occupies over 391MB of disk space.

While GSK has corrected their failure to submit initially the investigator-completed endpoint CRFs, we still do not have the key information from them in machine-readable form. While these CRFs include large free-text fields that usually are not entered into SAS data sets, they also include structured fields that are very amenable to electronic manipulation. Given the size of this study, electronic manipulation of study data is the only practical approach.

Appendix 4: RECORD Adjudication Comments

April 12, 2010

Version 1.2

For readjudication of any RECORD endpoints we are using the definitions from the final RECORD CEC Charter with the following supplements added because of problems with or inadequacies of the definitions or in the referrals for adjudication or data collection processes:

1. Unknown deaths. While the CEC Charter was amended to define all unknown deaths as CV deaths, we believe that counting all unknown deaths as CV deaths potentially introduces noise and is inappropriate for a noninferiority study. Furthermore, the CEC appears to have applied unusually strict criteria, not detailed in the CEC Charter, for accepting the cause of death, e.g., they adjudicated a well-documented fall from a roof as an unknown death. Hence we have modified and supplemented the CEC definition of CV death as follows:
 - a. We will count sudden deaths as CV deaths for the primary analyses of CV deaths. We will count non-sudden, unknown deaths as non-CV deaths for the primary analyses of CV deaths. We will perform sensitivity analyses counting non-sudden, unknown deaths as CV deaths.
 - b. We will accept reasonable, consistent documentation of the cause of death to differentiate CV from non-CV deaths.
 - i. We will count in-hospital deaths for which a cause is documented or reported as due to the cause. If the cause is only reported as possible (or similar language) we will have to judge whether the cause is plausible based on all available evidence.
 - ii. We will count out-of-hospital deaths for which a cause is documented or reported as due to the cause in the following circumstances:
 1. If the documentation for the cause is strong, i.e., autopsy.
 2. If the cause of death is consistent with a well-documented terminal illness, i.e., death from lung cancer in a patient with reported metastatic lung cancer.
 3. If the cause of death is consistently reported without suggestions of alternative causes, e.g., we will count the death reported as a fall from a roof as a non-CV death.
 4. Out-of-hospital “MI” or “acute cardiac insufficiency” deaths are particularly problematic. We believe that sudden, unknown deaths are reported as such even in the absence of suggestive signs or symptoms. We will count them as follows: If signs or symptoms of MI, i.e., chest pain, or acute heart failure, e.g., dyspnea, are documented, we will count the death as MI or heart failure. Otherwise we will count the death as sudden death.

- c. The CEC ultimately used a rigid, complex definition of sudden death as having one of the following: 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 (known that the patient did not have any signs or symptoms 24 hours before the death occurred). For the CEC differentiating sudden from unknown death was not critical because both were counted as CV deaths. For us differentiating them is important for the primary analysis. We will differentiate out-of-hospital, unknown deaths into sudden and non-sudden (only unknown) according to the following guidelines:
 - i. We will count deaths for which minimal or incomplete information are available, e.g., only the year or month and year are reported, as unknown deaths.
 - ii. We will count out-of-hospital deaths for which the date is reported but the only report is vague, like “found dead in the morning by wife” or “reported dead by neighbor” as follows: If there are suggestions of suddenness and unexpectedness, e.g., “found dead in the morning by wife” in a patient without a documented terminal illness, then we will count the death as a sudden death. Otherwise we will count the death as an unknown death.
2. Myocardial infarctions. The CEC Charter states that “Acute Myocardial Infarction will be adjudicated according to the definition in the document: ‘Myocardial Infarction redefined- A consensus documents of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. EHJ vol. 21; 1502-1513’”. However, the CEC Charter then describes criteria of hospitalization PLUS biomarker elevations PLUS one of the following: typical symptoms of cardiac ischemia or new ECG findings. These restrictive criteria exclude MIs for which biomarkers were either not obtained because of death prior to drawing or for which biomarkers were obtained at the hospital but the results never forwarded to the CEC. They also ignore MIs confirmed on autopsy. We will use the full criteria from the Universal Definition of MI as summarized in the table below:

Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
 - Symptoms of ischaemia;
 - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
 - Development of pathological Q waves in the ECG;
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary 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.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than $3 \times$ 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than $5 \times$ 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

3. Events not referred for adjudication or with incomplete data collections. Events not referred for adjudication are problematic because we frequently do not have all of the information needed to address the specific requirements in the CEC Charter definitions, e.g., the site did not complete a MIUA CRF and the CRO did not direct the sites to report troponin and other biomarker values for suspected MIs. For these events with incomplete data collections we will not apply the CEC Charter definitions with our supplements strictly; we will base our decisions upon our evaluation of all available evidence.
4. Endpoint dates. The protocol and the CEC charter do not discuss how the CEC will adjudicate endpoint dates. At a CEC meeting on December 10, 2003 (the minutes of which we obtained after April 8, 2010), the CEC stated that they would adjudicate endpoint events as follows: “The date of onset was discussed, as there have been discrepancies between the SAE onset date, endpoint onset date and admission date. It was agreed that in case of hospitalisation, the date of admission to the hospital will always be taken as the date of the endpoint. So if for example a patient reported chest

pain for 3 days at admission to the hospital and that is adjudicated as Unstable Angina, the endpoint date is the hospitalization and not the onset of symptoms. The previous agreement regarding consecutive events (February 2001 minutes) will remain the same. 'In case of consecutive events it was decided that death is always the primary endpoint. So for example if a patient has an MI, Heart Failure, Stroke, Death, the time to death will be captured. In case of consecutive events, where the patient survives, the time to first event will be captured.' For consecutive events where there is no death the situation is as follows: The date of onset of the endpoint leading to hospitalisation will be the date of hospitalization. For any subsequent events that occur during the same hospitalisation the date of onset of each subsequent event will be the date of onset of the event, as reported by the investigator."

We consider these endpoint date adjudication rules to be unacceptable. For example, consider two patients who suffer a MI on the same date, one of whom survives and the other of whom dies 15 days later. By the CEC rules the patient who survives will have an endpoint 15 days earlier than the patient with the more severe endpoint—death! While we would not expect these differences in dates to affect the time-to-first-event analyses greatly, we believe we should use the more appropriate analysis. Furthermore, depending upon censoring rules for events occurring after discontinuation of treatment, these rules could greatly affect results.

We will try to correct dates of onset to the dates of first symptoms or signs leading to the event. For deaths we will include an event dated according to the first symptoms or signs if the date of death is not the same as the date of first symptoms or signs leading to death. For the example given in the paragraph above, we would count the same event date for MI events in each patient.

Appendix 5: RECORD Adjudication Differences – Cardiovascular (CV) Deaths

We summarize in this appendix the differences in adjudications of CV deaths between the CEC and us. Please note the following:

- GSK classifies unknown deaths as CV deaths. We count them as non-CV deaths if the cause of death is truly unknown and not sudden and unexpected. If the unknown death had a reported CV cause, we considered it and classified the death as CV if reasonably documented. We counted sudden and unexpected deaths as CV deaths. For differences in the CEC-adjudicated unknown deaths we summarize below only those cases that we classified as non-CV.
- Forty-four deaths occurred while the patient was on survival status only follow-up. The CEC did not adjudicate them.

We show in Table 1 the cross-tabulation of the CEC's and our adjudications of CV deaths. We summarize in Table 2 the deaths that we adjudicated differently than the CEC did.

Table 1: Cross-tabulation of CV and non-CV Deaths by CEC and FDA

CEC	FDA		
	non-CVD	CVD	Total
non-CVD	118	2	120
CVD	15	116	131
not adjudicated	37	7	44
Total	170	125	295

CEC = GSK Clinical Endpoint Committee

CVD = cardiovascular death

Table 2: Summaries of Deaths Adjudicated Differently

#	Description	CEC	FDA
1	drowning death confirmed on autopsy	unknown	drowning
2	died from fall from roof while painting called accidental	unknown	accident
3	death from national death register or hospital database (both mentioned) but no other information	unknown	unknown
4	hospitalized febrile, confused, treated pneumonia but also 6mm subdural & subarachnoid blood on scan; sudden unconsciousness with deviated eyes day 3 called brainstem stroke by neurologist	non-CV	stroke
5	investigator reported patient died per authorities no other information	unknown	unknown
6	died day unknown no other information	unknown	unknown
7	investigator reported died of stroke due to pancreatic cancer; cancer reported 7 months earlier	unknown	unknown
8	died at home no details	unknown	unknown
9	investigator informed by patient's physician of death, no other information	unknown	unknown
10	died at home; forensic autopsy no evidence for MI or other CV cause, concluded diabetes & alcohol abuse	unknown	unknown
11	death from diabetic register no other information	unknown	unknown
12	died post-op colon cancer resection followed by sepsis, leg amputation, multiorgan failure	heart failure	non-CV
13	died in hospital of lung infection, no other information	unknown	non-CV
14	died unknown no details	unknown	unknown
15	died at home attributed by family to dehydration from gastroenteritis	unknown	unknown
16	drowning death confirmed on autopsy	unknown	drowning
17	hospitalized for chest pain, dyspnea, fever; pericardial & pleural effusions; improved then deteriorated, treated with pressors & died; attributed to thyroid cancer but nodule on echo not confirmed as cancer & no metastases	non-CV	CV

Appendix 6: RECORD Adjudication Differences – Myocardial Infarction (MI)

We summarize in this appendix the differences in adjudications of MIs between the CEC and us. Please note the following:

- We adjudicated probable MI deaths regardless of whether biomarkers were available. We accepted autopsy evidence of a new infarct while the CEC appears to have ignored this information. For out-of-hospital deaths we also considered death certificate causes of death and physician reports of MI deaths.
- Similarly, we adjudicated as MIs several cases that the CEC had adjudicated as “recent MI”. These cases typically had chest pain for which the patient did not seek hospitalization immediately. Hence they do not satisfy the GSK primary endpoint criterion of being a CV hospitalization. While not in the GSK primary endpoint (which we reject for other reasons), we believe that they should be counted as MIs when analyzing MIs.
- For MIs there is only one case (#1 below) that the CEC adjudicated as an MI and we did not. All of the rest are MIs that we have added. As we have discussed in Appendix 3 Study Conduct, the CEC appears to have applied a “high bar” for MIs (and strokes). We judge that the net effect of these “high bars” for the most serious events de-emphasized their contributions to the GSK primary endpoint relative to less serious CV hospitalizations such as hypertensive emergencies and paroxysmal atrial fibrillation and variably determined events such as “urgent” CV procedures.

We show in Table 1 the cross-tabulation of the CEC’s and our adjudications of MIs. We summarize in Table 2 the MI cases that we adjudicated differently than the CEC did.

Table 1: Cross-tabulation of MIs Adjudicated by CEC and FDA

CEC	FDA		
	not MI	MI	Total
not MI	4,304	23	4,327
MI	1	119	120
Total	4,305	142	4,447

Table 2: Summaries of MI Cases Adjudicated Differently

#	Description
1	CEC adjudicated MI: hospitalized for pneumonia, MI diagnosed based on elevated CK and troponin, no typical ischemic symptoms, ECG changes - see Appendix 1, Case R
2	hospitalized with recurrent episodes of ischemic pain, ecg changes, afib, bedside troponin positive adjudicated unstable angina
3	hospitalized for burn, recovering, sudden cardiac arrest with failed resuscitation, clinical diagnosis of MI, pulmonary edema and severe coronary atherosclerosis on autopsy
4	an MI SAE (chest pain, elevated troponin) was deleted 16 months later and never referred for adjudication - see Appendix 1 Case A

#	Description
5	retrosternal pain, hypertension, ischemia on ecg, troponin negative but CK-MB "23.6" ULN 12, CK-MB fraction 12% ULN 5%
6	hospitalized 13d for MI starting 21apr05 not adjudicated because confused with 8d hospitalization for HF 16-23may05 adjudicated not CV because insufficient information
7	sudden onset dyspnea at home, ventricular tachycardia resuscitated x2, pulmonary edema, CK-MB 25%, "positivity of cardiospecific enzymes" adjudicated heart failure but not MI
8	hospitalized for pulmonary embolus, arrests 4d later, fresh cardiac infarct on autopsy
9	arrhythmia, sudden death while hospitalized for GI bleeding reported as MI but documentation poor, adjudicated unknown
10	hospitalized for chest pain, dyspnea, afib; heart failure, ischemic changes on ecg, akinesia on echo, biomarkers not reported
11	sudden onset dyspnea, heart failure post colon surgery, CK-MB 647 ULN 25, arrested and died, adjudicated non-CV
12	died at home per general practitioner, acute myocardial infarction cause of death on death certificate
13	died at home observed with chest pain, sudden death; called MI, adjudicated other CV cardiac arrest
14	hospitalization for heart failure in Oct adjudicated as other CV recent MI although documentation on MI SAE from Sep lacking
15	dyspnea then hospitalized due to ECG changes evolving anterior infarct but ECGs not provided diagnosed anterior MI and one adjudicator recent MI
16	chest pain, anterior ischemia on ECG, one CK normal no other biomarkers adjudicated recent MI '0; discharge summary also mentions MI '03 but no record
17	chest pain ended 3d prior to hospitalization, 3 mm ST depression in V3-6, troponin 0.24 ULN 0.2
18	elevated cardio-specific enzymes post-CABG described as possible small MI; MI referenced in discharge summaries from later hospitalizations
19	hospitalized with increased heart failure, chest pain, troponin 0.07 ULN 0.03, died
20	retrosternal pain, dyspnea but not hospitalized until ECG showed changes consistent with MI, hypokinesia on echo, no cardiac biomarkers reported
21	chest pain, ischemia on ECG, troponin 0.06 ULN 0.01
22	severe chest pain Dec but not hospitalized until Mar with front wall negative T waves, adjudicated recent MI
23	described patient driving, had MI, hit a tree; ventricular fibrillation initial rhythm, died emergency room
24	chest pain, T-inversions ECG, elevated troponin 0.03 (called doubtful) but thrombus on angiography

Appendix 7: RECORD Adjudication Differences – Stroke

We summarize in this appendix the differences in adjudications of strokes between the CEC and us. Please note the following:

- Several of the strokes did not involve an immediate hospitalization. The CEC did not adjudicate them and we list them below as “NA*” (not adjudicated) in the CEC column.
- One stroke was reported while the patient was on survival status only. Hence the CEC did not adjudicate it. We include it in Table 1 but not in Table 2.

We show in Table 1 the cross-tabulation of the CEC’s and our adjudications of strokes. We summarize in Table 2 the stroke cases that we adjudicated differently than the CEC did.

Table 1: Cross-tabulation of Strokes Adjudicated by CEC and FDA

CEC	FDA		
	no stroke	stroke	Total
no stroke	4,323	15	4,338
stroke	3	106	109
Total	4,326	121	4,447

Table 2: Summaries of Stroke Cases Adjudicated Differently

#	Description	CEC	FDA
1	initial report of death 2005 unknown adjudicated unknown; note from 2007 reported subarachnoid bleed not readjudicated	no	yes
2	hospitalized for confusion, left parietal infarct on scan of indeterminate age (no prior history of stroke); post-hospital developed right sided numbness, falling to right; not hospitalized, called stroke by neurologist on outpatient visit	NA*	yes
3	short loss of consciousness, hemiparesis lasting >24h, dizziness; not hospitalized until 4d later, no scan or neuro exam reported although stroke diagnosed	no	yes
4	severe stroke hospitalized for 36 days no other information obtained - see Appendix 1, Case D	no	yes
5	hospitalized for angina and unable to perform exercise test because of stroke residual; atrial fibrillation started 4m earlier, with stroke during one episode no hospitalization recorded	NA*	yes
6	hospitalized febrile, confused, treated pneumonia but also 6mm subdural & subarachnoid blood on scan; sudden unconsciousness with deviated eyes day 3 called brainstem stroke by neurologist	no	yes
7	sudden onset expressive aphasia followed by grand mal seizure; hospital CT scan negative but expressive aphasia noted 4-5d after discharge	no	yes

#	Description	CEC	FDA
8	acute onset nausea, ataxia, nystagmus; hospitalized 14d with improvement but residual ataxia, no scan	no	yes
9	stroke AE changed to hemiparesis AE; hospitalized 2m later for carotid stenosis with stroke plus left arm & leg weakness noted	NA*	yes
10	history of stroke and traumatic subdural hematoma prior to randomization; hospitalized for aphasia of uncertain onset with scan unchanged from previous (subdural, old infarcts)	yes	no
11	complained of difficulty closing left eye, numbness left cheek; hospitalized with only finding slight reduced tactile sensation left cheek, scan negative	yes	no
12	hospitalized for left leg and hand numbness reported TIA but adjudicated non-CV because discharge summary poor; residual effects of stroke are mentioned in discharge summary 22m later - no baseline history of stroke/TIA	no	yes
13	became confused, disoriented in cath lab, "subacute" lesion on stroke, diagnosed completed stroke by neurologist	no	yes
14	left arm hemiparesis reported stroke AE (not SAE) because not hospitalized	NA*	yes
15	left-sided weakness reported <24h on CRF, resolving but no duration in discharge summary, scan negative	yes	no
16	intracerebral hematoma deleted from SAE CRF, also "epilepsy"; hospitalized focal neurologic signs and intracerebral hemorrhage on CT scan - see Appendix 1, Case C	no	yes
17	sudden dizziness, headache, visual disturbance not hospitalized reported as AE; right occipital lesion on MRI 6m later	NA*	yes

*NA = not adjudicated by CEC because not hospitalized immediately

Appendix 8: Analysis Plan for the RECORD Study

Version 1.3, May 19, 2010

The RECORD study had a complex, flawed design and a flawed execution—see our comments on the protocol and on the study conduct for the details. The sponsor’s original endpoint is both flawed and not consistent with the concerns raised by the external meta-analyses. For these reasons we believe that we can not use the sponsor’s analysis plan but must create one that addresses the flaws. Our plan addresses the appropriate statistical analysis, endpoints, treatment arms, analysis populations, and censoring rules.

Primary Statistical Analysis

Because of the varying entry and exit times and occurrences of multiple events in the same patient, we planned to analyze the endpoints by time-to-first-event using the logrank statistic for estimating probability and Cox regressions for estimating hazard ratios and for covariate inclusions (for sensitivity analyses). Because, as a Division statistician commented, the logrank test does not estimate confidence intervals and the primary analysis is one for noninferiority, we will copy the sponsor and use Cox regressions for all time-to-event analyses.

Endpoints

The primary endpoint for RECORD was time to first event of CV hospitalization or CV death. We advise against using CV hospitalization as part of a primary endpoint for three reasons: (1) CV hospitalizations include a wide range of disorders, e.g., valvular heart disease, many of which are unlikely to be affected by one drug—this will introduce noise. (2) Adjudicating CV hospitalizations is problematic because of the wide range of CV and possible CV reasons. (3) Hospitalizations for CV procedures are particularly problematic because the performance of CV procedures such as angioplasties may be influenced as much by physician factors as by patient or disease conditions. We discuss these three reasons in more detail in our comments on the protocol.

For drugs about which the CV effects are unclear, we favor the standard CV death, MI, stroke (MACE) endpoint as discussed in the 2008 Guidance “Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.” We favor MACE both because it captures the most significant events for the leading causes of CV morbidity and mortality in the US and because its components are “hard” events that are well defined and should be reliably ascertained.

However, for rosiglitazone we have some prior evidence regarding CV effects: The Nissen meta-analysis raised the question of whether rosiglitazone increases MI rates. Conversely, GSK has alleged that the drug may lower blood pressure and decrease stroke rates. Typically we do not include components in a composite endpoint that go in different directions. Finally, HF is a known adverse effect of PPAR-gamma agonists but relative risk and effects upon HF mortality could be defined better. Hence we consider the most appropriate safety endpoints for RECORD to be the MACE components analyzed separately, i.e., MI, stroke, CV death (plus the MACE composite as a secondary endpoint), and HF (all events).

We will perform our primary analyses using our re-adjudicated events that include both the CEC-adjudicated events and those that were not submitted for CEC adjudication. For comparison we will also analyze the CEC-adjudicated events and the site-reported events. For MIs we will perform sensitivity analyses of MI-related events, i.e., MI+sudden CV death+arrests, +AHF+HF deaths, and +ventricular arrhythmia/syncope/angina/ CAD/ACS SAEs. For HF we will perform sensitivity analyses of HF hospitalizations, hospitalizations with HF contributing, and HF deaths.

Finally, we observed that sites reported atrial fibrillation with a wide variety of terms, e.g., arrhythmia, tachyarrhythmia, TAF, etc., and that the sponsor did not code it specifically. We recoded atrial fibrillation based on the complete information in the CRFs—not just the investigator verbatim terms. We included events of worsening atrial fibrillation even if the patient has a history of atrial fibrillation at baseline. Because atrial fibrillation is associated with HF, we will present analyses of time-to-first atrial fibrillation events to complement the HF analyses.

Treatment Arms

As we discussed in our comments regarding the protocol, RECORD is actually two studies done in parallel: one comparing initial add-on therapy with rosiglitazone to initial add-on sulfonylurea in the baseline metformin patients and the other comparing initial add-on therapy with rosiglitazone to initial add-on metformin in the baseline sulfonylurea patients. That the two studies are not exactly comparable is shown by the differences in baseline characteristics summarized elsewhere in our review. From a strict statistical viewpoint we should analyze the two studies separately before combining them through a meta-analytic type approach. However, a looser clinical view might consider RECORD to be one study comparing add-on rosiglitazone to an appropriate diabetic drug active control. The sponsor has taken this latter approach but does recognize the imbedded two studies by proposing a primary analysis of a Cox regression with strata for the baseline metformin or sulfonylurea use and one cofactor for rosiglitazone randomization.

For our primary analyses we will follow the approach used by the sponsor and use a Cox regression with strata for baseline sulfonylurea/metformin use. However, to recognize completely the study design, we will also analyze the two studies independently. Finally, similar to the sponsor's plan, we will perform Cox regressions modeling the strata and treatment interactions but also using exploratory covariates.

Analysis Populations

RECORD is a non-inferiority study. Hence we can not automatically assume that a true intention-to-treat (ITT) approach is the most appropriate. For non-inferiority studies, an on-treatment approach must also be considered because patients off treatment can not possibly have an acute drug effect and hence including them will bias towards the null. While the original protocol defined the primary study population as “All Randomized Patients”, an early amendment changed it to “All Randomized and Treated Patients”. A secondary analysis was proposed to be done using the “Per Protocol Population”. The protocol does not define these populations further. The RECORD “per protocol” population does not represent an on-treatment

population (as it does for most protocols) because, per protocol, rosiglitazone could be discontinued in patients in the rosiglitazone arms in as few as 16 weeks if the HbA1c was elevated—see our comments on the protocol for more details.

Given the ambiguities regarding the “per protocol” or “on treatment” population for RECORD, we have a slight preference for using the ITT population for our primary analyses. We also have a slight preference for using a true ITT population, i.e., all randomized, rather than the all randomized and treated patients to which the sponsor changed. However, we also note that if the results for the all randomized and treated differ even minorly from the all randomized, then the study has definite problems with interpretation. Similarly, if the rosiglitazone exposures in the ITT population are substantially different than those in the on treatment population, then the study has definite problems with interpretation. Finally, as we discuss in our comments on the protocol, adequate follow-up for CV events, i.e., by face-to-face patient-site visits, varied. We discuss the analysis issues related to rosiglitazone exposures in more detail below regarding censoring rules.

Censoring Rules

RECORD had problems both regarding rosiglitazone exposure and regarding follow-up. Hence censoring rules regarding when to stop counting patient events are critical. The sponsor’s Report Analysis Plan dated March 13, 2009 (the only version submitted initially) refers to “All Randomized and Treated Patients” as the “Intent-to-treat population” and clarifies that “all available follow-up from start of randomised treatment through to study end” will be used, including post-dual therapy follow-up. It clarifies the “per protocol” analysis as “on-randomised-dual-combination treatment” and excluding “triple therapy for subjects in the RSG arm.” It also provides for “A supplementary on-randomised-treatment analysis of the primary endpoint will also include all events/follow-up up to 30 days after last dose of randomised treatment (dual therapy) for those subjects who have discontinued dual therapy and continued follow-up for CV events.”

We believe that treating the RSG arms and the control arms differently is not appropriate. The treatment phases as defined in the protocol are also problematic because their durations are defined post-randomization. How long a patient remained in the initial randomized dual treatment phase was likely dependent upon the patient’s comorbid conditions, including CV conditions: Clinically comorbid conditions contribute to poor diabetic control so patients with CV conditions such as worsening heart failure or angina may be more likely to progress from dual treatment to triple treatment or to insulin therapy. We will use the treatment phases for secondary analyses but not for the primary analyses.

When to stop counting events, e.g., at discontinuation of treatment or some arbitrary time thereafter, is not clear. For another CV outcome study (the LIFE study comparing losartan to atenolol in patients with hypertension and LVH), event rates did not stabilize until 90 days after discontinuation of study drug. Whether this delayed stabilization reflects a prolonged biologic effect or uncertainly in date collections or a combination of these two factors we can only speculate. We will examine stabilization of event rates post-discontinuation in RECORD as well and base our post-discontinuation cutoff on results from both RECORD and LIFE.

The RECORD protocol specified annual visits with quarterly phone contacts and an end of study visit. However, it also allowed investigators discretion in changing the frequencies or types of visits. Unfortunately this discretion resulted in some patients only being followed by phone contacts for many years, including the end of study visit. We do not believe phone contacts are optimal for determining CV events and would have preferred that the protocol schedule be maintained more rigorously. Because the protocol specified discretionary phone contacts and because some phone contacts are reasonable for the RECORD CV follow-up phases, i.e., after randomized study drug was discontinued, we will include phone contacts in our determinations of censoring times. However, we will also perform sensitivity analyses restricted to patient visits, CV events, and deaths.

Our plan for censoring for the primary analyses is the following;

- Use a true ITT (as randomized) approach with evaluation in all arms for equal follow-up durations.
- To achieve equal durations for endpoints other than all-cause mortality, censor follow-up in all arms at the study day prior to the day on which the percentage of good follow-up falls below 90% provided that the exposure time in the rosiglitazone arms is 80% or greater. We consider the good follow-up date for a patient who did not withdraw consent for CV follow-up and, for a control arm patient, who did not have any rosiglitazone or pioglitazone use to be the latest of the following: (1) the end of the study for patients who had an adjudicated death and for whom the cause of death was identified or who have an adequately described sudden death; (2) the date of the last visit or phone contact with the patient, excluding ones during survival-only follow-up; or (3) the discharge date of an adjudicated hospitalization, excluding ones with insufficient information to discriminate a CV from a non-CV hospitalization. For a patient who withdrew consent to follow-up or a control arm patient with rosiglitazone or pioglitazone use the good follow-up date is the earlier of the above or the date on which consent was withdrawn or, for a control arm patient, the date on which rosiglitazone or pioglitazone was started.
- If the rosiglitazone exposure time at 90% good follow-up is less than 80%, use the duration of follow-up at which the rosiglitazone exposure is 80% for the primary analyses. For event censoring for exposure time see our discussion of event censoring regarding phases below.
- For all cause mortality use the 80% rosiglitazone exposure time.

We will perform sensitivity analyses using the following variations in censoring:

- Variations on the good follow-up ITT approach:
 - Censoring follow-up based on good follow-up percentages of 80% and 95% as well as using all available good follow-up.
 - Using 90% good follow-up and rosiglitazone exposure times of 90% and 67%
 - Ending good follow-up n days after a rosiglitazone arm patient discontinues rosiglitazone (n will be determined based on CV AE rates after discontinuing

- Restricting patient contacts to face-to-face patient-site visits as estimated by vital sign recordings
- Ignoring rosiglitazone or pioglitazone use in the control arms
- Using all available survival follow-up for all cause mortality
- Dual randomized treatment phase
- Rosiglitazone triple treatment phase with matching durations of follow-up in the control arms

For these treatment phase analyses as well as the exposure time analyses we believe that we should not censor events on the treatment end day or the exposure drop day for the following reasons: For another CV outcome study (the LIFE study comparing losartan to atenolol in patients with hypertension and LVH), event rates did not stabilize until 90 days after discontinuation of study drug. Whether this delayed stabilization reflects a prolonged biologic effect or uncertainly in date collections or a combination of these two factors we can only speculate. We will examine stabilization of event rates post-discontinuation in RECORD as well and base our post-discontinuation cutoff on results from both RECORD and LIFE. Note that the sponsor is proposing 30-days for one of their analyses so we will include 30-days post treatment as one of our sensitivity analyses.

Subgroup and Covariate Analyses

We plan to perform exploratory analyses for a variety of subgroups and covariates. These analyses will include but are not limited to the following:

- Age and gender (race is 99% white)
- Region
- Use and dosage of statins
- Heart disease history at baseline

Appendix 9: Treatment Assignments for Examples

Table 1: Appendix 1 Case Examples

case	arm
A	rosiglitazone
B	rosiglitazone
C	rosiglitazone
D	rosiglitazone
E	control
F	rosiglitazone
G	control
H	rosiglitazone
I	control
J	control
K	rosiglitazone
L	control
M	rosiglitazone
N	rosiglitazone
O	control
P	control
Q	rosiglitazone
R	control
S	control
T	control

Table 2: Appendix 5 CV Death Disagreements

#	arm
1	control
2	control
3	rosiglitazone
4	rosiglitazone
5	rosiglitazone
6	control
7	control
8	control
9	rosiglitazone
10	control
11	rosiglitazone
12	control
13	control
14	rosiglitazone
15	control
16	control
17	rosiglitazone

Table 3: Appendix 6 MI Disagreements

#	arm
1	control
2	control
3	rosiglitazone
4	rosiglitazone
5	rosiglitazone
6	rosiglitazone
7	rosiglitazone
8	control
9	rosiglitazone
10	rosiglitazone
11	rosiglitazone
12	rosiglitazone
13	rosiglitazone
14	rosiglitazone
15	rosiglitazone
16	rosiglitazone
17	rosiglitazone
18	rosiglitazone
19	rosiglitazone
20	rosiglitazone
21	rosiglitazone
22	control
23	rosiglitazone
24	control

Table 4: Appendix 7 Stroke Disagreements

#	arm
1	control
2	rosiglitazone
3	rosiglitazone
4	rosiglitazone
5	control
6	rosiglitazone
7	rosiglitazone
8	rosiglitazone
9	control
10	control
11	control
12	rosiglitazone
13	rosiglitazone
14	rosiglitazone
15	control
16	rosiglitazone
17	rosiglitazone

Appendix 10: Abbreviations

<u>Abbreviation</u>	<u>Description</u>
AE	adverse event
af, afib	atrial fibrillation
AMI	acute myocardial infarction
AST	aspartate aminotransferase
CABG	coronary artery bypass graft (operation)
CAD	coronary artery disease
CEC	Clinical Endpoint Committee
CEVA	Clinical Event Validation and Adjudication (Services) at Quintiles-Dublin
CHF	congestive heart failure
CK, CPK	creatine (phospho)kinase
CK-MB	creatine kinase-myocardial band
CRF	case report form
CT	computerized (axial) tomography (scan)
ctl	control (arm or arms)
CV	cardiovascular
CVO	cardiovascular outcomes
CVO/TSS	CV outcomes/Tracking Substudy - phase following the randomized treatment phase during which patients were followed for CV outcomes
d	day
DRQ	data resolution query (regarding CRF entries)
ECG	electrocardiogram
ECHO	echocardiography
EP	endpoint
FDA	Food and Drug Administration
GP	general practitioner
GSK	GlaxoSmithKline
HF	heart failure
HR	hazard ratio
IHD	ischemic heart disease
LBBB	left bundle branch block (on ECG)
LVH	left ventricular hypertrophy
m, mo	month - durations in analyses are based on a 30d month
MACE	major adverse CV events, typically CV death, MI, & stroke
MET	metformin
MI	myocardial infarction
mr	metformin stratum, rosiglitazone randomized
MRI	magnetic resonance imaging
ms	metformin stratum, sulfonylurea randomized
NHS	National Health Service
non-CV	non-cardiovascular
PE	pulmonary embolism
PEP	primary endpoint
PEY	person exposure year
PPAR	peroxisome proliferator-activated receptor
PTCA	percutaneous transluminal coronary angiography
QDUB	Quintiles-Dublin, the CEC Coordinating Center

<u>Abbreviation</u>	<u>Description</u>
RAP	Reporting and Analysis Plan (GSK)
RBBB	right bundle branch block (on ECG)
ros, RSG	rosiglitazone
RTP	randomized treatment phase
rx	treatment
SAE	serious adverse event
SAS	Statistical Analysis System
SC	Steering Committee
sm	sulfonylurea stratum, metformin randomized
sMI	silent myocardial infarction
sr	sulfonylurea stratum, rosiglitazone randomized
SSO	survival status only
SU	sulfonylurea
TIA	transient ischemic attack
TSS	Tracking Substudy
UA	unstable angina
UK	United Kingdom
ULN	upper limit of normal
w, wk	week
y, yr	year

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
NDA-21071	SUPPL-36	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T
NDA-21071	SUPPL-37	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

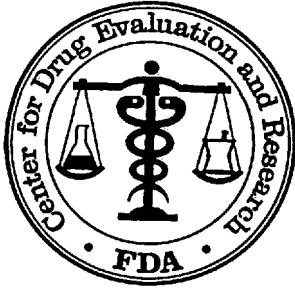
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THOMAS A MARCINIAK
06/14/2010

NORMAN L STOCKBRIDGE
06/15/2010

Dr. Marciniak identified numerous valid issues with the design and conduct of RECORD. These issues leave much in doubt and thus undermine one's ability to take much comfort from the safety findings. It is less clear to me whether, despite its shortcomings, one can interpret RECORD as showing new evidence of the harm of rosiglitizone.



OFFICE OF DRUG EVALUATION – I

Date: June 15, 2010

NDA: 21-071; suppl 35, 36, 37
Avandia (rosiglitazone)

From: Ellis F. Unger, M.D.
Deputy Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Evaluation and Research, FDA

To: The File

Background:

The Division of Metabolism and Endocrinology Products (DMEP) consulted the Division of Cardiovascular and Renal Products (DCaRP) on the RECORD trial, submitted as a supplement to NDA 21-071.

The questions for the consultant were:

1. Were the event definitions appropriate for the components of the primary endpoint, and for other defined major adverse cardiovascular events?
2. Was the adjudication process for major adverse cardiovascular events acceptable?
3. After start of the trial, more patients in the rosiglitazone group initiated a statin than did patients in the overall comparator group. Can you suggest additional analyses to further explore this issue?
4. If the consulting cardiologist notes additional important cardiologic issues which may affect the interpretation of the trial results or the proposed PI language, additional input is welcome.

The purpose of this memorandum is to emphasize, and perhaps deemphasize, some of the major points highlighted in the Division of Cardiovascular and Renal Products consultative memorandum of Dr. Thomas Marciniak, dated June 14, 2010.

Design:

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. The trial 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).

Subjects with type 2 diabetes and inadequate control of hyperglycemia (hemoglobin A_{1c} ≥ 7 and $\leq 9\%$) despite metformin or sulfonylurea monotherapy were randomized 1:1 to the addition of rosiglitazone or the alternate drug (i.e., a sulfonylurea if already on metformin; metformin if already on a sulfonylurea). Randomization was blocked and managed centrally with an interactive voice response telephone system, stratified by background treatment. The starting dose of rosiglitazone was 4 mg per day. The choice of sulfonylurea (glimepiride, gliclazide, or glyburide) and starting dose of sulfonylurea (and metformin) were according to local practice.

Given the expected progression of disease over the length of the trial and the anticipated need for intensification of therapy over time, an open-label design was selected – necessary because of the difference between groups in rescue mediations, in particular, the disparate types of sulfonylureas (drugs, formulations, and doses) to be used in different regions, and the different strategies for use of insulin. The impracticality of carrying on a long-term study with double-dummy insulin was also a major consideration in the open-label design. There are a number of problems associated with an open-label trial design, and they are discussed below.

Inclusion Criteria:

Principal inclusion criteria were age 40 – 75 years, body mass index $>25 \text{ kg/m}^2$, and hemoglobin A_{1c} ≥ 7 and $\leq 9\%$ on maximally tolerated doses of background therapy for 2 months. Major exclusion criteria were use of insulin, previous use of a PPAR- γ agonist, hospitalization for a major cardiovascular event within 3 months, planned cardiovascular intervention, and heart failure (a diagnosis of heart failure, or on specific treatment for heart failure). Patients on diuretics alone could be enrolled.

Management of Hyperglycemia/Progression of Disease:

Subjects were to have a target hemoglobin A_{1c} of $\leq 7\%$. Subjects with hemoglobin A_{1c} exceeding 7% at any point after 8 weeks were to have their dose of the study medication increased, if tolerated (the rosiglitazone dose could be doubled from 4 to 8 mg daily). If, despite titration of rosiglitazone or the comparator, hemoglobin A_{1c} was $\geq 8.5\%$ on two consecutive occasions >1 month apart, subjects were to receive rescue therapy; however, the rescue strategies differed for the 2 treatment groups. For subjects randomized to rosiglitazone, a third oral agent was to be added (sulfonylurea or metformin). If control remained inadequate, rosiglitazone was to be discontinued and insulin begun, with or without continued sulfonylurea and/or metformin. Subjects in the comparator group were to have insulin added, alone, or in combination with sulfonylurea or metformin. (At the time of approval in Europe, concomitant use of rosiglitazone with insulin was not advised.)

Study Visits:

Study visits were scheduled at screening and baseline (after a 4-week run-in program; time of randomization), and then every 2 months through 1 year, every 3 months for the second year, and then every 4 months. Subjects who discontinued study agents were to have visits annually, based on the day of the baseline visit. Subjects who withdrew from randomized treatment were to be contacted annually. The planned median follow-up was 6 years.

Monitoring/Collection of Events:

The study was monitored by Quintiles, Bracknell, UK. An independent data safety monitoring board reviewed unblinded data at approximately 6-month intervals.

Deaths and cardiovascular events were identified through adverse event reporting at study visits. Data were obtained by Quintiles and provided to a clinical endpoint committee coordinating center (also known as the Clinical Endpoint Validation and Adjudication group—CEVA), managed by Quintiles, with study treatment identifiers removed. Communications then took place between CEVA and the unblinded investigator, to confirm that endpoint criteria were met. If CEVA determined that the event met the protocol-defined criteria of a potential endpoint, the endpoint dossier was submitted to the independent clinical endpoint committee (CEC), which made determinations of endpoints, blinded to treatment assignment.

According to the sponsor, a number of measures were taken to ensure that all potential endpoints were reported to CEVA. Dr. Marciniak expresses the strong view, however, that referral for adjudication was inadequate. In appendix 3 on page 95 of his review (Table 4), he shows examples of 8 events that should have been sent for CEC adjudication, but were not. Given the complexities of some of the events, it could be argued whether the event would have met the criteria for an endpoint. However, that is exactly Dr. Marciniak's point: these cases should have been sent to the CEC so that the facts could have been debated by experts, blinded to treatment assignment. He also notes that all 8 events occurred in subjects in the rosiglitazone group, suggesting that the biases anticipated in an open-label study were, in fact, operational in RECORD.

Although not specifically mentioned in Dr. Marciniak's consultative memo, these examples highlight a fundamental problem with the adverse event reporting paradigm for RECORD: The CEC was only given the opportunity to debate endpoint events when the investigator (and presumably the CEVA) agreed that a potential endpoint event had occurred. In essence, they mostly had the opportunity to *downgrade* events that the investigators considered to be potential endpoints. By plan therefore, the CEC did not have the opportunity to consider adverse events that investigators believed fell short of the threshold for an endpoint, and *upgrade* them. In an open-label non-inferiority study, one would have wanted to CEC to "cast a wide net," and have the potential to upgrade events that investigators did not deem to be endpoints, as well as downgrade events that failed to meet standard criteria.

Study Endpoints:

The primary endpoint was time to first occurrence of cardiovascular hospitalization or cardiovascular death. The primary hypothesis was to be tested with a non-inferiority approach and a margin of 1.2 for the hazard ratio (if the 95% confidence interval [CI] of the upper bound was <1.2, non-inferiority could be claimed).

There were numerous secondary endpoints, some with multiple parameters, and many planned to be assessed at multiple time points. They could be broadly divided into two categories:

Endpoints related to cardiovascular outcomes and microvascular events:

- Time to all cause mortality endpoints

- Time to first occurrence of definite heart failure
- Time to first occurrence of all cause mortality, myocardial infarction, stroke, definitive congestive heart failure, and unstable angina
- Time to first occurrence of cardiovascular death, myocardial infarction, stroke and unstable angina
- Time to first occurrence of the combined cardiovascular death and/or cardiovascular hospitalization and microvascular events (diabetes related)
- Frequency of combined endpoints of cardiovascular death and/or cardiovascular hospitalization and microvascular events (diabetes related)
- Time to first occurrence of microvascular events (diabetes related)

Endpoints related to glycemic control, metabolic status, blood pressure, and economic parameters:

- Change from baseline in HbA1c, fasting plasma glucose (FPG), insulin, pro-insulin and urinary albumin:creatinine ratio from baseline to 18 months, 3 years, and end of study
- Proportion of patients achieving pre-defined targets ($FPG \leq 7.0\text{mmol/L}$ and hemoglobin $A_{1c} \leq 7.0\%$) of glycemic control after 18 months, 3 years, and end of study
- time to failure of glycemic control on dual combination therapy, defined as an hemoglobin $A_{1c} \geq 8.5\%$, following at least 8 weeks on maximum tolerated dose of add-on treatment and a confirmatory hemoglobin $A_{1c} \geq 8.5\%$ at least 4 weeks later
- Time to addition of a third oral therapy for rosiglitazone combination groups or switch to insulin for metformin and SU combination groups
- Time to initiation of treatment with insulin
- Change from baseline in insulin resistance and beta cell function as estimated using the homeostasis model assessment at 18 months, 3 years, and end of study
- Percentage change from baseline in lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and free fatty acids), PAI-1 antigen, fibrinogen, Apo-B and C Reactive Protein (CRP) and change from baseline in total cholesterol /HDL-cholesterol and LDL-cholesterol /HDL-cholesterol at 18 months, 3 years, and end of study
- Change from baseline in 24 hour ambulatory blood pressure parameters at 6 and 12 months
- Change from baseline in responses from the Diabetes Symptom Checklist (Hyperglycemia, Hypoglycemia, Neurology, Cardiology, Psychology, Ophthalmology) at 3 years and study end
- Number per 1000 patient-days in pharmacoeconomic endpoints

All endpoints were to be tested with a 2-sided test with $\alpha = 0.05$. *There was no plan to deal with multiplicity.*

Critique of Study Design and Analytic Plan:

Dr. Marciniak has noted a number of limitations and concerns regarding the RECORD design in his Appendix 2, beginning on page 78 of his review memorandum. His major criticisms are summarized below, along with some of my own:

1. Open-Label Design

Clearly, the open-label design is the most important limitation of RECORD. Dr. Marciniak opines that the study could have been placebo-controlled and blinded, but on this point I mostly disagree with Dr. Marciniak. I have some sympathy for those who designed the trial. Given the differences between groups with respect to rescue mediations, in particular, the variety of

sulfonylureas used across regions (different drugs, formulations, and doses) and the different strategies for use of insulin, blinding would have been extremely difficult. The impracticality of carrying on a long-term study with double-dummy insulin was a major consideration as well. Although I do not share Dr. Marciniak's view that the trial could have been blinded, I share his concerns regarding the consequences.

Ascertainment bias can be a critical issue with open-label trial designs. In RECORD, given that the investigators, contract research organization, and sponsor were aware of (or had access to) treatment assignment, the interpretation of a subject's clinical findings, decisions on ordering confirmatory investigations (cardiac enzymes, imaging studies, etc.), and threshold for reporting events could have been affected by bias. Moreover, queries by the monitoring staff were made with potential knowledge of treatment assignment; all discussions between study staff or Quintiles personnel and the investigators were, *by definition*, with knowledge of treatment assignment.

Clinical trialists worry about biases related to investigators' financial conflicts of interest, but investigators can be inherently biased towards demonstrating safety of a test drug irrespective of any financial involvement. If the goal of a study is to demonstrate the safety of a drug with respect to a particular type of event, and a subject experiences an untoward event, the investigator must accept some measure of responsibility for the outcome, at least subconsciously, for if the event was drug-related, it might not have occurred had she/he not enrolled the subject. This is not to say that investigators do not follow Good Clinical Practice (GCP); it is only to make the point that they subscribe to GCP in the presence of possible subconscious biases.

Dr. Marciniak has identified a number of concerns in his memorandum, making the case that ascertainment bias was operational in RECORD, acting in favor of rosiglitazone. Based on the points, above, I would say that such biases are actually *expected*. That is why double-blind trials are demanded, when feasible! The question is really whether these biases were controlled and/or neutralized. Although Dr. Marciniak comes to the conclusion that redaction of endpoint dossiers for the CEC was adequate, the CEC surely could not adjudicate what they did not see. By design, the CEC was given the opportunity to downgrade events that the investigator and CEVA deemed to be potential endpoints (i.e., classify them as non-endpoints). The CEC did not adjudicate events when the collective view of the investigator and CEVA was that the event failed to meet the criteria for an endpoint event. Thus, no matter how well blinded the CEC might have been, it could neither compensate for, nor prevent, ascertainment bias. As such, many of the results of RECORD should be interpreted in light of the potential for ascertainment bias, a byproduct of the open-label design.

Of note, however, from my own review of the data I find it reassuring that the fractions of deaths deemed to be cardiovascular in nature by the CEC were virtually the same in the two treatment groups (44% and 45% in the rosiglitazone and control groups, respectively). If biases were operational in classifying deaths as cardiovascular in etiology (and therefore endpoint events), one would expect a lower percentage of deaths classified as cardiovascular in the rosiglitazone group. This was not the case here, and I gain moderate assurance that such biases were not, in fact, extant in RECORD.

2. Design Complexities

Dr. Marciniak points out that there were a number of study phases in RECORD, the length of which was determined by failure to meet goal with respect to hemoglobin A_{1c}, prompting increases in dose or changes in therapy. For example, some subjects whose hyperglycemia was poorly controlled on rosiglitazone, sulfonylurea, and metformin were switched to insulin; in others, insulin was added to all three.

Dr. Marciniak notes that it is difficult to interpret a true intent-to-treat (ITT) analysis with evaluation of all randomized patients observed for equal duration, or at a fixed time post-randomization, with the study treatment remaining as randomized. Given that changes in therapies may be associated with particular patient characteristics and outcome events, interpretation is challenging.

I would argue that the primary analysis should be conducted on the “as-treated” population for a non-inferiority study (see # 9, below).

3. Change in Visit Schedule

Protocol amendment 7, dated February 27, 2006, Section 3.4.1, relaxed the frequency of patients visits: “If it will help to retain a patient in the study, the investigator can modify the frequency and schedule of assessments in the CV Outcomes phase (Post-Randomised Treatment Phase) to a ‘modified schedule’ agreeable to the patient. For example, the annual clinic visit could be optional and the patient contacted only by telephone (ideally every 4 months, but this is flexible and the frequency of contact can be increased or decreased to fit in with the patient).”

This amendment, coupled with some lack of clarity in the case report forms (CRFs) and human errors, caused ambiguities with the final dates of follow-up in some subjects. Dr. Marciniak’s review found errors in the CRFs of 8 of 100 randomly selected subjects. In terms of the importance of this, the last date of follow-up impacts only the censoring date and not whether or not a subject experienced an event; thus, the results are unlikely to be importantly affected by these errors. Nevertheless, the 8% figure seems disturbingly high.

4. Exclusion of Higher Risk Subjects

Dr. Marciniak opined that the RECORD entrance criteria appear to define a typical, inadequately controlled, type 2 diabetic population. He noted, however, that exclusion of patients hospitalized for a major cardiovascular event within 3 months, patients scheduled for a major cardiovascular intervention, or the presence of gangrene or treatment for heart failure contributed to the low CV event rates that concerned the RECORD Steering Committee and that external critics of RECORD have noted. This occurs not infrequently in clinical trials, where exclusion criteria and intensive monitoring lead to event rates lower than expected, based on those predicted from “real world” experience.

5. Primary Endpoint

For the assessment of cardiovascular safety of a drug, Dr. Marciniak points out that the standard endpoint of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke (Major Adverse Cardiovascular Event: MACE) is generally favored, as discussed in FDA’s “Guidance for Industry on Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes,” December, 2008. MACE captures the most significant cardiovascular events, and its components are “hard” events that are relatively well-

defined and reliably ascertained. The 1° endpoint of RECORD was time to first cardiovascular hospitalization or cardiovascular death, and the former component is somewhat problematic.

Dr. Marciniak notes the following issues with the use of cardiovascular hospitalizations as a component of the 1° endpoint in RECORD, and I agree with his concerns:

- a. Cardiovascular hospitalizations include a wide range of disorders, including some that are unlikely to be affected by the drug, e.g., need for valve replacement. Inclusion of hospitalizations for disorders not related to the drug introduces “noise” that biases the results towards the null, i.e., towards a finding of non-inferiority.
- b. Adjudication of cardiovascular hospitalizations can be difficult. Subjects frequently don't present with a single cause for admission. The original protocol discussed adjudication of some but not all categories of cardiovascular hospitalizations. Dr. Marciniak observed problems with missed adjudications when multiple events occurred during the same hospitalization.
- c. Hospitalizations for cardiovascular procedures may be strongly influenced by local practice patterns, physician preferences, and economics. Restriction of the endpoint to only “urgent” cardiovascular procedures, as was attempted in RECORD, may reduce the contribution of physician factors, but it introduces problems related to the determination of “urgent.” Dr. Marciniak noted inconsistent endpoint determination for cardiovascular procedures in a few cases (see Appendix 3 of Dr. Marciniak's memorandum).

6. Secondary Endpoints

This was not a criticism of Dr. Marciniak, but there were literally dozens of secondary endpoints (considering that some had multiple sections and some were to be assessed at multiple time points). No adjustments were planned for multiplicity. Given that there were no plans to deal with multiplicity in a statistical sense, the secondary endpoints should be considered exploratory in nature.

7. Definition of Myocardial Infarction

The CEC Charter states that criteria for determination of acute myocardial infarction (AMI) would 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” (*J Am Coll Cardiol.* 2000;36:959-69). The definition included hospitalization, plus biomarker elevations, plus typical symptoms of cardiac ischemia or new pathological ECG findings. Dr. Marciniak notes that these criteria are somewhat restrictive: they would fail to count MIs for which biomarkers were not obtained because of death, or for which biomarker results were obtained but never forwarded to the CEC. They would not include out-of-hospital deaths due to MI (these would be counted as CV deaths, but in the absence of biomarkers, they would not be counted as MIs.) The criteria would not include MIs confirmed at autopsy, whether or not the subject was hospitalized. Dr. Marciniak opines that less restrictive criteria would have been more appropriate for RECORD.

I have to disagree with Dr. Marciniak on this point. As he correctly notes (see 5a, above), “noise” biases towards the null, which works in favor of showing non-inferiority here. Thus, it is desirable to apply strict criteria when possible, in order to avoid “noise.” The diagnostic criteria for MI have evolved over time, and much careful thought and consideration have gone into their

standardization. The framers of RECORD selected standard, contemporary criteria for defining MIs. Although one can always go back retrospectively, apply modified (and seemingly reasonable) diagnostic criteria, and argue that particular events should have been counted or excluded, these amount to post-hoc explorations, and their value seems inherently limited.

8. Endpoint Dates

Dr. Marciniak points out that neither the protocol nor the CEC Charter discussed how the CEC would adjudicate endpoint dates. The CEC deliberated on this on a few occasions, and their agreements were captured in their minutes. By their agreements, in case of hospitalization, the date of admission to the hospital would be taken as the date of the endpoint. In case of consecutive events leading to death, they decided that death would always be the primary endpoint, and the date of death would be taken as the date of the endpoint. Dr. Marciniak considers two subjects who suffer an MI on the same date, with one surviving and the other dying 15 days later. By the CEC rules, the subject who survives will have an endpoint 15 days earlier than the subject with the more severe endpoint—death. He notes that these differences in dates should not greatly affect the time-to-first-event analyses, and I agree – subtle differences in timing will not meaningfully affect the results.

9. Analysis Population

Dr. Marciniak points out considerable ambiguity regarding the analysis population to be used for the analysis of the 1^o endpoint (“all randomized patients,” “all randomized and treated patients,” and the “per protocol population”). He suggests that the analysis approach must take into account: the duration of rosiglitazone treatment; the post-randomization nature of the protocol treatment phases; the imprecision of dates; and the nature of the follow-up.

The RECORD protocol states that the analyses of cardiovascular outcomes will be assessed using the “all randomized and treated patients” population, defined as patients who were randomized and received at least one dose of add on study medication.

A safety examination is inherently a non-inferiority analysis, and for RECORD I would argue that the “as treated” population is most appropriate for such analyses, with the ITT analysis providing supplementary information. When subjects are able to start and stop the study agent and/or switch treatments, and when there is potential for informative censoring, considerable planning is required to define analyses of the “as treated” population. It is not clear that such planning was undertaken for the creation of the RECORD’s analytic plan.

10. Handling of Withdrawals

The CEC Charter states that subjects discovered to have died between the date of their complete withdrawal from the study and attempts by the site to contact them regarding the tracking sub-study should not be reported as endpoints to the CEC, because such subjects have officially withdrawn from RECORD. The CEC further noted that subjects who agreed to provide only survival status data after completely withdrawing from RECORD should not be reported as endpoints to the CEC.

Dr. Marciniak objects to this approach (Appendix 2, section 2.18, page 89 of his memorandum), and notes that it is critical to maximize follow-up for optimal interpretation of the study; the CEC’s statements allow informative censoring in this open label study; investigators could declare that subjects with significant cardiovascular morbidity and randomized to rosiglitazone

are completely withdrawn from RECORD. This would make death – typically viewed as the “hardest” endpoint – subject to bias.

He also points out that these statements contradict the protocol, which states that “**Every effort should be made to follow up patients who withdraw completely from the study**” and “At the end of the study, and if possible, the investigator will review public records (e.g., the National Death Registry) to ascertain if the patient is alive or dead. Survival status on as many patients as possible is considered crucial information for the success of this study.”

The optimum length of follow-up presents some complex issues. For a therapy that exerts an irreversible effect on the cardiovascular system (e.g., anthracycline antibiotics), long-term follow-up, even after the drug is discontinued, may be desirable. Conversely, for a therapy with reversible deleterious effects, follow-up long after the drug is discontinued provides a bias towards the null, in this case, a bias towards showing non-inferiority. In practice, when the cardiovascular safety of a drug is unknown, the mechanism and reversibility of untoward effects (if any) are unknown, and it is not clear how long subjects should be followed after discontinuation of the drug. Such would have been the case in RECORD.

Study Results:

Recruitment occurred from April 2001 to April 2003, with 4447 subjects randomized at 364 centers in Europe, Australia, and New Zealand. Final study visits were conducted in December, 2008.

Baseline characteristics:

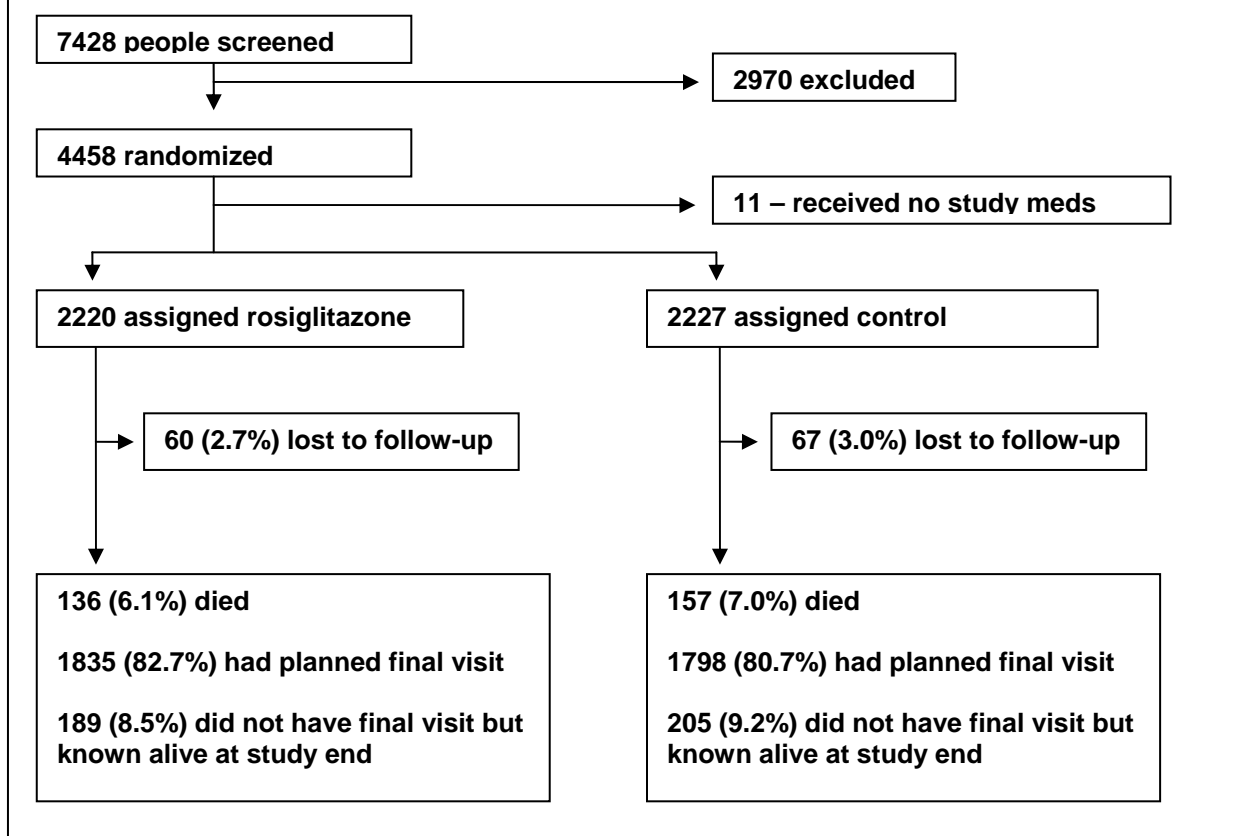
Baseline characteristics are well-described by the sponsor and were well-balanced between the rosiglitazone and control groups; there were a number of imbalances in characteristics between subjects taking metformin and sulfonylurea at baseline. Relative to patients treated with metformin at baseline, patients on a sulfonylurea at baseline were, on average, 1.7 years older, 8.7 kg lighter in body mass, and less likely to be a smoker (14.1% versus 17.7%). Fasting plasma glucose was higher in patients who received a sulfonylurea at baseline (183 versus 171 mg/dL), their duration of diabetes was 1.7 years longer, and greater percentages had ischemic heart disease (19.6% versus 15.1%) and peripheral vascular disease (10.5% versus 7.9%). These differences suggest that the presence of some patient characteristics led to preferential use of metformin or a sulfonylurea.

Follow-up:

According to the sponsor, 88.7% of subjects completed cardiovascular follow-up for the 1^o endpoint, and this figure was essentially the same in both treatment groups. With respect to mortality, vital status was known in all but 2.9% of subjects; again, this fraction was the same in both treatment groups.

Figure 1 summarizes subject flow in RECORD (slightly modified from sponsor with the addition of percentages):

Figure 1: Subject Disposition in RECORD



Primary Endpoint:

According to the sponsor's analysis, 14.5% of subjects in both treatment groups experienced an endpoint event, for a hazard ratio of 0.99, 95% CI 0.85 to 1.16. Results were similar in both strata. Because the upper limit of the 95% CI is <1.2, the study met its goal for a demonstration of non-inferiority. The sponsor's summaries of first events and all events contributing to the primary endpoint are provided for the ITT population in Tables 1 and 2, respectively.

It is important to note that the 1.16 upper bound of the 95% CI is relatively close to 1.20. If 7 events are added to the rosiglitazone group and 7 events are subtracted from the control group, the criterion for non-inferiority is no longer met. Assuming that ascertainment bias was operational in this unblinded study, the finding of non-inferiority on the primary endpoint should be accepted with some uncertainty.

Conversely, on the side of providing additional reassurance, it is worth noting that the protocol-specified boundary of 1.20 is arbitrary. FDA's "Guidance for Industry on Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," December, 2008, recommends 1.3 as the upper bound of the 95% CI for the estimated risk ratio for cardiovascular events (we acknowledge that 1.3 is also arbitrary!). To have exceeded FDA's recommended upper bound of 1.3, there would need to have been a net change of approximately 40 events, e.g., 20 additional events in the rosiglitazone group, and 20 fewer in

the control group. To have shown inferiority, that is, statistically significantly more events in the rosiglitazone group, approximately 24 events would have to be added to the rosiglitazone group, and 24 events would have to be subtracted from the comparator group.

In summary, the results seem only marginally robust to the protocol-defined limit of 1.2 for the upper bound of the 95% CI of the hazard ratio, but robust to FDA's newer 1.3 standard. There is no evidence of harm here, and this fact seems incontrovertible.

Table 1: Summary of First Events Contributing to CV Death or CV Hospitalization

	Combined RSG n=2220 subjects with events (%)	MET/SU n=2227 subjects with events (%)
CV Death or Hospitalization	321 (14.5)	323 (14.5)
CV Death	33 (1.5)	39 (1.8)
Acute MI	3 (0.1)	4 (0.2)
CHF	2 (0.1)	0 (0)
Sudden death	8 (0.4)	8 (0.4)
Acute vascular events	0 (0)	2 (0.1)
Other CV mortality	2 (0.1)	1 (0)
Death: presumed CV cause (insufficient data)	18 (0.8)	24 (1.1)
CV Hospitalisation	288 (13)	284 (12.8)
Acute MI	53 (2.4)	46 (2.1)
Unstable angina pectoris	20 (0.9)	21 (0.9)
CHF	39 (1.8)	19 (0.9)
Stroke	43 (1.9)	56 (2.5)
Transient ischaemic attack	9 (0.4)	9 (0.4)
Invasive cardiovascular procedure	24 (1.1)	25 (1.1)
Amputation of extremities	1 (0)	10 (0.4)
Other CV hospitalisation	99 (4.5)	98 (4.4)

Table 2: Summary of Total Events for Individual Components of CV Death or CV Hospitalization
(Note: Some subjects have multiple events; therefore, the numbers are not additive.)

	Combined RSG n=2220 subjects with events (%)	MET/SU n=2227 subjects with events (%)
CV Death	60 (2.7)	71 (3.2)
Acute MI	7 (0.3)	10 (0.4)
CHF	10 (0.5)	2 (0.1)
Sudden death	8 (0.4)	12 (0.5)
Acute vascular events	1 (0)	10 (0.4)
Other CV mortality	6 (0.3)	4 (0.2)
Death: presumed CV cause (insufficient data)	28 (1.3)	33 (1.5)
CV Hospitalisation	483 (21.8)	490 (22)
Acute MI	66 (3)	57 (2.6)
Unstable angina pectoris	28 (1.3)	28 (1.3)
CHF	69 (3.1)	36 (1.6)
Stroke	51 (2.3)	67 (3)
Transient ischaemic attack	10 (0.5)	10 (0.4)
Invasive cardiovascular procedure	99 (4.5)	116 (5.2)
Amputation of extremities	6 (0.3)	23 (1)
Other CV hospitalisation	154 (6.9)	153 (6.9)

All-cause Mortality:

In light of RECORD's open-label design and its susceptibility to ascertainment bias, the importance of all-cause mortality, a measure that is relatively insensitive to bias, looms large, especially because the majority of deaths in patients with type 2 diabetes are cardiovascular in nature. Importantly, in the meta-analysis by Nissen and Wolski (*N Engl J Med.* 2007; 356:2457-71), there was a strong and disturbing trend for excess mortality in the rosiglitazone groups. For cardiovascular mortality, the odds ratio was 1.64, 95% CI 0.98 to 2.74; $p=0.06$. For all-cause mortality, the odds ratio was 1.18, 95% CI 0.89 to 1.55; $p=0.24$.

According to the sponsor's accounting in RECORD, all-cause mortality was 6.1% in the rosiglitazone group and 7.0% in the comparator group, with a hazard ratio of 0.86 (95% CI 0.68 to 1.08). Given that all-cause mortality is a "hard endpoint" that is insensitive to bias, these figures seem reassuring on their face.

Dr. Marciniak's accounting of deaths is not materially different from that of the sponsor; however, he does not find the results reassuring. This is because he is reluctant to consider subjects who did not have their planned final visit, but were said by the sponsor to be "known alive at study end," as confirmed alive. There were 189 and 205 such subjects in the rosiglitazone and control groups, respectively. When these subjects are considered together with subjects lost to follow-up (60 and 67 subjects in the rosiglitazone and control groups, respectively), it can be said that 11.7% of subjects had incomplete follow-up. Thus, Dr. Marciniak's skepticism regarding the strength of the all-cause mortality finding hinges on whether or not one believes that subjects said to be "known alive at study end" were, in fact, alive.

If one accepts the sponsor's word on this (and I do), the data seem reassuring. I have difficulty accepting Dr. Marciniak's view, which is that one should not trust the sponsor's ascertainment of vital status for subjects who did not undergo their final planned study visit.

Nevertheless, there remain 60 and 67 subjects in the rosiglitazone and control groups, respectively, who were lost to follow-up (approximately 3% per group) and whose vital status is unknown and unknowable.

If these 127 subjects were unselected and the mortality rate for subjects with known disposition was extrapolated to them, one would expect approximately 8 deaths in these 127 subjects (~7% X 127). Of course these subjects are not unselected – they were lost to follow-up for a reason, and their mortality rate could be much higher than 6-7%. Thus, it is germane to consider how the unknown numbers of deaths in these subjects could influence the relative risk of all-cause mortality in the trial.

For the upper bound of the 95% CI for the relative risk of death to exceed 1.2, there would need to have been a differential of approximately 16 deaths between subjects lost to follow-up in the rosiglitazone and control groups. For example, 16 additional deaths in the 60 subjects (27%) in the rosiglitazone group versus zero of 67 (0%) in the control group, or 21 additional deaths in the rosiglitazone group (35%) and 5 (7%) in the control group would cause the upper bound of the 95% CI to exceed 1.2. To exceed an upper bound of 1.3, the level recommended in FDA guidance, the imbalance would have to have been even greater.

Such striking imbalances may be plausible, but they seem highly unlikely. I disagree, therefore, with Dr. Marciniak's interpretation of all-cause mortality. I deem the results of RECORD to be reassuring with respect to all-cause mortality, an endpoint essentially unaffected by ascertainment bias in an open-label study. Moreover, this finding seems critically important, given the almost statistically significant excess in mortality found in the meta-analysis of Nissen and Wolski.

Other Notable Findings:

Major Adverse Cardiovascular Events (MACE)

For MACE, results of analyses performed by the sponsor and Dr. Marciniak were similar. The sponsor calculated a hazard ratio of 0.91 (95% CI 0.73 to 1.13); Dr. Marciniak's results were 1.07 (95% CI 0.86 to 1.33). Thus, the sponsor's calculated upper bound of the 95% CI is well below 1.3; following Dr. Marciniak's adjudication of MIs, his upper bound does exceed 1.3, but only slightly (1.33).

Heart Failure

The trial confirmed the previously recognized risk of heart failure, where hospitalizations and deaths related to heart failure were more numerous in the rosiglitazone group. For heart failure hospitalizations, both the sponsor and Dr. Marciniak found hazard ratios slightly in excess of 2, and statistically significant. For heart failure deaths, Dr. Marciniak found a hazard ratio of 3.8, with 95% CI 1.3 to 11.

Myocardial Infarction

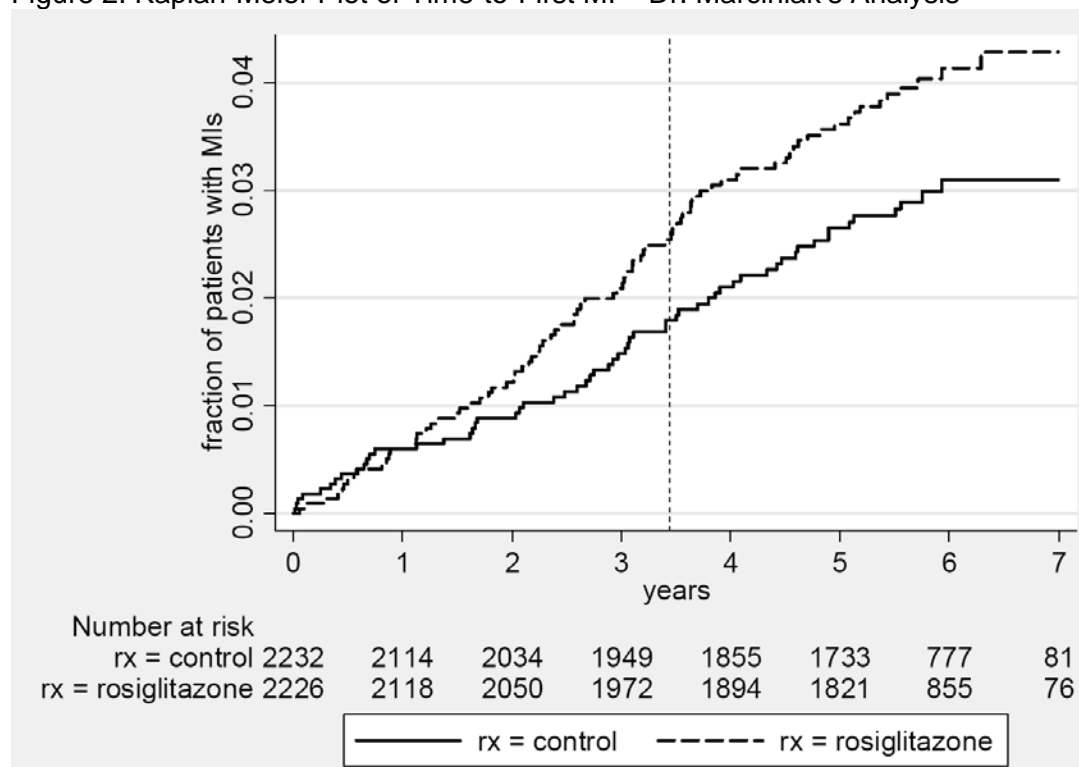
Although the principal finding of the meta-analysis of Nissen and Wolski was an excess risk of myocardial infarction (MI), RECORD was not powered to demonstrate non-inferiority on MIs.

Per the sponsor's analysis, acute MI (fatal and non-fatal) occurred in 64 and 56 subjects in the rosiglitazone and control groups, respectively, for a hazard ratio of 1.14, 95% CI 0.80 to 1.63. The sponsor makes the point that although there were 8 more subjects with fatal or non-fatal myocardial infarction in the rosiglitazone group, the overall number of subjects with a fatal MI at any time on study was higher in the control group (10) than in the rosiglitazone group (7).

As noted above (# 7, Definition of Myocardial Infarction, page 7 of this memorandum), Dr. Marciniak commented that the diagnostic criteria used for MI in RECORD were somewhat restrictive: they would fail to count events when biomarkers were not obtained because of death, or obtained but never forwarded to the CEC. They would not include MIs confirmed at autopsy. He opined that less restrictive criteria would have been more appropriate for RECORD.

After retrospectively applying modified diagnostic criteria, his adjudication added 19 MIs to the rosiglitazone group and 4 to the control group, while subtracting 1 event from the control group. (The net effect was to add 19 events to the rosiglitazone group, and 3 to the control group. This is a total of 22 events. Compared to the 120 events identified in the study, this represents an 18% increase.) Results of Dr. Marciniak's post hoc analysis are shown in Figure 2.

Figure 2: Kaplan-Meier Plot of Time-to-First MI – Dr. Marciniak's Analysis



Dr. Marciniak calculates a hazard ratio of 1.38, with 95% CI 0.99 to 1.93. Although the hazard ratio is substantially higher than the sponsor's, the difference is not statistically significant.

There may be some merit in re-adjudicating MIs in RECORD; however, there are reasons why diagnostic criteria are strictly defined and enshrined in the protocol, reasons why adjudication committees are actually committees (i.e., more than a single individual), and reasons why scrupulous blinding is essential for these committees to perform their duties correctly.

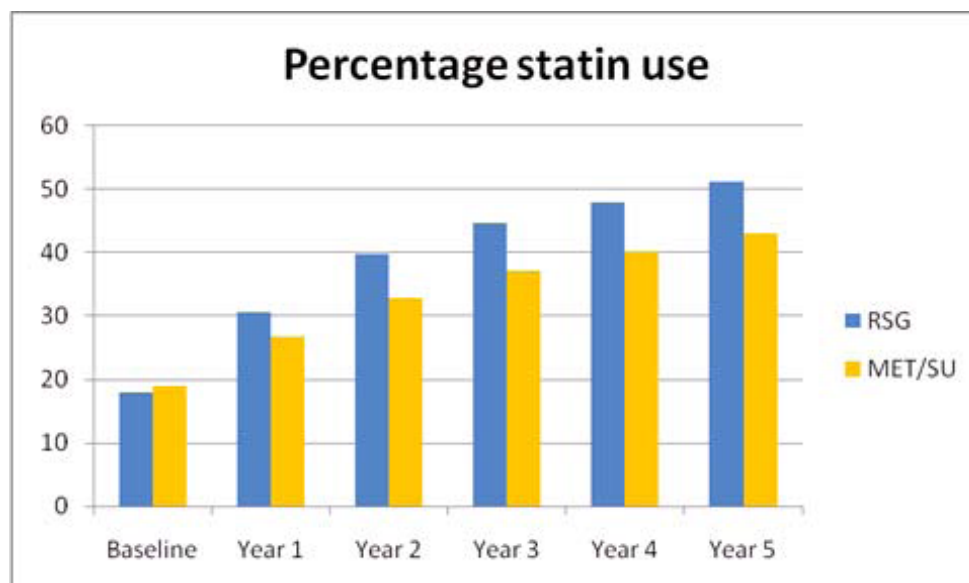
My view of MIs in RECORD is that the findings are neither reassuring nor concerning. I am not surprised that, using modified criteria, Dr. Marciniak was able to increase the number of MIs by 18%; I am somewhat concerned that nearly all of them were in the rosiglitazone group.

Statin Use

Although rosiglitazone increases LDL-cholesterol, it is thought to preferentially increase the concentration of larger, possibly less atherogenic LDL particles. It also increases HDL-cholesterol (and tends to preserve the ratio). Thus, rosiglitazone's overall effects are unknown.

Statin use increased as a function of time during RECORD, and was greater in the rosiglitazone group by approximately 7-8% absolute. At the end of year 5, statin use was 51% in the rosiglitazone group, versus 43% in the control group (Figure 3). Dr. Marciniak noted that the interpretation of statin use in RECORD was difficult. I would note that the imbalance in statin use tends to favor the rosiglitazone group, given the known cardiovascular effects of statins.

Figure 3: Sponsor's Analysis of Statin Use by Time



Overall Conclusion on Cardiovascular Safety in RECORD:

Dr. Marciniak expressed his view of RECORD this way: "We judge that there are sufficient issues with the study design that introduce biases, particularly towards the null, that we can not

rely upon RECORD to provide reassurances regarding the effects of rosiglitazone upon CV risk.”

Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products, provided these comments on Dr. Marciniak’s consultative memorandum: “Dr. Marciniak identified numerous valid issues with the design and conduct of RECORD. These issues leave much in doubt and thus undermine one’s ability to take much comfort from the safety findings. It is less clear to me whether, despite its shortcomings, one can interpret RECORD as showing new evidence of the harm of rosiglitazone.”

My view is that RECORD was an unusually complex, open-label, non-inferiority, cardiovascular safety trial. Interpretation of the results is not straightforward:

- The open-label design made the trial susceptible to ascertainment bias. Dr. Marciniak found imbalances in misinterpretations and errors in the translation of data from the primary CRFs to analysis datasets; these imbalances favored rosiglitazone and are compatible with bias.
- Discontinuations and crossovers make it difficult to define and analyze an “as treated” population, the population most appropriate for analysis in a non-inferiority safety study.
- The imbalance in statin use seems consequential, and favors rosiglitazone slightly.
- None of the secondary endpoints were designed to be tested in a statistically rigorous way. All should be considered exploratory.

Because of these issues, the results on the primary endpoint (time to first cardiovascular death or cardiovascular hospitalization) are not entirely conclusive. Conversely, the findings on all-cause mortality seem readily interpretable and important in RECORD, and they favor rosiglitazone – almost reaching statistical significance (hazard ratio 0.86; 95% CI 0.68 to 1.08, $p=0.19$). If the almost significant excess in cardiovascular mortality for rosiglitazone found in the meta-analysis of Nissen and Wolski is viewed as a hypothesis for future study, that hypothesis is not substantiated by the results of RECORD. With respect to cardiovascular safety, the strength of reassurance provided by RECORD can (and will) be debated, but, aside from the known risk of heart failure, the study does not appear to demonstrate harm.

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
NDA-21071	SUPPL-36	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T
NDA-21071	SUPPL-37	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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/s/

ELLIS F UNGER
06/15/2010

ADVISORY COMMITTEE CLINICAL BRIEFING DOCUMENT

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

New Drug Application 21071
Avandia® (rosiglitazone maleate)

Karen Murry Mahoney, MD, FACE
Division of Metabolism and Endocrinology Products

9 Jun 2010

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I. Introduction

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:

“AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.”

Among the safety concerns for RSG has been a possible increased risk of myocardial ischemic events, such as angina or myocardial infarction.

In January 2004, the World Health Organization's (WHO's) Uppsala Drug Monitoring Center published a notification of a review of postmarketing safety reports regarding thiazolidinediones (TZDs) and cardiac disease in the WHO newsletter Signal. The WHO undertook this review in response to elevated reporting ratios for the TZDs for some cardiac events, including cardiac failure, cardiomegaly, myocardial ischemia, myocardial infarction and angina pectoris. In 2005, GlaxoSmithKline (GSK), the manufacturer of Avandia®, began to develop an analysis plan regarding cardiac events in its controlled clinical trial database. On 4 August 2006, GSK submitted Supplement 22 to the Avandia® NDA; this supplement contained the results of GSK's analyses of pooled data from its completed randomized controlled diabetes clinical trials, which numbered 42 at that time. The submission also included the study report for an observational balanced cohort study.

The Agency also conducted its own meta-analysis in 2006 and 2007. This possible risk of myocardial ischemia was the subject of a July 2007 Advisory Committee meeting, at which the meta-analysis was discussed, as was emerging data from some large longterm clinical trials. In November 2007, the Full

Prescribing Information (FPI) for Avandia® was changed, and the following information was added to a Boxed Warning:

“A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.”

Additional information regarding the meta-analysis of the 42 relatively small, short-term trials and the three large, longterm trials, was included in the Warnings section of the FPI. Subsequently, the Agency also added a Medication Guide for patients, which described this potential risk and other safety information regarding RSG.

One of the three large, longterm trials for which data were available at the time of the 2007 Advisory Committee Meeting was RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia). Data from an interim analysis of RECORD were included in the updated labeling for RSG in November 2007. The RECORD trial is now complete, and a study report has been submitted and is under review by the Agency.

In a supplement submitted 25 Aug 2009, the applicant (GlaxoSmithKline, hereafter referred to as GSK), seeks to change sections of the Full Prescribing Information related to the cardiovascular safety of RSG, based on the results of the completed RECORD study.

This briefing document will present the following information:

- A preliminary clinical review of the RECORD trial
- A discussion of potential limitations to interpretability of the RECORD trial.
- A summary of the information that was available to the committee at the time of the 2007 Advisory Committee Meeting (in Appendices, Section IV)
- A summary from other sources of information regarding the cardiovascular safety of rosiglitazone that have become available since the 2007 Advisory Committee Meeting (in Appendices, Sections V and VI)

II. Preliminary Clinical Review of the RECORD Study

II.A. Background

The RECORD study was initiated in 2001 as a postmarketing commitment for the European Agency for the Evaluation of Medicinal Products (EMA). The study design was approved by the EMA's Committee for Proprietary Medicinal Products (CPMP), which is now called the Committee for Medicinal Products for Human Use (CHMP), in October 2001.

At the time of the interim analysis of RECORD, a great deal of concern was expressed regarding the low event rate up to that point, and some felt that the trial would be uninterpretable to the extent that it should not continue, although this was not the overall position of the FDA.

Now that the study report has been submitted, a primary focus of the review for this briefing document was to provide information which would allow the Committee to discuss whether the results of the trial are, in fact, interpretable. In addition to a summary of the preliminary findings of the trial, a separate summary is provided that discusses concerns which might limit interpretability (Section II.F).

II.B. Design

At the time of initiation of RECORD, the EMEA indication for rosiglitazone was for the treatment of “type 2 diabetes mellitus inadequately controlled on maximum or maximum tolerated doses of metformin or sulfonylurea alone”. The intent of the design of RECORD was to evaluate the cardiovascular safety of the drug during use consistent with this indication. The study was not conducted under a U.S. Investigational New Drug Application (IND).

Study title: “Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD): a longterm, open-label randomized study in patients with type 2 diabetes, comparing the combination of rosiglitazone and either metformin or sulfonylurea with metformin plus sulfonylurea on cardiovascular endpoints and glycemia”

Primary objective: Compare the time to reach the combined endpoint of cardiovascular death or cardiovascular hospitalization between patients treated with RSG and patients not treated with RSG, in patients with type 2 diabetes who are inadequately controlled on either MET or SU alone.

Study population: Patients with type 2 diabetes with HbA1c $>7\%$ and $\leq 9\%$, who were inadequately controlled on maximum permitted or maximum tolerated doses of background monotherapy (metformin, glibenclamide, gliclazide or glimepiride alone). Patients must have received an oral glucose lowering agent for a minimum of 6 months, and must have received their current oral glucose lowering agent at the maximum permitted or maximum tolerated dose for at least 2 months prior to visit 1.

General description of study design: This was a multicenter, randomized, open-label, parallel group study. 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.

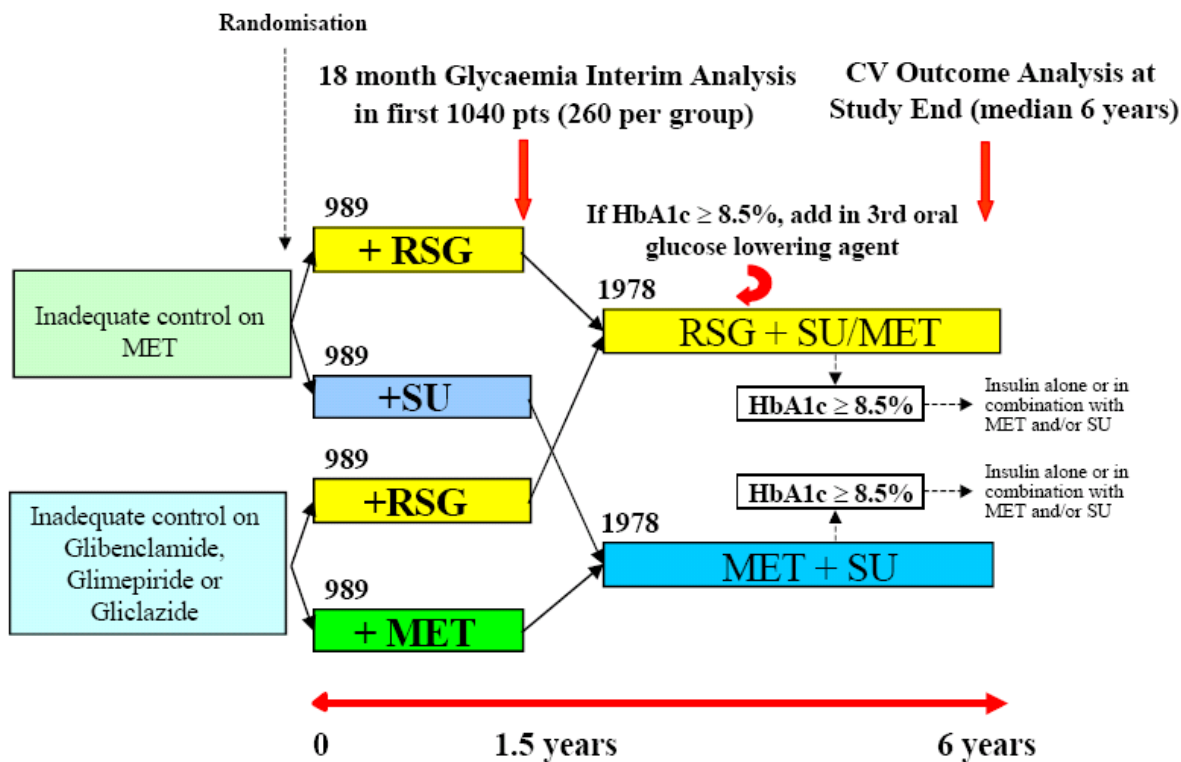
Throughout study, target hemoglobin A1c (HbA1c) was to be $\leq 7\%$. After 8 weeks of treatment, if a patient's HbA1c was $>7\%$, the investigator was to increase the dose of study medication. If tolerated, RSG was to be titrated to a dose of 8 mg/day, administered as 4 mg BID, in order to achieve a HbA1c of 7%. Doses of MET and SU were to be titrated to the maximum allowable dose approved by regulatory authority of the country in which the study site was located, also to achieve a HbA1c of 7%.

If a patient's HbA1c remained $\geq 8.5\%$ 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 $\geq 8.5\%$, 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 $\geq 8.5\%$, 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 following figure illustrates the study phases from randomization through initiation of insulin in both treatment groups.

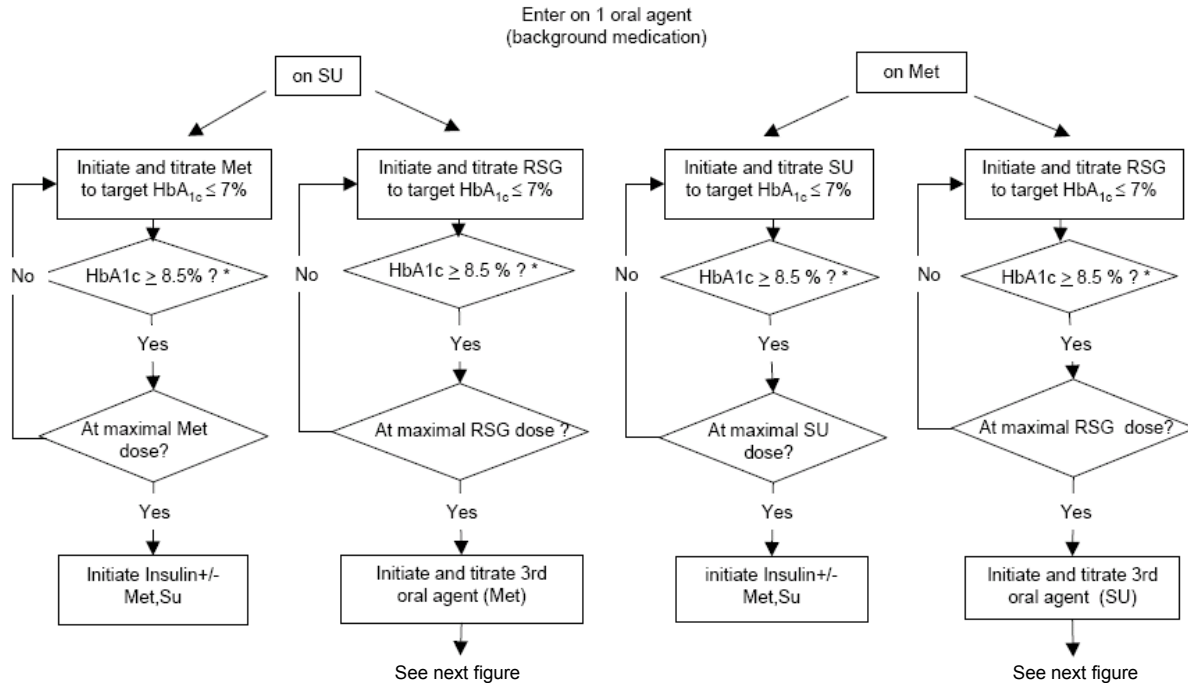
Figure II.B.1: Study Design From Randomization Through Initiation of Insulin



Source: Applicant's Figure 1, pg 28, RECORD protocol with Amendment 7, 27 Feb 2006

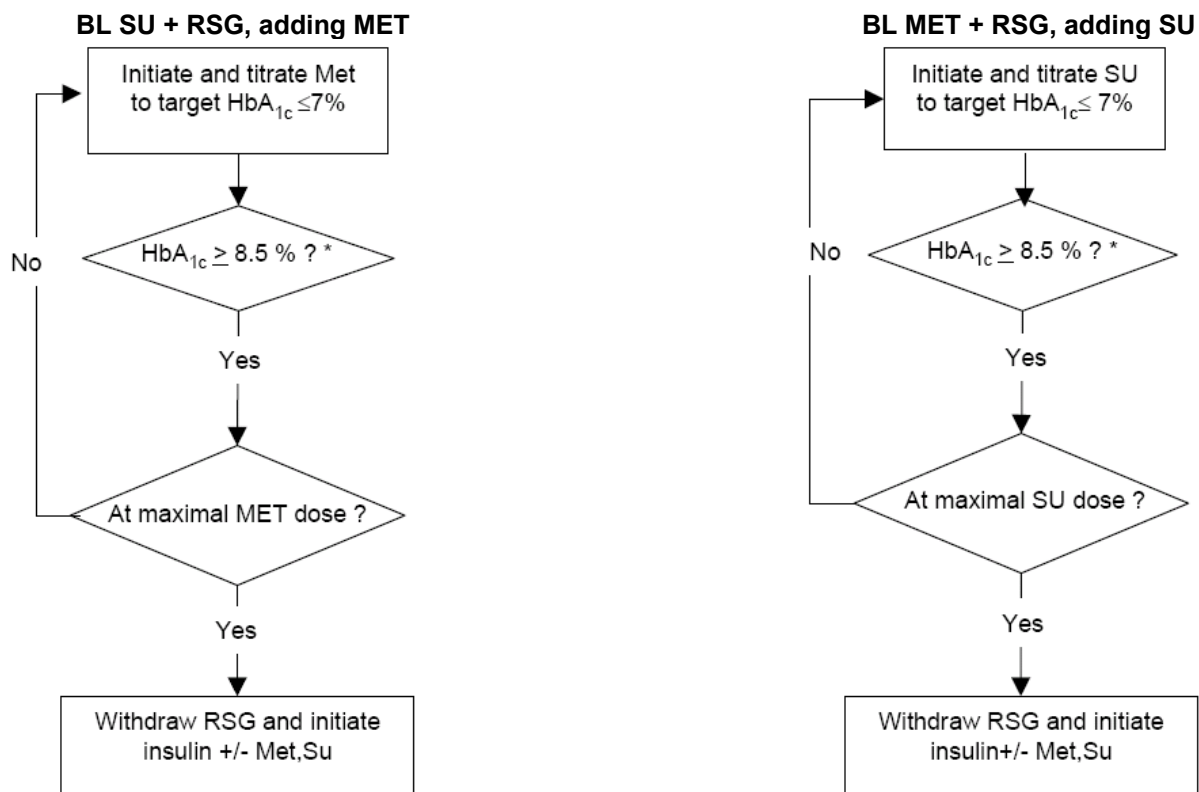
The following two figures illustrate the algorithm for add-on study medication:

Figure II.B.2: Algorithm for Addition of Study Medication From Randomization Through Triple Therapy



Source: Applicant's Figure 2, pg 32, RECORD protocol with Amendment 7, 27 Feb 2006

Figure II.B.3: Algorithm for Addition of Insulin after Triple Therapy Phase in Rosiglitazone Groups



Source: Applicant's Figure 2, pg 33, RECORD protocol with Amendment 7, 27 Feb 2006

The following tables summarize study procedures.

Table II.B.1: Abbreviated Table of Study Procedures, Screening Through Month 12

Study period →	Run-in		Treatment period					
Visit number →	1 (scrn)	2 (BL)	3	4	5	6	7	8
Week or Month (relative to baseline) →	-4 wks	0	2 mo	4 mo	6 mo	8 mo	10 mo	12 mo
Informed consent, complete H&P, incl/excl criteria check, waist/hip circumf, ht, serum beta hCG (women of childbearing potential)	X							
VS, wt	X	X	X	X	X	X	X	X
Fasting blood draw ¹	X	X	X	X	X	X	X	X
Urine for alb:cr		X			X			X
12-lead ECG	X							X
24-hr ambulatory BP		X			X			X
Dispense study med; dosing instruction; titration if indicated per protocol		X	X	X	X	X	X	X
Adverse experience checks		X	X	X	X	X	X	X
Concomitant medication check (rx only)	X	X	X	X	X	X	X	X
Diabetic diet and exercise education	X							
Diabetic diet and exercise review		X	X	X	X	X	X	X

Source: Applicant's Table 1, pg 35, RECORD protocol Amendment 7, 27 Feb 2006
Abbreviations: alb = albumin, BP = blood pressure, circumf = circumference, cr = creatinine, ECG = electrocardiogram, H&P = history and physical examination, hCG = human chorionic gonadotropin, ht = height, med = medication, rx = prescription, VS = vital signs, wt = weight
¹ In addition to routine chemistry and hematology, transaminases were measured as required per each country's guidelines for liver monitoring for RSG.

Table II.B.2: Abbreviated Table of Study Procedures, Months 15-44

Visit number →	9	10	11	12	13	14	15	16	17
Month (relative to baseline) →	15	18	21	24	28	32	36	40	44
Complete physical exam, ECG				X			X		
VS, wt	X	X	X	X	X	X	X	X	X
Waist/hip circumf				X			X		
Fasting blood draw	X	X	X	X	X	X	X	X	X
Urine for alb:cr		X		X			X		
Dispense study med; dosing instruction; titration if indicated per protocol	X	X	X	X	X	X	X	X	X
Adverse experience checks	X	X	X	X	X	X	X	X	X
Concomitant medication check (rx only)	X	X	X	X	X	X	X	X	X
Diabetic diet and exercise review	X	X	X	X	X	X	X	X	X

Source: Applicant's Table 1a, pg 36, RECORD protocol Amendment 7, 27 Feb 2006
Abbreviations: alb = albumin, circumf = circumference, cr = creatinine, ECG = electrocardiogram, rx = prescription, VS = vital signs, wt = weight

Table II.B.3: Abbreviated Table of Study Procedures, Month 48 Through Year 7

Visit number →	18	19	20	21	22	23	24	25	26	End of Tx Visit
Month (relative to baseline) →	48	52	56	60	64	68	72	76	80	Appr 84 ²
Complete physical exam, ECG	x			x			x			X
VS, wt	x	x	x	x	x	x	x	x	x	X
Waist/hip circumf	x			x			x			X
Fasting blood draw ¹	x	x	x	x	x	x	x	x	x	X
Urine for alb:cr	x			x			x			X
Dispense study med; dosing instruction; titration if indicated per protocol	x	x	x	x	x	x	x	x	x	
Adverse experience checks	x	x	x	x	x	x	x	x	x	X
Concomitant medication check (rx only)	x	x	x	x	x	x	x	x	x	X
Diabetic diet and exercise review	x	x	x	x	x	x	x	x	x	
Study conclusion record ¹										X

Source: Applicant's Table 1b, pgs 37-8, RECORD protocol Amendment 7, 27 Feb 2006

Abbreviations: alb = albumin, circumf = circumference, cr = creatinine, ECG = electrocardiogram, rx = prescription, VS = vital signs, wt = weight

¹ Minimum duration of participation in study was 60 months, and maximum was 84 months. If patient was recruited later in study, i.e. <84 months before the conclusion of the study, last scheduled visit could have been <84 months, but no <60 months.

Inclusion criteria:

- Type 2 diabetes mellitus as defined by 1999 WHO criteria
- Men or women, ages 40-75 years
- HbA1c >7.0% to ≤9.0% at Visit 1
- On an oral glucose lowering agent for at least 6 months prior to Visit 1
- For at least 2 months prior to Visit 1, patient had been on a stable dose of metformin monotherapy or SU monotherapy, at maximum allowed or maximum tolerated doses as specified below in "background diabetes medication". There were to be no changes in the MET or SU dose during the run-in phase.
- BMI >25 kg/m²
- If female, were to have been postmenopausal or using specified contraceptive methods (see RECORD protocol Amendment 7, pg 46, 27 Feb 2006).

Exclusion criteria:

- On any diabetes mellitus (DM) medication other than SU or MET
- Use of a combination of 2 or more oral diabetes medications during the 6 months prior to study
- Prior use of insulin (except during pregnancy or acute use in hospitalization, trauma or infection)
- Prior use of any TZD or PPAR gamma agonist
- Hospitalization for a major CV event in the 3 months prior to study; scheduled for a major CV intervention, or current gangrene
- Heart failure
- Systolic blood pressure (BP) >180 mmHg or diastolic BP >105 mmHg while receiving "optimal antihypertensive therapy according to local practice"
- Fasting triglycerides (TG) >12 mmol/L (1062 mg/dL)
- Serum creatinine >130 µmol/L (1.47 mg/dL)
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or alkaline phosphatase (alk phos) >2.5x ULRR (upper limit of reference range)
- Hemoglobin (Hb) <11 g/dL for men or <10 g/dL for women, or hemoglobinopathy

- Active alcohol or drug use in past 6 months
- Pregnancy or breast feeding, or plans for either during study

There was a provision in the protocol that if the first HbA1c test was “so high that in the investigator’s judgment it was likely to compromise patient safety”, the patient could be switched to insulin at that earlier point. This rarely occurred in the trial (see Table II.D.2.e).

For patients who had intercurrent illnesses that might have a major effect on glycemic control, HbA1c tests were to be performed after resolution of the intercurrent illness.

Patients who were receiving metformin and who had two consecutive serum creatinine values >130 $\mu\text{mol/L}$ (1.47 mg/dL) were to have the metformin discontinued. If HbA1c control was inadequate after discontinuation of metformin, action depended on the patient’s other current diabetes medications:

- SU only: add or substitute insulin
- SU + insulin: titrate insulin
- RSG only: add SU; if still inadequate, add insulin (with or without continued SU) and stop RSG
- RSG + SU: add insulin (with or without continued SU) and stop RSG
- Insulin only: titrate insulin

Add-on study medication doses could be reduced during study for tolerability problems. In general, the dose of the background MET or SU was to remain the same throughout study, unless the patient experienced “unacceptable” side effects (e.g. hypoglycemia, gastrointestinal intolerance), in which case the investigator could reduce the dose. Other antidiabetic agents were prohibited.

During study, the coordinators noted that some patients were withdrawing from study, and were not having collection of follow-up data. Protocol Amendment 7 (27 Feb 2006) added a tracking sub-study to contact these patients and obtain their consent for collection of CV outcomes information.

Primary efficacy variable: Time to reach the combined endpoint of cardiovascular death and/or cardiovascular hospitalization. The primary study population was the “all randomized and treated” population, i.e. all patients who were randomized and received at least one dose of study medication.

Secondary cardiovascular and diabetes-related complications outcomes included:

- Time to all-cause mortality
- Time to first occurrence of congestive heart failure
- Time to first occurrence of all-cause mortality, myocardial infarction (MI), stroke, congestive heart failure or unstable angina
- Time to first occurrence of CV death, MI, stroke or unstable angina
- Time to first occurrence of CV death, CV hospitalization or diabetes-related microvascular complication
- Time to first occurrence of diabetes-related microvascular complication
- Time to failure of glycemic control on dual oral combination therapy, defined as HbA1c $\geq 8.5\%$ following at least 8 weeks on maximum tolerated dose of add-on treatment and a confirmatory HbA1c $\geq 8.5\%$ at least 4 weeks later
- Time to addition of third oral agent for RSG group, or addition of insulin for MET/SU group
- Time to initiation of insulin

Secondary glycemic, metabolic and other outcomes included:

- Change from baseline in HbA1c, fasting plasma glucose, insulin, pro-insulin and urinary albumin:creatinine ratio; measured to 18 months (interim analysis in subset of patients), 3 years (all patients), and study end (all patients).

- Proportion of patients (pts) achieving HbA1c $\leq 7\%$ and proportion achieving fasting plasma glucose (FPG) ≤ 7 mmol/L (126 mg/dL), at 18 mo (interim analysis in subset of patients), 3 years (all pts), and study end (all pts).
- Change from baseline in lipid parameters (total cholesterol [TC], high density lipoprotein cholesterol [HDL], low density lipoprotein cholesterol [LDL], triglycerides, free fatty acids, TC:HDL, LDL:HDL), plasminogen activator inhibitor 1 (PAI-1) antigen, fibrinogen, apolipoprotein (Apo) B and C-reactive protein. Measured to 18 mo (interim analysis in subset of patients), 3 years (all pts), and study end (all pts).
- Change from baseline in 24-hour ambulatory blood pressure parameters at 6 months and 12 months.
- Change from baseline in certain homeostasis model assessment parameters
- Pharmacoeconomic endpoints
- Change from baseline in responses from a Diabetes Symptom Checklist

In general, this briefing document focuses on primary and secondary cardiovascular endpoints, with brief discussion of some other endpoints.

Background diabetes medication:

- Patients entering on metformin were to have been taking a dose of at least 1.7 gm/day for at least 2 months prior to screening Visit 1.
- Patients entering on sulfonylurea were to have been taking one of the following three sulfonylureas for at least 2 months prior to Visit 1. These 3 SUs constituted 90% of sulfonylurea use in Europe at the time of initiation.
 - Glibenclamide, at least 15 mg/day nonmicronized, or 10.5 mg/day micronized
 - Gliclazide, at least 240 mg/day standard release formulation, or 90 mg/day modified release formulation
 - Glimepiride, at least 4 mg/day

Patients who were taking lower doses of MET or SU could also be eligible if they had proven intolerance to higher doses. Minimum doses for patients who had intolerance were:

- MET, 1 gm/day
- Glibenclamide, 7.5 mg/day nonmicronized, or 5.25 mg/day micronized
- Gliclazide, 120 mg/day standard release formulation, or 45 mg/day modified release formulation
- Glimepiride, 2 mg/day

Doses of background medication were to remain unchanged throughout study.

Add-on medication doses:

- Add-on RSG was to be initiated at 4 mg/day. If up-titration was required per protocol (see above), the dose was increased to 4 mg BID
- Add-on SU and MET were to be initiated per local practice, and according to the locally available dosage strengths. If up-titration was required per protocol, the dose was increased as needed to achieve a HbA1c $\leq 7\%$, in line with local titration practices, up to the maximum allowable dose in the locality.

The initial power calculations for RECORD assumed a combined annualized event rate for the primary endpoint of 11% (3% CV death and 8% CV hospitalization). The applicant stated that this event rate was derived from the diabetes population in the CARE (Cholesterol and Recurrent Events, Goldberg 1998) and MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes substudy of Heart Outcomes Prevention Evaluation study, HOPE investigators, 2000) studies (Source: RECORD protocol with amendment 7, pg 92, 27 Feb 2006). The applicant stated that the combined annualized event rate exceeded 11% for similar events over a comparable duration in these studies. This event rate

assumption resulted in a calculated power of 99.2% to exclude a hazard ratio of 1.20, which was the 95% confidence interval upper bound target chosen for the study. At interim, the actual primary endpoint event rate was 3.1%, leading to concerns that the study would be underpowered. However, conditional power calculations (under varying assumption scenarios) conducted by FDA Biometrics indicated that, at interim, the study still had reasonable power for analyses of the primary endpoint.

The trial design for RECORD was somewhat complicated, and had multiple phases that may need explanation in order to convey an adequate understanding of patient disposition. In some cases, the name assigned to a particular phase of the trial is not intuitively descriptive of the population involved in that phase. Therefore, for some phases, the clinical reviewer has expanded on the phase name used by the applicant.

RECORD had the following phases:

- Run-in. In this phase, the patients remained on their entry medication (MET or SU), and a diet and exercise regimen was reinforced.
- Randomized treatment-dual therapy phase. The clinical reviewer refers to this phase as the “dual oral therapy phase” in the briefing document. At the beginning of this phase, patients inadequately controlled on MET were randomized to receive either RSG or SU. Patients inadequately controlled on SU were randomized to receive either RSG or MET. Investigators were given guidelines to treat patients to a target HbA1c of <7%, by adjusting the dose of the add-on study medication. Patients on dual oral therapy who had an HbA1c $\geq 8.5\%$ on two consecutive occasions at least 1 month apart had therapy added (see next bullet).
- Randomized dual/triple therapy “phase”: Not all patients went on additional therapy; as mentioned in the previous bullet, only those patients who were inadequately controlled on randomized dual oral therapy had a third agent added/substituted. Specifically, patients who were uncontrolled on RSG + MET had SU added; uncontrolled patients in the RSG + SU had MET added; and uncontrolled patients in the MET + SU group had insulin added (with or without continuing MET or SU). If a patient in an RSG group remained uncontrolled on triple oral therapy, RSG was withdrawn and insulin was added to (or substituted for) MET and/or SU. This was because RECORD was a European study, and the combination of RSG and insulin was not approved in Europe at the time of initiation of RECORD. In the study, some data are presented for the total patient-time populations on oral therapy. For the RSG group, this could be either dual or triple oral therapy, and the clinical reviewer refers to this as “dual/triple”. For the MET/SU group, this would always be dual oral therapy.
- Once a patient required insulin, they were no longer considered to be on their randomized treatment. This meant that there would likely be a different duration of time on randomized treatment for the RSG and MET/SU groups, since RSG group patients had a trial of triple oral therapy prior to the switch to insulin, but uncontrolled patients in the MET/SU group did not have the addition of a third oral agent prior to initiation of insulin. The RECORD trial began prior to the availability of most oral agents other than MET and SU, and therefore a third approved oral agent (other than acarbose) was not available for this group.
- Post-randomized-treatment/ cardiovascular outcomes “phase”. The clinical reviewer refers to this as the “PRT/CVO” phase. Patients who withdrew from the randomized treatment phase due to the initiation of insulin, or for other reasons, continued to be followed for cardiovascular events. The applicant called this “phase” of the study the “CV Outcomes Assessment Phase”. This nomenclature was potentially somewhat confusing, because in study tables, the use of this term could lead the reader to mistake the correct number of patients who had cardiovascular outcomes data collected. All patients had CV outcomes data collected throughout study, whether on-therapy or post-therapy. Patients in this post-therapy phase were also to have continued monitoring of serious adverse events (SAEs), liver enzymes, ECG and glycemic control. Visits were to occur annually, on the approximate anniversary of the patient’s randomization date (source RECORD protocol Amendment 7, pg 39, 27 Feb 2006). In between annual visits, patients were to have a telephone contact every 4 months to inquire about SAEs and hospitalization for cardiovascular events. See below for the types of CV

events which were to be counted. There were no restrictions on diabetes treatments during this phase, except that patients could not receive another PPAR gamma agonist, such as pioglitazone.

- “Survival status only phase”: Following Protocol Amendment 7, patients who withdrew from randomized treatment and refused consent for monitoring of liver enzymes or glycemic control were asked to consent to updates on their survival status. This could be done via contacts with a third party (e.g. relative, doctor) nominated by the patient. For patients who refused any further contact, the applicant attempted to obtain survival status information from other sources, e.g. National Death Registries or other public records.
- “Tracking substudy”: As part of Protocol Amendment 7, the applicant also attempted to contact patients who had withdrawn prior to Amendment 7, and to obtain their consent to be followed for CV events. If they refused consent for this, they were asked to consent to be followed for survival status only.

The specific types of CV events that were assessed during the PRT/CVO follow-up phase included:

- Death following heart failure or MI; sudden death; death due to acute vascular event
- Hospitalization due to MI, CHF, stroke, unstable angina pectoris, TIA, invasive CV procedure, amputation of extremities; or hospitalization for other CV or “undefined” CV reason.

Please see Figures II.B.1-3 for an illustration of the study phases from randomization through initiation of insulin.

Analyses were performed using the following populations:

- Intention-to-treat: Included all patients who were randomized and received at least one dose of study medication. Patient-time included all study time until death or loss to follow-up. This included all medication treatment phases (dual oral therapy portion, triple-therapy portions, and time on insulin). The applicant performed ITT analyses for the primary endpoint and all secondary endpoints.
- “Per-protocol dual oral combination therapy”: “Per-protocol” analyses were actually based on a subset of patient-time rather than a subset of patients per se. These analyses included all patients in the ITT population, and included only patient-time on dual combination therapy. It excluded time on triple therapy and insulin. The applicant performed analyses using this subset of patient-time for the primary endpoint and some secondary endpoints.
- “Per-protocol + 30 days”. Analyses for this subset of patient-time included all patient-time in the “per-protocol dual oral combination therapy” subset, plus an additional 30 days for each patient. This was done for the primary endpoint.

The flow from the time an investigative site noted an event through the various channels until the event ended up in the study report was very complex, as displayed in the following two figures.

Figure II.B.4: Event Reporting Flow From Investigative Site Through Database Lock

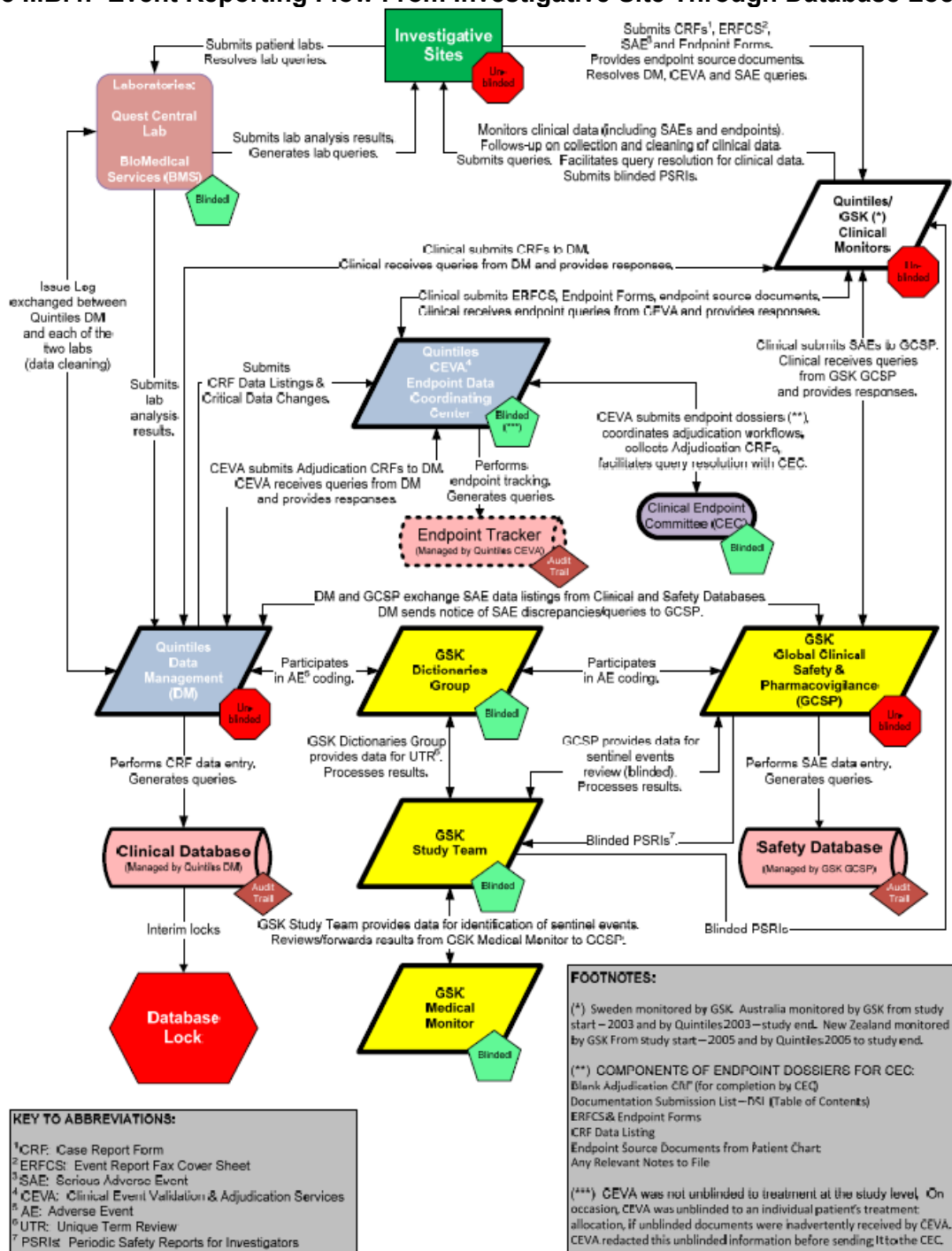
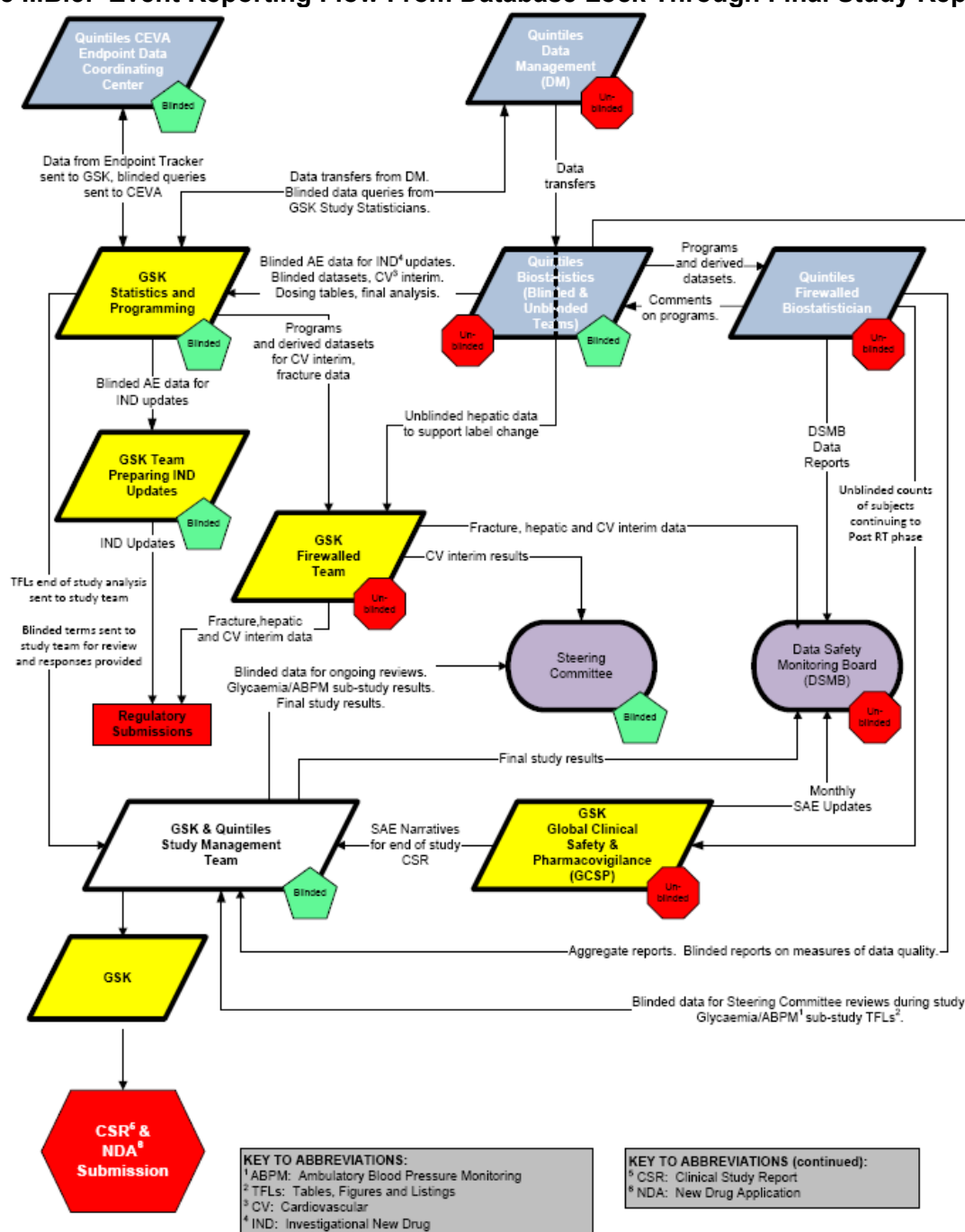


Figure II.B.5: Event Reporting Flow From Database Lock Through Final Study Report



Source: Applicant's Figure, beg pg 2, NDA 21071 submission 26 Apr 2010

Several observations can be made from these diagrams:

- Event reporting flow was complex. The numerous steps involved left room for error at multiple junctures.
- Multiple steps in the event reporting flow were unblinded, leaving open the possibility of reporting bias
- The Endpoint Data Coordinating Center, Clinical Endpoint Committee, and Statistics and Programming Team were blinded to treatment assignment. Blinding of these entities was important for trial integrity.

- An audit trail was to be maintained at key steps, including tracking of events that were submitted as potential endpoints; and data entry and queries for the clinical and safety databases. These audit trails are useful in FDA's inspection process to assess for ascertainment and event tracking.

Adjudication:

An independent Clinical Endpoints Committee (CEC) was appointed. They were to review all potential CV hospitalizations and CV deaths in blinded fashion and determine if the events met prespecified definitions.

All potential CV events referred for adjudication were to be classified as CV or non-CV. The protocol states that "all events (including death) will be considered to be of CV origin unless there is compelling evidence to indicate otherwise".

In general, all potential CV hospitalizations were also to be reported as SAEs. However, the protocol stated that hospitalizations for invasive CV procedures or amputation of extremities were to be reported as study endpoints but not as SAEs. The event leading to the hospitalization for the procedure was to be reported as an AE, or as an SAE if the event did not meet the definition of an AE. Although the clinical reviewer acknowledges that not all elective hospitalizations are due to serious adverse events, in general, any event with hospitalization involved is considered to be a serious adverse event in most clinical trials.

Cardiovascular Event Definitions:

Cardiovascular Death Definition:

Cardiovascular death was defined as any death for which an unequivocal noncardiovascular cause could not be established. Cardiovascular deaths included those following heart failure and MI; sudden death, and death due to acute vascular events. Deaths for which a cause could not be established were classified as "unknown deaths", but were counted as CV deaths for the primary endpoint.

Death following heart failure was defined as due to the onset and progression of symptoms of definite heart failure (as defined below).

Sudden death was 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 (this presumes that it is known that the patient did not have any signs or symptoms within the 24 hours before death; otherwise, the death is classified as of unknown cause)

Death due to vascular causes was defined as due to aortic dissection, aortic aneurysm, pulmonary embolism, stroke or "any other vascular cause".

Definition of cardiovascular hospitalization endpoints:

Hospitalization was defined as an admission to the hospital involving a change in date. Cardiovascular hospitalization was further defined as hospitalization for cardiac and/or macrovascular causes excluding routine or planned visits not associated with a worsening of the disease conditions of the patient. No change in date was required for unplanned ambulatory percutaneous cardiovascular intervention.

Cardiovascular hospitalization categories included hospitalizations for the following:

- acute MI
- definite CHF
- stroke
- unstable angina pectoris
- transient ischemic attack
- invasive cardiovascular procedure or amputation of extremities (did not include amputation related to trauma)
- other CV or undefined CV reasons

Acute MI was adjudicated according to a joint European Society of Cardiology and American College of Cardiology definition published in 2000 (Joint ESC/ACC Committee 2000). Elements of MI included elevation of cardiac biomarkers (troponin I or troponin T >ULN; or CK-MB ≥ 2 x ULN; or CK >2x ULN), plus one of the following:

- “typical symptoms of cardiac ischemia”, or
- new pathological ECG findings as defined in the aforementioned article.

Hospitalization for heart failure was defined as a new hospitalization for heart failure requiring a change in current medication (e.g. a change in dose, or intravenous [IV] medication, or addition of a new class of medication specific for the treatment of heart failure), in the context of new symptoms and signs and objective evidence of cardiac dysfunction.

Hospitalization for stroke was defined as hospitalization plus rapidly developed clinical signs of focal (or in certain circumstances 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. This included patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage or cerebral ischemic necrosis. It did not include secondary stroke events resulting from blood disease (e.g. leukemia or polycythemia vera); stroke symptoms from brain tumors or brain metastases; secondary stroke from trauma; or peripheral lesions that caused localizing neurologic deficits or coma. Circumstances under which global disturbance of cerebral function could be considered a sign of stroke were specified as applying to patients with subarachnoid hemorrhage or deep coma, but excluding coma of systemic vascular origin such as shock, Stokes-Adams syndrome or hypertensive encephalopathy.

Definite focal signs for the stroke definition included:

- unilateral or bilateral motor impairment
- unilateral or bilateral sensory impairment
- aphasia/dysphasia (nonfluent speech)
- hemianopia
- diplopia
- forced gaze (conjugate deviation)
- dysphagia of acute onset
- apraxia of acute onset
- ataxia of acute onset
- perception deficit of acute onset

The following were considered as *not* acceptable as sole evidence of focal dysfunction for the stroke definition:

- dizziness or vertigo
- localized headache
- blurred vision of both eyes
- dysarthria (slurred speech)

- impaired cognitive function (including confusion)
- impaired consciousness
- seizures

Hospitalization for angina pectoris was defined as hospitalization plus:

- cardiac ischemic symptoms necessitating treatment but not qualifying as MI by cardiac biochemical markers
- treatment with parenteral heparin and/or nitrates and/or beta blockers and/or a IIB/IIIA antagonist and/or antiplatelet agents

Hospitalization for TIA was defined as hospitalization for sudden onset of focal neurological deficit with complete recovery within 24 hours.

Hospitalization for invasive cardiovascular procedure or amputation of extremities was defined as hospitalization plus:

- surgical or nonsurgical revascularization of coronary, carotid or peripheral arteries for the treatment of acute/unstable conditions or deterioration of the patient, or
- amputation of extremities due to macrovascular peripheral vascular disease related to diabetes. Amputation due to trauma was excluded.

Microvascular events:

The CEC did not review or adjudicate microvascular events. Definitions for diabetes-related microvascular complications were provided to, and events were reported by, investigators.

Eye complications that were counted as diabetes-related microvascular complications included:

- new therapeutic intervention (laser coagulation carried out for the first time) for the treatment of diabetic retinopathy (worsening of existing retinopathy not counted)
- cataract extraction
- new blindness in either eye

Renal complications that were counted as diabetes-related microvascular complications included:

- end-stage renal disease necessitating dialysis or kidney transplantation
- death due to end-stage renal disease

Any new foot ulcer counted as a diabetes-related microvascular complication.

II.C. Demographics, Disposition and Exposure

A total of 4447 patients were randomized and received at least one dose of study medication. Among patients entering the study on background metformin, 1117 were randomized to the addition of RSG, and 1105 were randomized to the addition of SU. Among patients entering the study on background SU, 1103 were randomized to the addition of RSG, and 1122 were randomized to the addition of MET. The total number of patients in the combined RSG group was 2220, and the total number of patients in the combined non-RSG (MET/SU) group was 2227.

II.C.1 Demographics and Baseline Characteristics

The following table displays baseline demographics.

Table II.C.1.a: Baseline Demographics and Patient Characteristics

Parameter	Overall		Bkgrd MET		Bkgrd SU	
	RSG N=2220	Met/SU N=2227	RSG N=1117	SU N=1105	RSG N=1103	MET N=1122
% Male gender	51.4	51.7	53.8	52.9	49.0	50.6
Age, y, mean	58.4	58.5	57.0	57.2	59.8	59.7
% Caucasian	99.1	98.7	98.9	98.4	99.3	99.1
% Black	0.2	0.4	0.3	0.5	0.2	0.3
% Asian	0.4	0.4	0.4	0.2	0.5	0.6
% Other race	0.3	0.4	0.4	0.9	0.1	0
Weight, kg, mean	89.3	88.8	93.5	93.3	85.0	84.3
BMI, kg/m ² , mean	31.5	31.4	32.8	32.7	30.3	30.1
Systolic BP, mmHg, mean	139.0	138.5	139.7	139.1	138.3	138.0
Diastolic BP, mmHg, mean	83.2	82.8	84.1	83.3	82.3	82.2
DM duration, y, mean	7.0	7.1	6.1	6.3	7.9	7.9
HbA1c, %, mean	7.9	7.9	7.8	7.8	8.0	8.0
Source: Applicant's Table 6.88, beg pg 5569, RECORD study report body						
Abbreviations: BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, HbA1c = hemoglobin A1c, y = years						

In general, baseline characteristics did not differ between rosiglitazone and comparator, either for the overall comparison or by stratum. Patients in the background MET stratum tended to have a higher body weight and a shorter duration of diabetes than did patients in the background SU stratum, but within each stratum, baseline characteristics were well-matched between RSG and comparator.

The clinical reviewer examined the above baseline demographics for patients who completed the study for primary endpoint follow-up and for patients who did not complete the study for primary endpoint follow-up. There was no difference between groups for most variables, except for slight numeric differences in baseline systolic blood pressure, as shown in the following table.

Table II.C.1.b: Baseline Systolic Blood Pressure for Patients Who Did and Did Not Complete Study for the Primary Endpoint

Stratum	RSG Grp	Comp Grp	Compl I° Endpt F/U SBP (SD)	Did Not Compl I° Endpt F/U SBP (SD)
Overall	All add-on RSG (1977 compl, 243 noncompl)		139.3 (15.2)	136.6 (14.6)
		All add-on comp (1968 compl, 259 noncompl)	138.8 (15.9)	136.5 (14.8)
Bkgrd MET	RSG (1011 compl, 106 noncompl)		140.0 (15.7)	136.3 (15.1)
		SU (988 compl, 117 noncompl)	139.5 (16.3)	135.3 (16.1)
Bkgrd SU	RSG (966 compl, 137 noncompl)		138.5 (14.5)	136.9 (14.2)
		MET (980 compl, 142 noncompl)	138.1 (15.5)	137.5 (13.6)

Table II.C.1.b: Baseline Systolic Blood Pressure for Patients Who Did and Did Not Complete Study for the Primary Endpoint

Stratum	RSG Grp	Comp Grp	Compl I° Endpt F/U SBP (SD)	Did Not Compl I° Endpt F/U SBP (SD)
Source: Applicant's Table 6.88, beg pg 5569, RECORD study report body SBP = systolic blood pressure SD = standard deviation				

The above table should be interpreted with caution, because of the small numbers of patients in the noncompleter group, and because of the nonrandomized nature of the groups being compared. Patients who did not complete follow-up for the primary endpoint tended to have had a slightly numerically (but not statistically significantly) lower systolic blood pressure at baseline. One would not expect a lower systolic blood pressure to be indicative of higher CV risk among patients who did not complete the study for follow-up for the primary endpoint.

Other baseline characteristics, including cardiovascular risk factors and medications, are discussed below.

The following table displays cardiovascular risk factors at baseline.

Table II.C.1.c: Baseline Cardiovascular Risk Factors which Occurred in At Least 3 Patients in Any Treatment Group

CV RF Category	RF Term	Overall		Bkgrd MET		Bkgrd SU	
		RSG N=2220 n (%)	MET/SU N=2227 n (%)	RSG N=1117 n (%)	SU N=1105 n (%)	RSG N=1103 n (%)	MET N=1122 n (%)
Any CV RF ¹	Any CV RF ¹ Term	2206 (99.4)	2206 (99.1)	1110 (99.4)	1095 (99.1)	1096 (99.4)	1111 (99.0)
Ischemic heart dz	Any IHD Term	383 (17.3)	389 (17.5)	171 (15.3)	164 (14.8)	212 (19.2)	225 (20.1)
	Angina, stable	227 (10.2)	230 (10.3)	105 (9.4)	86 (7.8)	122 (11.1)	144 (12.8)
	Angina, unstable	20 (0.9)	30 (1.3)	7 (0.6)	16 (1.4)	13 (1.2)	14 (1.2)
	MI	104 (4.7)	114 (5.1)	50 (4.5)	62 (5.6)	54 (4.9)	52 (4.6)
	PTCA	68 (3.1)	66 (3.0)	38 (3.4)	40 (3.6)	30 (2.7)	26 (2.3)
	"Ischemic heart disease"	129 (5.8)	115 (5.2)	51 (4.6)	40 (3.6)	78 (7.1)	75 (6.7)
	Atherosclerosis	19 (0.9)	16 (0.7)	6 (0.5)	9 (0.8)	13 (1.2)	7 (0.6)
	Atherosclerosis, heart	25 (1.1)	22 (1.0)	3 (0.3)	9 (0.8)	22 (2.0)	13 (1.2)
Cerebrovascular dz	Any cerebrovasc dz term	98 (4.4)	94 (4.2)	49 (4.4)	41 (3.7)	49 (4.4)	53 (4.7)
	TIA	51 (2.3)	47 (2.1)	27 (2.4)	25 (2.3)	24 (2.2)	22 (2.0)
	Stroke	55 (2.5)	53 (2.4)	26 (2.3)	20 (1.8)	29 (2.6)	33 (2.9)
Peripheral vascular dz	Any PVD term	197 (8.9)	213 (9.6)	80 (7.2)	96 (8.7)	117 (10.6)	117 (10.4)
	PVD	112 (5.0)	119 (5.3)	36 (3.2)	42 (3.8)	76 (6.9)	77 (6.9)
	Femoral bypass	51 (2.3)	51 (2.3)	26 (2.3)	32 (2.9)	25 (2.3)	19 (1.7)
	PVD including intermittent claudication	58 (2.6)	62 (2.8)	28 (2.5)	32 (2.9)	30 (2.7)	30 (2.7)
Htn	Any htn term	1775 (80.0)	1788 (80.3)	906 (81.1)	898 (81.3)	869 (78.8)	890 (79.3)
	Hypertension	1416 (63.8)	1423 (63.9)	727 (65.1)	719 (65.1)	689 (62.5)	704 (62.7)
	Hypertensive heart disorder	4 (0.2)	2 (0.1)	3 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)
	Essential hypertension	48 (2.2)	48 (2.2)	23 (2.1)	16 (1.4)	25 (2.3)	32 (2.9)
	Elevated blood pressure	2 (0.1)	4 (0.2)	2 (0.2)	3 (0.3)	0	1 (0.1)
	Hypertensive renal dz	3 (0.1)	0	2 (0.2)	0	1 (0.1)	0
	Elev BP without hx htn ²	308 (13.9)	311 (14.0)	155 (13.9)	159 (14.4)	153 (13.9)	152 (13.5)
Lipid disorder	Any lipid disorder term	2116 (95.3)	2089 (93.8)	1072 (96.0)	1045 (94.6)	1044 (94.7)	1044 (93.0)
	"Elevated cholesterol/triglycerides"	251 (11.3)	250 (11.2)	144 (12.9)	135 (12.2)	107 (9.7)	115 (10.2)
	Hyperlipemia	458 (20.6)	469 (21.1)	254 (22.7)	253 (22.9)	204 (18.5)	216 (19.3)
	Lipid metab disorder	120 (5.4)	114 (5.1)	65 (5.8)	59 (5.3)	55 (5.0)	55 (4.9)

Table II.C.1.c: Baseline Cardiovascular Risk Factors which Occurred in At Least 3 Patients in Any Treatment Group

CV RF Category	RF Term	Overall		Bkgrd MET		Bkgrd SU	
		RSG N=2220 n (%)	MET/SU N=2227 n (%)	RSG N=1117 n (%)	SU N=1105 n (%)	RSG N=1103 n (%)	MET N=1122 n (%)
	No known hx lipid disorder but on lipid-lowering meds	18 (0.8)	25 (1.1)	9 (0.8)	10 (0.9)	9 (0.8)	15 (1.3)
	Abnl lipids without hx lipid disorder ³	1254 (56.5)	1214 (54.5)	592 (53.0)	580 (52.5)	662 (60.0)	634 (56.5)
	Chol elev	37 (1.7)	46 (2.1)	23 (2.1)	18 (1.6)	14 (1.3)	28 (2.5)
	TG elev	12 (0.5)	13 (0.6)	6 (0.5)	6 (0.5)	6 (0.5)	7 (0.6)
Smoking	Any smoking term	928 (41.8)	882 (39.6)	521 (46.6)	512 (46.3)	407 (36.9)	370 (33.0)
	Current smoker	363 (16.4)	343 (15.4)	199 (17.8)	194 (17.6)	164 (14.9)	149 (13.3)
	Previous smoker	565 (25.5)	539 (24.2)	322 (28.8)	318 (28.8)	243 (22.0)	221 (19.7)
Congestive heart failure	Any HF term	12 (0.5)	9 (0.4)	4 (0.4)	4 (0.4)	8 (0.7)	5 (0.4)
	Heart failure	11 (0.5)	9 (0.4)	4 (0.4)	4 (0.4)	7 (0.6)	5 (0.4)

Source: Applicant's Table 6.89, beg pg 5593, RECORD study report body
Abbreviations: cerebrovasc = cerebrovascular, chol = cholesterol, CV = cardiovascular, DBP = diastolic blood pressure, dz = disease, elev = elevated, HF = heart failure, htn = hypertension, IHD = ischemic heart disease, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angiography, PVD = peripheral vascular disease, RF = risk factor, SBP = systolic blood pressure, TG = triglycerides, TIA= transient ischemic attack
1 Any of the RFs listed in this table
2 No reported history of hypertension, but baseline SBP >130 mmHg or DBP >80 mmHg
3 No history of lipid disorder and on no lipid meds, but any of the following: LDL≥2.6 mmol/L; TG≥2.3 mmol/L; HDL<1.03 mmol/L (men); HDL <1.29 mmol/L (women)

The following table displays those baseline cardiovascular risk factors which occurred with a difference of 2% or more between groups in any comparison.

Table II.C.1.d: Baseline Cardiovascular Risk Factors which Occurred With a Frequency Difference of at Least 2% Between Any Comparator Groups

CV RF Category	RF Term	Overall		Bkgrd MET		Bkgrd SU	
		RSG N=2220 n (%)	MET/SU N=2227 n (%)	RSG N=1117 n (%)	SU N=1105 n (%)	RSG N=1103 n (%)	MET N=1122 n (%)
Lipid disorders	Abnl lipids without hx lipid disorder ¹	1254 (56.5)	1214 (54.5)	592 (53.0)	580 (52.5)	662 (60.0)	634 (56.5)
Smoking	Any smoking term	928 (41.8)	882 (39.6)	521 (46.6)	512 (46.3)	407 (36.9)	370 (33.0)

Source: Applicant's Table 6.89, beg pg 5593, RECORD study report body
Abbreviations: abnl = abnormal, CV = cardiovascular, hx = history of
1 No history of lipid disorder and on no lipid meds, but any of the following: LDL≥2.6 mmol/L; TG≥2.3 mmol/L; HDL<1.03 mmol/L (men); HDL <1.29 mmol/L (women)

Abnormal baseline lipid laboratory values without a prior known history of a lipid disorder, and a history of having smoked, occurred slightly numerically more frequently among RSG-treated patients for the overall comparison, and for RSG patients compared to MET patients in the background SU stratum. These differences were not statistically significantly different. Even had they been significant, they would not have conferred a baseline advantage to RSG, because they would have increased baseline risk for CV events among RSG patients.

The clinical reviewer examined the above baseline CV RFs for patients who completed the study for primary endpoint follow-up and for patients who did not complete the study for primary endpoint follow-up.

There was no difference between groups for most variables, except for slight numeric differences for some terms, as shown in the following table.

Table II.C.1.e: Baseline Cardiovascular Risk Factors For Which There Was a Frequency Difference Between Treatment Groups of at Least 3% Between Patients Who Did and Did Not Complete Primary Endpoint Followup

Risk Factor Term	Stratum	Tx ¹	Compl I° Endpt F/U	Did Not Compl I° Endpt F/U
Any ischemic heart disease term	Overall	RSG	334 (16.9)	49 (20.2)
		MET/SU	339 (17.2)	50 (19.3)
	Bkgrd MET	RSG	151 (14.9)	20 (18.9)
		SU	147 (14.9)	17 (14.5)
Angina, stable	Overall	RSG	183 (18.9)	29 (21.2)
		MET	192 (19.6)	33 (23.2)
	Bkgrd MET	RSG	93 (9.2)	12 (11.3)
		SU	78 (7.9)	8 (6.8)
Any cerebrovascular dz term	Overall	RSG	104 (10.8)	18 (13.1)
		MET	121 (12.3)	23 (16.2)
	Bkgrd MET	RSG	48 (4.7)	1 (0.9)
		SU	38 (3.8)	3 (2.6)
Any PVD term	Overall	RSG	43 (4.5)	6 (4.4)
		MET	48 (4.9)	5 (3.5)
	Bkgrd MET	RSG	171 (8.6)	26 (10.7)
		MET/SU	183 (9.3)	30 (11.6)
PVD	Overall	RSG	71 (7.0)	9 (8.5)
		SU	88 (8.9)	8 (6.8)
	Bkgrd MET	RSG	100 (10.4)	17 (12.4)
		MET	95 (9.7)	22 (15.5)
PVD (including intermittent claudication)	Overall	RSG	97 (4.9)	15 (6.2)
		MET/SU	100 (5.1)	19 (7.3)
	Bkgrd MET	RSG	31 (3.1)	5 (4.7)
		SU	39 (3.9)	3 (2.6)
Any hypertension term	Overall	RSG	66 (6.8)	10 (7.3)
		MET	61 (6.2)	16 (11.3)
	Bkgrd MET	RSG	49 (2.5)	9 (3.7)
		MET/SU	52 (2.6)	10 (3.9)
Hypertension	Overall	RSG	26 (2.6)	2 (1.9)
		SU	27 (2.7)	5 (4.3)
	Bkgrd MET	RSG	23 (2.4)	7 (5.1)
		MET	25 (2.6)	5 (3.5)
Any lipid disorder	Overall	RSG	1592 (80.5)	183 (75.3)
		MET/SU	1583 (80.4)	205 (79.2)
	Bkgrd MET	RSG	827 (81.8)	79 (74.5)
		SU	807 (81.7)	91 (77.8)
Hyperlipemia	Overall	RSG	765 (79.2)	104 (75.9)
		MET	776 (79.2)	114 (80.3)
	Bkgrd MET	RSG	1270 (64.2)	146 (60.1)
		MET/SU	1260 (64.0)	163 (62.9)
Any lipid disorder	Overall	RSG	665 (65.8)	62 (58.5)
		SU	645 (65.3)	74 (63.2)
	Bkgrd MET	RSG	605 (62.6)	84 (61.3)
		MET	615 (62.8)	89 (62.7)
Hyperlipemia	Overall	RSG	1890 (95.6)	226 (93.0)
		MET/SU	1852 (94.1)	237 (91.5)
	Bkgrd MET	RSG	972 (96.1)	100 (94.3)
		SU	936 (94.7)	109 (93.2)
Hyperlipemia	Overall	RSG	918 (95.0)	126 (92.0)
		MET	916 (93.5)	128 (90.1)
	Bkgrd MET	RSG	409 (20.7)	49 (20.2)
		MET/SU	426 (21.6)	43 (16.6)
	Bkgrd MET	RSG	233 (23.0)	21 (19.8)

Table II.C.1.e: Baseline Cardiovascular Risk Factors For Which There Was a Frequency Difference Between Treatment Groups of at Least 3% Between Patients Who Did and Did Not Complete Primary Endpoint Followup

Risk Factor Term	Stratum	Tx ¹	Compl I° Endpt F/U	Did Not Compl I° Endpt F/U
		SU	230 (23.3)	23 (19.7)
	Bkgrd SU	RSG	176 (18.2)	28 (20.4)
		MET	196 (20.0)	20 (14.1)
Lipid metab disorder	Overall	RSG	108 (5.5)	12 (4.9)
		MET/SU	101 (5.1)	13 (5.0)
	Bkgrd MET	RSG	62 (6.1)	3 (2.8)
		SU	50 (5.1)	9 (7.7)
	Bkgrd SU	RSG	46 (4.8)	9 (6.6)
		MET	51 (5.2)	4 (2.8)
Abnl lipids without hx lipid disorder ²	Overall	RSG	1120 (56.7)	134 (55.1)
		MET/SU	1067 (54.2)	147 (56.8)
	Bkgrd MET	RSG	532 (52.6)	60 (56.6)
		SU	519 (52.5)	61 (52.1)
	Bkgrd SU	RSG	588 (60.9)	74 (54.0)
		MET	548 (55.9)	86 (60.6)
Ever smoker	Overall	RSG	829 (41.9)	99 (40.7)
		MET/SU	788 (40.0)	94 (36.3)
	Bkgrd MET	RSG	472 (46.7)	49 (46.2)
		SU	459 (46.5)	53 (45.3)
	Bkgrd SU	RSG	357 (37.0)	50 (36.5)
		MET	329 (33.6)	41 (28.9)
Current smoker	Overall	RSG	317 (16.0)	46 (18.9)
		MET/SU	299 (15.2)	44 (17.0)
	Bkgrd MET	RSG	179 (17.7)	20 (18.9)
		SU	169 (17.1)	25 (21.4)
	Bkgrd SU	RSG	138 (14.3)	26 (19.0)
		MET	130 (13.3)	19 (13.4)
Previous smoker	Overall	RSG	512 (25.9)	53 (21.8)
		MET/SU	489 (24.8)	50 (19.3)
	Bkgrd MET	RSG	293 (29.0)	29 (27.4)
		SU	290 (29.4)	28 (23.9)
	Bkgrd SU	RSG	219 (22.7)	24 (17.5)
		MET	199 (20.3)	22 (15.5)

Source: Applicant's Table 6.89, beg pg 5593, RECORD study report body

Abbreviations: abnl = abnormal, chol = cholesterol, CV = cardiovascular, cerebrovasc = cerebrovascular, dz = disease, elev = elevated, HF = heart failure, htn = hypertension, hx = history of, IHD = ischemic heart disease, metab = metabolism, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, RF = risk factor, TG = triglycerides, TIA = transient ischemic attack

1 For the numbers of patients in each stratum arm who did and did not complete primary endpoint follow-up, refer to Table II.C.1.b above

2 No history of lipid disorder and on no lipid meds, but any of the following: LDL \geq 2.6 mmol/L; TG \geq 2.3 mmol/L; HDL $<$ 1.03 mmol/L (men); HDL $<$ 1.29 mmol/L (women)

Yellow shading indicates a \geq 3% difference between pts who completed CV f/u and those who did not, within a rosiglitazone group. Pink shading indicates a \geq 3% difference between pts who completed CV f/u and those who did not, within a non-RSG comparator group.

The above table should be interpreted with caution, because of the small numbers of patients in the noncompleter group, and because of the nonrandomized nature of the groups being compared.

Regarding baseline ischemic heart disease terms, overall, the presence of any reported baseline ischemic heart disease condition was slightly numerically more common among patients who did not complete CV follow-up than among patients who did complete CV follow-up. However, this was true both for RSG and comparator.

A baseline history of hypertension occurred numerically more commonly among patients who completed CV follow-up than among those who did not, particularly among RSG groups. This would not suggest a pattern of loss to follow-up of patients at CV risk due to hypertension from the RSG group.

A baseline history of a lipid disorder occurred numerically more commonly among patients who completed CV follow-up than among those who did not. However, this was true both for RSG and comparator.

A baseline history of being a past smoker occurred numerically more commonly among patients who completed CV follow-up than among those who did not. However, this was true both for RSG and comparator.

Patients who did not complete CV follow-up from the RSG group did not appear to have had higher baseline CV risk than patients who did not complete CV follow-up from the MET/SU group. Therefore, from a baseline CV risk standpoint, one would not expect the RSG group patients who left CV follow-up to have been potential “high event rate contributors” compared to the MET/SU patients who left CV follow-up. Systematic (or differential) loss of high CV risk patients from the RSG group did not appear to occur.

The overall baseline cardiovascular risk of the RECORD population was low compared to other cardiovascular outcomes studies involving patients with type 2 diabetes (see Section II.F.2).

The following table displays cardiovascular medications at baseline.

Table II.C.1.f: Baseline Cardiovascular Medications

CV Med Category	CV Med	RSG N=2220 n (%)	MET/SU N=2227 n (%)
Any CV med		1630 (73.4)	1627 (73.1)
Any lipid-lowering med		522 (23.5)	531 (23.8)
	Statins	399 (18.0)	424 (19.0)
	Fibrates	130 (5.9)	119 (5.3)
Any CV med other than lipid-lowering meds		1445 (65.1)	1453 (65.2)
Any diuretic		445 (20.0)	471 (21.1)
	Thiazide	374 (16.8)	399 (17.9)
	Loop	72 (3.2)	71 (3.2)
	Potassium-sparing	34 (1.5)	36 (1.6)
	Aldosterone antagonist	23 (1.0)	18 (0.8)
Any alpha blocker		67 (3.0)	71 (3.2)
Any beta blocker		517 (23.3)	482 (21.6)
	Selective	395 (17.8)	354 (15.9)
	Nonselective	123 (5.5)	131 (5.9)
Any calcium channel blocker		430 (19.4)	483 (21.7)
	Dihydropyridines	325 (14.6)	374 (16.8)
	Nondihydropyridines	107 (4.8)	111 (5.0)
Any renin-angiotensin system med		1059 (47.7)	1034 (46.4)
	ACEI	936 (42.2)	907 (40.7)
	A2RB	130 (5.9)	131 (5.9)
Any nitrate		132 (5.9)	140 (6.3)
Any vasodilator		93 (4.2)	88 (4.0)
Coumarin		39 (1.8)	24 (1.1)
Digitalis		29 (1.3)	20 (0.9)
Any antiarrhythmic		10 (0.5)	12 (0.5)
Any antiplatelet med		448 (20.2)	422 (18.9)
	ASA	436 (19.6)	406 (18.2)
	Dipyridamole	12 (0.5)	10 (0.4)

Table II.C.1.f: Baseline Cardiovascular Medications

CV Med Category	CV Med	RSG N=2220 n (%)	MET/SU N=2227 n (%)
	Clopidogrel	5 (0.2)	9 (0.4)
	Ticlopidine	4 (0.2)	6 (0.3)
Source: Applicant's Table 6.90, beg pg 5605, RECORD study report body Abbreviations: A2RB = angiotensin-2 receptor blocker, ACEI = angiotensin converting enzyme inhibitor, med = medication			

Overall, cardiovascular medications were well-balanced at baseline. This was also true by stratum (Source: Applicant's Table 6.90, beg pg 5609).

The clinical reviewer examined the above baseline CV medications for patients who completed the study for primary endpoint follow-up and for patients who did not complete the study for primary endpoint follow-up. There was no difference between groups for most medications, except for slight numeric differences for some medications, as shown in the following table.

Table II.C.1.g: Baseline Cardiovascular Medication Use For Which There Was a Frequency Difference Between Treatment Groups of at Least 3% Between Patients Who Did and Did Not Complete Primary Endpoint Followup

CV Med Category	CV Med	Stratum	Tx ¹	Compl I° Endpt F/U	Did Not Compl I° Endpt F/U
Any lipid lowering medication		Overall	RSG	463 (23.4)	59 (24.3)
			MET/SU	473 (24.0)	59 (22.8)
		Bkgrd MET	RSG	270 (26.7)	29 (27.4)
			SU	257 (26.0)	35 (29.9)
		Bkgrd SU	RSG	193 (20.0)	30 (21.9)
	Statins		MET	215 (21.9)	24 (16.9)
		Overall	RSG	355 (18.0)	44 (18.1)
			MET/SU	376 (19.1)	48 (18.5)
		Bkgrd MET	RSG	217 (21.5)	25 (23.6)
			SU	208 (21.1)	31 (26.5)
Any CV med other than lipid-lowering		Bkgrd SU	RSG	138 (14.3)	19 (13.9)
			MET	168 (17.1)	17 (12.0)
		Overall	RSG	1295 (65.5)	150 (61.7)
			MET/SU	1284 (65.2)	169 (65.3)
		Bkgrd MET	RSG	685 (67.8)	66 (62.3)
			SU	660 (66.8)	79 (67.5)
		Bkgrd SU	RSG	610 (63.1)	84 (61.3)
			MET	624 (63.7)	90 (63.4)
	Beta blockers	Overall	RSG	347 (17.6)	48 (19.8)
			MET/SU	315 (16.0)	39 (15.1)
Beta blockers	Selective beta blockers	Bkgrd MET	RSG	185 (18.3)	26 (24.5)
			SU	160 (16.2)	17 (14.5)
		Bkgrd SU	RSG	162 (16.8)	22 (16.1)
			MET	155 (15.8)	22 (15.5)
		Overall	RSG	111 (5.6)	12 (4.9)
	Nonselective beta blockers		MET/SU	115 (5.8)	16 (6.2)
		Bkgrd MET	RSG	62 (6.1)	1 (0.9)
			SU	55 (5.6)	9 (7.7)
		Bkgrd SU	RSG	49 (5.1)	11 (8.0)
			MET	60 (6.1)	7 (4.9)
Any CCB		Overall	RSG	387 (19.6)	43 (17.7)
			MET/SU	439 (22.3)	44 (17.0)
		Bkgrd MET	RSG	209 (20.7)	22 (20.8)
			SU	242 (24.5)	20 (17.1)
		Bkgrd SU	RSG	178 (18.4)	21 (15.3)
			MET	197 (20.1)	24 (16.9)

Table II.C.1.g: Baseline Cardiovascular Medication Use For Which There Was a Frequency Difference Between Treatment Groups of at Least 3% Between Patients Who Did and Did Not Complete Primary Endpoint Followup

CV Med Category	CV Med	Stratum	Tx ¹	Compl I° Endpt F/U	Did Not Compl I° Endpt F/U
	Dihydropyridines	Overall	RSG	287 (14.5)	38 (15.6)
			MET/SU	339 (17.2)	35 (13.5)
		Bkgrd MET	RSG	158 (15.6)	20 (18.9)
	Bkgrd SU	Overall	SU	189 (19.1)	15 (12.8)
			RSG	129 (13.4)	18 (13.1)
			MET	150 (15.3)	20 (14.1)
	Nondihydropyridines	Overall	RSG	101 (5.1)	6 (2.5)
			MET/SU	102 (5.2)	9 (3.5)
		Bkgrd MET	RSG	51 (5.0)	2 (1.9)
	Bkgrd SU	Overall	SU	54 (5.5)	5 (4.3)
			RSG	50 (5.2)	4 (2.9)
			MET	48 (4.9)	4 (2.8)
Any renin-angiotensin system med	Overall	Overall	RSG	951 (48.1)	108 (44.4)
			MET/SU	917 (46.6)	117 (45.2)
		Bkgrd MET	RSG	519 (51.3)	52 (49.1)
	Bkgrd SU	Overall	SU	470 (47.6)	57 (48.7)
			RSG	432 (44.7)	56 (40.9)
			MET	447 (45.6)	60 (42.3)
ACEI	Overall	Overall	RSG	843 (42.6)	93 (38.3)
			MET/SU	808 (41.1)	99 (38.2)
		Bkgrd MET	RSG	454 (44.9)	45 (42.5)
	Bkgrd SU	Overall	SU	415 (42.0)	45 (38.5)
			RSG	389 (40.3)	48 (35.0)
			MET	393 (40.1)	54 (38.0)
A2RB	Overall	Overall	RSG	114 (5.8)	16 (6.6)
			MET/SU	113 (5.7)	18 (6.9)
		Bkgrd MET	RSG	68 (6.7)	8 (7.5)
	Bkgrd SU	Overall	SU	57 (5.8)	12 (10.3)
			RSG	46 (4.8)	8 (5.8)
			MET	56 (5.7)	6 (4.2)
Nitrates	Overall	Overall	RSG	108 (5.5)	24 (9.9)
			MET/SU	118 (6.0)	22 (8.5)
		Bkgrd MET	RSG	52 (5.1)	7 (6.6)
	Bkgrd SU	Overall	SU	47 (4.8)	7 (6.0)
			RSG	56 (5.8)	17 (12.4)
			MET	71 (7.2)	15 (10.6)
Vasodilator	Overall	Overall	RSG	83 (4.2)	10 (4.1)
			MET/SU	73 (3.7)	15 (5.8)
		Bkgrd MET	RSG	39 (3.9)	3 (2.8)
	Bkgrd SU	Overall	SU	34 (3.4)	3 (2.6)
			RSG	44 (4.6)	7 (5.1)
			MET	39 (4.0)	12 (8.5)
Digitalis	Overall	Overall	RSG	26 (1.3)	3 (1.2)
			MET/SU	14 (0.7)	6 (2.3)
		Bkgrd MET	RSG	11 (1.1)	1 (0.9)
	Bkgrd SU	Overall	SU	5 (0.5)	6 (5.1)
			RSG	15 (1.6)	2 (1.5)
			MET	9 (0.9)	0
Any antiplatelet med	Overall	Overall	RSG	406 (20.5)	42 (17.3)
			MET/SU	375 (19.1)	47 (18.1)
		Bkgrd MET	RSG	239 (23.6)	21 (19.8)
	Bkgrd SU	Overall	SU	208 (21.1)	27 (23.1)
			RSG	167 (17.3)	21 (15.3)
			MET	167 (17.0)	20 (14.1)
ASA	Overall	Overall	RSG	396 (20.0)	40 (16.5)
			MET/SU	364 (18.5)	42 (16.2)
		Bkgrd MET	RSG	232 (22.9)	21 (19.8)
	Bkgrd SU	Overall	SU	206 (20.9)	24 (20.5)
			RSG	164 (17.0)	19 (13.9)
			MET	158 (16.1)	18 (12.7)

Table II.C.1.g: Baseline Cardiovascular Medication Use For Which There Was a Frequency Difference Between Treatment Groups of at Least 3% Between Patients Who Did and Did Not Complete Primary Endpoint Followup

CV Med Category	CV Med	Stratum	Tx ¹	Compl I° Endpt F/U	Did Not Compl I° Endpt F/U
<p>Source: Applicant's Table 6.90, beg pg 5605, RECORD study report body</p> <p>Abbreviations: A2RB = angiotensin-2 receptor blocker, ACEI = angiotensin converting enzyme inhibitor, ASA = aspirin, CCB = calcium channel blocker, med = medication</p> <p>¹ For the numbers of patients in each stratum arm who did and did not complete primary endpoint follow-up, refer to Table II.C.1.b above</p> <p>Yellow shading indicates a ≥3% difference between pts who completed CV f/u and those who did not, within a rosiglitazone group. Pink shading indicates a ≥3% difference between pts who completed CV f/u and those who did not, within a non-RSG comparator group.</p>					

The above table should be interpreted with caution, because of the small numbers of patients in the noncompleter group, and because of the nonrandomized nature of the groups being compared.

Baseline use of calcium channel blockers, ACEIs and aspirin was numerically more common among patients who completed CV followup than among patients who did not complete CV followup. This did not appear to differ between RSG and non-RSG groups.

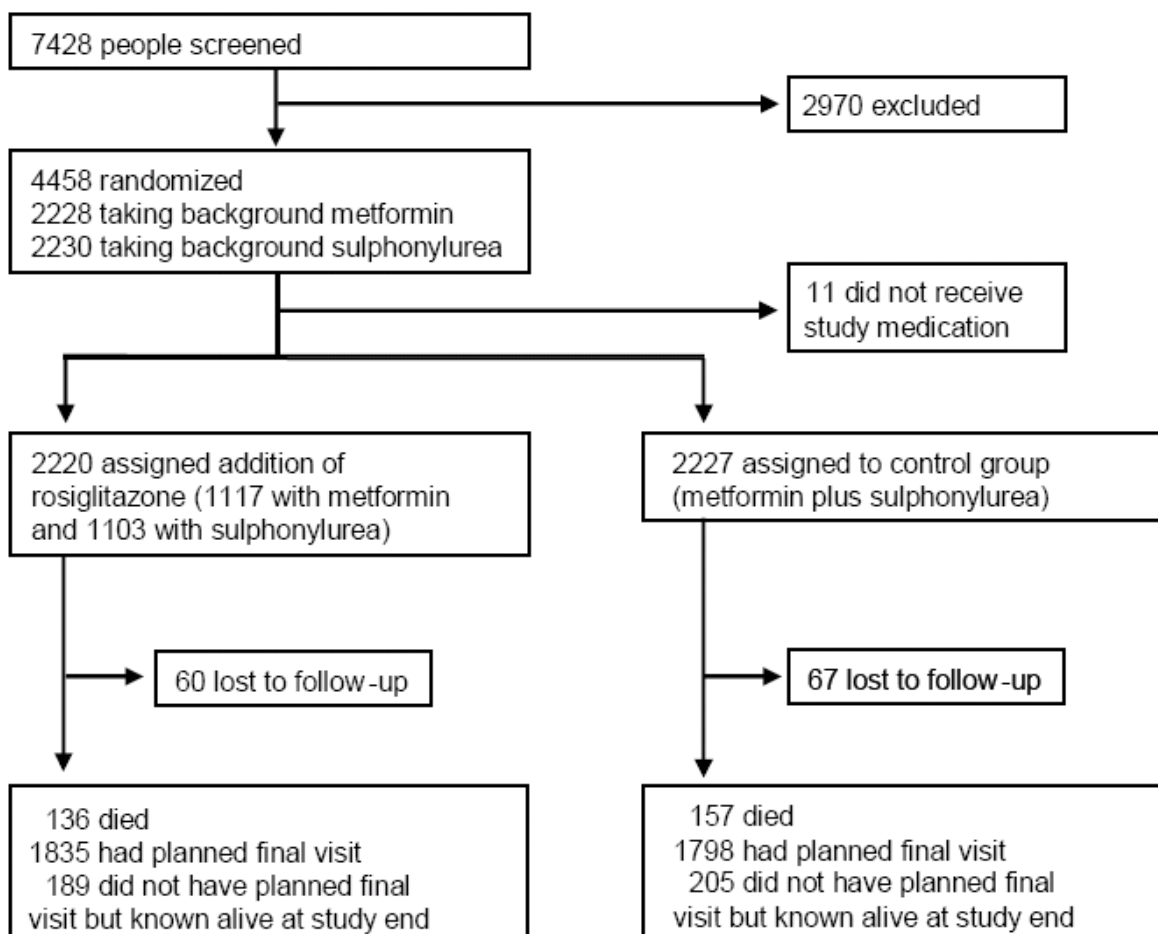
Baseline nitrate use was numerically more common among patients who did not complete CV followup than among patients who did complete CV followup for all treatment groups. This was primarily accounted for by patients from the background SU group, in which both the add-on RSG and add-on MET groups displayed this difference, i.e. a numerically higher percentage of noncompleters with a history of baseline nitrate use than completers with a history of baseline nitrate use.

Overall, there did not appear to be a pattern, based on baseline CV medication use among those who did and did not leave study, to suggest that high CV risk patients were preferentially lost from the RSG group.

II.C.2. Disposition and Exposure

The following figure summarizes the numbers of patients who were randomized and treated; and the numbers of patients who died, were lost to follow-up, completed study, or did not complete study but had known vital status at study end.

Figure II.C.2.a: Overview of Patient Flow in RECORD



Source: Applicant's Figure 2, RECORD study report body

The following table summarizes vital status at study end.

Table II.C.2.a: Summary of Vital Status at Study End

Stratum	Treatment (N)	Alive n (%)	Dead n (%)	Vital Status Unconfirmed n (%)
Overall	All (N=4447)	4027 (90.6)	293 (6.6)	127 (2.9)
	Combined RSG (N=2220)	2024 (91.2)	136 (6.1)	60 (2.7)
	Combined MET/SU (N=2227)	2003 (89.9)	157 (7.0)	67 (3.0)
Background MET	All bkgrd MET (N=2222)	2031 (91.4)	140 (6.3)	51 (2.3)
	Add-on RSG (N=1117)	1027 (91.9)	68 (6.1)	22 (2.0)
	Add-on SU (N=1105)	1004 (90.9)	72 (6.5)	29 (2.6)
Background SU	All bkgrd SU (N=2225)	1996 (89.7)	153 (6.9)	76 (3.4)
	Add-on RSG (N=1103)	997 (90.4)	68 (6.2)	38 (3.4)
	Add-on MET (N=1122)	999 (89.0)	85 (7.6)	38 (3.4)

Source: Applicant's Table 6.7, beg pg 3210, RECORD study report body

Vital status ascertainment during applicant's "study end window", 24 Aug 2008 to 24 Dec 2008

Overall, vital status was known for 97.1% of patients at study end, with similar percentages of patients with unknown vital status by study stratum.

The following table displays the last known disposition (i.e. reason for prior withdrawal) of patients for whom vital status was unknown at study end.

Table II.C.2.b: Last Known Disposition (Reason for Prior Withdrawal) for Patients for Whom Vital Status Was Unknown at Study End

Reason for Prior Withdrawal	Overall			Bkgrd MET			Bkgrd SU		
	Total (N=127)	RSG (N=60)	Met/SU (N=67)	Total (N=51)	RSG (N=22)	SU (N=29)	Total (N=76)	RSG (N=38)	MET (N=38)
Adverse event	8 (6.3)	1 (1.7)	7 (10.4)	4 (7.8)	1 (4.5)	3 (10.3)	4 (5.3)	0	4 (10.5)
Lost to follow-up	28 (22.0)	16 (26.7)	12 (17.9)	13 (25.5)	7 (31.8)	6 (20.7)	15 (19.7)	9 (23.7)	6 (15.8)
Patient withdrew at own request	62 (48.8)	30 (50.0)	32 (47.8)	26 (51.0)	10 (45.5)	16 (55.2)	36 (47.4)	20 (52.6)	16 (42.1)
Other reason given	22 (17.3)	9 (15.0)	13 (19.4)	7 (13.7)	4 (18.2)	3 (10.3)	15 (19.7)	5 (13.2)	10 (26.3)
Unknown withdrawal reason	7 (5.5)	4 (6.7)	3 (4.5)	1 (2.0)	0	1 (3.4)	6 (7.9)	4 (10.5)	2 (5.3)

Source: Applicant's Table 6.7, beg pg 3210, RECORD study report body

Among patients who had unconfirmed vital status at study end, the most common prior reason for study discontinuation had been that the patient had withdrawn at their own request, which had occurred for 49% of patients who had unconfirmed vital status at study end. This percentage was somewhat higher for patients treated with SU in the background MET stratum, at 55%; and slightly lower for patients treated with MET in the background SU stratum, at 42%.

The following table summarizes the numbers of patients who completed or withdrew from cardiovascular follow-up.

Table II.C.2.c: Summary of Follow-up for Cardiovascular Events

	RSG N=2220 n (%)	MET/SU N=2227 n (%)
Completed CV follow-up to final visit (includes both the main study and the tracking substudy)	1835 (82.7)	1798 (80.7)
Completed CV follow-up to final visit (main study only)	1796 (80.9)	1764 (79.2)
Died	111 (5.0)	139 (6.2)
Withdrew from CV follow-up (total) ³	274 (12.3)	290 (13.0)
Withdrew from CV follow-up after having a primary endpoint event	31 (1.4)	31 (1.4)
Withdrew from CV follow-up without having had a primary endpoint event ²	243 (10.9)	259 (11.6)
Completed follow-up for primary endpoint analysis ¹	1977 (89.1)	1968 (88.4)

Source: Applicant's Table 7, pg 93; Table 6.8, pg 3213; Table 6.21, pg 3826; RECORD study report body

1 Includes patients who had at least one primary endpoint event, or had no event and completed CV follow-up to study end, or had no event but a non-CV death terminated follow-up. Includes some tracking substudy patients

2 See Table II.C.2.f below for vital status of these patients at end of study

3 See Table II.C.2.e below for reasons for withdrawal from CV follow-up

In total, 86% of patients in the RSG group, and 85% of patients in the MET/SU group, completed study to the final visit in the main study, or died. When one adds those patients who withdrew, but not until they had already had a primary endpoint event, 87% of patients in the RSG group, and 87% of patients in the MET/SU group, completed follow-up for the primary endpoint analysis. This means that they either completed the study to the final visit in the main study; or they died; or they withdrew, but not until they had already had a primary endpoint event. If one adds the patients from the tracking substudy, these numbers are 89% for the RSG group and 88% for the MET/SU group. If one adds those patients for

whom vital status could be confirmed, 97% of patients in both the RSG and MET/SU groups had confirmed vital status at end of study.

Each of these classifications of follow-up provides a different kind of information. For follow-up for total mortality, information is available for 97% of patients. For cardiovascular follow-up for primary endpoint events throughout study, information is available for 89% of patients. For cardiovascular follow-up to the final visit in the main study, information is available for 87% of patients.

Over 95% of patients completed >90% of protocol-specified study visits. The following table displays the percentage of patients who completed various percentages of planned study visits.

Table II.C.2.d: Distribution of Percentage of Protocol-Specified Study Visits Completed				
Percentage¹ of Protocol-Specified Postbaseline Study Visits Completed	Bkgrd MET		Bkgrd SU	
	RSG N=1117	SU N=1105	RSG N=1103	MET N=1122
0%	3 (0.3)	8 (0.7)	13 (1.2)	12 (1.1)
>0-50%	2 (0.2)	0	1 (0.1)	1 (0.1)
>50-60%	0	0	0	2 (0.2)
>60-70%	0	1 (0.1)	0	3 (0.3)
>70-80%	9 (0.8)	4 (0.4)	9 (0.8)	9 (0.8)
>80-90%	25 (2.2)	20 (1.8)	16 (1.5)	27 (2.4)
>90-<100%	508 (45.5)	474 (42.9)	499 (45.2)	497 (44.3)
100%	570 (51.0)	598 (54.1)	565 (51.2)	571 (50.9)
Mean (SD)	97.3 (4.3)	97.6 (3.3)	97.4 (3.9)	97.2 (4.5)
Median	100	100	100	100
Source: Applicant's Table 2278.10.1, NDA 21071 subm 20 May 2010 1 For subjects who withdrew from study or died, number of available visits was determined by number of scheduled visits from baseline to time of withdrawal or death. For subjects who re-entered study via tracking substudy, number of available visits was determined by number of scheduled visits from baseline to time of withdrawal plus number of visits available when patient entered tracking substudy.				

As noted in the previous description of the study design, the protocol permitted some study visits to be completed by telephone rather than in person, and the above table includes these telephone visits as well as in-person visits.

The following table presents the reasons for withdrawal for patients who withdrew from CV follow-up.

Table II.C.2.e: Reasons for Withdrawal for Patients who Withdrew from Cardiovascular Follow-up			
		Combined RSG	Combined MET/SU
		Total N=2220; n w/d fr CV = 274	Total N=2227; n w/d fr CV = 290
		# (% of total N)	# (% of total N)
Adverse event		15 (0.7)	19 (0.9)
Lost to follow-up		54 (2.4)	55 (2.5)
Subject withdrew at own request		118 (5.3)	126 (5.7)
Moved to survival status follow-up only		59 (2.7)	61 (2.7)

Table II.C.2.e: Reasons for Withdrawal for Patients who Withdrew from Cardiovascular Follow-up			
		Combined RSG	Combined MET/SU
		Total N=2220; n w/d fr CV = 274	Total N=2227; n w/d fr CV = 290
		# (% of total N)	# (% of total N)
Other (subsets at right)		28 (1.3)	29 (1.3)
	Subject moved¹	6 (0.3)	5 (0.2)
	Poor compliance¹	5 (0.2)	3 (0.1)
	Prohibited glucose lowering med¹	0	4 (0.2)
	Site closed¹	8 (0.4)	12 (0.5)
	Other¹	9 (0.4)	5 (0.2)
Source: Applicant's Table 6.11, pg 3506, RECORD study report body			
1 Subset of "Other"			

The distribution of reasons for withdrawal from cardiovascular follow-up was similar for the RSG and MET/SU groups.

The following table presents the vital status at end of study for all patients who withdrew from cardiovascular follow-up, and for those who withdrew without having had a primary endpoint event.

Table II.C.2.f: Vital Status at End of Study for All Patients Who Withdrew from Cardiovascular Follow-up, and For Those Who Withdrew Without Having Had a Primary Endpoint Event				
	Total Withdrawals From CV Follow-up		Withdrawals Without Having Had a Primary Endpoint Event	
	Combined RSG	Combined MET/SU	Combined RSG	Combined MET/SU
	Total N=2220; n w/d = 274	Total N=2227; n w/d = 290	Total N=2220; n w/d without I° = 243	Total N=2227; n w/d without I° = 259
	# (% of total N)	# (% of total N)	# (% of total N)	# (% of total N)
Alive	189 (8.5)	205 (9.2)	172 (7.7)	186 (8.4)
Dead	25 (1.1)	18 (0.8)	14 (0.6)	13 (0.6)
Vital status unconfirmed	60 (2.7)	67 (3.0)	57 (2.6)	60 (2.7)
Source: Applicant's Table 6.8, pg 3213; and Table 6.11, pg 3506; RECORD study report body				

The majority (77%) of all patients who withdrew from cardiovascular follow-up did have vital status determined at end of study. The percentages of patients who were known to be alive, to have died, and to have had vital status unconfirmed, were similar between treatment groups. Most (89%) of the patients who withdrew from CV follow-up had not yet had a primary event. Among those patients, the majority (77%) did have vital status determined at end of study, and vital status confirmation was similar between treatment groups.

The following table summarizes the total patient-years of follow-up.

Table II.C.2.g: Total Patient-Years of Follow-up, Overall and by Stratum

Follow-up Category	Overall			Bkgrd MET			Bkgrd SU		
	RSG N=2220	MET/SU N=2227	Total Overall N=4447	RSG N=1117	SU N=1105	Total Bkgrd MET N=2222	RSG N=1103	MET N=1122	Total Bkgrd SU N=2225
Vital status follow-up	12969	12870	25839	6506	6397	12903	6463	6473	12936
Cardiovascular follow-up	12338	12272	24610	6228	6146	12375	6110	6126	12236
Dual/triple randomized combination treatment follow-up	10849	10209	21058	5504	5165	10670	5344	5044	10388
Dual randomized combination treatment (dual oral therapy) follow-up	9279	10209	19488	4753	5165	9918	4526	5044	9570
Lost for CV events follow-up ¹	925	982	1907	381	410	791	544	573	1116
Lost for vital status follow-up ²	231	302	533	82	117	199	149	186	334
Source: Applicant's Table 6.16, beg pg 3814, RECORD study report body									

Regarding overall results, for the patient-time category of cardiovascular follow-up, patient-time was similar for RSG and MET/SU. Total follow-up on randomized therapy (dual/triple) was slightly greater for RSG than for MET/SU (ratio 1.06). For the patient-time category of dual oral randomized combination treatment, the ratio of RSG group patient-years to MET/SU group years was 0.91. Relative follow-up by stratum was similar to that for the overall comparison.

The majority of total cardiovascular follow-up occurred on randomized therapy, with 88% for RSG (75% dual, 13% triple), and 83% for MET/SU.

When considering patient-years by stratum and by individual endpoint, proportions were similar to that seen for overall follow-up (source applicant's Table 7.4, beg pg 5878, RECORD study report body).

Two tables follow which summarize patient follow-up by patient-time interval. The first table includes all patient-time for which there was follow-up for cardiovascular events. The second table includes only time on randomized therapy, and displays time on dual oral therapy and triple oral therapy separately.

Table II.C.2.h: Summary of Follow-up by Patient-Time Interval, All Follow-up for Cardiovascular Events (Percentage of Patients Who Had Specified Durations of Follow-up by Six Month Intervals)

Patient-Year Interval	Overall		Bkgrd MET		Bkgrd SU	
	RSG N=2220 n (%)	MET/SU N=2227 n (%)	RSG N=1117 n (%)	SU N=1105 n (%)	RSG N=1103 n (%)	MET N=1122 n (%)
≤0.5	51 (2.3)	60 (2.7)	23 (2.1)	25 (2.3)	28 (2.5)	35 (3.1)
>0.5 and ≤1.0	32 (1.4)	19 (0.9)	14 (1.3)	5 (0.5)	18 (1.6)	14 (1.2)
>1.0 and ≤2.0	53 (2.4)	66 (3.0)	18 (1.6)	22 (2.0)	35 (3.2)	44 (3.9)
>2.0 and ≤3.0	53 (2.4)	59 (2.6)	29 (2.6)	27 (2.4)	24 (2.2)	32 (2.9)
>3.0 and ≤4.0	61 (2.7)	61 (2.7)	29 (2.6)	35 (3.2)	32 (2.9)	26 (2.3)
>4.0 and ≤5.0	56 (2.5)	72 (3.2)	25 (2.2)	42 (3.8)	31 (2.8)	30 (2.7)
>5.0 and ≤6.0	1010 (45.5)	1006 (45.2)	573 (51.3)	542 (49.0)	437 (39.6)	464 (41.4)
>6.0 and ≤7.0	825 (37.2)	794 (35.7)	368 (32.9)	364 (32.9)	457 (41.4)	430 (38.3)
>7.0	79 (3.6)	90 (4.0)	38 (3.4)	43 (3.9)	41 (3.7)	47 (4.2)
Total % pts with >5.0 y total CV f/u	86.3	84.9	87.6	85.8	84.7	83.9
Mean exposure per pt, yrs (SD)	5.56 (1.48)	5.51 (1.53)	5.58 (1.38)	5.56 (1.40)	5.54 (1.58)	5.46 (1.64)
Median exposure per pt, yrs	5.74	5.72	5.70	5.69	5.97	5.81
Total PY	12338	12272	6228	6146	6110	6126

Source: Applicant's Table 6.17, beg pg 3817, RECORD study report body

Median total follow-up per patient for cardiovascular events, in years, was similar for RSG (5.74) and MET/SU (5.72). For the first 6 months of patient-time, a slightly numerically higher percentage of patients withdrew from the MET/SU group than from the RSG group. From Months 6-12, a slightly numerically higher percentage of patients withdrew from the RSG group than from the MET/SU group. After 12 months, there did not appear to be a pattern of differential loss from either arm. The percentage of patients with >5.0 years of followup was 86.3 for the RSG group and 84.9 for the MET/SU group. Results by strata were similar.

Table II.C.2.i: Summary of Follow-up by Patient-Time Interval, Time on Randomized Therapy Only (Percentage of Patients Who Had Specified Durations of Follow-up by Six Month Intervals)

Patient-Year Interval	Overall			Bkgd MET			Bkgd SU		
	RSG N=2220		Comp N=2227	RSG N=1117		Comp N=1105	RSG N=1103		Comp N=1122
	RSG Du/Tr n (%)	RSG Du n (%)	MET/SU n (%)	RSG Du/Tr n (%)	RSG Du n (%)	SU n (%)	RSG Du/Tr n (%)	RSG Du n (%)	MET n (%)
≤0.5	95 (4.3)	140 (6.3)	113 (5.1)	46 (4.1)	66 (5.9)	40 (3.6)	49 (4.4)	74 (6.7)	73 (6.5)
>0.5 and ≤1.0	74 (3.3)	175 (7.9)	66 (3.0)	31 (2.8)	80 (7.2)	20 (1.8)	43 (3.9)	95 (8.6)	46 (4.1)
>1.0 and ≤2.0	123 (5.5)	219 (9.9)	178 (8.0)	54 (4.8)	98 (8.8)	90 (8.1)	69 (6.3)	121 (11.0)	88 (7.8)
>2.0 and ≤3.0	118 (5.3)	181 (8.2)	165 (7.4)	60 (5.4)	99 (8.9)	84 (7.6)	58 (5.3)	82 (7.4)	81 (7.2)
>3.0 and ≤4.0	132 (5.9)	154 (6.9)	176 (7.9)	66 (5.9)	75 (6.7)	94 (8.5)	66 (6.0)	79 (7.2)	82 (7.3)
>4.0 and ≤5.0	171 (7.7)	182 (8.2)	205 (9.2)	87 (7.8)	88 (7.9)	112 (10.1)	84 (7.6)	94 (8.5)	93 (8.3)
>5.0 and ≤6.0	877 (39.5)	715 (32.2)	792 (35.6)	490 (43.9)	404 (36.2)	416 (37.6)	387 (35.1)	311 (28.2)	376 (33.5)
>6.0 and ≤7.0	581 (26.2)	416 (18.7)	495 (22.2)	260 (23.3)	189 (16.9)	231 (20.9)	321 (29.1)	227 (20.6)	264 (23.5)
>7.0	49 (2.2)	38 (1.7)	37 (1.7)	23 (2.1)	18 (1.6)	18 (1.6)	26 (2.4)	20 (1.8)	19 (1.7)
Total % pts with >5.0 y f/u on rand rx	67.9	52.6	59.5	69.3	54.7	60.1	66.6	50.6	58.7
Mean PY (SD)	4.89 (1.91)	4.18 (2.19)	4.58 (1.99)	4.93 (1.84)	4.25 (2.13)	4.67 (1.87)	4.85 (1.98)	4.10 (2.24)	4.50 (2.09)
Median PY	5.65	5.33	5.61	5.65	5.36	5.63	5.66	5.07	5.58
Total PY	10849	9279	10209	5504	4753	5165	5344	4526	5044

Source: Applicant's Table 6.18, beg pg 3820, RECORD study report body

The pattern in the above table may be reflective of the asymmetric study design with regard to the prespecified 3rd agent, and of the reluctance of patients in the MET/SU group to add insulin promptly to dual oral therapy as specified in the protocol for patients who were failing glycemic control on MET+SU. As mentioned earlier, for patients in the RSG group who failed glycemic control (had 2 consecutive HbA1cs ≥8.5%), the specified 3rd agent was oral (MET for the background SU group, and SU for the background MET group). For the MET/SU group, the 3rd agent was insulin. However, the applicant reports that there was reluctance on the part of patients and investigators to initiate insulin per the timing specified in the protocol. Therefore, patients in the RSG group generally had a 3rd agent added promptly, but patients in the MET/SU group did not. Therefore, patients moved out of the “dual oral therapy only” phase somewhat faster in the RSG group than in the MET/SU group. This is reflected in the above table, where in the rows for the shorter time periods of follow-up, i.e. those patients with 3 or fewer years of follow-up, numerically more patients were leaving dual oral therapy in the RSG group than in the MET/SU group. However, these RSG patients were moving into triple oral therapy and continuing in their randomized groups. As time progressed, patients in the MET/SU group did eventually begin to have insulin added, and therefore were no longer in the dual oral therapy phase. Because of these two trends, there were more patients with follow-up of >5 years for RSG (67.9%) than comparator (59.5%) when one considers all randomized therapy time (i.e. time on both dual and triple oral therapy), but there were more comparator patients (59.5%) than RSG patients (52.6%) who completed >5.0 years on dual oral therapy alone. Diabetes is a progressive disease, and it is the norm to require the addition and/or substitution of multiple glycemic control agents over time.

The following two tables summarize completion status and reasons for withdrawal from follow-up during randomized treatment, and following randomized treatment. Because of the asymmetric study design, a higher percentage of patients in the RSG group remained on randomized therapy (triple oral therapy) compared to patients in the MET/SU group, who had insulin as their 3rd agent and by study design were no longer considered to be on randomized treatment once insulin was initiated. Therefore, there were fewer RSG patients in the “cardiovascular follow-up only” (i.e. post-randomized therapy phase, PRT/CVO) of the study.

Table II.C.2.j: Summary of Completion Status and Reasons for Withdrawal from Follow-up During Randomized Treatment, ITT Population

Completion Status	Withdrawal Reason	RSG n (%)	MET/SU n (%)	Total n (%)
Entered randomized treatment phase		2220 (100)	2227 (100)	4447 (100)
Completed study to final visit in randomized treatment ¹ phase		1344 (60.5)	1131 (50.8)	2475 (55.7)
Died ²		77 (3.5)	92 (4.1)	169 (3.8)
Discontinued study drug and entered post-randomized-therapy CV outcomes follow-up (PRT/CVO)		597 (26.9)	798 (35.8)	1395 (31.4)
Discontinued study drug and did not enter PRT/CVO		202 (9.1)	206 (9.3)	408 (9.2)
	Adverse event	13 (0.6)	16 (0.7)	29 (0.7)
	Lost to follow-up	32 (1.4)	31 (1.4)	63 (1.4)
	Withdrew at own request	96 (4.3)	97 (4.4)	193 (4.3)
	Moved to survival status follow-up only	36 (1.6)	37 (1.7)	73 (1.6)
	Patient moved	4 (0.2)	5 (0.2)	9 (0.2)
	Poor compliance	5 (0.2)	2 (0.1)	7 (0.2)
	Prohibited glucose-lowering medication	0	2 (0.1)	2 (<0.1)
	Site closed	8 (0.4)	11 (0.5)	19 (0.4)
	Other	8 (0.4)	5 (0.2)	13 (0.3)

Source: Applicant's Table 12, pg 97, RECORD study report body

1 Randomized treatment phase includes dual/triple oral treatment for RSG, but only dual oral for MET/SU.

2 Death terminated follow-up during randomized treatment phase and while still eligible for serious adverse event reporting.

Overall, 56% of patients completed study to final visit in the randomized treatment phase (61% for RSG, 51% for MET/SU). Type 2 diabetes mellitus is a progressive disease; in practice, most patients require multiple antidiabetic agents for control over time. The difference between the RSG and MET/SU groups is due to the asymmetric study design, as described above. The most common reason for withdrawal from CV follow-up was patient withdrawal at their own request. Reasons for withdrawal were similar between groups. These percentages and reasons for withdrawal were similar by stratum (source applicant's Table 6.13, beg pg 3513, RECORD study report body).

The following table summarizes completion status and reasons for withdrawal during the post-randomized-treatment/ cardiovascular outcomes phase (PRT/CVO).

Table II.C.2.k: Summary of Completion Status and Reasons for Withdrawal During the Post-Randomized Treatment/ Cardiovascular Outcomes (PRT/CVO) Phase, ITT Population

Completion Status	Withdrawal Reason	RSG N=2220 n (%)	MET/SU N=2227 n (%)	Total N=4447 n (%)
Entered post-randomized treatment/ CV outcomes (PRT/CVO) phase		597 (26.9)	798 (35.8)	1395 (31.4)
Completed study to final visit in PRT/CVO phase		491 (22.1)	667 (30.0)	1158 (26.0)
Died in PRT/CVO phase ¹		34 (1.5)	47 (2.1)	81 (1.8)
Withdrew from PRT/CVO phase		72 (3.2)	84 (3.8)	156 (3.5)
	Adverse event	2 (0.1)	3 (0.1)	5 (0.1)
	Lost to follow-up	22 (1.0)	24 (1.1)	46 (1.0)
	Withdrew at own request	22 (1.0)	29 (1.3)	51 (1.1)
	Moved to survival status follow-up only	23 (1.0)	24 (1.1)	47 (1.1)
	Patient moved	2 (0.1)	0	2 (<0.1)
	Poor compliance	0	1 (<0.1)	1 (<0.1)
	Prohibited glucose-lowering medication	0	2 (0.1)	2 (<0.1)
	Site closed	0	1 (<0.1)	1 (<0.1)
	Other	1 (<0.1)	0	1 (<0.1)

Source: Applicant's Table 13, pg 98, RECORD study report body

¹ Death terminated follow-up during randomized treatment phase and while still eligible for serious adverse event reporting.

In the above table, the relative percentage of RSG and MET/SU patients who completed study within the PRT/CVO phase, and who died during this phase, is reflective of the asymmetric study design, with a higher percentage of patients in the MET/SU group. When one takes into account the numbers of patients who actually entered the PRT/CVO phase for each treatment group, the percentages of patients are similar by treatment group for RSG vs MET/SU (completers in PRT/CVO 82% vs 84%; died in PRT/CVO 5.7% vs 5.9%; withdrew from PRT/CVO 12% vs 11%). Results were similar by stratum (source applicant's Table 6.13, beg pg 3514, RECORD study report body).

The following table displays reasons for discontinuation of randomized dual oral combination therapy.

Table II.C.2.l: Summary of Completion Status and Reasons for Withdrawal From Randomized Dual Oral Combination Therapy

Completion Status	Tx and CV F/U Status After D/C	Reason for D/C of Rand Dual Oral Rx	RSG N=2220 n (%)	MET/SU N=2227 n (%)	Total N=4447 n (%)
Completed study to final visit on randomized dual oral combo therapy			1003 (45.2)	1131 (50.8)	2134 (48.0)
Died during randomized dual oral combo therapy			69 (3.1)	92 (4.1)	161 (3.6)
Discontinued randomized dual oral combination therapy (includes addition/substitution of 3 rd agent)			1148 (51.7)	1004 (45.1)	2152 (48.4)
	Started triple therapy or insulin		615 (27.8)	373 (16.7)	988 (22.2)
	Moved to PRT/CVO for reason other than insulin initiation		360 (16.2)	425 (19.1)	785 (17.7)
	Withdrew from PRT/CVO		173 (7.8)	206 (9.3)	379 (8.5)
		Insulin initiated	64 (2.9)	377 (16.9)	441 (9.9)

Table II.C.2.I: Summary of Completion Status and Reasons for Withdrawal From Randomized Dual Oral Combination Therapy

Completion Status	Tx and CV F/U Status After D/C	Reason for D/C of Rand Dual Oral Rx	RSG N=2220 n (%)	MET/SU N=2227 n (%)	Total N=4447 n (%)
		Triple oral study medication initiated	553 (24.9)	0	553 (12.4)
		Adverse event (fatal or nonfatal)	278 (12.5)	300 (13.5)	578 (13.0)
		ALT >3x ULRR	3 (0.1)	2 (0.1)	5 (0.1)
		“Continued participation presents safety risk due to medical condition”	16 (0.7)	19 (0.9)	35 (0.8)
		Prohibited glucose-lowering medication	15 (0.7)	59 (2.6)	74 (1.7)
		Patient admitted to longterm healthcare facility	5 (0.2)	3 (0.1)	8 (0.2)
		Lost to follow-up	36 (1.6)	43 (1.9)	79 (1.8)
		High HbA1c	6 (0.3)	48 (2.2)	54 (1.2)
		High HbA1c, insulin refused	2 (0.1)	15 (0.7)	17 (0.4)
		Add-on study drug stopped for >2 wks	8 (0.4)	6 (0.3)	14 (0.3)
		Poor compliance	18 (0.8)	23 (1.0)	41 (0.9)
		Patient moved	16 (0.7)	18 (0.8)	34 (0.8)
		Patient withdrew at own request	150 (6.8)	137 (6.2)	287 (6.5)
		Withdrawal reason not reported	14 (0.6)	14 (0.6)	28 (0.6)
		Other	33 (1.5)	32 (1.4)	65 (1.5)

Source: Applicant’s Table 15, pg 100, RECORD study report body

A smaller percentage of patients in the overall RSG group (45%) completed study on dual oral therapy than did patients in the MET/SU group (51%). This may have been due to the asymmetric study design, in which patients on RSG who were not well-controlled on dual oral therapy could add a 3rd oral agent, whereas patients on MET/SU were forced to add or substitute insulin. A total of 25% of RSG group patients left the dual oral therapy phase due to the initiation of triple oral study drug therapy, while 17% of MET/SU patients left dual oral therapy due to initiation of insulin. This occurred in spite of the fact that patients in the RSG group were reaching dual agent glycemic failure at a slower rate than patients in the MET/SU group, as presented in Figure II.C.2.b below. When one combines the categories of reasons for discontinuation that are related to glycemic control or death, the difference between RSG and MET/SU is somewhat less marked for reasons for these types of glycemic-control-related discontinuation, at 32% vs 27% (categories of insulin initiation; triple therapy initiation; prohibited glucose-lowering medication; high HbA1c; “high HbA1c, insulin refused”; and death).

Similar numbers of patients discontinued dual oral therapy due to adverse events (RSG 12.5% vs MET/SU 13.5%). A total of 3.1% of RSG-treated patients died during dual oral therapy, while 4.1% of MET/SU-treated patients died during dual oral therapy.

The following table displays the above reasons for discontinuation from randomized dual oral combination therapy by stratum.

Table II.C.2.m: Summary of Completion Status and Reasons for Withdrawal From Randomized Dual Oral Combination Therapy, By Stratum

Completion Status	Tx and CV F/U Status After D/C	Reason for D/C of Rand Dual Oral Rx	Bkgrd MET		Bkgrd SU	
			RSG N=1117	SU N=1105	RSG N=1103	MET N=1122
Completed study to final visit on randomized dual oral combo therapy			540 (48.3)	573 (51.9)	463 (42.0)	558 (49.7)
Died during randomized dual oral combo therapy			34 (3.0)	44 (4.0)	35 (3.2)	48 (4.3)
Discontinued randomized dual oral combination therapy (includes addition/substitution of 3 rd agent)			543 (48.6)	488 (44.2)	605 (54.9)	516 (46.0)
	Started triple therapy or insulin		283 (25.3)	202 (18.3)	332 (30.1)	171 (15.2)
	Moved to PRT/CVO for reason other than insulin initiation		187 (16.7)	200 (18.1)	173 (15.7)	225 (20.1)
	Withdrew from PRT/CVO		73 (6.5)	86 (7.8)	100 (9.1)	120 (10.7)
		Insulin initiated	27 (2.4)	204 (18.5)	37 (3.4)	173 (15.4)
		Triple oral study medication initiated	257 (23.0)	0	296 (26.8)	0
		Adverse event (fatal or nonfatal)	150 (13.4)	135 (12.2)	128 (11.6)	165 (14.7)
		ALT >3x ULRR	3 (0.3)	0	0	2 (0.2)
		"Continued participation presents safety risk due to medical condition"	7 (0.6)	9 (0.8)	9 (0.8)	10 (0.9)
		Prohibited glucose-lowering medication	7 (0.6)	36 (3.3)	8 (0.7)	23 (2.0)
		Patient admitted to longterm healthcare facility	3 (0.3)	3 (0.3)	2 (0.2)	0
		Lost to follow-up	20 (1.8)	22 (2.0)	16 (1.5)	21 (1.9)
		High HbA1c	4 (0.4)	27 (2.4)	2 (0.2)	21 (1.9)
		High HbA1c, insulin refused	0	10 (0.9)	2 (0.2)	5 (0.4)
		Add-on study drug stopped for >2 wks	3 (0.3)	1 (0.1)	5 (0.5)	5 (0.4)
		Poor compliance	10 (0.9)	11 (1.0)	8 (0.7)	12 (1.1)
		Patient moved	8 (0.7)	5 (0.5)	8 (0.7)	13 (1.2)
		Patient withdrew at own request	60 (5.4)	53 (4.8)	90 (8.2)	84 (7.5)
		Withdrawal reason not reported	2 (0.2)	2 (0.2)	12 (1.1)	12 (1.1)
		Other	16 (1.4)	14 (1.3)	17 (1.5)	18 (1.6)

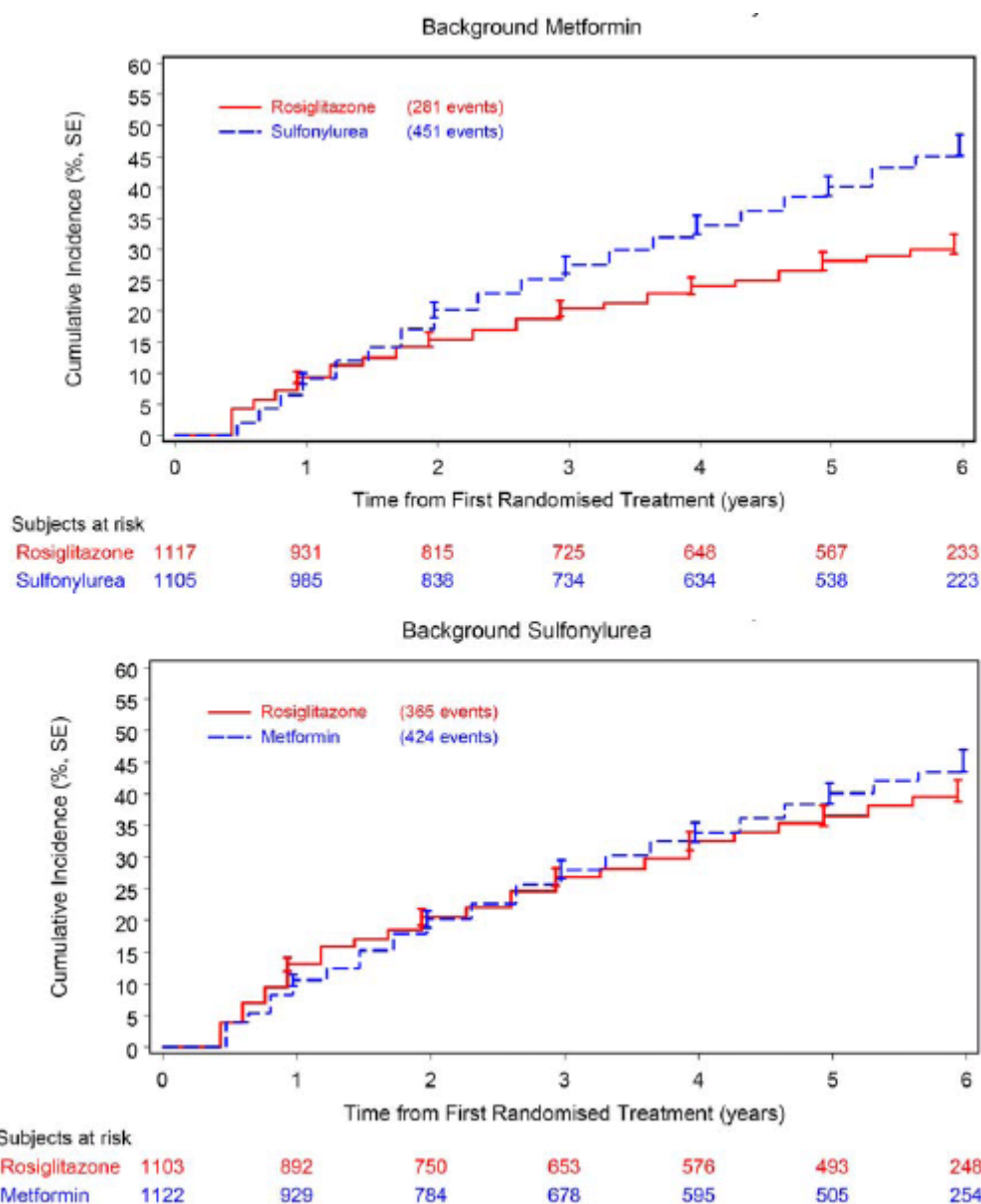
Source: Applicant's Table 16, pg 101, RECORD study report body

By stratum, there was a greater difference between RSG and comparator for the background SU stratum (which compared RSG to MET) than for the background MET stratum (which compared RSG to SU). In the background SU stratum, 42% of patients completed study on dual oral therapy for RSG, and 50% of MET patients did so. The difference between completion status between the background SU and background MET strata was accounted for by the percentage of patients in the background SU stratum who left dual oral therapy due to either initiation of triple therapy or insulin (30% for RSG, 15% for MET).

In Tables II.C.2.I and II.C.2.m above, it appears that a higher proportion of patients left the dual oral therapy phase due to the initiation of the protocol-defined 3rd agent for the RSG group than for the MET/SU group. For the RSG group, the protocol-defined 3rd agent was either MET or SU, with patients

in the background MET group adding SU and patients in the background SU group adding MET. For the overall MET/SU comparator group, the protocol-defined 3rd agent was insulin, which could either be added or substituted. From the observation of a higher proportion of RSG group patients receiving the protocol-defined 3rd agent, one might think that protocol-defined glycemic failure occurred earlier or in more patients for the RSG group than for the MET/SU group. However, this did not appear to be the case, as illustrated in the following figures:

Figure II.C.2.b: Cumulative Incidence of Time to Failure of Glycemic Control

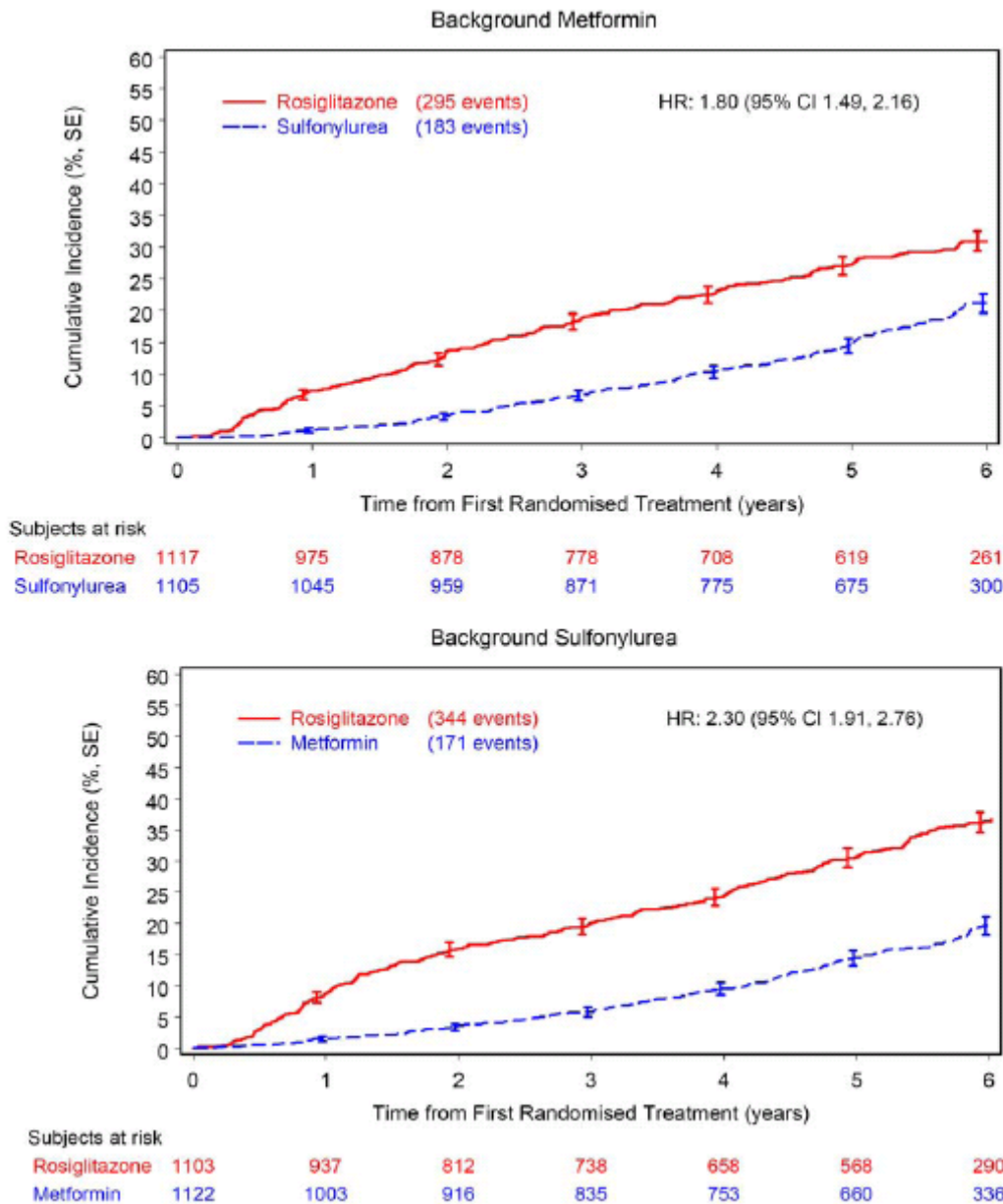


Source: Applicant's Figure 27, pg 193, RECORD study report body. Glycemic control failure defined as two consecutive HbA1c values of $\geq 8.5\%$, or HbA1c $\geq 8.5\%$ at a single visit, following which the patient was either moved to the PRT/CVO phase or triple therapy was started.

Protocol-defined glycemic failure actually occurred more commonly among comparator group patients than among RSG group patients. Among patients in the background MET stratum, 25% of add-on RSG patients had glycemic failure over the course of the study, compared to 41% of patients in the add-on SU arm. For the background SU stratum, the values were 33% for RSG and 38% for MET. However,

although more patients failed glycemic control in the MET/SU group, fewer received their protocol-defined 3rd agent, as illustrated in the following figures:

Figure II.C.2.c: Cumulative Incidence of Time to Addition of Third Oral Agent/Switch to Insulin



Source: Applicant's Figure 28, pg 195, RECORD study report body

The applicant postulates that this may have been due to reluctance of patients to initiate insulin. Additional information was requested from the applicant regarding this, including information on instructions to investigators regarding timing of the addition of 3rd agents, and whether there was recording of reasons for non-addition of the protocol-specified 3rd agents. On 30 Apr 2010, the applicant responded that the protocol and case report forms did not specify that the reason should be recorded for not adding/substituting a 3rd agent after glycemic failure. Therefore, the applicant could not determine precisely why glycemic-failure-prompted addition/substitution of the 3rd agent was less likely to occur for comparator, despite a higher rate of glycemic failure for comparator. The applicant continued to postulate that reluctance of patients to add insulin could have been a contributing factor. Part of the issue could also be related to Protocol Amendment 5, which had specific instructions regarding “cases

where patients and/or doctors express a strong reluctance to switch patients to insulin therapy despite them having reached the upper permitted level of glycemia". This amendment permitted increases in the dose of background sulfonylurea, changes in the formulation of type of sulfonylurea, and increases in the dose of add-on MET or SU to the maximum locally permitted dose. Therefore, patients could have delayed insulin initiation for an extended period of time while attempts at these interventions occurred.

This observation regarding time to initiation of a third agent might be expected to have more importance if one were considering a glycemic control efficacy claim related to it than if one were considering a safety claim. From a cardiovascular safety standpoint, one question would be whether a delay in initiation of insulin in the MET/SU group would have resulted in a higher HbA1c, and thus in a higher CV risk. However, multiple large recent diabetes trials (ACCORD Study Group 2009; ADVANCE Collaborative Group 2008; Duckworth 2009 [VADT]) have failed to show a significant effect of tight glycemic control on the rate of major adverse cardiovascular events in patients with type 2 diabetes. Another question would be whether insulin could have a negative effect on cardiovascular outcomes, which could affect the risk in the comparator group.

When considering the patient-time period of dual/triple therapy, discontinuations through this time period were more common among comparator-treated patients than among RSG-treated patients, with the difference being accounted for by more insulin initiations in the MET/SU group. The following abbreviated table presents these differences. Other types of reasons for discontinuation of dual/triple therapy were similar in frequency between RSG and MET/SU, and by-stratum results were also similar, and are included in the referenced source table.

Table II.C.2.n: Summary of Completion Status and Reasons for Withdrawal From Randomized Dual/Triple Therapy				
Completion Status	Reason for D/C of Rand Dual/Triple Rx	RSG N=2220 n (%)	MET/SU N=2227 n (%)	Total N=4447 n (%)
Completed study to final visit on dual/triple therapy		1344 (60.5)	1131 (50.8)	2475 (55.5)
Died during dual/triple therapy		77 (3.5)	92 (4.1)	169 (3.8)
Discontinued dual/triple combination therapy (includes addition/substitution of insulin)		799 (36.0)	1004 (45.1)	1803 (40.5)
	Insulin initiated	154 (6.9)	377 (16.9)	531 (11.9)
	Adverse event (fatal or nonfatal)	337 (15.2)	300 (13.5)	637 (14.3)
	Prohibited glucose-lowering medication	18 (0.8)	59 (2.6)	77 (1.7)
	High HbA1c	10 (0.5)	48 (2.2)	58 (1.3)
	High HbA1c, insulin refused	4 (0.2)	15 (0.7)	19 (0.4)
	Patient withdrew at own request	176 (7.9)	137 (6.2)	313 (7.0)
Source: Applicant's Table 17, pg 102, RECORD study report body				

Interest has been expressed in the amount of exposure and number of events which occurred in RECORD compared to exposure and event numbers in the original meta-analysis which was the basis of the original concern regarding the cardiovascular safety of rosiglitazone. The overall RECORD trial, and the RECORD patient-time population which included only time on randomized dual oral therapy, both included more patient-time and more events than all combined trials in the 2007 meta-analysis. The following table displays this information for the RECORD patient-time population which included only time on randomized dual oral therapy.

Table II.C.2.o: Patient-Year Exposure and Number of Events, RECORD Dual Oral Therapy Time Period and 2007 Meta-Analysis (All Trials)

Endpoint	RECORD Dual Rx Only		2007 Meta-Analysis	
	RSG N=2220 PY=9279 n (%) [rate/100 PY]	Comp N=2227 PY=10209 n (%) [rate/100 PY]	RSG N=8604 PY=4143 n (%) [rate/100 PY]	Comp N=5633 PY=2675 n (%) [rate/100 PY]
MACE	94 (4.2) [1.0]	117 (5.2) [1.1]	63 (0.7) [1.5]	38 (0.7) [1.4]
MI	47 (2.1) [0.5]	44 (2.0) [0.4]	45 (0.5) [1.1]	20 (0.4) [0.7]
Stroke	32 (1.4) [0.3]	51 (2.3) [0.5]	13 (0.2) [0.3]	18 (0.3) [0.7]
CV Death	23 (1.0) [0.2]	34 (1.5) [0.3]	18 (0.2) [0.4]	7 (0.1) [0.3]
Total Mortality	29 (1.3) [0.3]	46 (2.1) [0.5]	28 (0.3) [0.7]	11 (0.2) [0.4]
Source: Applicant's Figure 7.2.1, pg 5674, RECORD study report body; Table 56, pg 151, RECORD study report body; NDA 21071 Advisory Committee briefing document for Jul 2007 AC mtg				

II.D. Results of Protocol-Specified Analyses

II.D.1. Cardiovascular Endpoints

II.D.1.a. Primary Endpoint

The primary endpoint was the time to first occurrence of adjudicated cardiovascular death or adjudicated cardiovascular hospitalization. The primary study population was the all randomized and treated population, i.e. those randomized patients who received at least one dose of study medication. If the upper bound of the 95% confidence interval (one-sided, $\alpha = 0.025$), for the hazard ratio of the combined endpoint of CV death/hospitalization for the RSG group relative to the MET/SU group fell below 1.2, then it was to be concluded that the RSG group was noninferior to the MET/SU group, per the protocol agreed upon by the EMEA.

The following table displays the applicant's results for the primary analysis:

Table II.D.1.a.i. Primary Analysis: Time to First Occurrence of Adjudicated Cardiovascular Death or Adjudicated Cardiovascular Hospitalization, ITT Population

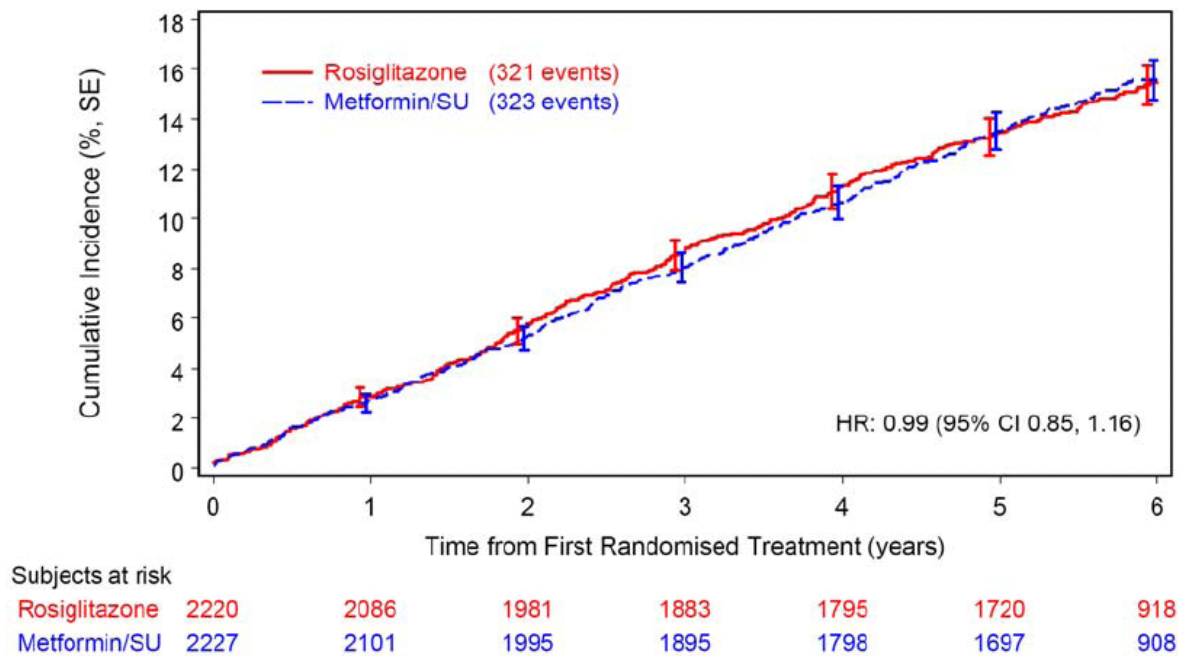
Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with an event	321 (14.5)	323 (14.5)
Rate per 100 patient-years ¹ (95% CI)	2.79 (2.49, 3.11)	2.81 (2.51, 3.13)
Primary analysis ² result: Hazard ratio (95% CI)	0.99 (0.85, 1.16)	
Non-inferiority p-value ³ for primary analysis	0.0164	
Absolute rate difference per 100 patient-years (95% CI)	-0.02 (-0.45, 0.41)	
Source: Applicant's Table 49, pg 142, RECORD study report body		
1 Patient-years up to first primary event		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		
3 p <0.05 is equivalent to the upper 95% confidence limit for the true hazard ratio <1.2 (rejects the null hypothesis that the HR is ≥1.2)		

The above result supports that one can reject the null hypothesis that the true hazard ratio is ≥ 1.2 . Thus, it appears that the primary objective of the study was met, i.e. to demonstrate that rosiglitazone does not

cause an increase in risk of 20% (or higher) for events of cardiovascular death or cardiovascular hospitalization. In fact, the point estimate of risk is <1 for rosiglitazone versus comparator.

The following figure presents the primary analysis result graphically.

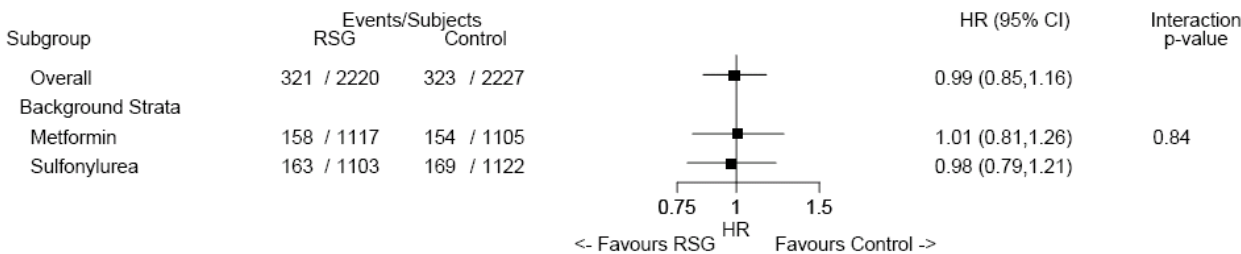
Figure II.D.1.a.i: Cumulative Incidence of Time to First Occurrence of Adjudicated Cardiovascular Death or Adjudicated Cardiovascular Hospitalization (ITT Population)



Source: Applicant’s Figure 7.4, pg 5678, RECORD study report body

The following Forest Plot displays the hazard ratio and 95% confidence interval for the overall result, and by background treatment stratum.

Figure II.D.1.a.ii: Forest Plot of Hazard Ratios for Rosiglitazone vs Comparator for Time to First Occurrence of Adjudicated Cardiovascular Death or Adjudicated Cardiovascular Hospitalization, Overall and by Background Treatment Stratum



Source: Applicant’s Figure 7.3, pg 5677, RECORD study report body

Results by stratum were similar to the overall result, with a nonsignificant p-value for interaction by baseline background diabetes treatment.

The following table summarizes first events contributing to the primary endpoint.

Table II.D.1.a.ii: Summary of First Events Contributing to Primary Endpoint

Component	Subcomponent	Combined RSG N=2220 PY=11523	Combined MET/SU N=2227 PY=11506
Any first event for primary endpoint	Combined all primary endpoint first events	321 (14.5)	323 (14.5)
Cardiovascular Death	Combined CV death	33 (1.5)	39 (1.8)
	Acute MI	3 (0.1)	4 (0.2)
	CHF	2 (0.1)	0
	Sudden death	8 (0.4)	8 (0.4)
	Acute vascular event	0	2 (0.1)
	Other CV mortality	2 (0.1)	1 (<0.1)
	Death from unknown cause (insufficient data)	18 (0.8)	24 (1.1)
Cardiovascular hospitalization	Combined CV hospitalization	288 (13.0)	284 (12.8)
	Acute MI	53 (2.4)	46 (2.1)
	Unstable angina pectoris	20 (0.9)	21 (0.9)
	CHF	39 (1.8)	19 (0.9)
	Stroke	43 (1.9)	56 (2.5)
	Transient ischemic attack	9 (0.4)	9 (0.4)
	Invasive cardiovascular procedures	24 (1.1)	25 (1.1)
	Amputation of extremities	1 (<0.1)	10 (0.4)
	Other CV hospitalization	99 (4.5)	98 (4.4)

Source: Applicant's Table 7.6, pg 5881, RECORD study report body

In general, the component first events for the primary endpoint occurred with similar frequency between treatment groups, with the exception of first primary endpoint events of hospitalization for heart failure, which occurred among 1.8% of RSG patients and 0.9% of MET/SU patients, and first primary endpoint events of stroke, which occurred among 1.9% of RSG patients and 2.5% of MET/SU patients.

The following table presents the results of the primary endpoint by study stratum, i.e. separated into groups by whether the patient's background medication was metformin or sulfonylurea.

Table II.D.1.A.iii: Primary Endpoint by Study Stratum

Parameter	Background MET		Background SU	
	Add-on RSG N=1117	Add-on SU N=1105	Add-on RSG N=1103	Add-on MET N=1122
Number (and percentage) of patients with an event	158 (14.1)	154 (13.9)	163 (14.8)	169 (15.1)
Rate per 100 PY ¹ (95% CI)	2.70 (2.29, 3.15)	2.67 (2.26, 3.12)	2.88 (2.45, 3.35)	2.95 (2.52, 3.43)
Hazard ratio (95% CI)	1.01 (0.81, 1.26)		0.98 (0.79, 1.21)	
Absolute rate difference per 100 PY (95% CI)	0.03 (-0.57, 0.62)		-0.07 (-0.70, 0.56)	

Source: Applicant's Table 65, pg 159 of RECORD study report body

1 Patient-years up to first primary event

2 Stratified (by background stratum) Cox Proportional Hazards Model: Time = treatment + stratum*treatment; HR is relative to respective control group

By the applicant's analysis, there was no evidence of a statistical interaction by baseline study stratum (p=0.84).

In general, the percentages of patients who completed cardiovascular event follow-up for the primary endpoint and those who withdrew from follow-up were similar between rosiglitazone and comparator, for the overall comparison and by stratum.

Table II.D.1.a.iv: Summary of Percentages of Patients Who Completed CV Follow-up for Primary Endpoint

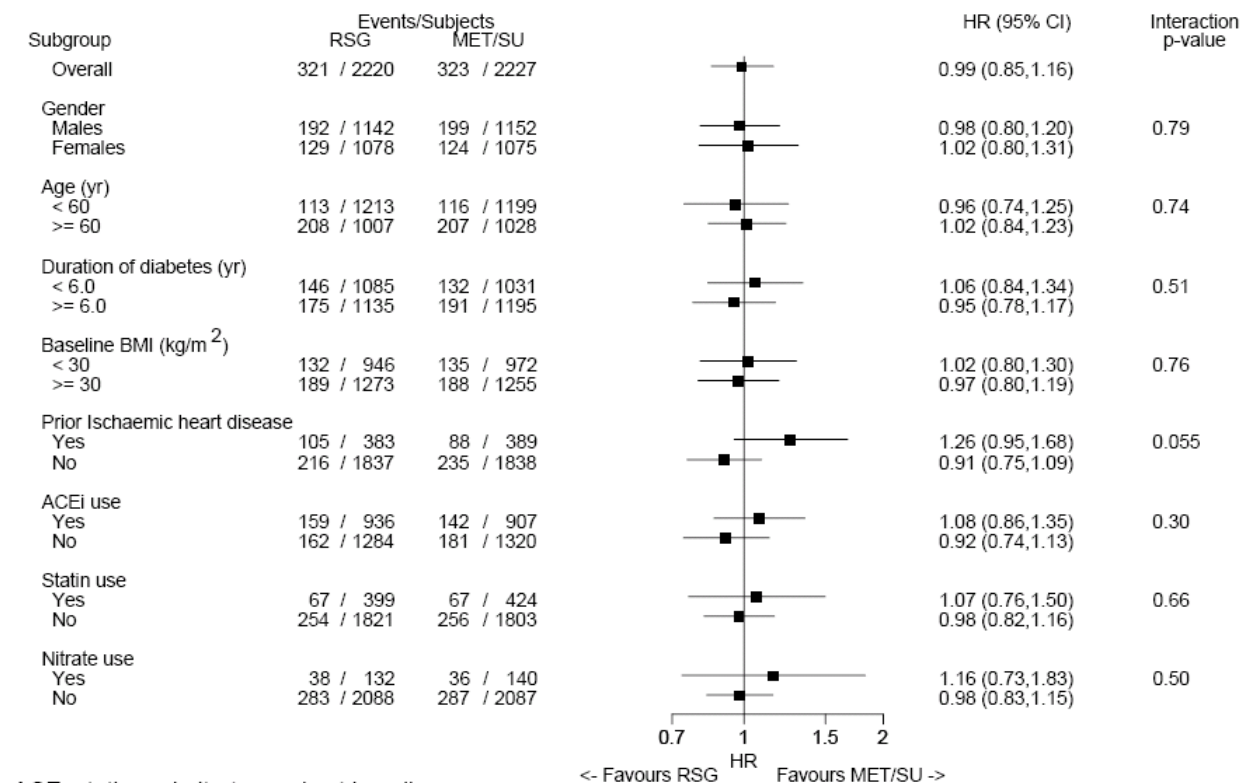
Follow-up Category	Overall		Bkgrd MET		Bkgrd SU	
	Combined RSG N=2220 n (%)	Combined MET/SU N=2227 n (%)	RSG N=1117 n (%)	SU N=1105 n (%)	RSG N=1103 n (%)	MET N=1122 n (%)
Patients with at least one adjudicated event	321 (14.5)	323 (14.5)	158 (14.1)	154 (13.9)	163 (14.8)	169 (15.1)
Patients with no event and who completed CV follow-up to final visit	1612 (72.6)	1589 (71.4)	830 (74.3)	806 (72.9)	782 (70.9)	783 (69.8)
Patients with no event, and for whom a noncardiovascular death terminated follow-up	44 (2.0)	56 (2.5)	23 (2.1)	28 (2.5)	21 (1.9)	28 (2.5)
Patients who had no event and withdrew from CV follow-up	243 (10.9)	259 (11.6)	106 (9.5)	117 (10.6)	137 (12.4)	142 (12.7)

Source: Applicant's Table 7.1, beg pg 5872, RECORD study report body

The applicant explored multiple baseline characteristics with regard to potential statistical interactions by the presence of these characteristics.

The following Forest Plot displays a summary of these analyses for statistical interactions by baseline characteristics, for the primary endpoint.

Figure II.D.1.a.iii: Forest Plot of Hazard Ratios for Time to First Occurrence of CV Death or CV Hospitalization by Baseline Subgroups



ACE, statin and nitrate use is at baseline

dart1: /bioenv/dart1/brl49653_3b/231_final/code/f_7_13_1_d.sas 14JUL09 08:59

Source: Applicant's Figure 7.13.1, pg 5685, RECORD study report body

No interactions were noted by baseline nitrate use ($p=0.50$) or baseline angiotensin converting enzyme inhibitor (ACEI) use ($p=0.30$). These particular baseline characteristics were of special interest, because the 2007 FDA meta-analysis had suggested a statistical interaction by baseline use of nitrates and ACEIs, and information regarding this was added to the RSG label at that time.

For a baseline history of ischemic heart disease, the interaction p -value was 0.055, with a higher point estimate (1.26) among those with a prior history of ischemic heart disease. Please see Section II.D.3.a for a discussion of the types of events which occurred among patients with prior ischemic heart disease. When one examined these events, the difference between RSG and comparator was primarily accounted for by heart failure events, with unstable angina events contributing to a lesser degree. Among patients with a prior history of ischemic heart disease, myocardial infarction rates did not differ between RSG and comparator, and point estimates for cardiovascular death and total mortality favored RSG.

The primary analyses for RECORD were done using the intention-to-treat principle. In addition, the applicant performed two types of "per-protocol" analyses, which may serve as sensitivity analyses and explore the question of whether the results might differ if one considers the drop-out rate and time on actual randomized therapy.

Table II.D.1.a.v: Time to First Occurrence of Adjudicated Cardiovascular Death or Adjudicated Cardiovascular Hospitalization, “Per Protocol” Population With Cut-Off at End of Randomized Dual Oral Combination Treatment

Parameter	Combined RSG N=2220 PY=8834	Combined MET/SU N=2227 PY=9761
Number (and percentage) of patients with an event	237 (10.7)	255 (11.5)
Rate per 100 patient-years ¹ (95% CI)	2.68 (2.35, 3.05)	2.61 (2.30, 2.95)
Hazard ratio ² (95% CI)	1.03 (0.86, 1.23)	
Non-inferiority p-value	0.0845	
Absolute rate difference per 100 patient-years (95% CI)	0.07 (-0.40, 0.54)	
Source: Applicant's Table 54, pg 148; and Table 7.1.3, pg 6195, RECORD study report body		
1 Patient-years up to first primary event		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

The point estimate for this analysis is similar to that obtained with the intention-to-treat approach. The upper bound of the 95% confidence interval for this analysis is 1.23. Because this is >1.2, if this had been the primary analysis method, this upper bound would have fallen slightly above that set for non-inferiority. Please see the discussion below of the MACE endpoint (with Table II.D.1.b.xvi) regarding this upper bound of 1.2 versus the upper bound of 1.3 used in the Agency’s Guidance regarding evaluation of the cardiovascular safety of drugs for type 2 diabetes mellitus.

The following table displays results for the primary endpoint, using a patient-time population of time on randomized dual oral therapy plus 30 days, to account for any additional events which may have occurred in the time period shortly after the patient moved out of the dual oral therapy phase.

Table II.D.1.a.vi: Time to First Occurrence of Adjudicated Cardiovascular Death or Adjudicated Cardiovascular Hospitalization, “Per Protocol” Population With Cut-Off 30 Days Beyond End of Randomized Dual Oral Combination Treatment

Parameter	Combined RSG N=2220 PY=8905	Combined MET/SU N=2227 PY=9818
Number (and percentage) of patients with an event	240 (10.8)	260 (11.7)
Rate per 100 patient-years ¹ (95% CI)	2.70 (2.36, 3.06)	2.65 (2.33, 2.99)
Hazard ratio ² (95% CI)	1.02 (0.85, 1.21)	
Non-inferiority p-value	0.0659	
Absolute rate difference per 100 patient-years (95% CI)	0.05 (-0.42, 0.52)	
Source: Applicant's Table 7.17, pg 6500; and Table 7.18, pg 6503, RECORD study report body		
1 Patient-years up to first primary event		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

Point estimates were similar for all three analysis population approaches. The results of this analysis, which adds 30 days of follow-up after cessation of randomized treatment, are similar to that in Table II.D.1.a.v above. The upper bound of the 95% confidence interval is 1.21.

It has been suggested that the intention-to-treat analysis is not the appropriate analysis, and that a more appropriate analysis would be some type of per protocol analysis which included only the period of time

during which patients were actually taking the randomized trial medications (sometimes referred to as a type of “as-treated” analysis). The FDA’s recent Guidance for Industry entitled “Noninferiority Clinical Trials” (Mar 2010) discusses limitations of intention-to-treat analysis, and of “as-treated” analyses in noninferiority clinical trials. This is a recent Guidance, and was not available at the time of design and initiation of RECORD. Because both an intention-to-treat and an “as-treated” approach have limitations, the Agency’s current recommendation is that both types of analyses be performed for noninferiority trials. In RECORD, the primary analysis used the intention-to-treat principle, and secondary analyses were performed using a “per protocol” (“as-treated”) patient-time population, which included only time on randomized dual oral therapy.

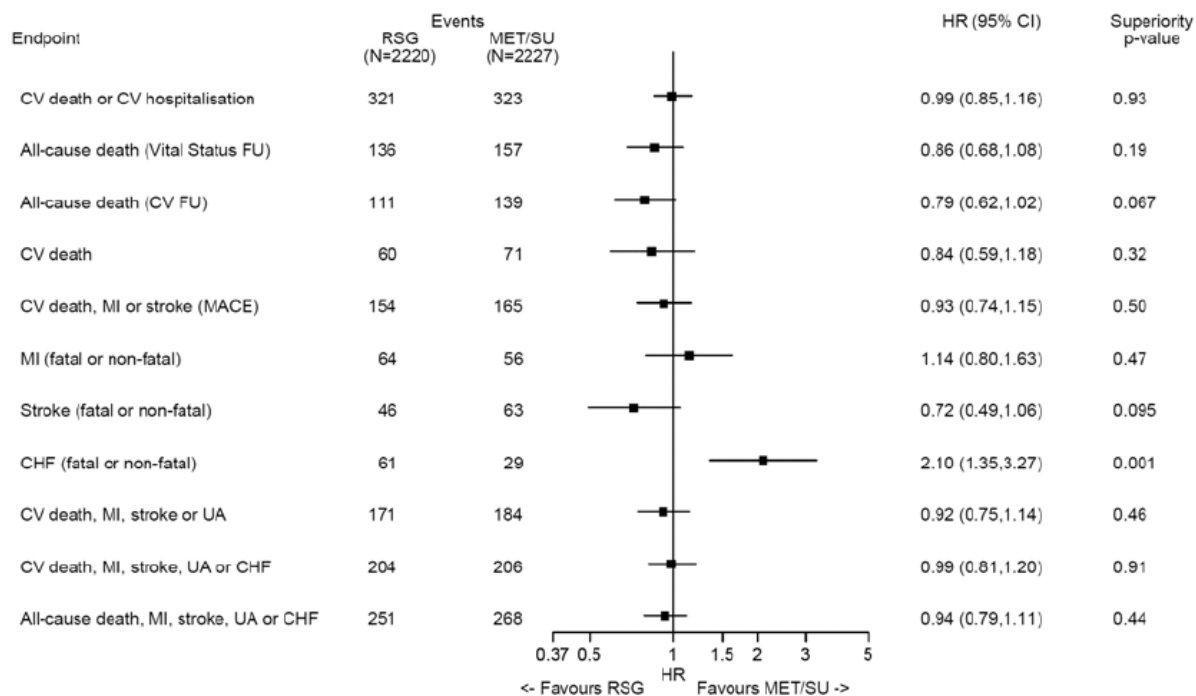
Overall, for the primary endpoint, when examining “per protocol” analyses which include only time on dual randomized therapy, with or without the subsequent 30 day period, point estimates are similar to those using the ITT population, and upper bounds of 95% confidence intervals do not increase greatly.

II.D.1.b. Secondary Cardiovascular Endpoints

Overview of Secondary Cardiovascular Outcomes

The following Forest Plot displays the applicant’s hazard ratios and 95% confidence intervals for the secondary cardiovascular outcomes by their model, using the ITT population. Heart failure occurred statistically significantly more commonly among rosiglitazone-treated patients than among comparator-treated patients. There were no other statistically significant differences between rosiglitazone and comparator. All other cardiovascular composites and components had point estimates <1, favoring rosiglitazone, except for myocardial infarction, which had a point estimate of 1.14, not favoring rosiglitazone, with a statistically nonsignificant result (95% CI 0.80, 1.63; p-value 0.47).

Figure II.D.1.b.i: Forest Plot of Hazard Ratios and 95% Confidence Intervals for Cardiovascular Outcomes, ITT Population



UA-unstable angina

Source: Applicant’s Figure 10, pg 161, RECORD study report body

The following table includes a summary of the results for these analyses, and includes information on absolute rate differences as well as hazard ratios, for the ITT population.

Table II.D.1.b.i: Summary of Adjudicated Cardiovascular Endpoints, ITT Population

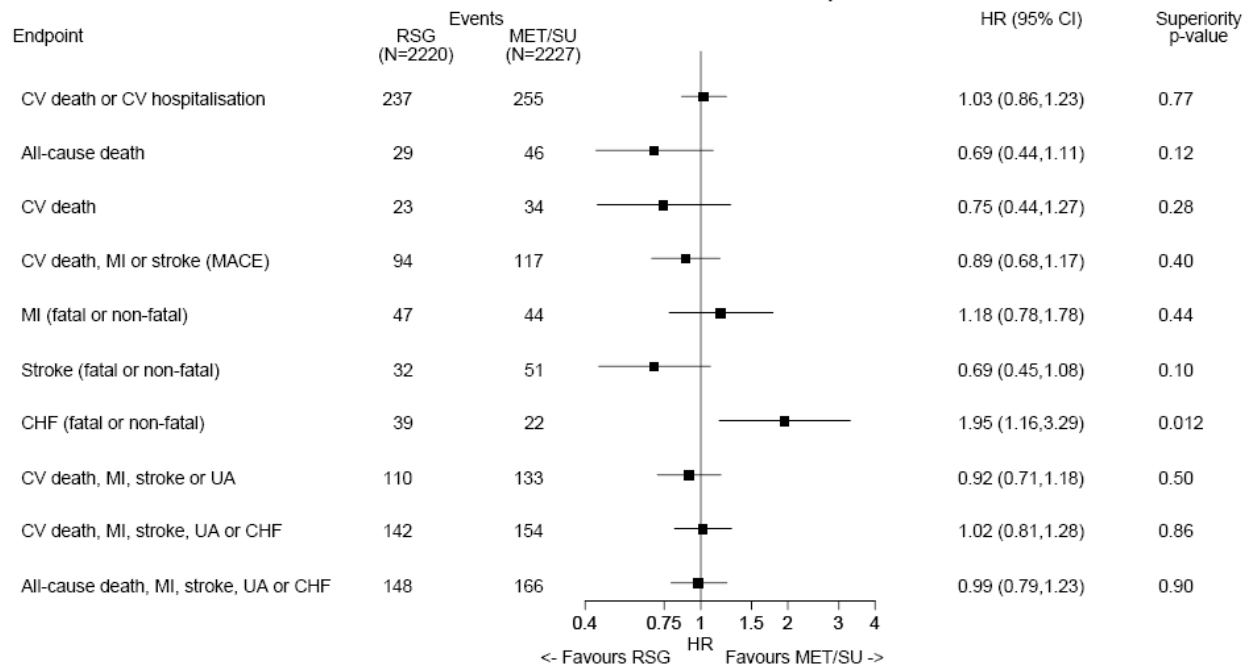
Endpoint	Combined RSG N=2220 n (%)	Combined MET/SU N=2227 n (%)	HR (95% CI)	Absolute Rate Difference per 100 PY (95% CI)
CV death or CV hosp	321 (14.5)	323 (14.5)	0.99 (0.85, 1.16)	-0.02 (-0.45, 0.41)
All-cause death (including vital status follow-up)	136 (6.1)	157 (7.0)	0.86 (0.68, 1.08)	-0.17 (-0.43, 0.09)
All-cause death (including CV follow-up but not patients who were in “vital status follow-up only” status	111 (5.0)	139 (6.2)	0.79 (0.62, 1.02)	-0.23 (-0.48, 0.02)
CV death	60 (2.7)	71 (3.2)	0.84 (0.59, 1.18)	-0.09 (-0.27, 0.09)
CV death, MI or stroke (“MACE”)	154 (6.9)	165 (7.4)	0.93 (0.74, 1.15)	-0.10 (-0.39, 0.19)
Myocardial infarction (fatal or nonfatal)	64 (2.9)	56 (2.5)	1.14 (0.80, 1.63)	0.06 (-0.11, 0.24)
Stroke (fatal or nonfatal)	46 (2.1)	63 (2.8)	0.72 (0.49, 1.06)	-0.14 (-0.31, 0.02)
Heart Failure (fatal or nonfatal)	61 (2.7)	29 (1.3)	2.10 (1.35, 3.27)	0.26 (0.11, 0.41)
CV death, MI, stroke or unstable angina	171 (7.7)	184 (8.3)	0.92 (0.75, 1.14)	-0.12 (-0.43, 0.19)
CV death, MI, stroke, unstable angina or HF	204 (9.2)	206 (9.3)	0.99 (0.81, 1.20)	-0.02 (-0.35, 0.32)
All-cause death, MI, stroke, unstable angina or HF	251 (11.3)	268 (12.0)	0.94 (0.79, 1.11)	-0.15 (-0.52, 0.23)

Source: Applicant’s Figure 7.1.1, pg 5671; Table 49, pg 142; Table 66, pg 162; Table 68, pg 163; Table 69, pg 165; Table 70, pg 166; Table 71, pg 168; Table 72, pg 171; Table 73, pg 173; Table 76, pg 176; Table 80, pg 180; and Table 81, pg 181 (RECORD study report body)

As discussed for the primary endpoint, analysis of events which occurred during the patient-time period which includes only dual oral combination therapy provides a sensitivity analysis which avoids the complicating factor of the asymmetric study design for addition of 3rd agents.

The following Forest Plot displays these endpoints for the “per-protocol” analyses, i.e. including only time on randomized dual oral combination therapy.

Figure II.D.1.b.ii: Forest Plot of Hazard Ratios and 95% Confidence Intervals for Cardiovascular Outcomes, “Per-Protocol” Analyses (Time on Randomized Dual Oral Combination Therapy Only)



Source: Applicant's Figure 7.2.1, pg 5674, RECORD study report body

The above analyses take into account the difference in total patient-time between the RSG and comparator groups for time on randomized dual oral therapy. Each of the estimates includes first events for the particular endpoint examined (and not only those first events that were included in the primary endpoint analysis). There are some small differences in point estimates between these analyses and the ITT analyses, but they are generally similar. Because point estimates for the ITT population analyses were often near 1, inclusion of time in the model shifted some point estimates from slightly below 1 to slightly above 1.

As with the ITT analyses, the only statistically significant result was for heart failure, and did not favor rosiglitazone. The per protocol analysis of the primary endpoint was discussed in the previous section. As with the ITT analysis, the point estimate for MI was >1 at 1.18, with an upper bound of 1.78 reflecting the smaller total number of MI events (120 ITT vs 91 PP).

The following table displays the above results, and includes absolute rate differences.

Table II.D.1.b.ii: Summary of Adjudicated Cardiovascular Endpoints, “Per-Protocol” Analyses (Time on Randomized Dual Oral Combination Therapy Only)

Endpoint	Combined RSG N=2220 n (%)	Combined MET/SU N=2227 n (%)	HR (95% CI)	Absolute Rate Difference per 100 PY (95% CI)
CV death or CV hosp	237 (10.7)	255 (11.5)	1.03 (0.86, 1.23)	0.07 (-0.40, 0.54)
All-cause death	29 (1.3)	46 (2.1)	0.69 (0.44, 1.11)	-0.14 (-0.31, 0.03)
CV death	23 (1.0)	34 (1.5)	0.75 (0.44, 1.27)	-0.09 (-0.24, 0.07)
CV death, MI or stroke (“MACE”)	94 (4.2)	117 (5.3)	0.89 (0.68, 1.17)	-0.13 (-0.43, 0.17)
Myocardial infarction (fatal or nonfatal)	47 (2.1)	44 (2.0)	1.18 (0.78, 1.78)	0.08 (-0.12, 0.27)
Stroke (fatal or nonfatal)	32 (1.4)	51 (2.3)	0.69 (0.45, 1.08)	-0.16 (-0.34, 0.03)
Heart Failure (fatal or nonfatal)	39 (1.8)	22 (1.0)	1.95 (1.16, 3.29)	0.21 (0.05, 0.37)
CV death, MI, stroke or unstable angina	110 (5.0)	133 (6.0)	0.92 (0.71, 1.18)	-0.11 (-0.43, 0.21)
CV death, MI, stroke, unstable angina or HF	142 (6.4)	154 (6.9)	1.02 (0.81, 1.28)	0.03 (-0.32, 0.39)
All-cause death, MI, stroke, unstable angina or HF	148 (6.7)	166 (7.5)	0.99 (0.79, 1.23)	-0.02 (-0.39, 0.34)

Source: Applicant’s Figure 7.2.1, pg 5674; Table 54, pg 148; Table 7.59, pg 7666; Table 7.65, pg 8270; Table 7.71, pg 8874; Table 7.77, pg 9478; Table 7.84, pg 10085; Table 7.94, pg 10701; Table 7.100, pg 11305; Table 7.106, pg 11909 and Table 7.112, pg 12513 (RECORD study report body)

Time to Cardiovascular Mortality (component of primary endpoint)

The following table displays the applicant’s analysis of time to death from cardiovascular causes.

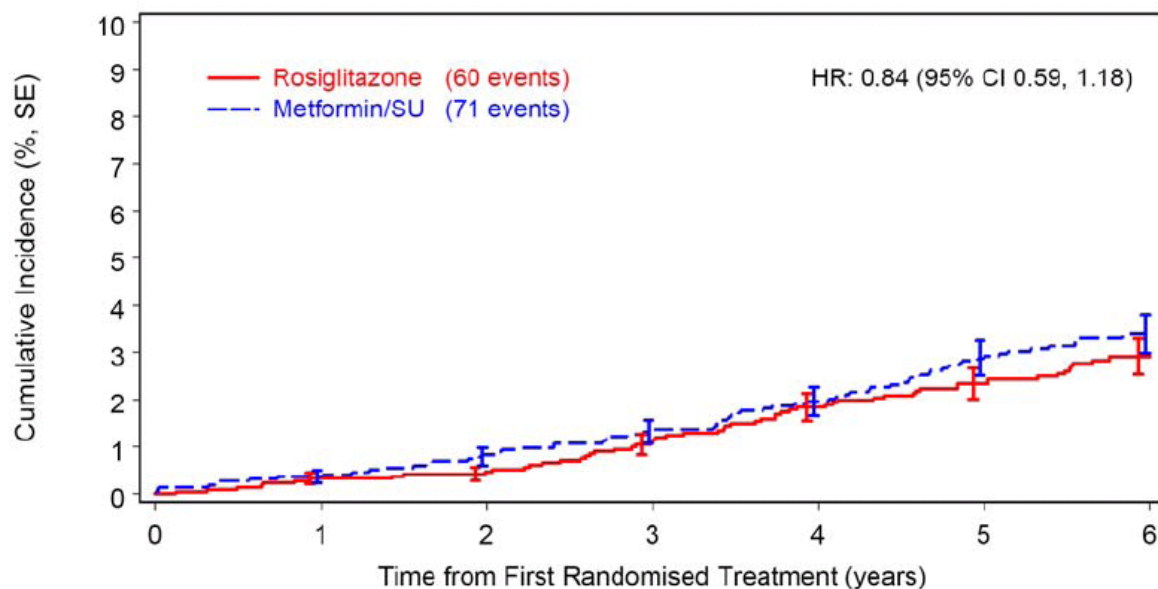
Table II.D.1.b.iii: Time to Death from Cardiovascular Causes, ITT Population

Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with CV death	60 (2.7)	71 (3.2)
Rate per 100 patient-years ¹ (95% CI)	0.49 (0.37, 0.63)	0.58 (0.45, 0.73)
Hazard ratio (95% CI) ²	0.84 (0.59, 1.18)	
p-value	0.3158	
Absolute rate difference per 100 patient-years (95% CI)	-0.09 (-0.27, 0.09)	
Source: Applicant’s Table 76, pg 176, RECORD study report body		
1 Patient-years up to first event		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

Using adjudicated results, the incidence of death from cardiovascular causes was lower among patients treated with RSG than among patients in the control group, but the difference was not statistically significant.

The following Kaplan Meier plot displays the results of the above analysis.

Figure II.D.1.b.iii: Cumulative Incidence of Time to Death from Cardiovascular Causes, ITT Population



Subjects at risk

Rosiglitazone	2220	2139	2084	2032	1972	1918	104
Metformin/SU	2227	2148	2085	2025	1965	1893	101

Source: Applicant's Figure 20, pg 176, RECORD study report body

The following table displays a summary of cardiovascular causes of death, using adjudicated results.

Table II.D.1.b.iv: Adjudicated Cardiovascular Causes of Death, ITT Population

CV Death Category	CV Death Subcategory	Combined RSG N=2220 n (%) ¹	Combined MET/SU N=2227 n (%) ¹
Any CV cause		60 (2.7)	71 (3.2)
Acute MI		7 (0.3)	10 (0.4)
CHF		10 (0.5)	2 (0.1)
Sudden death		8 (0.4)	12 (0.5)
Acute vascular events	Any acute vascular event	1 (<0.1)	10 (0.4)
	Stroke	0	5 (0.2)
	Other vascular events	1 (<0.1)	5 (0.2)
Other CV mortality		6 (0.3)	4 (0.2)
Presumed CV cause (insufficient data per applicant)		28 (1.3)	33 (1.5)

Source: Applicant's Table 77, pg 177, RECORD study report body

¹ Number and percentage of patients who died from a given category of cardiovascular event

Death from congestive heart failure occurred among 10 (0.5%) of RSG group patients, and among 2 (<0.1%) of combined MET/SU group patients. Death from stroke occurred among no RSG group patients and among 5 MET/SU group patients. For other causes of cardiovascular death, the incidence was similar between RSG and MET/SU, or was numerically higher for MET/SU.

The category of “presumed cardiovascular cause” presents a challenge because it contains a substantial percentage of overall cardiovascular deaths (47% of RSG group CV deaths and 46% of MET/SU CV deaths). If these deaths were in fact not CV in etiology, the addition of these deaths to the analytic pool could dilute the overall analysis. The applicant reported that these cases did not have adequate data to meet adjudication criteria for cardiovascular cause of death, and thus, per protocol, were to be included as cardiovascular deaths. However, in order to address the issue of dilution, the applicant’s steering committee chairman performed a post hoc blinded review of these cases and assigned a cause of death for each case. The following table lists those causes of death by treatment group.

Table II.D.1.b.v: Steering Committee Chairman’s Assigned Causes of Death after Post Hoc Blinded Review of Cardiovascular Deaths Classified as “Presumed Cardiovascular Cause” Due to Insufficient Adjudication Data

Cause of Death Category	Cause of Death Subcategory	RSG	MET/SU
All cases categorized as “presumed CV cause” due to insufficient data	All “presumed CV cause” deaths	28	33
Sudden death	All sudden death	7	7
	Sudden death	5	6
	Sudden cardiac death	2	1
Myocardial infarction	All myocardial infarction	6	3
	Myocardial infarction	4	3
	Myocardial ischemia	1	0
	Coronary artery disease	1	0
CHF	All CHF	3	2
	Cardiac failure congestive	2	1
	Cardiac failure	1	0
	Cardiac failure acute	0	1
Stroke	All stroke	2	4
	Cerebrovascular accident	1	3
	Cerebral infarction	1	0
	Ruptured cerebral aneurysm	0	1
Other CV Mortality	All other CV	3	4
	Pulmonary embolism	1	2
	Ventricular arrhythmia	1	0
	Cardiovascular insufficiency	0	2
	Cardiac disorder	1	0
Unknown death	Any unknown death	6	7
Non-CV death	Any non-CV death	1	6
	Respiratory failure	0	1
	Alcohol abuse	0	1
	Lung infection	0	1
	Drowning	0	2
	Fall	1	1

Source: Applicant’s Table 78, pg 178, RECORD study report body

By these post hoc adjudications, it appears that a total of 7 of these deaths were actually non-cardiovascular (RSG group n=1; MET/SU group n=6). This would change the total numbers of cardiovascular deaths to 59 (2.7%) for the RSG group, and 65 (2.9%) for the combined MET/SU group.

The following table displays the “per protocol” analysis, which included only time on randomized dual oral combination treatment.

Table II.D.1.b.vii: Time to Death from Cardiovascular Causes, “Per Protocol” Population With Cut-Off at End of Randomized Dual Oral Combination Treatment

Parameter	Combined RSG N=2220 PY=9283	Combined MET/SU N=2227 PY=10215
Number (and percentage) of patients with CV death	23 (1.0)	34 (1.5)
Rate per 100 patient-years ¹ (95% CI)	0.25 (0.16, 0.37)	0.33 (0.23, 0.47)
Hazard ratio ² (95% CI)	0.75 (0.44, 1.27)	
p-value	0.2817	
Absolute rate difference per 100 patient-years (95% CI)	-0.09 (-0.24, 0.07)	
Source: Applicant's Table 7.105, pg 11906; and Table 7.106, pg 11909, RECORD study report body		
1 Patient-years up to death		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

Results from this analysis were similar to those for the ITT analysis. The rate of CV death events for this analysis was somewhat lower for the randomized dual combination therapy patient-time population (0.25 RSG, 0.33 MET/SU) than for the ITT population (0.49 RSG, 0.58 MET/SU). The relative rate between RSG and MET/SU was similar, however. The applicant states that the lower rate on dual therapy occurred because, for some out-of-hospital deaths, it was sometimes not possible to confirm whether the patient was actually on randomized dual therapy at the time of death. This rate difference was also noted when examining total deaths on randomized therapy. However, for nonfatal events, rates were similar during the ITT and dual therapy patient-time periods; dual therapy status could more easily be confirmed for patients who survived an event and returned for follow-up than for patients who died outside of the hospital.

Cardiovascular Hospitalization

The applicant did not provide a separate analysis of time to cardiovascular hospitalization. Cardiovascular events which contributed to first events of cardiovascular hospitalization for the primary endpoint are summarized in Table II.D.1.a.ii above in the section regarding the primary endpoint. The various types of events which contributed to cardiovascular hospitalizations (e.g. MI, stroke, CHF, amputation, etc), each had their own analysis.

Time to First Occurrence of Myocardial Infarction (Fatal or Nonfatal)

The following table displays the applicant's analysis of myocardial infarction for the ITT population.

Table II.D.1.b.viii: Time to First Occurrence of Myocardial Infarction (Fatal or Nonfatal), ITT Population

Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with any MI	64 (2.9)	56 (2.5)
Rate per 100 patient-years ¹ (95% CI)	0.53 (0.40, 0.67)	0.46 (0.35, 0.60)
Hazard ratio (95% CI) ²	1.14 (0.80, 1.63)	
p-value	0.4725	
Absolute rate difference per 100 patient-years (95% CI)	0.06 (-0.11, 0.24)	

Source: Applicant's Table 71, pg 168, RECORD study report body

1 Patient-years up to first MI event

2 Cox proportional hazards model, stratified by background stratum. Time = treatment

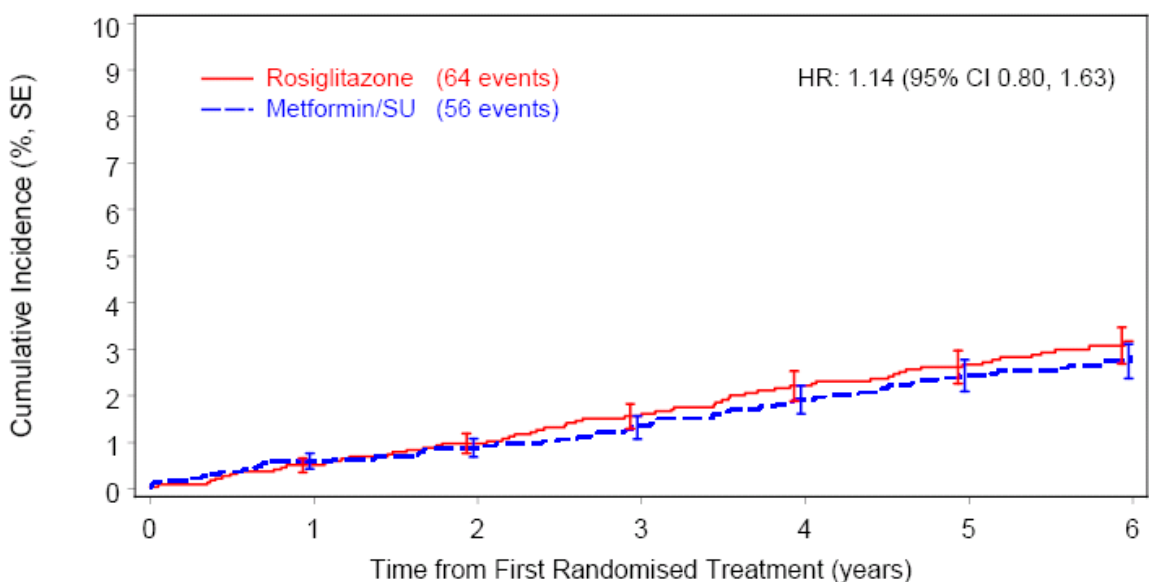
First events of myocardial infarction occurred numerically, but not statistically significantly, more commonly among patients in the RSG group than among patients in the MET/SU group.

For first events contributing to this analysis, 4 first events of MI were fatal in the overall RSG group, and 4 were fatal in the overall comparator group.

Using adjudicated results, when considering all events of MI (not only first events), a total of 7 (0.3%) of patients in the overall RSG group died from myocardial infarction, while 10 (0.4%) of patients in the overall comparator group died from MI.

The following figure displays the cumulative incidence of MI.

Figure II.D.1.b.iv: Kaplan Meier Cumulative Incidence Curves for Time to First Occurrence of Adjudicated Acute Myocardial Infarction, ITT Population



Subjects at risk

Rosiglitazone 2220 2128 2066 2005 1937 1879 1012

Metformin/SU 2227 2141 2074 2005 1936 1858 996

Source: Applicant's Figure 7.22, pg 5702, RECORD study report body

For the first two years, there was no difference in the cumulative incidence of MI between RSG and MET/SU. After Year 2, there was a numeric point estimate difference between RSG and MET/SU, not favoring RSG. The vertical bars in the figure represent the standard error of the point estimate at each specified time point, and do not represent confidence intervals.

The following table displays myocardial infarction by study stratum.

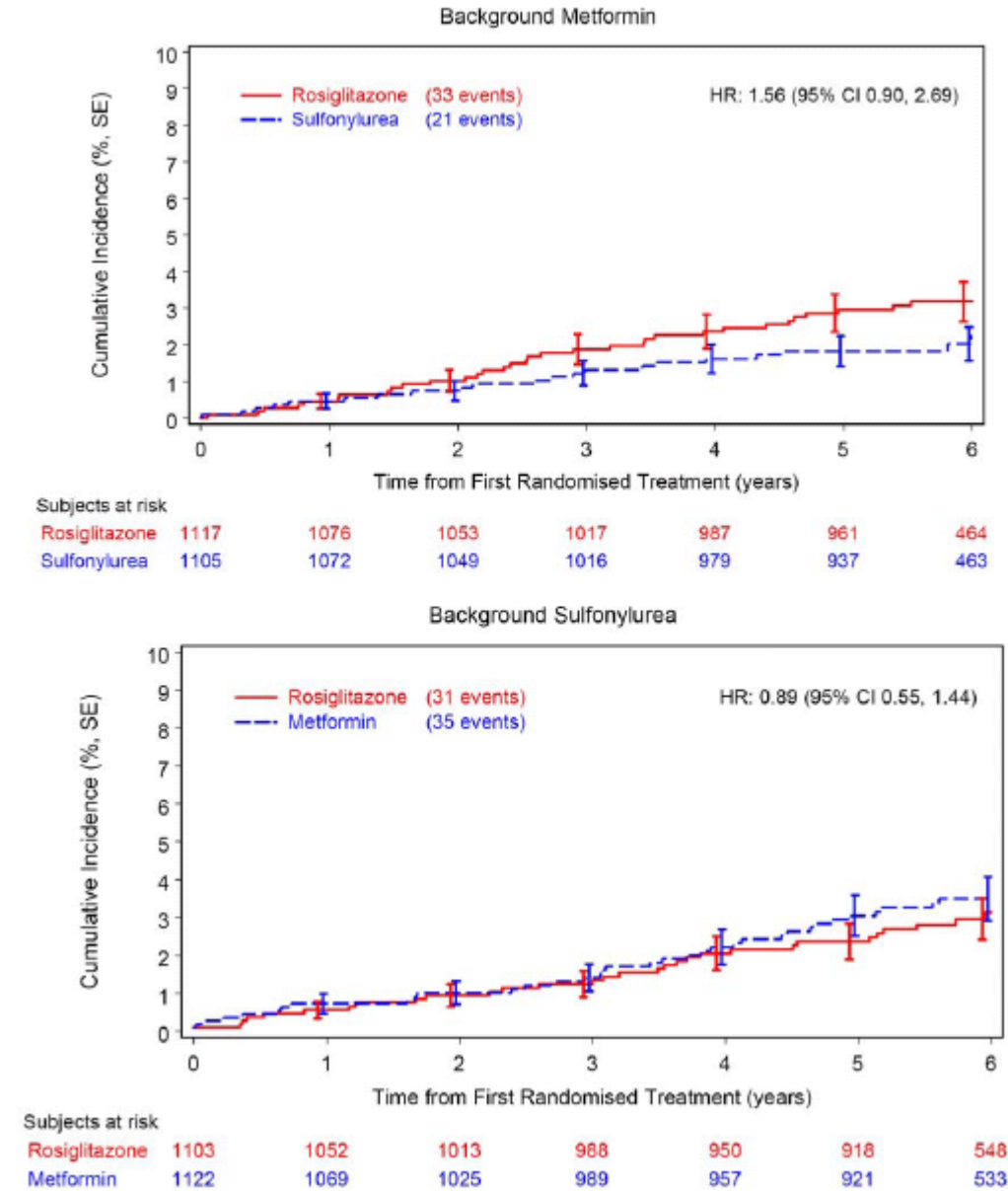
Table II.D.1.b.ix: First Events of Myocardial Infarction (Fatal or Nonfatal) by Study Stratum, ITT Population

Parameter	Background MET		Background SU	
	Add-on RSG N=1117 PY=6147	Add-on SU N=1105 PY=6093	Add-on RSG N=1103 PY=6028	Add-on MET N=1122 PY=6054
Number (and percentage) of patients with an event	33 (3.0)	21 (1.9)	31 (2.8)	35 (3.1)
Rate per 100 PY (95% CI)	0.54 (0.37, 0.75)	0.34 (0.21, 0.52)	0.51 (0.35, 0.73)	0.58 (0.40, 0.80)
Hazard ratio (95% CI)	1.56 (0.90, 2.69)		0.89 (0.55, 1.44)	
Absolute rate difference per 100 PY (95% CI)	0.19 (-0.04, 0.43)		-0.06 (-0.33, 0.20)	
Source: Applicant's Tables 7.80 (beg pg 9781) and 7.81 (beg pg 9784), RECORD study report body				

By study stratum, the point estimate for the comparison of RSG to SU remained >1 at 1.56, while the point estimate for the comparison of RSG to MET was <1, at 0.89. For both strata, the difference between RSG and comparator was not statistically significant.

The following Kaplan-Meier curves display cumulative incidence of MI by background stratum.

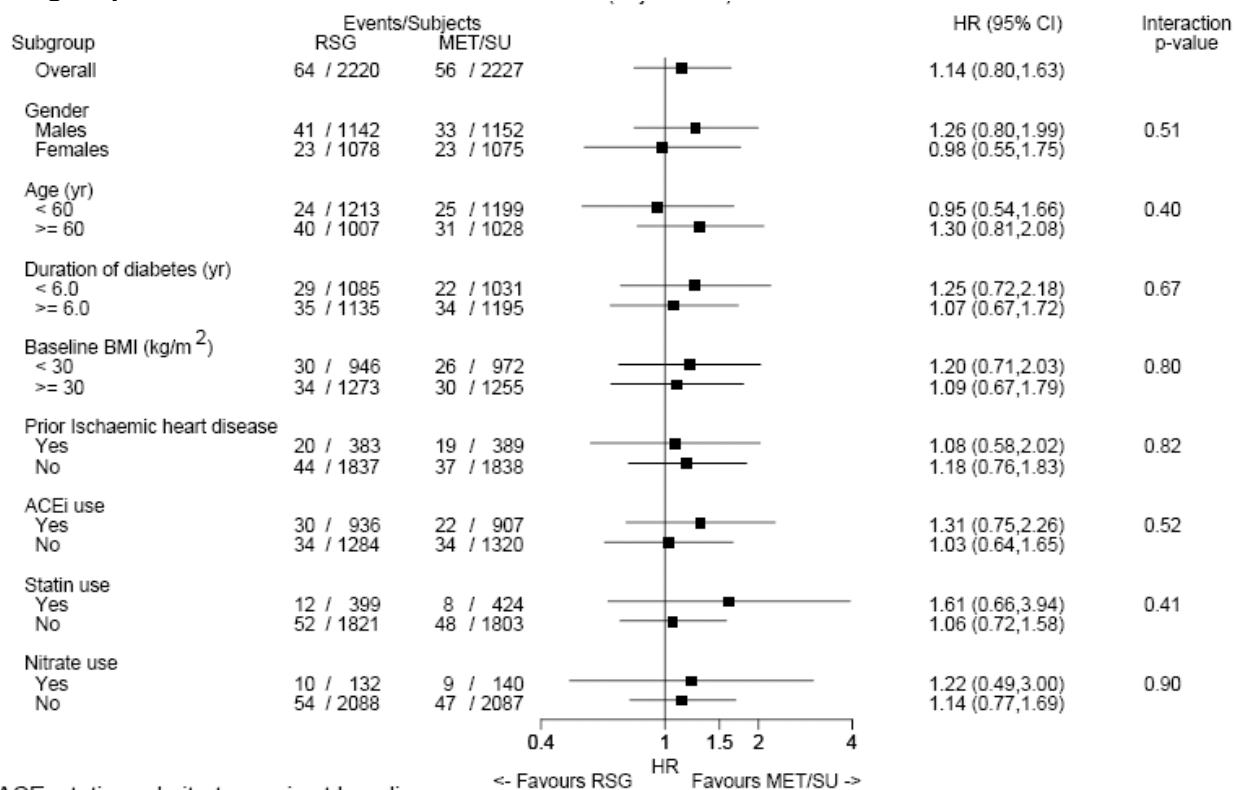
Figure II.D.1.b.v: Cumulative Incidence Curves for Time to First Occurrence of Adjudicated Acute Myocardial Infarction by Background Stratum, ITT Population



Source: Applicant's Figure 16, pg 170, RECORD study report body

The following Forest Plot displays the incidence of myocardial infarction by subgroups of baseline characteristics.

Figure II.D.1.b.vi: Forest Plot of Hazard Ratios for Rosiglitazone Relative to Comparator for Time to First Occurrence of Acute Myocardial Infarction (Adjudicated, Fatal or Nonfatal) by Baseline Subgroups



ACE, statin and nitrate use is at baseline

Source: Applicant's Figure ah2257.1, subm 1 Feb 2010

In general, there was no evidence of a statistical interaction by baseline subgroup, with all interaction p-values being ≥ 0.4 . Most point estimates were >1 , and all 95% confidence intervals included 1. Unlike the observation for the primary endpoint, there was no evidence of a statistical interaction by baseline history of ischemic heart disease (p-value 0.8) for the MI endpoint.

The following table displays the incidence and rate of MI through the end of randomized dual oral combination therapy (the "per protocol" treatment period).

Table II.D.1.b.x: Myocardial Infarction (Fatal or Nonfatal) Through End of Randomized Dual Oral Combination Therapy (“Per Protocol” Time Period)

		Overall		Bkgrd MET		Bkgrd SU	
		RSG N=2220 PY=9189	MET/SU N=2227 PY=10146	RSG N=1117 PY=4713	SU N=1105 PY=5144	RSG N=1103 PY=4476	MET N=1122 PY=5002
Number and percentage of patients with event		47 (2.1)	44 (2.0)	23 (2.1)	16 (1.4)	24 (2.2)	28 (2.5)
Rate per 100 PY (95% CI)		0.51 (0.38, 0.68)	0.43 (0.32, 0.58)	0.49 (0.31, 0.73)	0.31 (0.18, 0.51)	0.54 (0.34, 0.80)	0.56 (0.37, 0.81)
First event fatality status?	Fatal n (%)	3 (0.1)	3 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)
	Nonfatal n (%)	44 (2.0)	41 (1.0)	22 (2.0)	15 (1.4)	22 (2.0)	26 (2.3)
Vital status at end of study among patients with nonfatal events	Alive n (%)	38/44 (86.4)	33/41 (80.5)	16/22 (72.7)	12/15 (80.0)	22/22 (100)	21/26 (80.8)
	Dead n (%)	6/44 (13.6)	8/41 (19.5)	6/22 (27.3)	3/15 (20.0)	0	5/26 (19.2)
First event nonfatal and died subsequently from adjudicated CV cause [n (%)]		3 (0.1)	6 (0.3)	3 (0.3)	3 (0.3)	0	3 (0.3)

Source: Applicant’s Table 7.83, beg pg 10082, RECORD study report body

The results of this “per protocol” analysis were similar to those for the ITT analysis.

For the overall group, the incidence and rate of MI was slightly numerically higher for the RSG group than for the comparator group, although 95% confidence intervals for rate ratios overlapped. The incidence among RSG-treated patients was 2.1%, and among comparator-treated patients was 2.0%. By stratum, the incidence ratio did not favor RSG numerically for the background MET stratum (HR 1.5 vs SU), but favored RSG numerically for the background SU stratum (HR 0.88 vs MET). For both strata, rate ratios overlapped between RSG and comparator. The percentage of events which were fatal did not differ substantially between treatment groups, nor did the percentage of patients who died subsequently.

Time to First Occurrence of Stroke (Fatal or Nonfatal)

The following table displays the applicant’s analyses for time to first occurrence of adjudicated stroke.

Table II.D.1.b.xi: Time to First Occurrence of Stroke (Fatal or Nonfatal), ITT Population

Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with any stroke	46 (2.1)	63 (2.8)
Rate per 100 patient-years ¹ (95% CI)	0.38 (0.28, 0.50)	0.52 (0.40, 0.67)
Hazard ratio (95% CI) ²	0.72 (0.49, 1.06)	
p-value	0.0953	
Absolute rate difference per 100 patient-years (95% CI)	-0.14 (-0.31, 0.02)	

Source: Applicant’s Table 72, pg 171, RECORD study report body

¹ Patient-years up to first stroke event

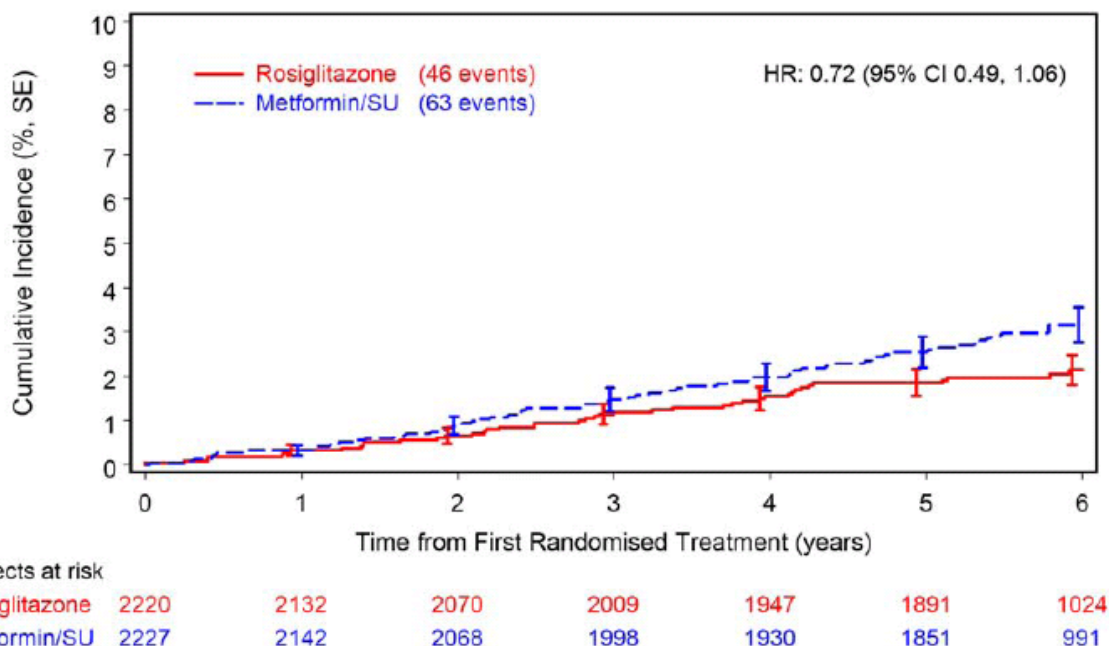
² Cox proportional hazards model, stratified by background stratum. Time = treatment

Stroke occurred numerically, but not statistically significantly, less commonly among RSG group patients than among MET/SU group patients.

Using adjudicated results, no patients in the overall RSG group suffered a fatal stroke, while 5 (0.2%) of patients in the overall comparator group had a fatal stroke.

The following figure displays the cumulative incidence of stroke.

Figure II.D.1.b.vii: Kaplan Meier Cumulative Incidence Curves for Time to First Occurrence of Adjudicated Stroke



Source: Applicant's Figure 18, pg 172, RECORD study report body

The following table displays stroke by study stratum.

Table II.D.1.b.xii: Stroke (Fatal or Nonfatal) by Study Stratum, ITT Population

Parameter	Background MET		Background SU	
	Add-on RSG N=1117 PY=6092	Add-on SU N=1105 PY=6009	Add-on RSG N=1103 PY=6052	Add-on MET N=1122 PY=6055
Number (and percentage) of patients with an event	21 (1.9)	32 (2.9)	25 (2.3)	31 (2.8)
Rate per 100 PY (95% CI)	0.34 (0.21, 0.52)	0.53 (0.36, 0.75)	0.41 (0.27, 0.61)	0.51 (0.35, 0.73)
Hazard ratio (95% CI)	0.64 (0.37, 1.12)		0.81 (0.48, 1.36)	
Absolute rate difference per 100 PY (95% CI)	-0.19 (-0.42, 0.05)		-0.10 (-0.34, 0.14)	

Source: Applicant's Tables 7.90 and 7.91, beg pg 10397, RECORD study report body

Results by stratum were similar to the overall result. The point estimate for the comparison of RSG to SU was somewhat lower than that for the comparison of RSG to MET, but both estimates favored RSG and 95% confidence intervals included 1 for both strata.

The following table displays the incidence and rate of stroke during the patient-time period that includes only time on randomized dual oral therapy.

Table II.D.1.b.xiii: Time to Stroke, “Per Protocol” Population With Cut-Off at End of Randomized Dual Oral Combination Treatment		
Parameter	Combined RSG N=2220 PY=9212	Combined MET/SU N=2227 PY=10137
Number (and percentage) of patients with stroke	32 (1.4)	51 (2.3)
Rate per 100 patient-years ¹ (95% CI)	0.35 (0.24, 0.49)	0.50 (0.37, 0.66)
Hazard ratio ² (95% CI)	0.69 (0.45, 1.08)	
p-value	0.10	
Absolute rate difference per 100 patient-years (95% CI)	-0.16 (-0.34, 0.03)	
Source: Applicant’s Table 7.93, pg 10698; and Table 7.94, pg 10701, RECORD study report body		
1 Patient-years up to death		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

The results of this “per protocol” analysis were similar to those for the ITT analysis. During randomized dual combination therapy, stroke occurred numerically, but not statistically significantly, less commonly among RSG group patients than among MET/SU group patients.

Time to First Occurrence of Congestive Heart Failure

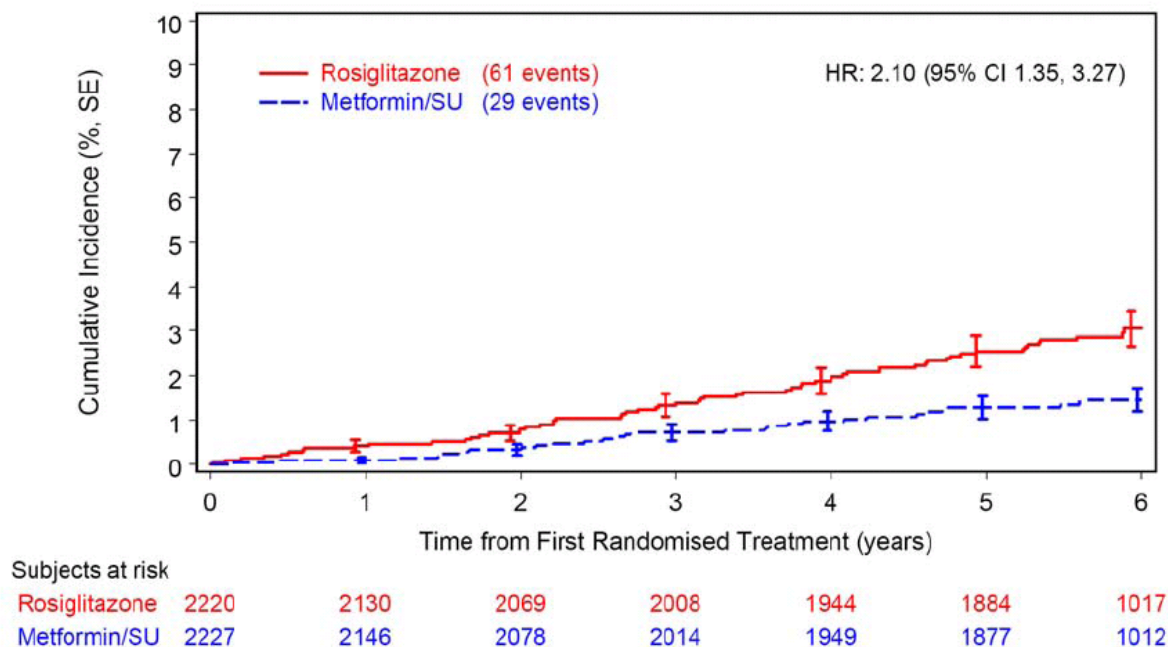
Events of heart failure (fatal or nonfatal) occurred at a statistically significantly higher rate among patients in the overall RSG group than among patients in the overall MET/SU group.

Table II.D.1.b.xiv: Time to First Occurrence of Heart Failure, ITT Population		
Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with any HF	61 (2.7)	29 (1.3)
Rate per 100 patient-years ¹ (95% CI)	0.50 (0.38, 0.64)	0.24 (0.16, 0.34)
Hazard ratio (95% CI) ²	2.10 (1.35, 3.27)	
p-value	0.001	
Absolute rate difference per 100 patient-years (95% CI)	0.26 (0.11, 0.41)	
Source: Applicant’s Table 73, pg 173, RECORD study report body		
1 Patient-years up to first HF event		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

Using adjudicated results, a total of 10 (0.5%) of patients in the overall RSG group died from heart failure, while 2 (0.1%) of patients in the overall comparator group died from heart failure.

The following Kaplan-Meier curves display the cumulative incidence of heart failure for the overall RSG group vs the overall MET/SU group.

Figure II.D.1.b.viii: Kaplan Meier Cumulative Incidence Curves for Time to First Occurrence of Heart Failure (Fatal or Nonfatal, Adjudicated)

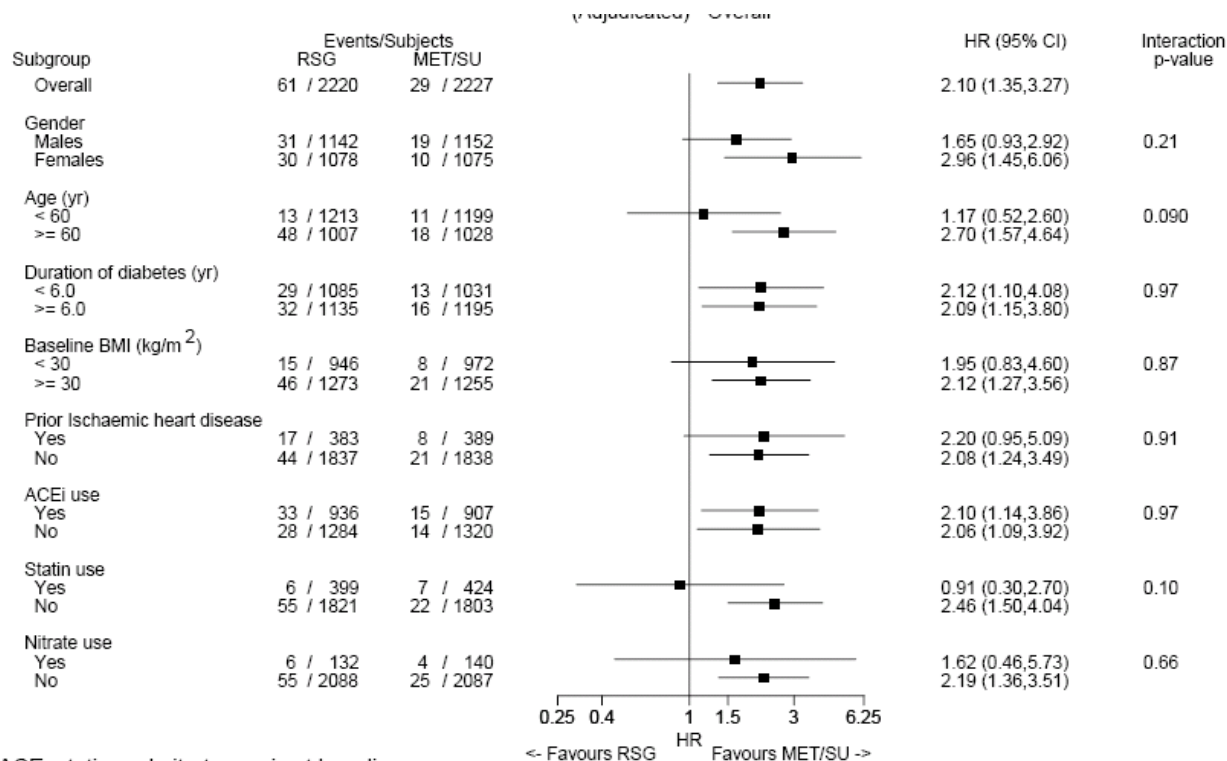


Source: Applicant's Figure 7.26, pg 5712, RECORD study report body

The difference between RSG and MET/SU for the occurrence of heart failure occurred early in study and widened throughout study.

The following figure displays the occurrence of heart failure by baseline subgroups. In general, the finding of a higher incidence of heart failure among RSG-treated patients was consistent across subgroups. Interaction p-values were <0.2 for age and baseline statin use, with a somewhat lower point estimate for patients under age 60 years and patients who were taking a statin at baseline. However, the numbers of events in these baseline subgroups were small, and 95% confidence intervals were wide and included 1. There was no evidence of a statistical interaction by baseline history of ischemic heart disease, ACEI use, or nitrate use.

Figure II.D.1.b.ix: Forest Plot of Hazard Ratios for Rosiglitazone Relative to Comparator for Time to First Occurrence of Heart Failure (Adjudicated, Fatal or Nonfatal) by Baseline Subgroups



ACE, statin and nitrate use is at baseline

Source: Applicant's Figure ah2257.2, subm 1 Feb 2010

The following table displays heart failure for the patient-time population that included only time on randomized dual oral therapy.

Table II.D.1.b.xv: Time to Heart Failure, "Per Protocol" Population With Cut-Off at End of Randomized Dual Oral Combination Treatment

Parameter	Combined RSG N=2220 PY=9235	Combined MET/SU N=2227 PY=10175
Number (and percentage) of patients with heart failure	39 (1.8)	22 (1.0)
Rate per 100 patient-years ¹ (95% CI)	0.42 (0.30, 0.58)	0.22 (0.14, 0.33)
Hazard ratio ² (95% CI)	1.95 (1.16, 3.29)	
p-value	0.01	
Absolute rate difference per 100 patient-years (95% CI)	0.21 (0.05, 0.37)	
Source: Applicant's Table 7.99, pg 11302; and Table 7.100, pg 11305, RECORD study report body		
1 Patient-years up to death		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

The results of this "per protocol" analysis were similar to those for the ITT analysis. Heart failure occurred statistically significantly more commonly among RSG group patients than among MET/SU group patients.

Time to First MACE

The following table displays the results of the applicant's MACE analyses.

Table II.D.1.b.xvi: Time to Occurrence of MACE (Nonfatal Myocardial Infarction, Nonfatal Stroke or Cardiovascular Death), ITT Population

Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with an event	154 (6.9)	165 (7.4)
Total number of events	177	195
Rate per 100 patient-years (95% CI)	1.28 (1.08, 1.50)	1.38 (1.17, 1.60)
Hazard ratio (95% CI)	0.93 (0.74, 1.15)	
p-value	0.499	
Absolute rate difference per 100 patient-years (95% CI)	-0.10 (-0.39, 0.19)	

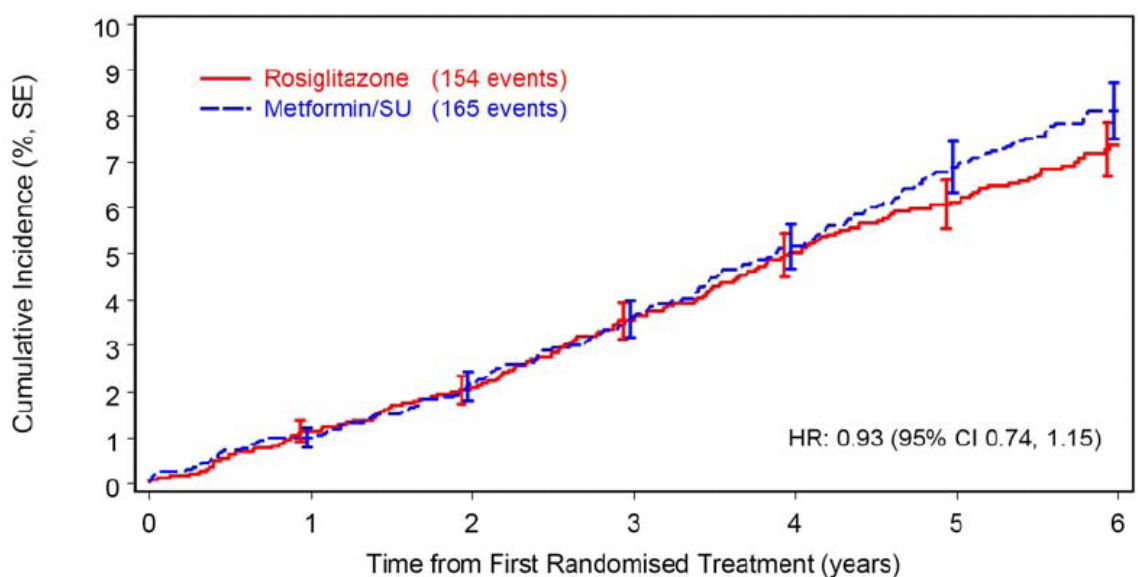
Source: Applicant's Table 66, pg 162, RECORD study report body

Using the applicant's model, there was not a statistically significant difference between rosiglitazone and comparator for the occurrence of a first event of MI, stroke or CV death; the point estimate for the hazard ratio favored rosiglitazone.

Because the upper bound of the 95% confidence interval of 1.15 is <1.3, this analysis would meet the criteria set by the FDA Guidance entitled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" (Dec 2008), in which the maximum specified upper bound is 1.3, for demonstration of lack of unacceptably increased cardiovascular risk.

The following Kaplan-Meier plot displays time to first MACE.

Figure II.D.1.b.x: Kaplan-Meier Cumulative Incidence Curves for Time to First Occurrence of MACE (MI, Stroke or CV Death)



Subjects at risk

Rosiglitazone	2220	2121	2052	1982	1912	1852	994
Metformin/SU	2227	2135	2057	1978	1901	1816	970

Source: Applicant's Figure 7.14, pg 5686, RECORD study report body

The following table displays the first component events which contributed to the MACE composite, and the vital status at end of study for patients whose first MACE was nonfatal.

Table II.D.1.b.xvii: Summary of First Events Contributing to Overall MACE Analysis, and Summary of Vital Status at End of Study for Patients with First MACE Nonfatal

Parameter	Category	Combined RSG N=2220 PY=12062 n (%) ¹	Combined MET/SU N=2227 PY=11993 n (%) ¹
First Event Contributing to MACE	CV Death	48/2220 (2.2)	51/2227 (2.3)
	Nonfatal MI	60/2220 (2.7)	51/2227 (2.3)
	Nonfatal stroke	46/2220 (2.1)	63/2227 (2.8)
Vital status at study end for patients with first MACE nonfatal	Alive	86/106 (81.1)	89/114 (78.1)
	Dead	20/106 (18.9)	24/114 (21.1)
	Vital status unconfirmed	0	1/114 (0.9)
First MACE nonfatal and patient subsequently died from adjudicated CV cause		12/2220 (0.5)	20/2220 (0.9)
Source: Applicant's Table 7.55, pg 7361, RECORD study report body ¹ Denominator for first events contributing to composite, and for CV death after MACE, is total for arm (2220 RSG, 2227 MET/SU). Denominator for vital status at end of study for patients with first nonfatal MACE = total number of first events of nonfatal MACE in arm (106 RSG, 114 MET/SU).			

The percentage of first events contributing to MACE which were cardiovascular deaths was similar between treatment groups. The percentage of first events which were MI was slightly higher for RSG than for MET/SU (2.7% vs 2.3%), and the percentage of strokes was slightly lower (2.1% vs 2.8%). Among patients who survived a first MACE, all but one patient had confirmed vital status at end of study, and most patients were still alive at end of study (81% for RSG and 79% for MET/SU). For RSG group patients 12/20 (60%) of deaths after a nonfatal MACE were due to CV causes, and for the MET/SU group, 20/24 (83%) of deaths after a nonfatal MACE were due to CV causes.

The following table displays MACE results by background stratum.

Table II.D.1.b.xviii: MACE by Background Stratum

Parameter	Background MET		Background SU	
	Add-on RSG N=1117 PY=6092	Add-on SU N=1105 PY=6009	Add-on RSG N=1103 PY=5970	Add-on MET N=1122 PY=5984
Number (and percentage) of patients with an event	78 (7.0)	76 (6.9)	76 (6.9)	89 (7.9)
Rate per 100 PY (95% CI)	1.28 (1.01, 1.60)	1.26 (1.00, 1.58)	1.27 (1.00, 1.59)	1.49 (1.19, 1.83)
Hazard ratio (95% CI)	1.01 (0.74, 1.39)		0.85 (0.63, 1.16)	
Absolute rate difference per 100 PY (95% CI)	0.02 (-0.39, 0.42)		-0.21 (-0.64, 0.21)	
Source: Applicant's Tables 7.55 (beg pg 7362) and 7.56 (beg pg 7365). RECORD study report body				

When considering the background MET stratum, the percentage of patients who had a first MACE event, and the rate of first MACEs, were similar between RSG and SU. When considering the background SU

stratum, the percentage of patients with a first MACE event, and the rate of first MACEs, were numerically, but not statistically significantly, lower for RSG group patients than for MET group patients.

When considering only time on randomized dual oral combination therapy (a “per protocol” analysis), the point estimate was slightly lower than that for the ITT population analysis, favoring RSG, and the upper bound of the 95% confidence interval was similar to that for the ITT population [HR 0.89 (95% CI 0.68-1.17, p-value 0.4016), absolute rate difference -0.13 (95% CI -0.43-0.17), treatment by stratum interaction p-value 0.9268]. As with the ITT analysis, the upper bound for the “per protocol” analysis of 1.17 would have met the criteria for demonstration of CV safety under the new diabetes CV safety evaluation Guidance.

Table II.D.1.b.xix: Time to First Event of Cardiovascular Death, Myocardial Infarction or Stroke (MACE), “Per Protocol” Population With Cut-Off at End of Randomized Dual Oral Combination Treatment

Parameter	Combined RSG N=2220 PY=9117	Combined MET/SU N=2227 PY=10067
Number (and percentage) of patients with MACE	94 (4.2)	117 (5.3)
Rate per 100 patient-years ¹ (95% CI)	1.03 (0.83, 1.26)	1.16 (0.96, 1.39)
Hazard ratio ² (95% CI)	0.89 (0.68, 1.17)	
p-value	0.40	
Absolute rate difference per 100 patient-years (95% CI)	-0.13 (-0.43, 0.17)	
Source: Applicant's Table 7.58, pg 7663; and Table 7.59, pg 7666, RECORD study report body		
1 Patient-years up to death		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

Time to First Occurrence of Microvascular Event

Analyses for microvascular events should be interpreted with caution, because the CEC did not review or adjudicate microvascular events. Definitions for diabetes-related microvascular complications were provided to, and events were reported by, investigators. Please see Section II.B for definitions used.

No events of end-stage renal disease, which was the definition used for renal microvascular disease, occurred in RECORD. Therefore, events were limited to diabetes-related eye and foot complications.

Table II.D.1.b.xx: Incidence of Microvascular Events, ITT Population

Type of Microvascular Event ¹	RSG N=2220 n (%)	MET/SU N=2227 n (%)	HR (95% CI)	p-value
Any	59 (2.7)	78 (3.5)	0.75 (0.54, 1.05)	0.0969
Eye	42 (1.9)	52 (2.3)	0.81 (0.54, 1.21)	0.2980
Foot	19 (0.9)	28 (1.3)	0.67 (0.37, 1.20)	0.1783
Source: Applicant’s Table 84, pg 185, RECORD study report body				
1 No cases of endstage renal disease occurred				

Overall, point estimates favored RSG for this endpoint, but the difference was not statistically significant. Results were similar by stratum (Applicant’s Table 7.118, beg pg 13118; Table 7.124, beg pg 13429; and Table 7.130, beg pg 14028; RECORD study report body).

As mentioned above, the definition used for renal microvascular complications was the development of endstage renal disease, which did not occur in any patients in RECORD. Microalbuminuria is often considered an early precursor of overt diabetic nephropathy. In RECORD, microalbuminuria was defined as a urinary albumin:creatinine ratio of ≥ 2.5 to <30 mg/mmol in men, and ≥ 3.5 to <30 mg/mmol in women. When examining microalbuminuria, 4.2% of RSG group patients and 5.3% of MET/SU patients developed new microalbuminuria between baseline and 60 months of study. In the background MET stratum, this occurred for 4.3% of RSG patients and 6.1% of SU patients. In the background SU stratum, this occurred for 4.1% of RSG patients and 4.6% of MET patients (Source: Applicant's Table 7.283, pg 19353, RECORD study report body). These data should be interpreted with caution because, in all stratum arms, missing values were common at 60 months (27-32% of patients).

II.D.2. Noncardiovascular Endpoints

II.D.2.a. Time to All-Cause Mortality

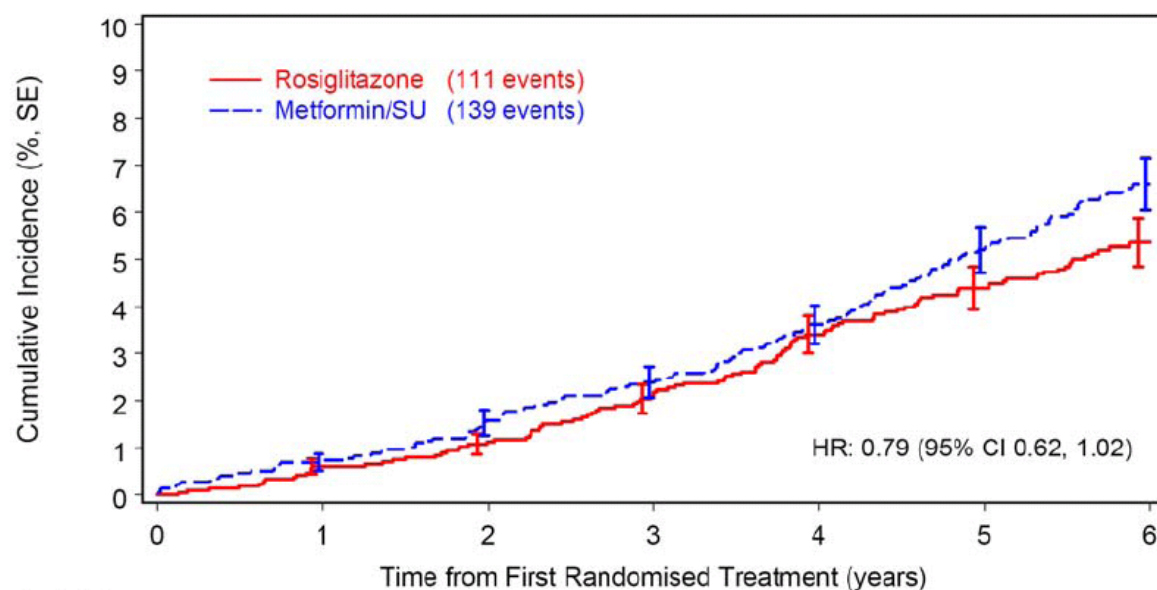
The following table displays the applicant's analyses for total mortality.

Table II.D.2.a.i: Time to Occurrence of Death from Any Cause, ITT Population		
Parameter	Combined RSG N=2220	Combined MET/SU N=2227
Number (and percentage) of patients with death	111 (5.0)	139 (6.2)
Rate per 100 patient-years ¹ (95% CI)	0.90 (0.74, 1.08)	1.13 (0.95, 1.34)
Hazard ratio ² (95% CI)	0.79 (0.62, 1.02)	
p-value	0.0673	
Absolute rate difference per 100 patient-years (95% CI)	-0.23 (-0.48, 0.02)	
Source: Applicant's Table 80, pg 180, RECORD study report body		
1 Patient-years up to death		
2 Cox proportional hazards model, stratified by background stratum. Time = treatment		

Death from any cause occurred numerically, but not statistically significantly, less frequently among RSG group patients than among MET/SU group patients.

The following Kaplan-Meier plots illustrate time to death for the ITT population.

Figure II.D.2.a: Cumulative Incidence of Time to Death, ITT Population



Subjects at risk							
Rosiglitazone	2220	2139	2084	2032	1972	1918	1042
Metformin/SU	2227	2148	2085	2025	1965	1893	1017

Source: Applicant's Figure 21, pg 180, RECORD study report body

The cumulative incidence of death was numerically lower among RSG group patients throughout study.

The following tables display analyses of death from any cause when considering only the time on randomized dual oral therapy.

Table II.D.2.a.ii: Time to Death from Any Cause, "Per Protocol" Population With Cut-Off at End of Randomized Dual Oral Combination Treatment

Parameter	Combined RSG N=2220 PY=9283	Combined MET/SU N=2227 PY=10215
Number (and percentage) of patients with an event	29 (1.3)	46 (2.1)
Rate per 100 patient-years ¹ (95% CI)	0.31 (0.21, 0.45)	0.45 (0.33, 0.60)
Hazard ratio ² (95% CI)	0.69 (0.44, 1.11)	
p-value	0.1247	
Absolute rate difference per 100 patient-years (95% CI)	-0.14 (-0.31, 0.03)	

Source: Applicant's Table 7.111, pg 12510; and Table 7.112, pg 12513, RECORD study report body

¹ Patient-years up to death

² Cox proportional hazards model, stratified by background stratum. Time = treatment

The results of this analysis were generally similar to those for the ITT population.

The rate of events of death for this analysis was lower for the randomized dual combination therapy patient-time population (0.31 RSG, 0.45 MET/SU) than for the ITT population (0.90 RSG, 1.13 MET/SU). The relative rate between RSG and MET/SU was similar, however, for the two patient-time populations. The applicant states that the lower rate on dual therapy occurred because, for some out-of-hospital

deaths, it was sometimes not possible to confirm whether the patient was actually on randomized dual therapy at the time of death. This rate difference was also noted when examining cardiovascular deaths on randomized therapy. However, for nonfatal events, rates were similar during the ITT and dual therapy patient-time periods; dual therapy status could more easily be confirmed for patients who survived an event and returned for follow-up than for patients who died outside of the hospital.

II.D.2.b. Change From Baseline in Hemoglobin A1c

The following table presents the change from baseline in HbA1c at each year of study, by baseline stratum.

Table II.D.2.b: Change from Baseline in HbA1c at Each Year of Study, ITT Population

HbA1c (%)	Treatment Group			
	Background MET		Background SU	
	RSG (N=1117)	SU (N=1105)	RSG (N=1103)	MET (N=1122)
N ¹	1096	1079	1073	1079
Baseline (mean ± SE)	7.82±0.020	7.83±0.020	7.96±0.023	7.97±0.022
Month 12				
Change ² from b/l (mean ± SE)	-0.50±0.023	-0.60±0.023	-0.57±0.027	-0.60±0.024
Difference from control mean (95% CI)	0.10 (0.04, 0.16)		0.03 (-0.04, 0.10)	
p-value	0.0024		0.3590	
Month 18				
Change ² from b/l (mean ± SE)	-0.51±0.026	-0.47±0.029	-0.57±0.029	-0.56±0.026
Difference from control mean (95% CI)	-0.04 (-0.11, 0.04)		-0.01 (-0.08, 0.07)	
p-value	0.3133		0.8380	
Month 24				
Change ² from b/l (mean ± SE)	-0.43±0.027	-0.32±0.030	-0.47±0.030	-0.39±0.029
Difference from control mean (95% CI)	-0.11 (-0.19, -0.03)		-0.08 (-0.16, 0)	
p-value	0.0083		0.0538	
Month 36				
Change ² from b/l (mean ± SE)	-0.30±0.030	-0.09±0.034	-0.39±0.033	-0.29±0.033
Difference from control mean (95% CI)	-0.21 (-0.30, -0.12)		-0.10 (-0.19, -0.01)	
p-value	<0.0001		0.0248	
Month 48				
Change ² from b/l (mean ± SE)	-0.32±0.033	0.02±0.039	-0.33±0.038	-0.21±0.035
Difference from control mean (95% CI)	-0.34 (-0.44, -0.24)		-0.11 (-0.22, -0.01)	
p-value	<0.0001		0.0247	
Month 60				
Change ² from b/l (mean ± SE)	-0.14±0.035	0.17±0.042	-0.24±0.039	-0.10±0.039
Difference from control mean (95% CI)	-0.31 (-0.42, -0.21)		-0.15 (-0.25, -0.04)	
p-value	<0.0001		0.0083	

Data Source: DS [Table 7.142](#)

1. Number of subjects with baseline value and at least one post-baseline value.
2. Model-adjusted change from baseline (b/l).

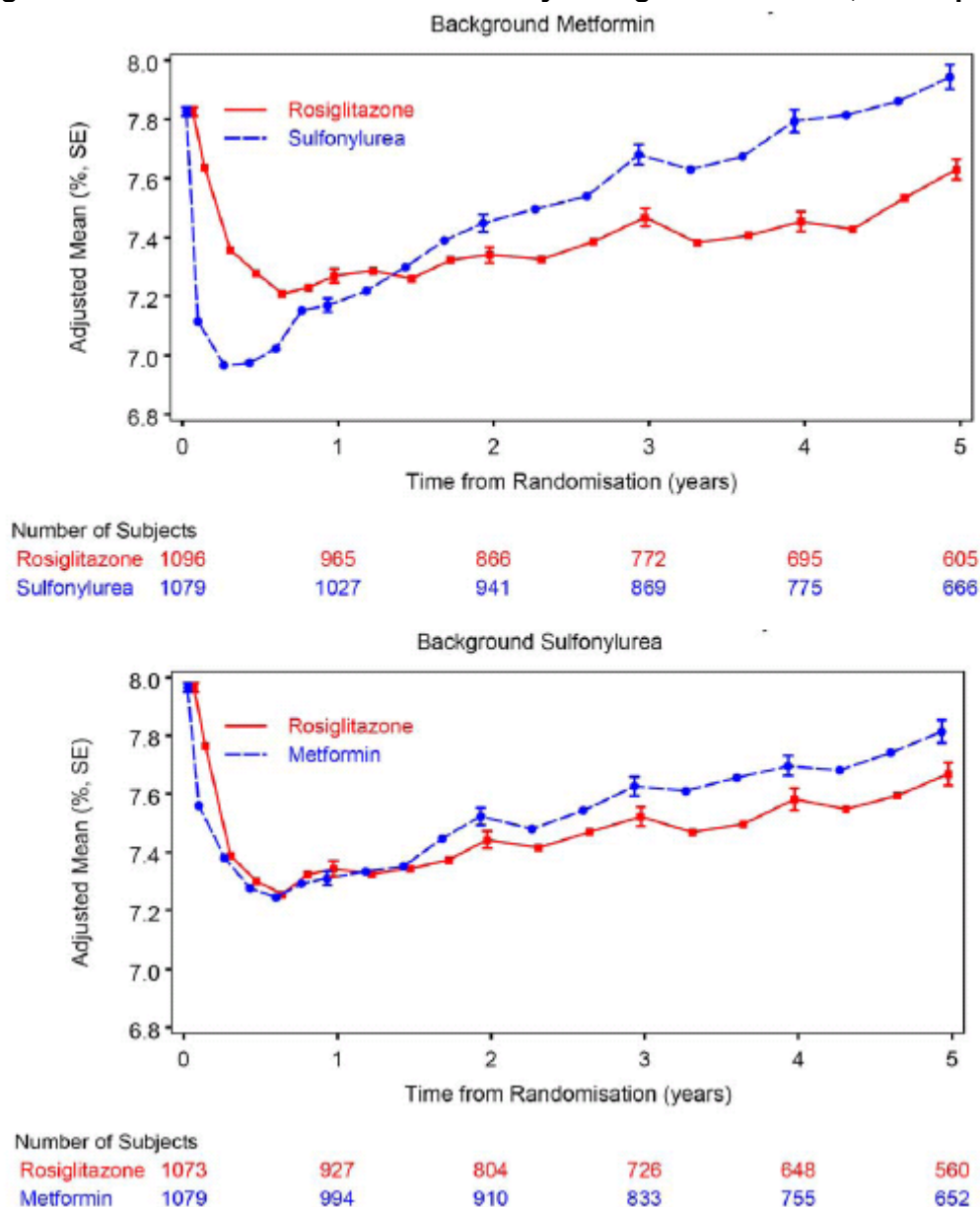
Source: Applicant's Table 87, pg 190, RECORD study report body

At Year 1, change from baseline in HbA1c was statistically significantly better for add-on sulfonylurea than for add-on RSG in the background MET group and similar between add-on MET and add-on RSG in the background SU group. Over the duration of study, the change from baseline in HbA1c became more favorable for RSG vs control, in comparison to both add-on SU and add-on MET. From Month 36 on,

this difference was statistically significant, favoring rosiglitazone over SU; and was statistically significant for RSG vs MET from Month 48 on. This add-on therapy result is consistent with that seen in the ADOPT trial, in which monotherapy failure was delayed longer with RSG than with MET or SU.

These findings are illustrated in the following figures, by background stratum.

Figure II.D.2.b: Mean HbA1c Over Time by Background Stratum, ITT Population



Source: Applicant's Figure 26, pg 189. RECORD study report body

II.D.2.d. Time to Failure of Glycemic Control on Dual Oral Combination Therapy

The applicant defined failure of glycemic control as two consecutive HbA1c values of $\geq 8.5\%$, or HbA1c $\geq 8.5\%$ at a single visit, following which the patient was either moved to the PRT/CVO phase, or triple therapy was started. The following table displays the number and percentage of patients who had glycemic failure, by stratum.

Table II.D.2.d.i: Summary of Glycemic Failure Status, Randomized Dual Oral Combination Therapy				
Glycemic Failure Status	Bkgrd MET		Bkgrd SU	
	RSG N=1117 n (%)	SU N=1105 n (%)	RSG N=1103 n (%)	MET N=1122 n (%)
Failed	281 (25.2)	451 (40.8)	365 (33.1)	424 (37.8)
Did not fail, and completed HbA1c assessment to final visit on randomized dual oral combination treatment	492 (44.0)	437 (39.5)	397 (36.0)	402 (35.8)
Did not fail, but discontinued randomized dual oral combination treatment prior to end of trial, or did not have HbA1c data	344 (30.8)	217 (19.6)	341 (30.9)	296 (26.4)
Source: Applicant's Table 89, pg 192, RECORD study report body				

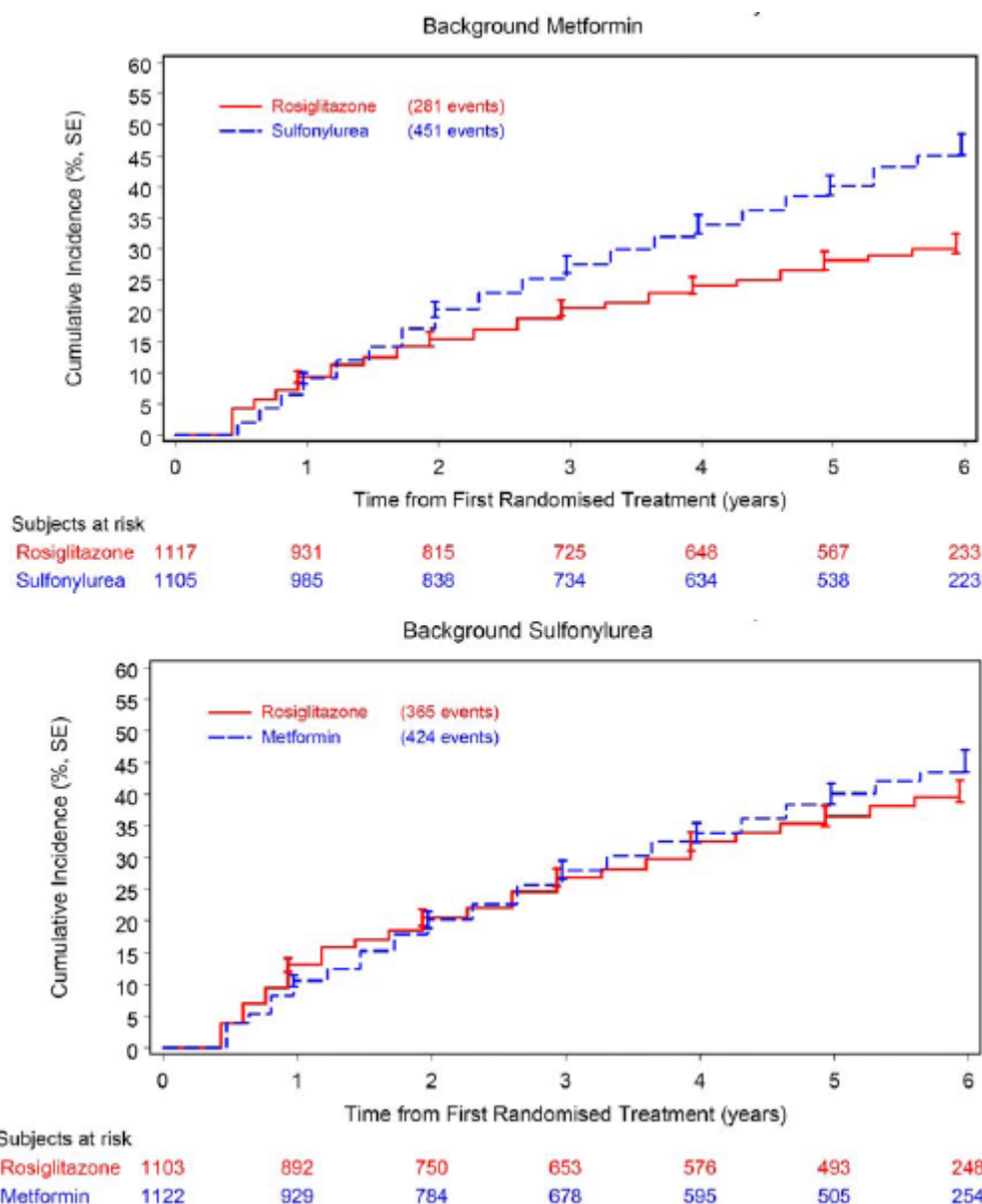
Overall, a lower percentage of patients in RSG groups failed glycemic control, particularly when compared to sulfonylurea. However, when further examining those patients who did not fail glycemic control, movement out of randomized dual oral therapy (or lack of HbA1c data) occurred somewhat more commonly among RSG-treated patients than among comparator-treated patients. The following table displays only those patients who did not fail glycemic control during randomized dual oral combination therapy, and displays the percentage who did and did not move out of randomized dual oral therapy (or lack HbA1c data). For the following table, the denominator used is that of the total number of glycemic control “nonfailers”.

Table II.D.2.d.ii: Disposition of Glycemic Control “Nonfailers”, Randomized Dual Oral Combination Therapy				
Disposition	Bkgrd MET		Bkgrd SU	
	RSG N=836 n (%)	SU N=654 n (%)	RSG N=738 n (%)	MET N=698 n (%)
Did not fail, and completed HbA1c assessment to final visit on randomized dual oral combination treatment	492 (58.9)	437 (66.8)	397 (53.8)	402 (57.6)
Did not fail, but discontinued randomized dual oral combination treatment prior to end of trial, or did not have HbA1c data	344 (41.1)	217 (33.2)	341 (46.2)	296 (42.4)
Source: Applicant's Table 89, pg 192, RECORD study report body				

As previously discussed, this was likely due to the asymmetric study design, in which the 3rd agent for RSG group patients was oral, and the 3rd agent for MET/SU group patients was insulin. The applicant reported reluctance on the part of patients and investigators to initiate insulin promptly after MET/SU group patients met criteria for addition of a third agent. For the RSG group, however, addition of a third agent did not meet with similar reluctance, possibly because that agent was oral rather than injected.

The following figures display time to glycemic failure by stratum.

Figure II.D.2.d: Cumulative Incidence of Time to Failure of Glycemic Control by Stratum



Source: Applicant's Figure 27, pg 193, RECORD study report body. Glycemic control failure defined as two consecutive HbA1c values of $\geq 8.5\%$, or HbA1c $\geq 8.5\%$ at a single visit, following which the patient was either moved to the PRT/CVO phase or triple therapy was started.

The difference between RSG and comparator was more marked for the comparison to SU than for the comparison to MET.

II.D.2.d. Time to Addition of a 3rd Oral Therapy for Rosiglitazone Combination Groups or Initiation of Insulin for Metformin + Sulfonylurea Combination Groups

Within both strata, addition of (or switch to) a third agent was more common among RSG-treated patients than among comparator-treated patients. Per protocol, the third agent for the RSG groups was oral, and the third agent for comparator groups was insulin. The applicant reports that reluctance to add insulin contributed to the lower rate of 3rd agent addition among comparator-treated patients, despite the

fact that comparator-treated patients appeared to fail glycemic control more often on dual oral therapy (see Figure II.C.2.b). The following table summarizes addition of third agents.

Table II.D.2.d: Summary of Addition of Third Glycemic Agent, ITT Population

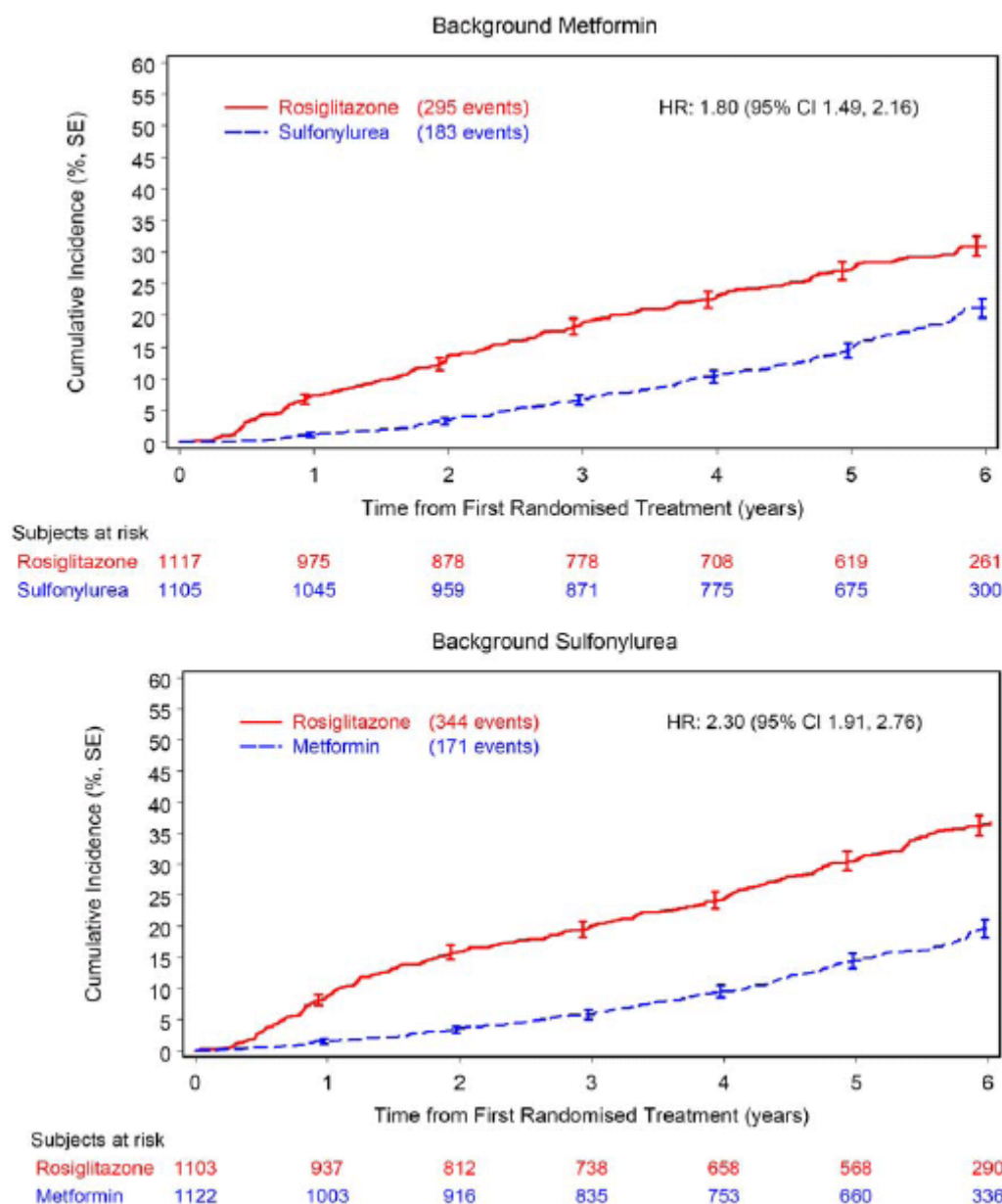
Stratum	Tx	Added 3 rd Agent n (%)	HR (95% CI)	p- value	First Event Triple Oral Therapy n (%)	First Event Insulin n (%)	Moved to Insulin from Triple Therapy n (%)
Bkgrd MET	RSG (N=1117)	295 (26.4)	1.8 (1.5, 2.2)	<0.0001	257 (23.0)	38 (3.4)	24 (2.1)
	SU (N=1105)	183 (16.6)			7 (0.6)	176 (15.9)	1 (<0.1)
Bkgrd SU	RSG¹ (N=1103)	344 (31.2)	2.3 (1.9, 2.8)	<0.001	296 (26.8)	49 (4.4)	53 (4.8)
	MET (N=1122)	171 (15.2)			6 (0.5)	165 (14.7)	0

Source: Applicant's Table 90, pg 194, RECORD study report body

1 One patient in the RSG + SU group initiated insulin and triple oral therapy on the same day, and is counted for each therapy

The following figures illustrate time to addition of a third agent.

Figure II.D.2.d: Cumulative Incidence of Time to Addition of Third Oral Agent/Switch to Insulin



Source: Applicant's Figure 28, pg 195, RECORD study report body

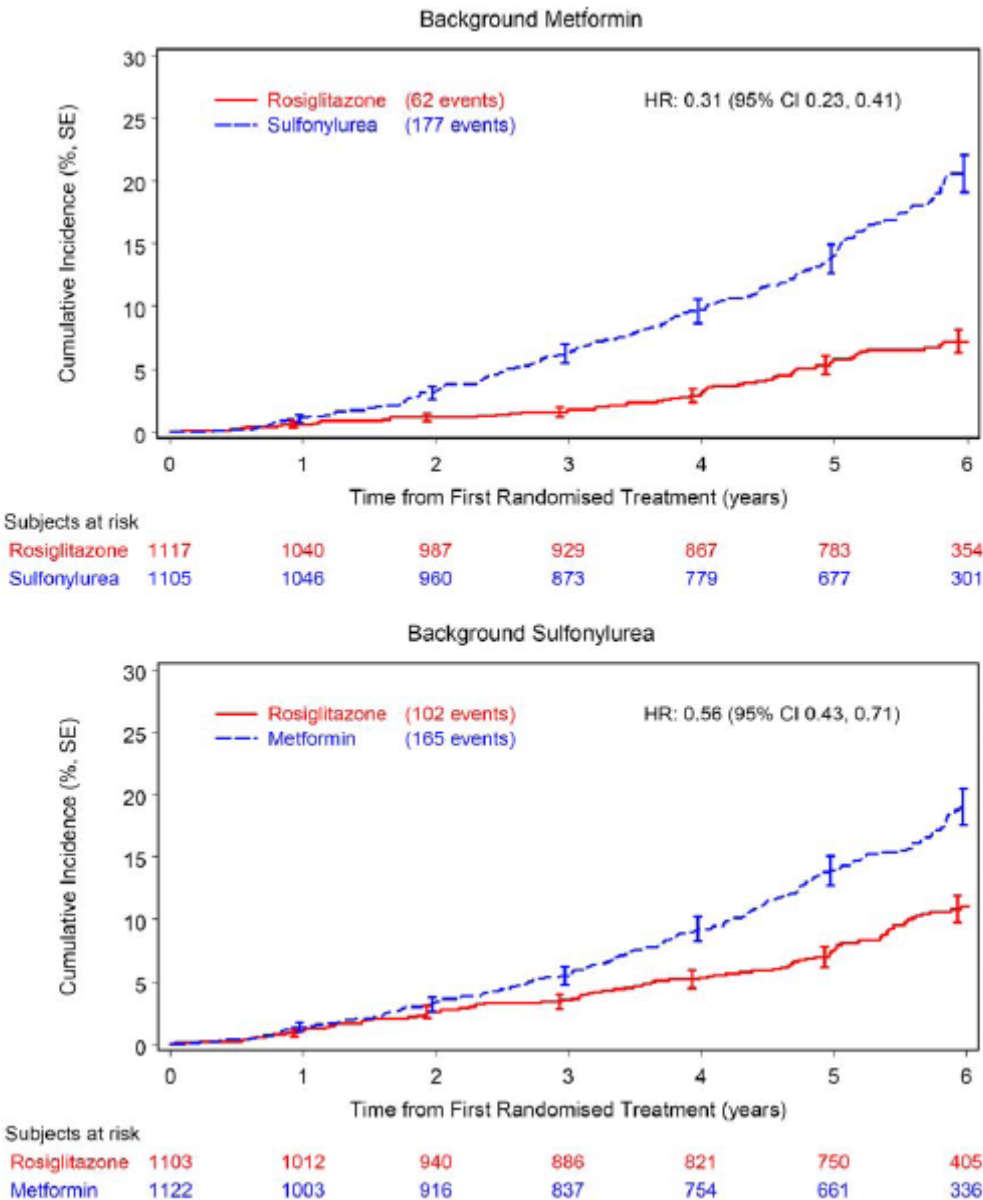
The pattern of a higher rate of 3rd agent initiation was similar by stratum. Curves began to separate at about 6 months of treatment. By 2-3 years of treatment, the cumulative difference between groups had reached a maximum. After that point, the cumulative incidence of addition of a 3rd agent continued to increase for both RSG and comparator, but at approximately the same rate for each group, until end of study.

II.D.2.e. Initiation of Insulin

As mentioned previously, after glycemic failure, the protocol-specified 3rd agent for the RSG group was oral, while the 3rd agent for the MET/SU group was insulin. For both strata, initiation of insulin was more common and occurred earlier among comparator-treated patients than among RSG-treated patients. For background MET stratum patients, 11% of add-on RSG patients and 25% of add-on SU patients initiated insulin. For background SU stratum patients, the values were 15% for add-on RSG and 23% for add-on

MET (Source: Applicant’s Table 91, pg 197, RECORD study report body). The p-value was <0.0001 for the difference between RSG and comparator for both strata. This finding must be considered in context of the asymmetric study design, in which insulin was essentially a 4th agent for RSG-treated patients, and a 3rd agent for comparator-treated patients. The following figures display time to initiation of insulin by stratum.

Figure II.D.2.e: Cumulative Incidence of Time to Initiation of Insulin from Randomized Dual/Triple Combination Therapy, ITT Population



Source: Applicant’s Figure 29, pg 198, RECORD study report body

As mentioned in the description of the trial design, there was a provision in the protocol that if the first HbA1c test was “so high that in the investigator’s judgment it was likely to compromise patient safety”, the patient could be switched to insulin at that earlier point. Concern has been expressed that this could have meant that patients would remain on randomized therapy for a very short period of time, e.g. 8 weeks. However, that did not occur in a significant number of patients, as suggested by the above

Kaplan-Meier curves in Figure II.D.2.e. In fact, only 17 total patients (0.4%) initiated insulin at less than 6 months of study, as illustrated in the following table:

Table II.D.2.e: Cumulative Events of Initiation of Insulin by Stratum

Time Interval (months)	Cumulative Events of Initiation of Insulin				Total Percentage of Pts With Insulin Initiated ¹
	Bkgrd MET		Bkgrd SU		
	RSG N=1117 Cumulative n	SU N=1105 Cumulative n	RSG N=1103 Cumulative n	MET N=1122 Cumulative n	
0-<6	4	3	4	6	0.4
6-<12	11	13	18	19	1.4
12-<18	16	27	31	36	2.5
18-<24	21	50	42	59	3.9
24-<30	30	77	51	72	5.2
30-<36	38	102	57	97	6.6
36-<42	48	123	74	121	8.2
42-<48	63	148	88	139	9.8
48-<54	84	176	99	165	11.8
54-<60	99	203	116	194	13.8
60-<66	120	235	141	217	16.0
66-<72	125	262	155	244	17.7
72-<78	126	273	165	257	18.5
78-<84	126	276	167	258	18.6
84-<90	126	276	168	259	18.6
90-<96	126	276	n/a	n/a	n/a

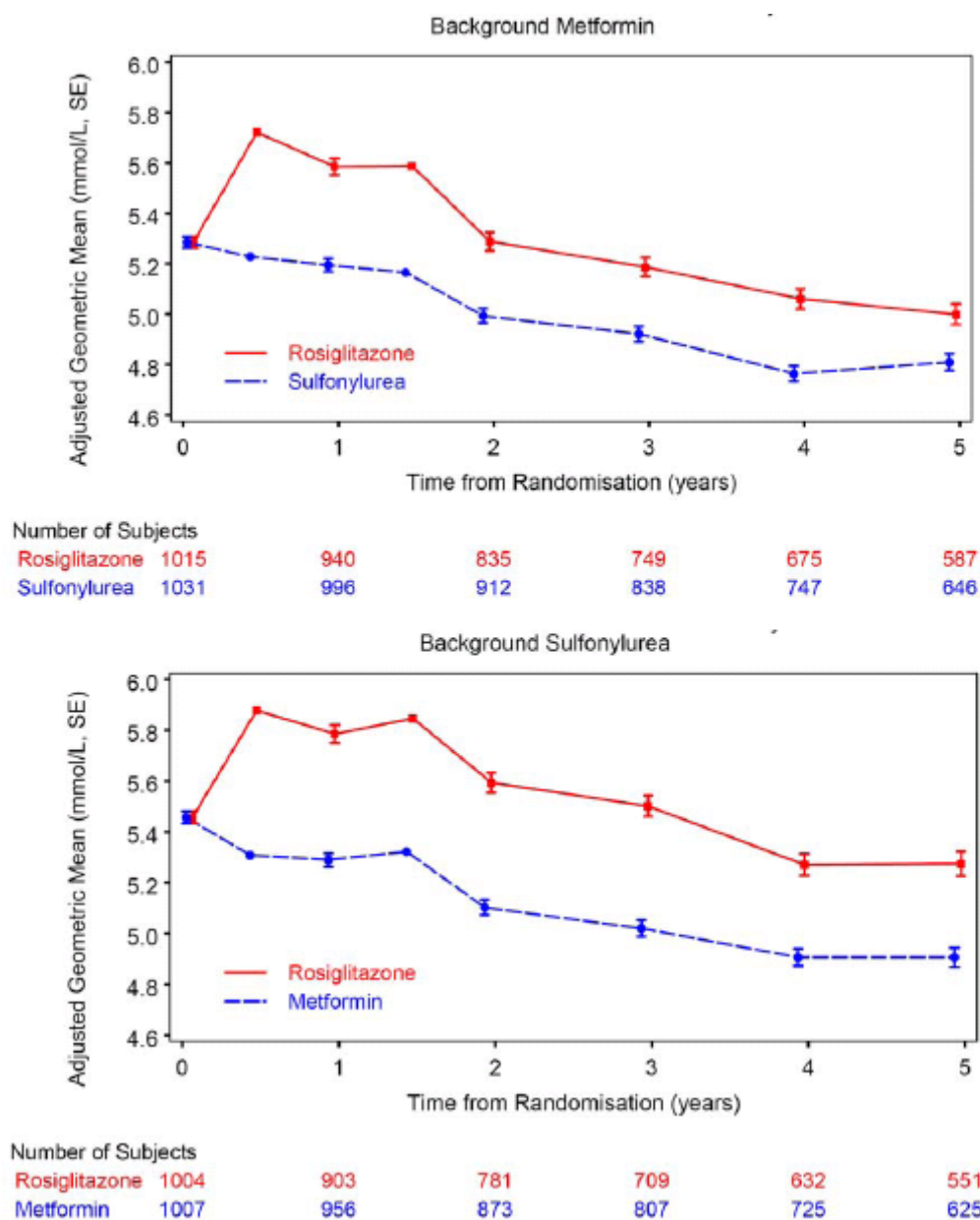
Source: Applicant's Table 7.159, beg pg 15655, RECORD study report body

¹ Percentage of total N (4447). Denominator does not exclude patients who died or withdrew.

II.D.2.f. Percent Change from Baseline in Total Cholesterol

Mean total cholesterol increased in RSG-treated patients in both strata within the first 6 months of study, then gradually declined over time. Mean total cholesterol in comparator-treated patients declined throughout study. Mean total cholesterol remained higher among RSG-treated patients than among comparator-treated patients throughout study, despite a higher rate of on-study initiation of statins among RSG-treated patients. The following figures display total cholesterol over time by stratum.

Figure II.D.2.f: Mean Total Cholesterol Over Time, Randomized Dual Oral Combination Treatment

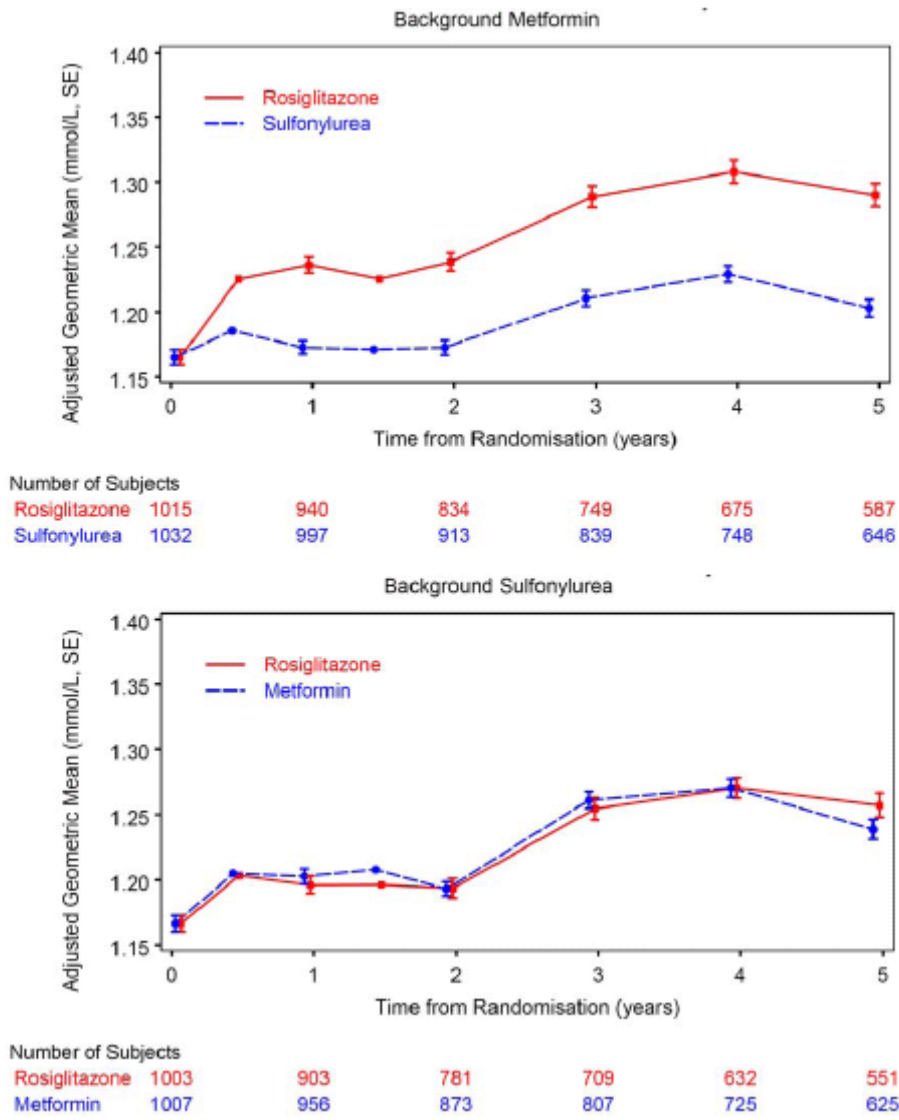


Source: Applicant's Figure 36, pg 213, RECORD study report body

II.D.2.g. Percent Change from Baseline in High Density Lipoprotein Cholesterol

Mean high-density lipoprotein (HDL) cholesterol values increased over time in all treatment groups. The increase was similar for RSG and MET group patients (p NS), and greater for RSG group patients than for SU group patients (p <0.0001 at all time points after baseline). The following figures display HDL cholesterol values over time.

Figure II.D.2.g: Mean High Density Lipoprotein Cholesterol Over Time, Randomized Dual Oral Combination Treatment

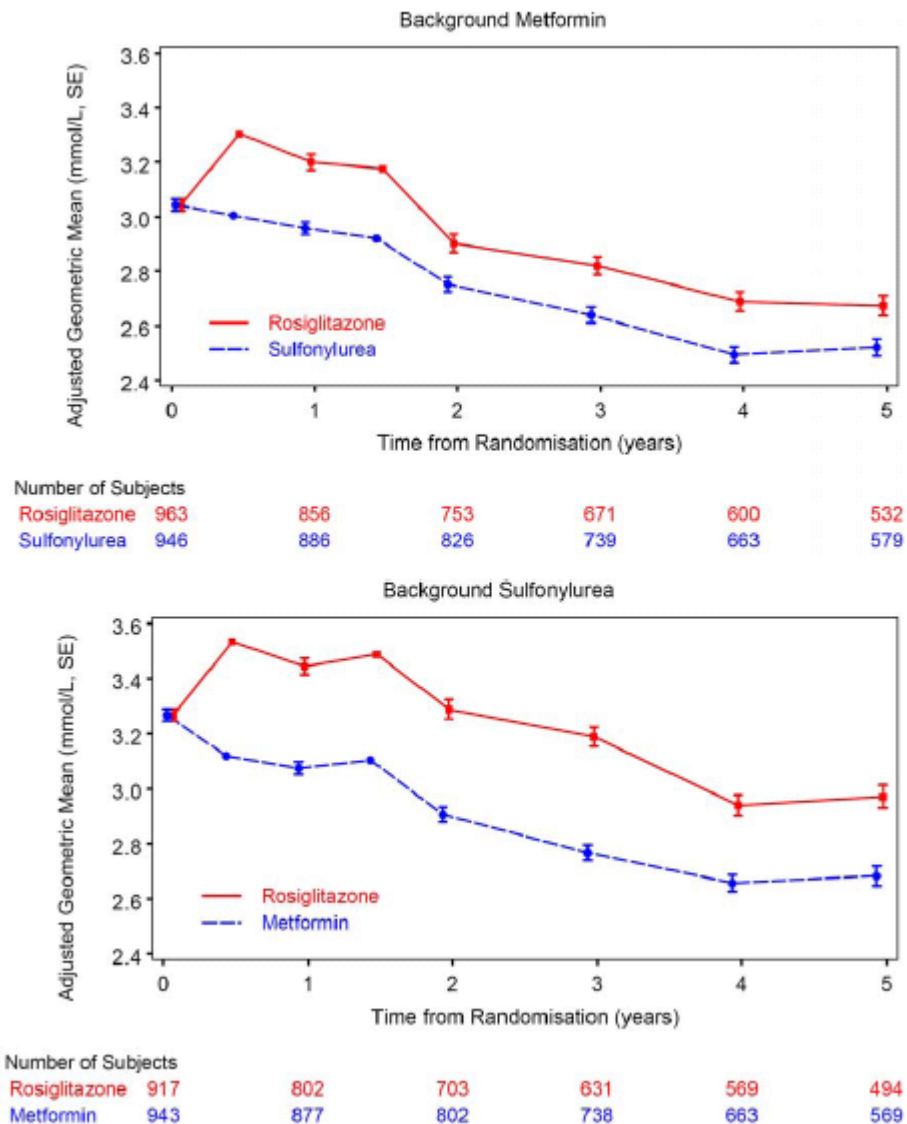


Source: Applicant's Figure 37, pg 215, RECORD study report body

II.D.2.h. Percent Change from Baseline in Low Density Lipoprotein Cholesterol

The pattern of change for LDL was very similar to that for total cholesterol, in that it increased in RSG-treated patients in both strata within the first 6 months of study, then gradually declined over time. Mean LDL in comparator-treated patients declined throughout study. Mean LDL remained higher among RSG-treated patients than among comparator-treated patients throughout study, despite a higher rate of on-study initiation of statins among RSG-treated patients. The following figures display LDL over time by stratum.

Figure II.D.2.h: Mean Low-Density Lipoprotein Cholesterol Over Time, Randomized Dual Oral Combination Treatment



Source: Applicant's Figure 38, pg 218, RECORD study report body

II.D.2.i. Percent Change from Baseline in C-Reactive Protein

Mean values for C-reactive protein declined over time in all treatment groups, and declined to a greater extent among RSG-treated patients than among comparator-treated patients in both strata.

Table II.D.2.i: Mean Percent Change (95% CI) in C-Reactive Protein Over Time by Stratum

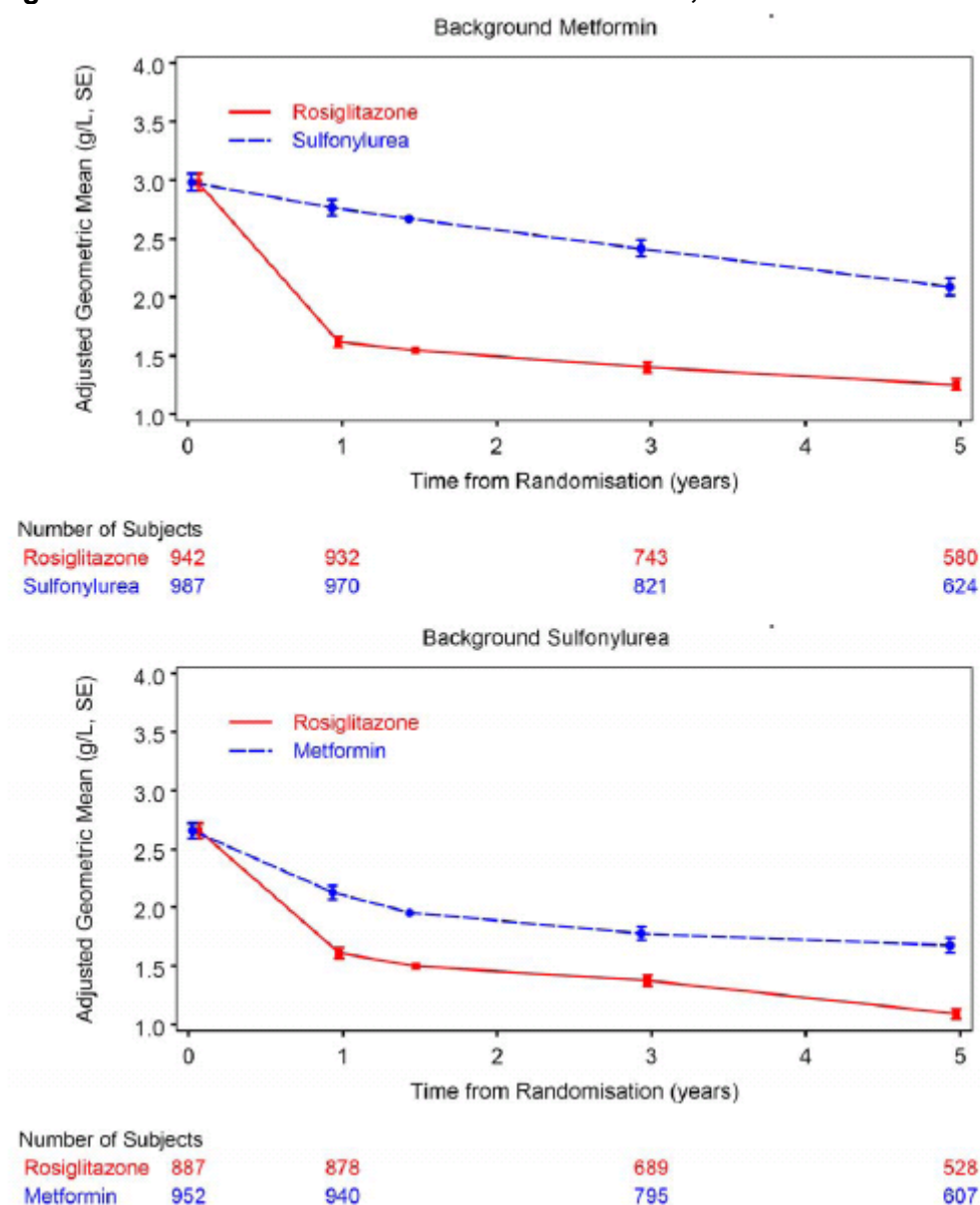
Month	Bkgrd MET			Bkgrd SU		
	RSG	SU	p-value	RSG	MET	p-value
12	-44.9 (-47.8, -41.8)	-5.9 (-10.3, -1.2)	<0.0001	-38.7 (-42.0, -35.1)	-19.1 (-23.3, -14.6)	<0.0001
18	-47.3 (-50.3, -44.2)	-9.1 (-13.8, -4.1)	<0.0001	-43.0 (-46.2, -39.8)	-25.7 (-29.6, -21.5)	<0.0001
36	-52.4 (-55.3, -49.2)	-17.8 (-22.4, -12.9)	<0.0001	-47.7 (-51.0, -44.2)	-32.4 (-36.4, -28.1)	<0.0001
60	-57.4 (-60.4, -54.2)	-28.9 (-33.7, -23.8)	<0.0001	-58.5 (-61.6, -55.2)	-36.3 (-41.0, -31.2)	<0.0001

Source: Applicant's Table 106, pg 236, RECORD study report body

Rosiglitazone is known to decrease CRP levels, beginning as early as 2 weeks after initiation. This effect is independent of glycemic control and statin use (Stocker 2007). Statins are also known to decrease CRP levels. In RECORD, the higher rate of statin addition in RSG-treated patients may have had an additive effect in reduction of CRP values.

The following figures display CRP over time.

Figure II.D.2.i: Mean C-reactive Protein Over Time, Randomized Dual Oral Combination Treatment



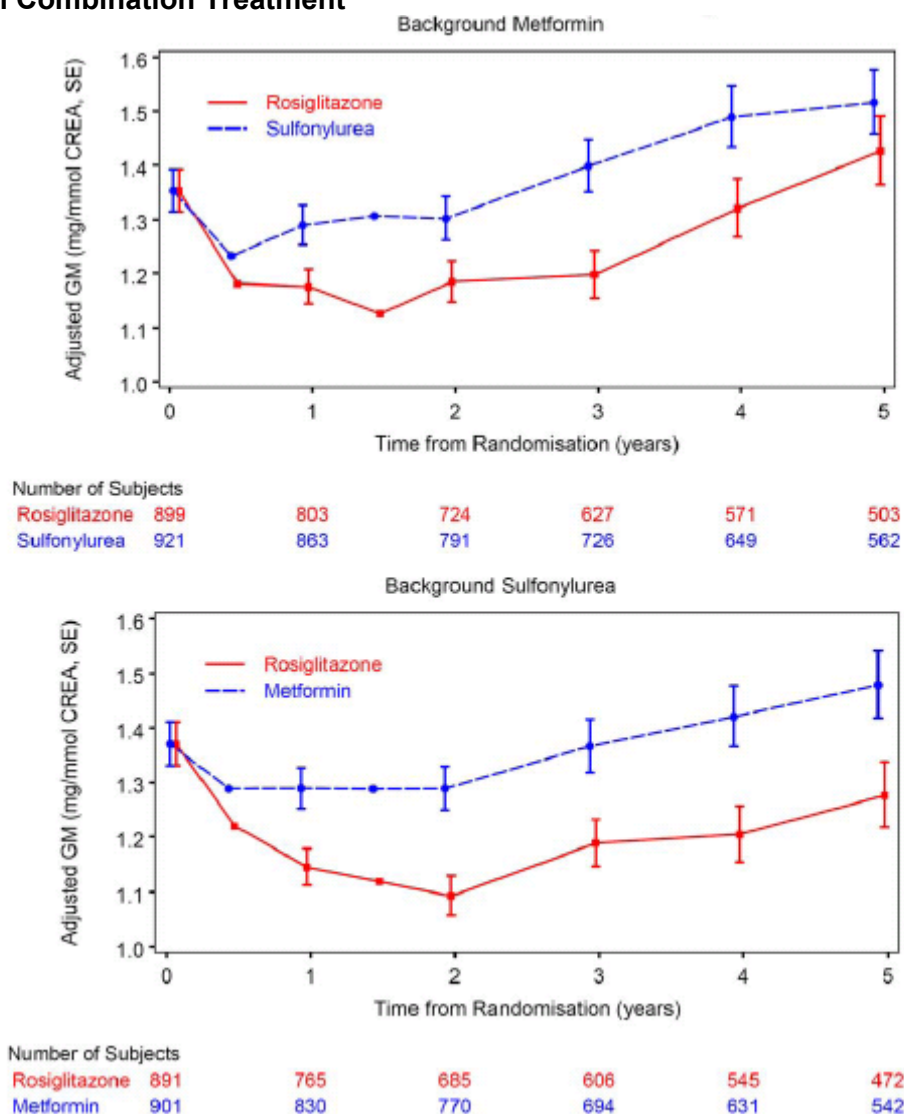
Source: Applicant's Figure 45, pg 235

Because the above figures do not include a postbaseline time point earlier than one year, it is not possible to determine if the greater decline in C-reactive protein for RSG-treated patients predated the difference in rate of initiation of statin between treatment groups.

II.D.2.j. Urinary Albumin:Creatinine Ratio

Urinary albumin:creatinine ratio (alb:cr) was a predefined endpoint. An increase in urinary albumin:creatinine ratio in a patient with diabetes is often seen in early diabetic nephropathy. At most timepoints throughout study, alb:cr favored RSG, with a statistically significant difference.

Figure II.D.2.j: Geometric Mean Urinary Albumin:Creatinine Ratio Over Time, Randomized Dual Oral Combination Treatment



Data Source: DS Figure 7.101.1 and DS Figure 7.101.2

Source: Applicant's Figure 48, pg 241, RECORD study report body

II.D.3. Additional Cardiovascular Endpoint Issues

II.D.3.a. Patients with Prior Ischemic Heart Disease

When examining only patients with a prior history of ischemic heart disease (IHD), 27% of patients in the overall RSG group experienced a primary endpoint event, while 23% of patients in the overall MET/SU group had a primary endpoint event. This difference was not statistically significant (incidence rate/100 PY 95% CIs 4.81-7.12 for RSG and 3.74-5.75 for MET/SU).

The following tables break down the primary endpoint by contributing first events, among patients with a history of ischemic heart disease.

Table II.D.3.a.i: Summary of First Events Contributing to Primary Endpoint (CV Death or CV Hospitalization) for Patients with a History of Ischemic Heart Disease at Baseline

Event Category	First Event	Overall		BL MET		BL SU	
		RSG N=383	MET/SU N=389	RSG + MET N=171	SU + MET N=164	RSG + SU N=212	MET + SU N=225
CV death or CV hosp	All	105 (27.4)	88 (22.6)	40 (23.4)	44 (26.8)	65 (30.7)	44 (19.6)
CV death	Any CV death	15 (3.9)	10 (2.6)	6 (3.5)	6 (3.7)	9 (4.2)	4 (1.8)
	MI	2 (0.5)	1 (0.3)	1 (0.6)	0	1 (0.5)	1 (0.4)
	CHF	1 (0.3)	0	0	0	1 (0.5)	0
	Sudden death	5 (1.3)	4 (1.0)	2 (1.2)	3 (1.8)	3 (1.4)	1 (0.4)
	Acute vascular events	0	1 (0.3)	0	1 (0.6)	0	0
	Other CV mortality	1 (0.3)	1 (0.3)	1 (0.6)	0	0	1 (0.4)
	Death unk cause (insuff data)	6 (1.6)	3 (0.8)	2 (1.2)	2 (1.2)	4 (1.9)	1 (0.4)
CV hosp	Any CV hosp	90 (23.5)	78 (20.1)	34 (19.9)	38 (23.2)	56 (26.4)	40 (17.8)
	MI	13 (3.4)	15 (3.9)	6 (3.5)	3 (1.8)	7 (3.3)	12 (5.3)
	Unstable angina	11 (2.9)	9 (2.3)	2 (1.2)	6 (3.7)	9 (4.2)	3 (1.3)
	CHF	11 (2.9)	4 (1.0)	5 (2.9)	2 (1.2)	6 (2.8)	2 (0.9)
	Stroke	10 (2.6)	7 (1.8)	6 (3.5)	5 (3.0)	4 (1.9)	2 (0.9)
	TIA	2 (0.5)	1 (0.3)	1 (0.6)	1 (0.6)	1 (0.5)	0
	Invasive CV procedure	9 (2.3)	11 (2.8)	6 (3.5)	3 (1.8)	3 (1.4)	8 (3.6)
	Amputation of extremity	1 (0.3)	1 (0.3)	0	1 (0.6)	1 (0.5)	0
	Other CV hosp	33 (8.6)	30 (7.7)	8 (4.7)	17 (10.4)	25 (11.8)	13 (5.8)

Source: Applicant's Table 2198.9, beg pg 19360, RECORD study report body

When examining events by strata, among patients on baseline sulfonylurea, there was a numerical difference between add-on RSG and add-on MET for the incidence of “other CV hospitalizations” among patients with a history of ischemic heart disease. The following table summarizes the reasons for these hospitalizations for the first events contributing to the primary endpoint.

Table II.D.3.a.ii: Summary of Reasons for “Other Cardiovascular Hospitalizations” Contributing to the Primary Endpoint Analysis for Patients with a History of Ischemic Heart Disease

Reason for “Other Cardiovascular Hospitalization”	Overall		BL MET		BL SU	
	RSG N=383	MET/SU N=389	RSG + MET N=171	SU + MET N=164	RSG + SU N=212	MET + SU N=225
All “other cardiovascular hospitalizations”	33 (8.6)	30 (7.7)	8 (4.7)	17 (10.4)	25 (11.8)	13 (5.8)
Ablation/pacemaker	0	1 (0.3)	0	1 (0.6)	0	0
Angina pectoris	12 (3.1)	10 (2.6)	4 (2.3)	6 (3.7)	8 (3.8)	4 (1.8)
Atrial fibrillation	4 (1.0)	7 (1.8)	3 (1.8)	4 (2.4)	1 (0.5)	3 (1.3)
Bradycardia	2 (0.5)	1 (0.3)	0	2 (1.2)	2 (0.9)	1 (0.4)
Deep venous thrombosis	2 (0.5)	2 (0.5)	0	2 (1.2)	2 (0.9)	0
Hypertensive emergency	5 (1.3)	2 (0.5)	1 (0.6)	0	4 (1.9)	2 (0.9)
Pericarditis	1 (0.3)	0	0	0	1 (0.5)	0

Table II.D.3.a.ii: Summary of Reasons for “Other Cardiovascular Hospitalizations” Contributing to the Primary Endpoint Analysis for Patients with a History of Ischemic Heart Disease

Reason for “Other Cardiovascular Hospitalization”	Overall		BL MET		BL SU	
	RSG	MET/SU	RSG + MET	SU + MET	RSG + SU	MET + SU
	N=383	N=389	N=171	N=164	N=212	N=225
Peripheral artery disease	2 (0.5)	2 (0.5)	0	1 (0.6)	2 (0.9)	1 (0.4)
Pulmonary embolism	1 (0.3)	3 (0.8)	0	2 (1.2)	1 (0.5)	1 (0.4)
Recent MI	1 (0.3)	1 (0.3)	0	0	1 (0.5)	1 (0.4)
Valve surgery/ valvular heart disease	3 (0.8)	1 (0.3)	0	1 (0.6)	3 (1.4)	0

Source: Applicant’s Table 2198.10, beg pg 19363, RECORD study report body

Reasons for “other CV hospitalizations” were spread out over a variety of diagnoses for patients with underlying IHD. For the baseline SU group, no one particular reason predominated to explain the difference in incidence between add-on RSG and add-on MET. Small numerical differences occurred for angina pectoris (3.8% RSG vs 1.8% MET), hypertensive emergency (1.9% vs 0.9%) and valve surgery/ valvular heart disease (1.4% vs 0%).

“Prior ischemic heart disease” could include multiple conditions, such as stable or unstable angina, myocardial infarction, coronary angioplasty, and terms such as “atherosclerosis”, “atherosclerosis heart”, “cardiovascular disease” and “ischemic heart disease”. When examining specific baseline ischemic heart disease terms, no specific type of prior ischemic heart disease event (e.g. myocardial infarction, stable angina, unstable angina) seemed to predispose to a future primary endpoint event. For patients with the nonspecific baseline term “ischemic heart disease”, a higher percentage of RSG group patients than comparator patients went on to have a primary endpoint event.

Table II.D.3.a.iii: Baseline Ischemic Heart Disease Conditions and Incidence of Primary Endpoint Events, ITT Population

Baseline Condition (MedDRA Preferred Term)	Overall RSG n/N ¹ (%)	Overall MET/SU n/N ¹ (%)
Stable angina	59/227 (26.0)	56/230 (24.3)
Myocardial infarction	37/104 (35.6)	35/114 (30.7)
Unstable angina	8/20 (40.0)	11/30 (36.7)
“Ischemic heart disease”	40/129 (31.0)	18/115 (15.7)

Source: Applicant’s Table 62, pg 157, RECORD study report body

1 Denominator = the total number of patients who had a baseline history of the designated ischemic heart disease condition

The above tables display only the first events which contributed to the primary endpoint among patients with a history of IHD. When examining individual endpoint events among patients with prior IHD, and taking into consideration all first events for a given endpoint (and not only first events which contributed to the primary endpoint) the differences between RSG and comparator were seen primarily in the occurrence of heart failure events (4% vs 2%), and to a lesser extent for hospitalizations for unstable angina (4% vs 3%). There was no difference between rosiglitazone and comparator for all-cause mortality, cardiovascular death, MI or stroke. The following tables display these results by prior IHD status, for the overall groups and the strata.

Table II.D.3.a.iv: Cardiovascular Endpoints by Baseline History of Ischemic Heart Disease (IHD), All First Events for Each Component Endpoint, Overall Rosiglitazone Group vs Overall Metformin/Sulfonylurea Group, ITT Population

Endpoint	Prior IHD		No Prior IHD	
	RSG N=383 n (%)	MET/SU N=389 n (%)	RSG N=1837 n (%)	MET/SU N=1838 n (%)
CV death or CV hosp	105 (27.4)	88 (22.6)	216 (11.8)	235 (12.8)
All-cause death	43 (11.2)	45 (11.6)	93 (5.1)	112 (6.1)
CV death	23 (6.0)	24 (6.2)	37 (2.0)	47 (2.6)
MI (fatal or nonfatal)	20 (5.2)	19 (4.9)	44 (2.4)	37 (2.0)
Stroke (fatal or nonfatal)	10 (2.6) ¹	9 (2.3)	36 (2.0)	54 (2.9)
CHF (fatal or nonfatal)	17 (4.4) ²	8 (2.1)	44 (2.4)	21 (1.1)
Unstable angina hospitalization	15 (3.9) ³	10 (2.6)	9 (0.5)	14 (0.8)

Source: Applicant's Table 2198.1, beg pg 19354; and Table 2198.2, beg pg 19357; RECORD study report body
1 Incidence rate/100 PY 95% CI = 0.24-0.91 for RSG and 0.20-0.83 for MET/SU
2 Incidence rate/100 PY 95% CI = 0.49-1.36 for RSG and 0.17-0.76 for MET/SU
3 Incidence rate/100 PY 95% CI = 0.42-1.24 for RSG and 0.23-0.90 for MET/SU

In the above table, the numerical imbalance in heart failure events (not favoring rosiglitazone) is slightly more pronounced in patients with a prior history of ischemic heart disease (4.4% RSG vs 2.1% MET/SU) than in patients without prior ischemic heart disease (2.4% RSG vs 1.1% MET/SU). For patients with prior ischemic heart disease, stroke and unstable angina hospitalization occurred numerically, but not statistically significantly, more frequently among RSG group patients than among MET/SU group patients, but for patients without a prior history of ischemic heart disease, the converse was seen. These differences consisted of a few events, and thus were not robust findings. For patients with prior ischemic heart disease, the 95% confidence intervals for the incidence rates for each of these endpoints overlapped between RSG and MET/SU. For other endpoint events, the pattern was similar between patients with and without prior IHD.

Table II.D.3.a.v: Cardiovascular Endpoints by Baseline History of Ischemic Heart Disease (IHD), All First Events for Each Component Endpoint, Background Metformin Group, ITT Population

Endpoint	Prior IHD		No Prior IHD	
	RSG + MET N=171 n (%)	SU + MET N=164 n (%)	RSG + MET N=946 n (%)	SU + MET N=941 n (%)
CV death or CV hosp	40 (23.4)	44 (26.8)	118 (12.5)	110 (11.7)
All-cause death	22 (12.9)	22 (13.4)	46 (4.9)	50 (5.3)
CV death	9 (5.3) ¹	13 (7.9)	21 (2.2)	20 (2.1)
MI (fatal or nonfatal)	11 (6.4) ²	4 (2.4)	22 (2.3)	17 (1.8)
Stroke (fatal or nonfatal)	6 (3.5)	7 (4.3)	15 (1.6)	25 (2.7)
CHF (fatal or nonfatal)	7 (4.1) ³	2 (1.2)	26 (2.7)	11 (1.2)
Unstable angina hospitalization	5 (2.9) ⁴	7 (4.3)	6 (0.6)	6 (0.6)

Source: Applicant's Table 2198.1, beg pg 19354; and Table 2198.2, beg pg 19357; RECORD study report body
1 Incidence rate/100 PY 95% CI = 0.45-1.89 for RSG + MET and 0.79-2.55 for SU + MET
2 Incidence rate/100 PY 95% CI = 0.62-2.21 for RSG + MET and 0.13-1.19 for SU + MET
3 Incidence rate/100 PY 95% CI = 0.32-1.62 for RSG + MET and 0.03-0.83 for SU + MET
4 Incidence rate/100 PY 95% CI = 0.18-1.31 for RSG + MET and 0.33-1.70 for SU + MET

The number of events for any given endpoint among IHD patients was small, and therefore caution should be used in interpreting this information. In the above table, the numerical imbalance in heart

failure events and myocardial infarction events (not favoring rosiglitazone) is slightly more pronounced, but not statistically significant, in patients with a prior history of ischemic heart disease than in patients without prior ischemic heart disease. These differences consisted of a few events, and thus were not robust findings. When examining CV deaths and unstable angina hospitalization, the incidence in patients without a prior history of ischemic heart disease is equal between treatment groups, but for patients with a prior history of ischemic heart disease, it favors RSG, although not statistically significantly so. For patients with prior ischemic heart disease, the 95% confidence intervals for the incidence rates for each of these endpoints overlapped between RSG and MET/SU. For other endpoint events, the pattern was similar between patients with and without prior IHD.

Table II.D.3.a.vi: Cardiovascular Endpoints by Baseline History of Ischemic Heart Disease (IHD), All First Events for Each Component Endpoint, Background Sulfonylurea Group, ITT Population

Endpoint	Prior IHD		No Prior IHD	
	RSG + SU N=212 n (%)	MET + SU N=225 n (%)	RSG + SU N=891 n (%)	MET + SU N=897 n (%)
CV death or CV hosp	65 (30.7) ¹	44 (19.6)	98 (11.0)	125 (13.9)
All-cause death	21 (9.9)	23 (10.2)	47 (5.3)	62 (6.9)
CV death	14 (6.6) ²	11 (4.9)	16 (1.8)	27 (3.0)
MI (fatal or nonfatal)	9 (4.2) ³	15 (6.7)	22 (2.5)	20 (2.2)
Stroke (fatal or nonfatal)	4 (1.9) ⁴	2 (0.9)	21 (2.4)	29 (3.2)
CHF (fatal or nonfatal)	10 (4.7) ⁵	6 (2.7)	18 (2.0)	10 (1.1)
Unstable angina hospitalization	10 (4.7) ⁶	3 (1.3)	3 (0.3)	8 (0.9)

Source: Applicant's Table 2198.1, beg pg 19354; and Table 2198.2, beg pg 19357; RECORD study report body

1 Incidence rate per 100 PY 95% CI = 5.18-8.55 for RSG + SU and 2.86-5.28 for MET + SU

2 Incidence rate per 100 PY 95% CI = 0.67-2.06 for RSG + SU and 0.46-1.63 for MET + SU

3 Incidence rate per 100 PY 95% CI = 0.37-1.52 for RSG + SU and 0.71-2.08 for MET + SU

4 Incidence rate per 100 PY 95% CI = 0.10-0.90 for RSG + SU and 0.02-0.60 for MET + SU

5 Incidence rate per 100 PY 95% CI = 0.43-1.66 for RSG + SU and 0.18-1.09 for MET + SU

6 Incidence rate per 100 PY 95% CI = 0.43-1.66 for RSG + SU and 0.05-0.73 for MET + SU

The number of events for any given endpoint among IHD patients was small, and therefore caution should be used in interpreting this information. In the above table, the numerical imbalance in heart failure events (not favoring rosiglitazone) is slightly more pronounced, but not statistically significant, in patients with a prior history of ischemic heart disease than in patients without prior ischemic heart disease. When examining CV deaths, stroke and unstable angina hospitalization, the incidence in patients without a prior history of ischemic heart disease was numerically, but not statistically significantly lower for RSG group patients than for MET group patients, but for patients with a prior history of ischemic heart disease, the incidence is slightly higher for RSG, although not statistically significantly so. These differences consisted of a few events, and thus were not robust findings. For myocardial infarction events in patients without prior ischemic heart disease, the incidence was slightly higher for RSG group patients than for MET group patients, but among patients with a prior history of ischemic heart disease, the incidence of MI was lower for RSG group patients than for MET group patients. For patients with prior ischemic heart disease, the 95% confidence intervals for the incidence rates for each of these endpoints overlapped between RSG and MET/SU.

Overall, for the primary endpoint, there was a suggestion of an interaction by the baseline presence of ischemic heart disease. When examining the types of cardiovascular events which occurred more commonly among patients with a prior history of ischemic heart disease, it appeared that the difference was accounted for by a higher rate of heart failure, and perhaps hospitalization for unstable angina, among baseline IHD patients than among patients without a prior IHD history. The number of events for any given endpoint among IHD patients was small, and therefore caution should be used in interpreting this information. No particular type of prior IHD event appeared to predispose to excess CV events.

II.D.3.b. Use of Cardiovascular Medications Over Time

In general, the use of cardiovascular medications increased over time in all strata.

The following table displays the number and percentage of patients who were taking cardiovascular medications over time in the study.

Table II.D.3.b: Number and Percentage of Patients Taking Cardiovascular Medications by Study Year, ITT Population

CV Medications at End of Years 1 to 5 of CV Follow-up, n (%)	CV Follow-up ¹					
	Baseline	End of Year 1	End of Year 2	End of Year 3	End of Year 4	End of Year 5
Completed to End of Year						
Combined RSG	2220	2145	2084	2032	1972	1918
MET/SU	2227	2149	2085	2025	1965	1892
Any Cardiovascular Medication						
Combined RSG	1630 (73.4)	1743 (81.3)	1772 (85.0)	1777 (87.5)	1753 (88.9)	1735 (90.5)
MET/SU	1627 (73.1)	1742 (81.1)	1756 (84.2)	1758 (86.8)	1728 (87.9)	1684 (89.0)
Lipid-lowering Medication						
Any medication						
Combined RSG	522 (23.5)	804 (37.5)	973 (46.7)	1038 (51.1)	1070 (54.3)	1102 (57.5)
MET/SU	531 (23.8)	704 (32.8)	812 (38.9)	874 (43.2)	908 (46.2)	933 (49.3)
Statins						
Combined RSG	399 (18.0)	656 (30.6)	829 (39.8)	908 (44.7)	944 (47.9)	981 (51.1)
MET/SU	424 (19.0)	574 (26.7)	685 (32.9)	752 (37.1)	788 (40.1)	813 (43.0)
Fibrates						
Combined RSG	130 (5.9)	166 (7.7)	166 (8.0)	163 (8.0)	156 (7.9)	157 (8.2)
MET/SU	119 (5.3)	147 (6.8)	153 (7.3)	152 (7.5)	152 (7.7)	156 (8.2)
Other						
Combined RSG	2 (<1)	6 (<1)	18 (<1)	29 (1.4)	34 (1.7)	38 (2.0)
MET/SU	2 (<1)	6 (<1)	16 (<1)	18 (<1)	26 (1.3)	25 (1.3)
Cardiovascular Medication						
Any medication						
Combined RSG	1445 (65.1)	1529 (71.3)	1549 (74.3)	1567 (77.1)	1551 (78.7)	1559 (81.3)
MET/SU	1453 (65.2)	1536 (71.5)	1552 (74.5)	1571 (77.6)	1551 (78.9)	1516 (80.1)
Any diuretic						
Combined RSG	445 (20.0)	590 (27.5)	673 (32.3)	723 (35.6)	747 (37.9)	781 (40.7)
MET/SU	471 (21.1)	544 (25.3)	590 (28.3)	623 (30.8)	662 (33.7)	667 (35.3)
Loop diuretics						
Combined RSG	72 (3.2)	126 (5.9)	163 (7.8)	188 (9.3)	198 (10.0)	217 (11.3)
MET/SU	71 (3.2)	83 (3.9)	100 (4.8)	105 (5.2)	123 (6.3)	137 (7.2)
CV Medications at End of Years 1 to 5 of CV Follow-up, n (%)	CV Follow-up ¹					
	Baseline	End of Year 1	End of Year 2	End of Year 3	End of Year 4	End of Year 5
Any alpha-blocker						
Combined RSG	67 (3.0)	74 (3.4)	78 (3.7)	86 (4.2)	91 (4.6)	93 (4.8)
MET/SU	71 (3.2)	92 (4.3)	97 (4.7)	111 (5.5)	111 (5.6)	112 (5.9)
Any beta-blocker						
Combined RSG	517 (23.3)	599 (27.9)	629 (30.2)	652 (32.1)	670 (34.0)	685 (35.7)
MET/SU	482 (21.6)	545 (25.4)	583 (28.0)	624 (30.8)	655 (33.3)	660 (34.9)
Any calcium channel blocker						
Combined RSG	430 (19.4)	471 (22.0)	481 (23.1)	513 (25.2)	522 (26.5)	539 (28.1)
MET/SU	483 (21.7)	548 (25.5)	559 (26.8)	580 (28.6)	627 (31.9)	625 (33.0)
Any renin-angiotensin system drug						
Combined RSG	1059 (47.7)	1155 (53.8)	1206 (57.9)	1236 (60.8)	1245 (63.1)	1272 (66.3)
MET/SU	1034 (46.4)	1154 (53.7)	1225 (58.8)	1259 (62.2)	1256 (63.9)	1261 (66.6)
Antiplatelet Medication						
Any anti-platelet medication						
Combined RSG	448 (20.2)	516 (24.1)	570 (27.4)	608 (29.9)	635 (32.2)	649 (33.8)
MET/SU	422 (18.9)	494 (23.0)	554 (26.6)	595 (29.4)	647 (32.9)	656 (34.7)
Acetylsalicylate						
Combined RSG	436 (19.6)	497 (23.2)	550 (26.4)	579 (28.5)	601 (30.5)	616 (32.1)
MET/SU	406 (18.2)	473 (22.0)	535 (25.7)	572 (28.2)	617 (31.4)	630 (33.3)
Clopidogrel						
Combined RSG	5 (<1)	16 (<1)	26 (1.2)	34 (1.7)	37 (1.9)	39 (2.0)
MET/SU	9 (<1)	20 (<1)	23 (1.1)	30 (1.5)	39 (2.0)	46 (2.4)
Ticlopidine						
Combined RSG	4 (<1)	8 (<1)	13 (<1)	16 (<1)	19 (<1)	18 (<1)
MET/SU	6 (<1)	9 (<1)	6 (<1)	9 (<1)	10 (<1)	11 (<1)
Dipyridamole						
Combined RSG	12 (<1)	13 (<1)	14 (<1)	16 (<1)	19 (<1)	22 (1.1)
MET/SU	10 (<1)	10 (<1)	9 (<1)	12 (<1)	13 (<1)	13 (<1)

Data Source: DS Table 6.70 and DS Table 6.77

1. Percentages are based on the number of subjects who completed each year of treatment (i.e. for End of Year 1, the percentages are based on the number of Year 1 completers)

Source: Applicant's Table 46, beg pg 137, RECORD study report

Over time, there were some differences between overall treatment groups in the use of certain classes of cardiovascular medications, e.g. statins, loop diuretics and calcium channel blockers. These classes are discussed further below.

Statin Use over Time

At the beginning of study, statin use was equal between treatment groups (18% in RSG grp, 19% in MET/SU grp). Over time, use of statins became more common among patients in the overall RSG group. At the end of cardiovascular follow-up, 50.7% of patients in the overall RSG group were taking a statin, compared to 42.2% of patients in the overall MET/SU group. This difference in statin use was apparent at Year 1, and from Year 2 on, the percentage difference in statin use remained stable over time, at approximately 7-8% at each time point. See Section II.F.4 for further discussion of this observation.

Loop Diuretic Use over Time

At beginning of study, 3.2% of patients in both overall treatment groups were using a loop diuretic. At end of cardiovascular follow-up, 11.3% of patients in the overall RSG group were using a loop diuretic, compared to 7.2% of patients in the MET/SU group. As with statin use, this difference between groups in loop diuretic use was apparent by Year 1, and remained at a stable difference of 3-4% from Year 2 on. Loop diuretic use was likely reflective of the higher incidence of heart failure among RSG group patients compared to MET/SU group patients.

Calcium Channel Blocker Use over Time

At beginning of study, there was a slight difference in use of calcium channel blockers between treatment groups (19.4% RSG, 21.7% MET/SU). Over time, this difference widened (approximately 3.5% difference at Years 2, 3 and 4; and approximately 5% difference at Years 4 and 5). At end of cardiovascular follow-up, 28.1% of patients in the combined RSG group were taking a calcium channel blocker, compared to 33.0% of patients in the MET/SU group. This difference may have been reflective of the higher systolic blood pressure seen among MET/SU group patients over study, and thus of the need for additional antihypertensive therapy in this group compared to the MET/SU group. The clinical significance of this difference in calcium channel blocker use is unknown, but greater attention to blood pressure control in the MET/SU group, if it occurred, would not be likely to bias the study in favor of RSG.

II.D.3.c. Other Issues With Potential Effects on the Interpretability of Cardiovascular Endpoint Information

Please see Section II.F for a discussion of several other issues which could potentially affect the interpretability of the findings of RECORD.

II.E. Noncardiovascular Safety Results

Noncardiovascular safety was reviewed, and the preliminary findings from RECORD were generally similar to those documented in current labeling. Because the focus of this Advisory Committee Meeting is on the cardiovascular safety of rosiglitazone, results for the review of noncardiovascular adverse events have not been included in the briefing document, but will be in the final review document for RECORD.

Although analyses of most categories of adverse events of special interest displayed very similar results to those in the current FPI, a difference in incidence of adverse renal events between treatment groups occurred in RECORD, and is not described in the current FPI.

Renal adverse events occurred less commonly among RSG-treated patients than among comparator-treated patients (rates per 100 PY during randomized dual oral therapy RSG 0.97 [0.78, 1.19], MET/SU 1.50 [1.27, 1.76]). The 95% confidence intervals for the incidence rates of renal events did not overlap for this comparison. Events of microalbuminuria (0.9% RSG vs 1.8% MET/SU) and albuminuria (0.1% RSG vs 0.8%) occurred numerically less frequently among RSG-treated patients than among comparator-treated patients; this was also true for both strata. Events of diabetic nephropathy occurred numerically less frequently among RSG-treated patients than among comparator-treated patients (1.0% vs 1.6%); and in the background SU stratum, diabetic nephropathy occurred numerically less frequently among RSG-treated patients than among MET-treated patients (0.9% vs 2.0%).

Several laboratory tests were included as efficacy endpoints, and are discussed in Section II.D.2.

Vital signs findings are not discussed with efficacy endpoints, and are briefly presented below.

The following table displays baseline values, and mean changes from baseline, in blood pressure and pulse during randomized treatment.

Table II.E.1: Baseline Values and Mean Changes from Baseline (Mean and SD), Blood Pressure and Heart Rate, Randomized Dual Oral Therapy Period

Month	SBP (mmHg)		DBP (mmHg)		HR (bpm)	
	RSG Du	Met/SU Du	RSG Du	Met/SU Du	RSG Du	Met/SU Du
BL	139.0 ± 15.1	138.5 ± 15.8	83.2 ± 8.3	82.8 ± 8.4	73.6 ± 8.5	73.8 ± 8.6
12	-1.8 ± 15.2	-0.8 ± 15.4	-1.8 ± 8.8	-0.9 ± 8.9	-0.4 ± 9.2	0.1 ± 9.3
18	-2.6 ± 15.8	-1.2 ± 16.4	-2.6 ± 9.2	-1.1 ± 9.7	-0.5 ± 8.9	-0.3 ± 9.0
24	-1.7 ± 15.5	-0.4 ± 16.3	-2.4 ± 9.3	-1.1 ± 9.5	-0.5 ± 9.3	-0.2 ± 9.7
36	-1.1 ± 16.4	-0.1 ± 16.8	-2.9 ± 9.5	-1.1 ± 9.7	-0.9 ± 9.4	0 ± 9.8
48	-2.2 ± 16.3	-1.6 ± 17.3	-3.5 ± 9.9	-2.3 ± 9.8	-0.8 ± 10.2	-0.5 ± 9.9
60	-2.8 ± 16.8	-1.6 ± 17.8	-4.0 ± 10.1	-2.8 ± 10.1	1.0 ± 10.1	-0.3 ± 10.3

Source: Applicant's Table 176, pg 340, RECORD study report body
DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure

Rosiglitazone was associated with slightly numerically greater declines from baseline in systolic blood pressure, diastolic blood pressure and heart rate, but standard deviations were large.

Rosiglitazone was associated with an increase in body weight compared to both SU and MET, as displayed in the following table.

Table II.E.2: Baseline Mean (SD), and Mean Change (SD) from Baseline in Body Weight (kg) During Randomized Dual Oral Therapy

Month	Bkgrd MET			Bkgrd SU		
	RSG	SU	p-value	RSG	MET	p-value
BL	93.5 ± 0.5	93.2 ± 0.5	n/a	85.1 ± 0.4	84.4 ± 0.4	n/a
12	1.9 ± 0.1	1.2 ± 0.1	0.0004	2.7 ± 0.1	-0.7 ± 0.1	<0.0001
18	2.2 ± 0.2	0.9 ± 0.1	<0.0001	3.1 ± 0.2	-0.9 ± 0.1	<0.0001
24	2.7 ± 0.2	0.9 ± 0.1	<0.0001	3.5 ± 0.2	-0.9 ± 0.1	<0.0001
36	3.2 ± 0.2	0.7 ± 0.2	<0.0001	3.8 ± 0.2	-1.4 ± 0.1	<0.0001
48	3.7 ± 0.2	0.0 ± 0.2	<0.0001	4.2 ± 0.2	-1.7 ± 0.2	<0.0001
60	3.9 ± 0.3	-0.5 ± 0.2	<0.0001	4.7 ± 0.2	-2.2 ± 0.2	<0.0001

Source: Applicant's Table 112, pg 246 RECORD study report body

II.F. Discussion of Concerns Which Might Limit Interpretability of RECORD

The RECORD trial has received an extraordinary amount of scrutiny. At the time of the 2007 Advisory Committee meeting regarding the cardiovascular safety of rosiglitazone, it was asserted that the trial might not provide useful information, primarily because of concerns regarding underpowering. There was a great need at the time of the 2007 AC for a source of adjudicated CV outcomes data to further evaluate the hypothesis generated by the meta-analysis of myocardial ischemic events, but it was felt that RECORD would be unlikely to be such a source. However, when the published trial results became available, they indicated that there had been adequate power. The announcement of the results was followed by extensive quotes in the public press regarding numerous additional possible limitations of the trial. Some of these putative limitations were somewhat speculative and dealt with hypothetical possibilities of trial misconduct and, although they may color the perception of the trial, cannot be evaluated in a scientific fashion. Some of the conjecture regarding possible trial misconduct could be applied to any clinical trial of any agent, and are not useful comments if the conjecture cannot be definitively assessed. However, some of the issues could be objectively evaluated, at least to some extent, either by the inspection process under the Division of Scientific Investigations, or by analysis of available data. The following section addresses some of the concerns which have been raised in the public press, and others that have been discussed by the FDA review team.

II.F.1. Overall Complexity of Trial Design

As stated earlier in this document, RECORD was designed as a postmarketing commitment study for the EMEA. The intent of the design of RECORD was to evaluate the cardiovascular safety of the drug during use consistent with the EMEA-approved indication and conditions of use at the time of study initiation. The resulting trial design was complex, and resulted in some challenges to interpretation.

In practice, most patients with type 2 diabetes require the progressive addition of medication over time. Most patients progress to require multiple oral agents, and eventually require insulin for adequate glycemic control. The RECORD trial began with patients who were inadequately controlled on maximum or maximum tolerated doses of MET or SU. Over time, it was expected that a significant percentage of patients would require a 3rd agent, and the protocol specified this. However, because RSG could not be administered with insulin, the 3rd agent for the RSG group was an oral agent (MET for patients on background SU, and SU for patients on background MET). If this triple oral therapy failed for RSG group patients, insulin could be added, but RSG then had to be discontinued. For patients in the MET/SU comparator group, the 3rd agent could not be RSG or another TZD, and other classes of oral agents were generally not available at that time. Therefore, the 3rd agent for the MET/SU comparator group was insulin. This meant that more patients in the MET/SU group might receive insulin, and they might receive it earlier, than patients in the RSG group. Therefore, the ITT population was expected to have some asymmetry in insulin use. In order to address this somewhat, sensitivity analyses were performed using the patient-time period of dual oral therapy only, and were generally consistent with the ITT analyses.

A noninferiority design was used, as the EMEA objective was to confirm that RSG did not carry an unacceptably higher CV risk than MET or SU. A noninferiority design has some limitations. Careful prespecification of the noninferiority margin is important, but challenging. In RECORD, the prespecified margin was conservative for the time of initiation of the study, calling for an upper bound of the 95% confidence interval of 1.2 for the hazard ratio for the primary endpoint. At that time, a typical upper bound was often 2.0 for safety findings, and interpretation of more stringent upper bounds was considered difficult because of problems with multiple testing for numerous safety endpoints.

In a noninferiority design, multiple factors can reduce assay sensitivity, including poor compliance with study medication, poor diagnostic criteria for the endpoint, and biased assessment of the endpoint. A superiority design has fewer difficulties with these issues. However, at the time of initiation of the study,

and continuing to this day, there is no diabetes drug that has been definitively shown to improve CV outcomes, and therefore there is no “gold standard” for a superiority comparison. Compliance with study medication is important in a noninferiority design, but one expects patients with diabetes to require additional medication over time, and once a patient with RSG failed oral therapy, insulin was required, which in turn required discontinuation of RSG under EMEA conditions of use at the time. The study did have blinded endpoint adjudication and prespecified endpoint definitions. However, the complexity of endpoint reporting and the open-label design (both discussed in following sections) could have resulted in room for errors or omissions in channeling of potential endpoint events to the endpoint adjudication committee. This concern was to be evaluated during extensive inspections by the Division of Scientific Investigations; the report for these inspections is pending as of 8 Jun 2010.

Additionally, in a noninferiority design, the standard analysis methods used for superiority trials have limitations. In superiority trials, the ITT approach is usually used, because it adheres to the randomization procedure and is generally conservative. However, in a noninferiority trial, including data after study drug discontinuation in the analysis can make a finding of equivalence more likely. Therefore, sensitivity analyses that exclude patients after they have discontinued study drug are often used. However, excluding these patients can bias the results in either direction. Therefore, in noninferiority trials, analyses are generally presented using both types of analysis approaches. This was done for the RECORD trial.

II.F.2. Assertion that the Rate of Myocardial Infarction was Low

In the RECORD trial, there were 120 events adjudicated as MI over 24,610 patient-years of cardiovascular follow-up. This equates to 4.9 adjudicated MIs per 1000 PY. Cross-study comparisons of event rates are difficult, because studies differ in the baseline cardiovascular risk of their included populations, and in their event definitions. The calendar year of initiation of the study can also be important, because cardiovascular care and attention to risk factors has improved in recent years, possibly leading to lower event rates. Thus, while underascertainment is a concern when one observes a difference in event rates between trials, other factors should also be considered.

The following table lists several trials which included patients with diabetes, which were conducted in the past 10 years, and in which adjudication of cardiovascular events occurred. Myocardial infarction rates and baseline cardiovascular risk factors are presented. Because a prior history of macrovascular disease is a strong risk factor for subsequent myocardial infarction, the table is arranged in descending order of the baseline percentage of patients with a prior macrovascular event history.

Table II.F.2: Myocardial Infarction Rates, Baseline History of Macrovascular Events, and Other Baseline Cardiovascular Risk Factors, Large Trials in Patients with Diabetes

	Adjud MI per 1000 PY	Any Prior Macro- vasc Event or Known CAD (%)	DM ≥10 yr (%)	Prior MI (%)	Mean Age (y)	% Male	SBP (mmHg)	LDL (mg/dL)	HbA1c (%)	Curr Smoker (%)	Ever Smoked (%)	DM Dur (y)
BARI-2D	20	100	43	32	62	70	132	96	7.7	22	54	10
IDEAL	19	100	28	100	63	78	140	116	6.5	16	60	8
TNT	19	100	35	57	63	73	135	96	7.4	11	62	9
PROACTIVE	17	100	44	47	62	67	144	112	7.8	14	45	8
APPROACH	15	100		24	61	68	129	90	7.2	17	37	5
SPARCL	7	78	36	<1	64	61	142	132		16	40	8
HPS	9	51	44	19	62	70	148	124	7.1	13	67	11
VADT	14	46	54	19	60	97	132	108	9.4	17	56	12
ACCORD	12	35	50	16	62	61	136	105	8.3	14	44	10
ADVANCE	6	32	36	12	66	57	145	120	7.5	14	41	8
RECORD	5	19	23	5	58	52	139	127	7.8	16	41	6
ASCOT LLA	6	8		0	64	76	165	127		20	61	
CARDS	6	0	33	0	62	68	144	117	7.8	23	66	8

Sources: ACCORD Study Group 2008, beg pg 2548; ADVANCE Collaborative Group 2008; Amarencio 2007; BARI 2D Study Group 2008; BARI 2D Study Group 2009; Colhoun 2004; Dormandy 2005; Duckworth 2009; Gerstein 2010; Heart Protection Study Collaborative Group 2003; Sever 2005; Shepherd 2006; NDA 19766, subm 13 Apr 2010; NDA 20702, subm 2010 04 16 and 2010 04 19

1 Action to Control Cardiovascular Risk in Diabetes

2 Median

3 Mean

4 Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

5 Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients with Cardiovascular History Trial

6 Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm, Diabetes Subpopulation

7 Bypass Angioplasty Revascularization Intervention in Type 2 Diabetes

8 Collaborative Atorvastatin Diabetes Study

9 Heart Protection Study, Diabetes Subpopulation

10 Incremental Decrease in Endpoints through Aggressive Lipid-lowering

11 Prospective Pioglitazone Clinical Trial in Macrovascular Events

12 Stroke Prevention by Aggressive Reduction in Cholesterol Levels

13 Treating to New Targets diabetes substudy

14 Veterans Affairs Diabetes Trial

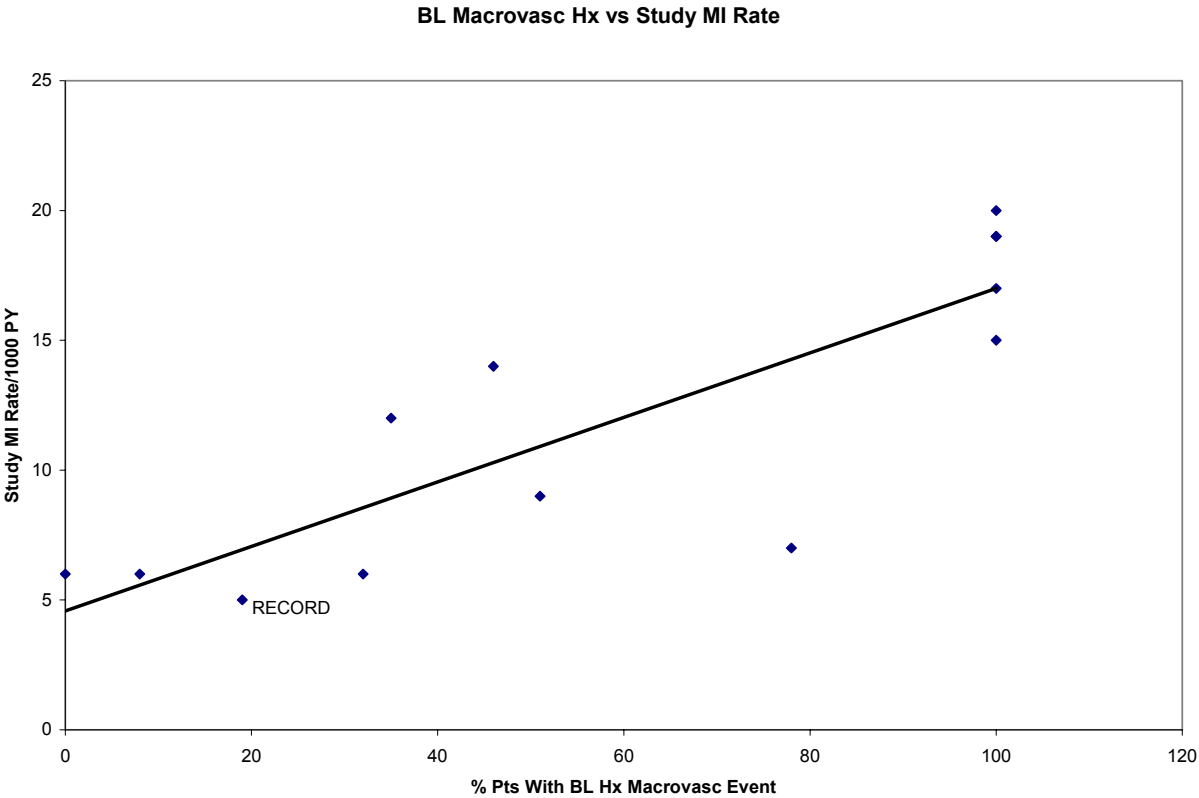
15 Patients with this condition were excluded

In the above table, it appears that the rate of MI in RECORD was in the range one might expect, given the relatively low risk population enrolled. The MI rate in RECORD falls in the range of that seen in other trials which included a similar proportion of patients with a history of macrovascular disease. Other strong risk factors for MI in patients with diabetes were also more common among patients in trials with higher study MI rates, such as a prior history of MI (unless specifically excluded) and duration of diabetes ≥10 years.

Dr. Hoberman performed analyses for the rate of MI observed in these studies vs baseline characteristics of a prior history of any macrovascular event, and vs a prior history of myocardial infarction. Pearson correlation coefficients (PCCs) confirmed a strong relationship between these baseline risk factors and subsequent MI, and the values for RECORD fell near the expected area of the plots. The PCC for baseline history of macrovascular event vs study MI rate was 0.843 (p 0.0003), and for baseline history of MI vs study MI rate was 0.803 (p 0.0017). Thus, although other factors could have contributed to the MI rate in RECORD, the low CV risk of the population was likely a contributor.

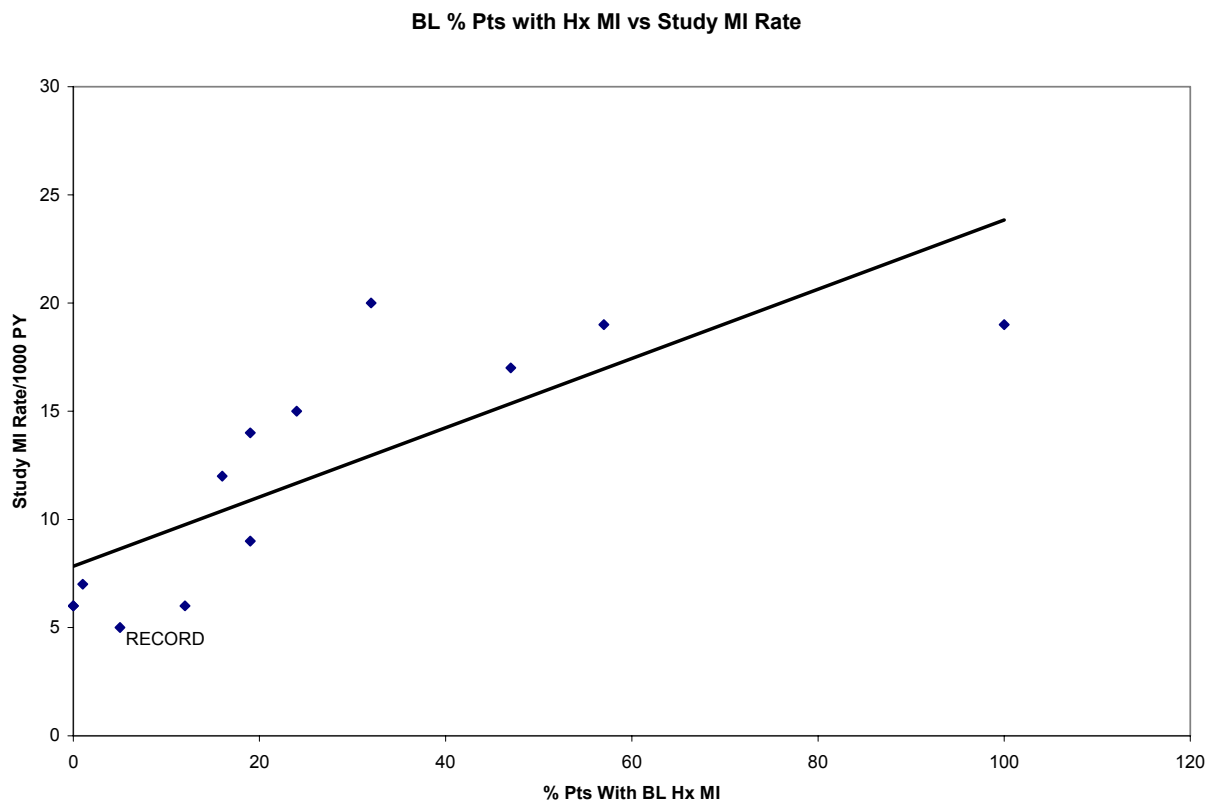
The following scatter plots illustrate this correlation.

Figure II.F.2.a: Scatter Plot of Baseline History of Macrovascular Disease (% Patients) vs Study Rate of Myocardial Infarction (Rate per 1000 PY), Large Trials in Patients with Diabetes



Source: Table II.F.2 above.

Figure II.F.2.b: Scatter Plot of Baseline History of Myocardial Infarction (% Patients) vs Study Rate of Myocardial Infarction (Rate per 1000 PY), Large Trials in Patients with Diabetes



Source: Table II.F.2 above.

The definition(s) used for adjudication of MI varied somewhat between these studies. As mentioned earlier, in RECORD, MI was adjudicated according to a joint European Society of Cardiology and American College of Cardiology definition published in 2000 (Joint ESC/ACC Committee 2000). Elements of MI included elevation of cardiac biomarkers (troponin I or troponin T >ULN; or CK-MB ≥ 2 x ULN; or CK >2x ULN), plus one of the following:

- “typical symptoms of cardiac ischemia”, or
- new pathological ECG findings as defined in the aforementioned article.

The clinical reviewer reviewed the available protocol documents regarding the definitions of MI that were used for adjudication in the above studies.

The MI definition used in IDEAL was similar to that used in RECORD.

For the ACCORD study, the definition used for acute MI was fairly similar to that used above for RECORD. However, in ACCORD, several other types of events were also adjudicated as MIs. For example, ACCORD had definitions for non-Q-wave MI, silent (unrecognized) MI, “probable” non-Q-wave MI, and definitions for MI after various interventions that differed from the definition used for acute MI (ACCORD Protocol 5 Jan 2009).

For BARI 2D, the definition used in RECORD would have been counted as an event, but there were also definitions for asymptomatic and non-Q-wave MIs (BARI 2D Protocol 2002).

For ASCOT-LLA and CARDS, there were several definitions for MI, which included varying combinations of ECG, biochemical, clinical and autopsy findings. Silent myocardial infarction was also included.

For PROactive, elevated cardiac biomarkers were not required for the definition of MI in all cases. Rather, patients were considered to have an MI if they met 2 of 3 criteria (symptoms, ECG evidence or an elevated serum marker) (NDA 21073, PROactive study report pg 8185, subm 24 Jan 2006). The Heart Protection Study had a similar definition (NDA 19766, subm date 13 Apr 2010).

For VADT, myocardial infarction was defined primarily on the basis of ECG findings, with confirmation by supporting documentation. Included were ECG definitions for non-Q-wave and silent MIs.

In general, the definition of MI used in other trials would have resulted in some events being counted as MIs that would not have met the definition used in RECORD. This difference might also have contributed to the somewhat lower rate of MI seen in RECORD. Because the RECORD MI definition, based on the Joint ESC/ACC definition in effect at the time, required elevated cardiac biomarkers, some patients whose medical records did not include documentation of biomarkers may not have met the definition of MI in RECORD, but may have met it in other studies where elevated biomarkers were not an absolute requirement, but rather were, for example, included in a “two out of three” list of elements that could define MI. In the latter case, a patient in another study whose medical records did not include documentation of elevated biomarkers could still be adjudicated to have an MI if they had a typical clinical history and ECG changes.

The Agency requested information from the applicant regarding patients for whom the above might have happened, i.e. patients who had a typical clinical history and ECG changes, but lacked results for biomarkers and were therefore adjudicated not to have had a myocardial infarction. The applicant responded on 4 Jun 2010. The applicant examined all potential endpoints that were sent for adjudication as possible myocardial infarctions, but were adjudicated not to have been an MI. There were 60 of these cases; 18 were adjudicated as noncardiovascular events, and 42 were adjudicated as cardiovascular events other than MI. Among these 60 cases, the applicant identified 1 patient (pt ID 38628) who fell into the category of having symptoms + ECG changes, but lacking biomarkers. The patient presented with “symptoms typically consistent with cardiac ischemia”. The ECG in the adjudication package was of poor quality, but a medical summary stated that the ECG had been read as “atrial fibrillation, non-Q-wave MI in the ventrolateral wall and apical myocardial infarction”. No biomarkers were provided, but thrombolytic therapy was administered. Upon initial adjudication, the two adjudicators had different opinions regarding whether this represented an MI. Therefore, the event went to the full adjudication committee and was adjudicated not to have met criteria for MI. It is possible that this event could have been deemed an MI in a study which used a different definition of MI.

Overall, it appears that, at least in part, the rate of MI in RECORD was low because it enrolled a low-risk population.

II.F.3. Open-Label Design

The open-label design of RECORD introduced a potential for investigator bias. Although this could be mitigated somewhat by the adjudication of events by a blinded endpoints committee, there remains concern for the possibility of unbalanced referral of events for adjudication. These concerns were a focus of inspections by the Division of Scientific Investigations. The final inspection report is pending as of 8 Jun 2010.

On 15 Apr 2010, DMEP sent an information request to GSK asking for clarification of which personnel at GSK were unblinded to treatment group prior to the prespecified post-study date on which analyses of data were to begin. On 17 May 2010, GSK responded that members of GSK’s Global Clinical Safety and

Pharmacovigilance (GCSP) Case Management Group who were involved in case processing of adverse events were unblinded to patient-level individual case report information, but did not participate in any study analyses. A physician member of the GCSP was also responsible for providing, as requested by the Data Safety Monitoring Board, monthly summaries of unblinded patient level event data. Another member of the GCSP was responsible for providing an Excel® spreadsheet of cumulative unblinded patient level RECORD SAEs to Quintiles every six months. Quintiles was the Contract Research Organization which was responsible for the administration of RECORD. A firewalled team within Statistics and Programming at GSK had access to unblinded patient level data for planned analyses of glycemic, blood pressure, and hepatic data. This team also conducted analyses of fracture data in November 2006 after concerns regarding this adverse event arose for thiazolidinediones. As described above, a separate firewalled Statistics and Programming team, which had not previously been assigned to RECORD, conducted the analyses for the nonprespecified interim cardiovascular analysis that was prompted by the publicity surrounding the 2007 Nissen meta-analysis. The firewall procedure for this team is described in Section II.F.12. After the analyses were done, the results were placed in a slide set which was shared with the DSMB, several GSK executives, and statisticians at the London School of Hygiene and Tropical Medicine who were involved in preparation of the manuscript.

Overall, it appears that efforts were made to maintain blinding in areas such as adjudication, programming and statistical analysis, but an effect of knowledge of treatment assignment by patients and caregivers cannot be excluded.

II.F.4. Higher Rate of Statin Initiation Among Rosiglitazone Group Patients

At the beginning of study, statin use was equal between treatment groups (18% in RSG grp, 19% in MET/SU grp). Over time, use of statins became more common among patients in the overall RSG group. At the end of cardiovascular follow-up, 50.7% of patients in the overall RSG group were taking a statin, compared to 42.2% of patients in the overall MET/SU group. This difference in statin use was apparent at Year 1, and from Year 2 on, the percentage difference in statin use remained stable over time, at approximately 7-8% at each time point.

A question arises as to whether more statin use in the RSG group may have affected the outcome of the study. Higher use of a drug known to decrease major cardiovascular events might make the true risk of RSG seem lower than it would be if statin use was equal between groups. In order to address this question, the applicant performed an analysis where they assumed that all patients who started a statin had the full 25% risk reduction that would be expected based on major cardiovascular outcomes studies of statins (Cholesterol Treatment Trialists' Collaborators 2005). The 8% difference in use of statins would be expected to alter the observed hazard ratio (0.99) by only 0.02, with no change in the significance of the non-inferiority conclusion (pg 356, RECORD study report body). Dr. Hoberman's analyses confirmed this.

Although statin use was higher in the RSG group over time, levels of low density lipoprotein cholesterol remained higher in the RSG group. Therefore, the differential statin use did not convey an LDL advantage for the RSG group. Statins may have other beneficial cardiovascular effects apart from lowering LDL, but these are less well-documented.

A question has arisen regarding whether there was a systematic effort to give more potent statins to rosiglitazone group patients, or to give higher doses to these patients. The Division of Metabolism and Endocrinology Products specifically queried the applicant regarding this in an information request on 15 Apr 2010. The applicant provided responses on 17 and 20 May 2010. The applicant stated that patients who developed elevated levels of LDL were not systematically identified, and that investigators did not receive any communications regarding which patients should start a statin, which statin should be used, or which statin dose should be used. Section 6.11.2 of the protocol specified that, at beginning of study,

patients were to be treated according to the 1999 European Diabetes Policy Group (EDPG) recommendations for management of lipids in patients with diabetes, and from that point onward, patients were to be managed according to subsequent versions of those EDPG recommendations.

The following table displays the types of statins that patients were on at Year 5 of study, and the mean dose.

Table II.F.4: Types of Statins Used and Mean Doses, End of Year 5 of Study

Statin	RSG N=1918		MET/SU N=1892		Ratio of Values ¹ RSG:MET/SU
	n (%) on Specified Statin	Mean Dose, mg (SD) of Specified Statin	n (%) on Specified Statin	Mean Dose, mg (SD) of Specified Statin	
Any statin	981 (51.1)		813 (43.0)		1.19
		n/a		n/a	n/a
Atorvastatin	327 (17.0)		263 (13.9)		1.22
		21.0 (14.8)		18.9 (12.2)	1.11
Cerivastatin	0		2 (0.1)		n/a
		0		0.2 (n/a)	n/a
Fluvastatin	59 (3.1)		31 (1.6)		1.94
		63.2 (21.8)		52.5 (25.1)	1.20
Lovastatin	30 (1.6)		16 (0.8)		2.00
		20.7 (7.4)		20.6 (5.7)	1.00
Pravastatin	37 (1.9)		27 (1.4)		1.36
		28.0 (14.9)		33.3 (13.6)	0.84
Rosuvastatin	53 (2.8)		43 (2.3)		1.22
		14.2 (13.8)		10.9 (3.5)	1.30
Simvastatin	535 (27.9)		457 (24.2)		1.15
		24.3 (12.6)		23.1 (11.4)	1.05
Source: Applicant's Table 3, pg 4; NDA 21071 subm 20 May 2010					
1 For the "n (%)" column, this is the ratio of the percentages of patients who were taking the specified statin. For the dose column, this is the ratio of mean doses					

In the above table, the most potent statins, in terms of LDL-lowering, would be rosuvastatin and atorvastatin. For both these drugs, the relative percentage (between RSG and MET/SU groups) of patients using the particular statin was similar to the overall relative percentage of patients using any statin. This was also true for the ratio of mean doses. Across all statins used, the ratio of mean dose between patients in the RSG group and patients in the MET/SU group was similar. Thus, it does not appear that patients in the RSG group systematically received more potent statins; or that when statins were initiated, that RSG group patients received higher doses of statin, compared to patients in the MET/SU group. The differences between the RSG and MET/SU group appear simply to be reflective of the overall higher rate of initiation of statins in the RSG group.

Dr. Hoberman explored the question of statin use in several ways.

First, he examined patients by baseline statin status, and looked at the incidence of primary events and timing of initiation of statins.

There were a total of 510 patients who were not taking a statin at baseline, and who eventually had a primary endpoint event. Dr. Hoberman examined the timing of initiation of statin for this group (no baseline statin, eventual primary endpoint event), specifically whether statin was initiated before or after the primary endpoint event. For patients who had a statin initiated at the time of or after an event, there

were 79 patients in the RSG arm and 71 patients in the control arm. For patients who had a statin initiated before their event, 76 were in the RSG arm and 55 were in the control arm.

There were 3114 patients who were not on a statin at baseline, and who did not have a primary endpoint event, split approximately equally between groups. A total of 671 (43%) of RSG patients and 492 (32%) of control group patients eventually received a statin.

There were 2180 patients who were never on a statin, either at baseline or during study. Among these patients, 99/995 (9.9%) of RSG patients and 130/1185 (11.0%) of MET/SU patients had a primary endpoint event (HR 0.92, upper bound of 95% CI 1.20). For MACE in this group, the HR was 0.74 with an upper bound of 1.08.

There were 578 patients who were taking a statin at baseline and never had an increase in dose. In this group, 17/258 (6.6%) of RSG group patients, and 13/320 (4.1%) of control group patients had a MACE.

Overall, although there was a concern that a higher rate of statin initiation in the RSG group may have biased results toward noninferiority, an analytical evaluation supports that the statistical effect would likely be small.

II.F.5. Power Concerns

As discussed in Sections IV.B and II.B, at the time of the 2007 interim analysis, concerns were expressed that the lower-than-expected event rate for RECORD at the time would result in inadequate power to assess the primary endpoint. However, at the end of the study, power was adequate for the primary endpoint, with an upper bound of the 95% confidence interval of 1.16.

As is usual in most clinical trials, the study was not powered for secondary endpoints, or for analyses involving only time on randomized treatment. Therefore, some uncertainty will remain for these endpoints and for the on-treatment patient-time population. In particular, because the upper bound of the 95% confidence interval for the hazard ratio for myocardial infarction was 1.63, RECORD cannot rule out an increased risk for myocardial infarction with RSG, although the 95% confidence interval includes 1. The study does not have the statistical power to address this and other secondary endpoint questions.

II.F.6. Concern Regarding Percentage of Patients Who Were Not Taking Original Randomized Dual Oral Combination Therapy at End of Study

RECORD was a 5-year study, and over time, drop-outs occurred, as discussed in Section II.C.2. Also, once insulin was begun, a patient was no longer considered to be on randomized therapy, because the combination use of insulin and RSG was not permitted in Europe at the time. Concern has been expressed regarding the effect of these drop-outs (and protocol-specified movements out of the classification of randomized therapy) on the outcome of the analyses, with the assertion that high drop-out rates could bias toward a non-inferiority conclusion. To address this concern, analyses were done on the “per protocol” (randomized dual oral combination therapy only) population, in addition to the primary analyses which used the intention-to-treat principle. This was done in order to examine the risk among patients who stayed on randomized treatment and did not drop out. Results of these analyses are summarized in Table II.D.1.b.ii. Qualitatively, the results of these analyses were very similar, with similar point estimates, to those obtained with the ITT population. Because the “dual oral therapy only” portion of the patient-time was shorter than the full study time included in the ITT analyses, and therefore there was less time for events to accrue, 95% confidence intervals were wider with the “dual oral therapy only” analyses than with the ITT analyses.

Additionally, the cardiovascular risk of the patients who withdrew from cardiovascular follow-up was examined, and was compared to that of patients who remained in study. The CV risk of patients who withdrew was also compared between treatment groups. Please see Tables II.C.1.b, II.C.1.e and II.C.1.g. After examination of baseline CV risk factors, baseline history of CV events, and baseline CV medication use, there did not appear to be evidence of preferential loss of high CV risk patients from the RSG group.

An assertion has been made in a published commentary that it is “mathematically implausible” that RSG could have been administered during 88% of the person-years of follow-up, when at end of study, 40% of patients were no longer taking RSG (Nissen 2010). However, the following information from Dr. Hoberman, demonstrates that 88% person-years of follow-up is correct.

Table II.F.6: Follow-up Time for Patients Who Were and Were Not Taking Rosiglitazone at End of Treatment, Rosiglitazone Arm		
	Taking RSG at End of Follow-up?	
	No N=876	Yes N=1344
Total follow-up time (patient-years)	4169	8176
Total follow-up time on RSG (patient-years)	2685	8176

From these numbers, one can calculate:

- The percentage of patients who were no longer taking RSG at end of study at $876/(876+1344) = 40\%$; and
- The percentage of patient-time spent on RSG at $(2685+8176)/(4169+8176) = 88\%$

While it would have been hypothetically desirable for all patients to be able to remain on randomized dual oral therapy until the end of trial, due to the progressive nature of type 2 diabetes, and the near-inevitable requirement for additional glycemic control therapy over time, this would be unrealistic for this length of trial. The use of analyses of both the ITT population and “dual oral therapy only” patient-time population addresses this concern somewhat, and results for these two analysis approaches were similar.

II.F.7. Concern Regarding the Percentage of Patients Who Were Lost to Follow-up

A total of 60 (2.7%) of RSG group patients had unknown vital status at end of study, while 67 (3.0%) of MET/SU patients had unknown vital status.

A discussion of the percentage of patients who were lost to follow-up requires clarification of the follow-up methods in the study.

For patients who withdrew (or were removed per protocol due to insulin initiation or other reasons) from randomized treatment prior to completion of the final study visit, the applicant had additional means of obtaining information on adverse events and vital status. Please see Section II.B for further description of these methods. Per protocol, patients were to have continued follow-up for cardiovascular events even after discontinuation of randomized treatment, with annual visits and telephone contacts every 4 months. Additionally, patients who actually withdrew from study were asked to consent to follow-up for survival status through a tracking substudy. For patients who refused consent, attempts were made to verify survival status through public records.

Please see Table II.C.2.c for a summary of the numbers of patients who were followed in the main study to the final visit, and the numbers of patients who had information obtained by these additional methods after withdrawal from study.

In total, 86% of patients in the RSG group, and 85% of patients in the MET/SU group, completed study to the final visit in the main study, or died. When one adds those patients who withdrew, but not until they had already had a primary endpoint event, 87% of patients in the RSG group, and 87% of patients in the MET/SU group, completed follow-up for the primary endpoint analysis. This means that they either completed the study to the final visit in the main study; or they died; or they withdrew, but not until they had already had a primary endpoint event. If one adds the patients from the tracking substudy, these numbers are 89% for the RSG group and 88% for the MET/SU group. If one adds those patients for whom vital status could be confirmed, 97% of patients in both the RSG and MET/SU groups had confirmed vital status at end of study.

Each of these classifications of follow-up provides a different kind of information. For follow-up for total mortality, information is available for 97% of patients. For cardiovascular follow-up for primary endpoint events throughout study, information is available for 89% of patients. For cardiovascular follow-up to the final visit in the main study, information is available for 87% of patients.

Concern has been expressed that it was possible that patients did not complete a large percentage of protocol-specified study visits. However, as displayed in Table II.C.2.d, over 95% of patients completed at least 90% of protocol-specified study visits.

Additionally, the clinical reviewer carefully examined the baseline cardiovascular risk factors of those patients who completed follow-up for the primary endpoint, and those who did not (see Tables II.C.1.b, II.C.1.e and II.C.1.g). Patients who did not complete CV follow-up from the RSG group did not appear to have had higher baseline CV risk than patients who did not complete CV follow-up from the MET/SU group. Therefore, from a baseline CV risk standpoint, one would not expect the RSG group patients who left CV follow-up to have been potential “high event rate contributors” compared to the MET/SU patients who left CV follow-up. Systematic (or differential) loss of high CV risk patients from the RSG group did not appear to occur.

Baseline CV medication use was also examined among those who did and did not leave study. There was not a pattern, based on baseline CV medication use among those who did and did not leave study, to suggest that high CV risk patients were preferentially lost from the RSG group.

II.F.8. Choice of the Primary Endpoint

Concern has been expressed regarding the choice of the primary endpoint, which was cardiovascular death or cardiovascular hospitalization. In particular, cardiovascular hospitalization may have limitations because:

- it may contain a wide range of disorders, some of which may be unlikely to be related to medication use
- patients may present with more than one cause for a hospitalization
- hospitalization for cardiac procedures may be driven by provider decisions rather than by CV events

The composite of cardiovascular death, MI or stroke (MACE) is more typically relied upon as the primary endpoint in large CV outcomes trials. This was evaluated as a secondary endpoint.

II.F.9. Possibility of Telephone Contact in Lieu of Some Visits

A concern has been expressed that the protocol permitted some study contacts to be made by telephone rather than in person. It is possible that fewer details of events would be elicited in a phone call than in a face-to-face study visit.

II.F.10. Concern Regarding Potential Effect of Complexity of Adverse Event Reporting Process on Ascertainment

Please see the event reporting flow diagrams in Figures II.B.4 and II.B.5. Several observations can be made from these diagrams:

- Event reporting flow was complex. The numerous steps involved left room for error (or under-reporting) at multiple junctures.
- Multiple steps in the event reporting flow were unblinded, leaving open the possibility of reporting bias.
- The Endpoint Data Coordinating Center, Clinical Endpoint Committee, and the Statistics and Programming Team were blinded to treatment assignment. Blinding of these entities was important for trial integrity.
- An audit trail was to be maintained at key steps, including tracking of events that were submitted as potential endpoints; and data entry and queries for the clinical and safety databases. These audit trails are useful in FDA's inspection process to assess for ascertainment and event tracking.

The Division of Scientific Investigations prepared in detail for its inspections to address these issues and others. As of 8 Jun 2010, the results of that inspection are pending.

II.F.11. Concern Regarding Possible “Cross-Over” Effect of Study Design

Concern has been expressed that “cross-over” might have been common in the RECORD trial, which might bias toward a noninferiority finding. In the RSG arm, patients who failed glycemic control on dual oral combination therapy were to have the other “nonbackground” oral agent added. That is, patients who failed glycemic control on MET + RSG were to have SU added, and patients who failed glycemic control on SU + RSG were to have MET added. In the MET/SU arm, the 3rd agent was insulin, and, per protocol, RSG would not have been added in this arm. This design was intended to mimic what would have occurred in “real-world” use under the approved indications in effect in Europe at the time of study initiation. The Agency requested information from the applicant whether any patients in the MET/SU arm had RSG added. A few patients in the MET/SU arm did receive RSG during the randomized treatment phase (during which time it would have been a prohibited medication), or during the post-randomized treatment phase, as displayed in the following table.

Table II.F.11: Summary of Rosiglitazone Use in Patients Randomized to the Add-On Metformin/Sulfonylurea Arm

Rosiglitazone Use Status	Treatment Phase	Category of Use	Metformin/Sulfonylurea Arm N=2227 PY=12,272.1	
			n (%)	RSG PY (% of total PY for arm)
No RSG use at any time during study			2139 (96.0)	12,100.5 (98.6)
RSG use at any time during study	Any treatment phase		88 (4.0)	171.6 (1.4)
	Randomized treatment phase	Any category of use	33 (1.5)	30.2 (0.2)
		Received as randomized treatment by mistake	4 (0.2)	15.1 (0.1)
		Received as prohibited medication	29 (1.3)	15.1 (0.1)
	Post-randomized treatment phase		71 (3.2)	141.4 (1.2)

Source: Applicant's Table 1, NDA 21071 subm 20 May 2010

In total, patients took RSG during 1.4% of patient-years in the MET/SU arm. Per Dr. Hoberman of FDA Biometrics, this amount of patient-time would not alter the results of analyses for the primary endpoint, MACE or MI.

Because of the asymmetric study design regarding addition of a 3rd agent, one cannot rule out some effect of the addition of a 3rd oral agent for patients in the RSG group. However, use of the ITT analysis method still generally permits a comparison of patients who were exposed to RSG to patients who were not exposed to RSG (although acknowledging the small percentage “cross-over” as above), and this was the intent of the “real-world” study design. Also, sensitivity analyses performed using the dual-oral-therapy-only time period generally avoid the problems associated with the asymmetric study design, and were consistent with the ITT findings.

It should perhaps be noted that the circumstance in which cross-over is particularly important is when one of the treatments is known to have a significant effect (either positive or negative) on the endpoint of interest. That was not the case in RECORD, where neither MET nor SU (nor insulin) has been shown definitively to increase or decrease cardiovascular events.

II.F.12. Potential Effect of Publicity and Interim Analysis on Outcome of RECORD

In May 2007, a highly publicized study-level meta-analysis suggested an increased risk of MI and CV death with RSG (Nissen 2007). This publication received a large amount of attention in the media and from Congress. Because of this, the RECORD investigators published an interim analysis (Home 2007), which did not demonstrate a significant difference between RSG and comparator at that point. Questions have arisen regarding whether investigator or patient behavior might have changed (either intentionally or unintentionally) after the publicity and interim analysis. Some explorations regarding this were conducted.

As discussed in Sections II.D.3.b and II.F.4, use of certain cardiovascular medications differed over time between treatment groups. However, this difference was apparent prior to the publicity surrounding RSG,

and did not change after the interim analysis. For example, the difference in statin use was apparent at Year 1 (prior to the interim analysis for all patients), and from Year 2 on (also prior to the interim analysis for all patients), the percentage difference in statin use remained stable over time, at approximately 7-8% at each time point. The same was also true for loop diuretic use and calcium channel blocker use.

A “firewall” was placed at the time of the 2007 interim analysis in order to maintain blinding at the analysis level. The firewall process was detailed by GSK on 17 May 2010 in response to an FDA information request from 15 Apr 2010. The analysis team consisted of two GSK statisticians and one GSK programmer who had not previously worked on RECORD. They were unblinded to patient-level cardiovascular endpoint data on 14 May 2007. An electronic firewall was established by creating a dedicated user group on a server; no one other than the 3 staff members in the user group could have “read” access to the directories used to store the datasets and outputs. This electronic firewall was maintained throughout the remaining duration of the RECORD study. Summary level results were communicated on a controlled basis prior to the interim publication, as described in Section II.F.3.

There has been an assertion that GSK could have made decisions regarding the end date, and planned analysis date, of RECORD based on ongoing (post-interim) knowledge of study results. On 15 Apr 2010, the Agency submitted an information request to GSK with several questions related to this issue. On 17 May 2010, GSK responded that the original planned date for the last patient visit had been May 2008, with data analyses planned for August 2008. However, study recruitment had not been uniform over the two year recruitment period, with more patients recruited in the second year. Based on dates of entry into study, it was calculated that, if the last patient visit occurred in May 2008, median duration of follow-up would be only 5.5 years, rather than the intended 6 years. Therefore, at a Steering Committee meeting on 26 Apr 2005, it was decided to extend the date for “last patient, last visit” to approximately November 2008, when it was expected that a median duration of follow-up of six years would have been reached. This Steering Committee meeting took place over two years prior to Dr. Nissen’s meta-analysis publication and over two years prior to GSK’s interim publication. Final study visits actually occurred over the four month period ending 26 Dec 2008, which included the period two months before and two months after the six-year median follow-up point was reached. The applicant states that decisions regarding when to stop the study and when to formally analyze the data were not made with knowledge of ongoing study results. Stopping criteria had been prespecified in the DSMB charter, and did not change after study initiation.

There has been an assertion in a published commentary (Nissen 2010) that the pattern of event rates reversed after the interim publication, from not favoring RSG to favoring RSG. Dr. Hoberman examined event rates before and after the interim analysis.

Table II.F.12.a: Adjudicated Primary Endpoint Events With Onset¹ Before and After Interim Analysis

	PY		Rate (Events per 100 PY)	
	Before IA	After IA	Before IA	After IA
RSG	9173	2357	2.9	2.2
MET/SU	9186	2327	2.9	2.5

Source: Dr. David Hoberman, FDA Biometrics, 10 May 2010

¹ Includes events which had onset before and after 2007 interim analysis. Some events had onset before the interim analyses, but were not adjudicated until after the interim analysis. These events would be included in the “before IA” columns above. These numbers may therefore differ from those in the published interim analysis, because some events which had already occurred had not yet been adjudicated.

Before the interim analysis, primary endpoint events were occurring at a similar rate in both arms. After the interim analysis, the event rate declined somewhat in both arms, and to a slightly numerically greater degree in the RSG arm.

The following table displays MI rates before and after the interim analysis.

Table II.F.12.b: Adjudicated Myocardial Infarction Events With Onset¹ Before and After Interim Analysis

	PY (# Events)		Rate (Events per 100 PY)	
	Before IA	After IA	Before IA	After IA
RSG	9240 (54)	2943 (10)	0.58	0.34
MET/SU	9255 (48)	2900 (8)	0.52	0.28

Source: Dr. David Hoberman, FDA Biometrics, 10 May 2010

¹ Includes events which had onset before and after 2007 interim analysis. Some events had onset before the interim analyses, but were not adjudicated until after the interim analysis. These events would be included in the “before IA” columns above. These numbers may therefore differ from those in the published interim analysis, because some events which had already occurred had not yet been adjudicated.

At interim, approximately 76% of the trial’s total patient-time had occurred in each arm. For both arms, the rate of onset of MI declined somewhat after the interim analysis. However, it declined to approximately the same degree, and there was not a reversal in the rates. That is, the rate of MI remained numerically somewhat higher in the RSG arm than in the MET/SU arm.

II.F.13. Inclusion of Deaths with Inadequate Data as Cardiovascular Deaths

As discussed in Section II.D.1.b, per protocol, deaths which had inadequate data for assessment of cause of death were presumed to be cardiovascular deaths and were included as events for the primary analysis. However, some of these deaths probably were not cardiovascular in origin. This was recognized by the Steering Committee. As presented in Table II.D.1.b.v, in order to address this, the Steering Committee Chairman performed a post hoc blinded review of these deaths and excluded those which appeared likely to be noncardiovascular in origin (1 RSG, 6 MET/SU). There remained inadequate data to assign a cause of death for a total of 6 other RSG and 7 other MET/SU deaths. This post hoc adjudication would change the total numbers of cardiovascular deaths to 59 (2.7%) for the RSG group, and 65 (2.9%) for the combined MET/SU group.

Inclusion of deaths with inadequate data or unknown cause as CV deaths is common in cardiovascular outcomes trials, but may increase the likelihood of a finding of noninferiority.

II.F.14. Use of an Active Comparator Rather than a Placebo

In RECORD, add-on RSG was compared to add-on MET and/or add-on SU. There was no placebo arm. The study was intended to evaluate RSG as an add-on medication under the conditions of use approved in EMEA countries at the time. In patients who are failing monotherapy, the addition of a placebo is not a treatment option. However, MET and SU have not been shown to have a CV benefit. If MET or SU is associated with CV risk, statistical equivalence of RSG would not be clinically meaningful.

II.F.15. Concern that a Provision That Allowed Earlier Initiation of Insulin for Patients with Very High Hemoglobin A1cs Could Have Resulted in Very Short Follow-up for Some Patients

As mentioned in the description of the trial design, there was a provision in the protocol that if the first HbA1c test was “so high that in the investigator’s judgment it was likely to compromise patient safety”, the patient could be switched to insulin at that earlier point. Concern has been expressed that this could have meant that patients would remain on randomized therapy for a very short period of time, e.g. 8 weeks. However, that did not occur in a significant number of patients. In fact, only 17 total patients (0.4%) initiated insulin at less than 6 months of study (see Table II.D.2.e).

II.F.16. Concern that Applicant May Have Altered Study Conduct Based on Unplanned Unblinded Applicant Analyses

A published commentary has expressed concern that the applicant may have performed non-prespecified analyses during the trial, and then altered conduct of the study based on knowledge of the outcomes of these analyses (Nissen 2010). The Agency has questioned the applicant extensively regarding this allegation, and the applicant has denied performing such analyses. The Division of Scientific Investigations also searched for evidence of such study conduct changes in its inspections, for which a final report is pending as of 8 Jun 2010. Please also see the discussion for Section II.F.12.

II.F.17. Findings From FDA Cardiology Consultation

The Division of Metabolism and Endocrinology Products consulted the Division of Cardiorenal Products, with the following consult questions:

- “1. Were the event definitions appropriate for the components of the primary endpoint, and for other defined major adverse cardiovascular events?
2. Was the adjudication process for major adverse cardiovascular events acceptable?
3. After start of the trial, more patients in the rosiglitazone group initiated a statin than did patients in the overall comparator group. Dr. David Hoberman of Biometrics is performing several analyses to explore the effect of this on interpretability of the trial results. Can you suggest additional analyses to further explore this issue?
4. If the consulting cardiologist notes additional important cardiologic issues which may affect the interpretation of the trial results or the proposed PI language, additional input is welcome.”

During the review process, the cardiology reviewer has expressed other concerns regarding study design and possible underascertainment. As of 8 Jun 2010, the consult report had not been received.

II.G. Summary of Preliminary Findings from RECORD

The RECORD study was a postmarketing commitment study for the European Agency for the Evaluation of Medicinal Products. The design was intended to evaluate the cardiovascular risk of rosiglitazone when used according to European labeling at the time of initiation of the study, and to compare rosiglitazone to the most commonly used drugs (metformin and sulfonylurea) which were available at the time for treatment of type 2 diabetes.

The study included patients with type 2 diabetes who had failed MET or SU monotherapy; those who had failed MET were randomized to receive either add-on RSG or add-on SU, and those who had failed SU were randomized to receive either add-on RSG or add-on MET. A total of 2,220 patients received add-on RSG, and 2,227 patients received one of the add-on regimens not containing RSG. At the time of study initiation, co-administration of insulin and RSG was not permitted under European labeling, and therefore there was an asymmetric study design for “rescue” medication after loss of glycemic control. For patients treated with add-on RSG who failed glycemic control, either MET or SU was to be added as a 3rd agent (MET if background was SU; SU if background was MET). For patients in the add-on MET/SU arm, the 3rd agent for addition/substitution after glycemic failure was insulin. If RSG group patients on triple oral therapy subsequently had loss of glycemic control, insulin was to be added but could not be coadministered with rosiglitazone, because this combination was not permitted in Europe at the time of study initiation. This asymmetry of design resulted in a longer potential time on oral agents for patients in the add-on RSG group than for patients in the add-on comparator group. The primary analysis population was the ITT population. However, additional analyses were performed for the patient-time period that included only randomized dual oral combination therapy. This provided

sensitivity analyses using a patient-time period that did not have the complicating factor of differential time to (and incidence of) insulin initiation.

The study was open-label, in that individual investigators and patients knew which drugs that patients were taking. However, adjudication of cardiovascular endpoints was performed by a blinded endpoint adjudication committee. Event definitions were prespecified.

A total of 4447 patients were randomized and received at least one dose of study medication. Among patients entering the study on background metformin, 1117 were randomized to the addition of RSG, and 1105 were randomized to the addition of SU. Among patients entering the study on background SU, 1103 were randomized to the addition of RSG, and 1122 were randomized to the addition of MET. The total number of patients in the combined RSG group was 2220, and the total number of patients in the combined non-RSG (MET/SU) group was 2227. At study end, vital status was known for 97.1% of patients, with equal distribution of loss to follow-up between stratified groups. Some of these patients for whom vital status was known had stopped going to study visits and vital status was ascertained by other means. When one excludes these patients, a total of 88.8% of RSG group patients and 87.8% of comparator group patients continued through study until final study visit or death.

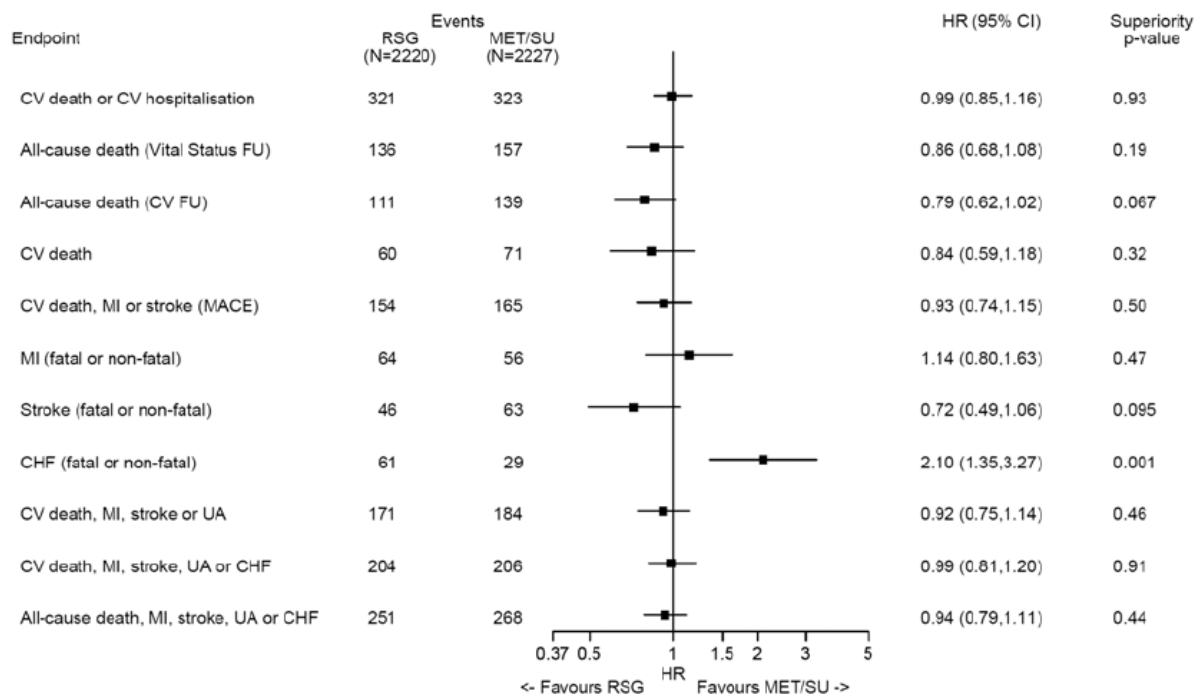
As is usual with patients with type 2 diabetes, additional therapy was required over time in a substantial proportion of patients. The combination of insulin and rosiglitazone was not permitted in Europe at the time of study initiation. Therefore, once a patient required insulin, they were no longer considered to be on their randomized therapy in either treatment group. A total of 61% of RSG patients and 51% of comparator group patients completed study to the final visit on randomized treatment. However, the proportion of total study cardiovascular follow-up time that was spent on randomized treatment was 88% for RSG (75% on dual oral, 13% on triple oral), and 83% for MET/SU (all on dual oral per asymmetric study design). Mean follow-up for CV risk, in patient-years, was similar for RSG (5.56) and MET/SU (5.51).

Baseline demographics and cardiovascular risk factors were balanced between treatment groups. The overall baseline cardiovascular risk of the population was low compared to other cardiovascular outcomes studies involving patients with type 2 diabetes. The clinical reviewer also examined the baseline demographics and CV risk factors of patients who did and did not complete study for the primary endpoint, in order to assess whether there was evidence of differential withdrawal of high CV risk patients from the RSG group. No pattern of differential risk among withdrawn patients was detected.

The primary endpoint was the time to first occurrence of adjudicated cardiovascular death or adjudicated cardiovascular hospitalization, among all patients who were randomized and received at least one dose of study medication. For this endpoint, the hazard ratio was 0.99, favoring rosiglitazone, with a 95% CI of 0.85-1.16. This upper bound of 1.16 met the prespecified noninferiority margin. Results by study stratum (background SU and background MET) were similar. Results using only time on randomized dual oral therapy were also similar (HR 1.02, 95% CI 0.85-1.21). Multiple baseline subgroups were analyzed, and there was no evidence of an interaction by baseline subgroup status for most categories, including for baseline nitrate use or angiotensin converting enzyme use. For a baseline history of ischemic heart disease, the interaction p-value was 0.055, with a higher point estimate (1.26) among those with a prior history of ischemic heart disease. When one examined the types of events which occurred more commonly among patients with ischemic heart disease, the difference between RSG and comparator was primarily accounted for by heart failure events, with unstable angina events contributing to a lesser degree. Among patients with a prior history of ischemic heart disease, myocardial infarction rates did not differ between RSG and comparator, and point estimates for cardiovascular death and total mortality favored RSG.

Multiple secondary cardiovascular endpoints were examined, as displayed in the following Forest plot.

Figure II.G.1: Forest Plot of Hazard Ratios and 95% Confidence Intervals for Cardiovascular Outcomes, ITT Population



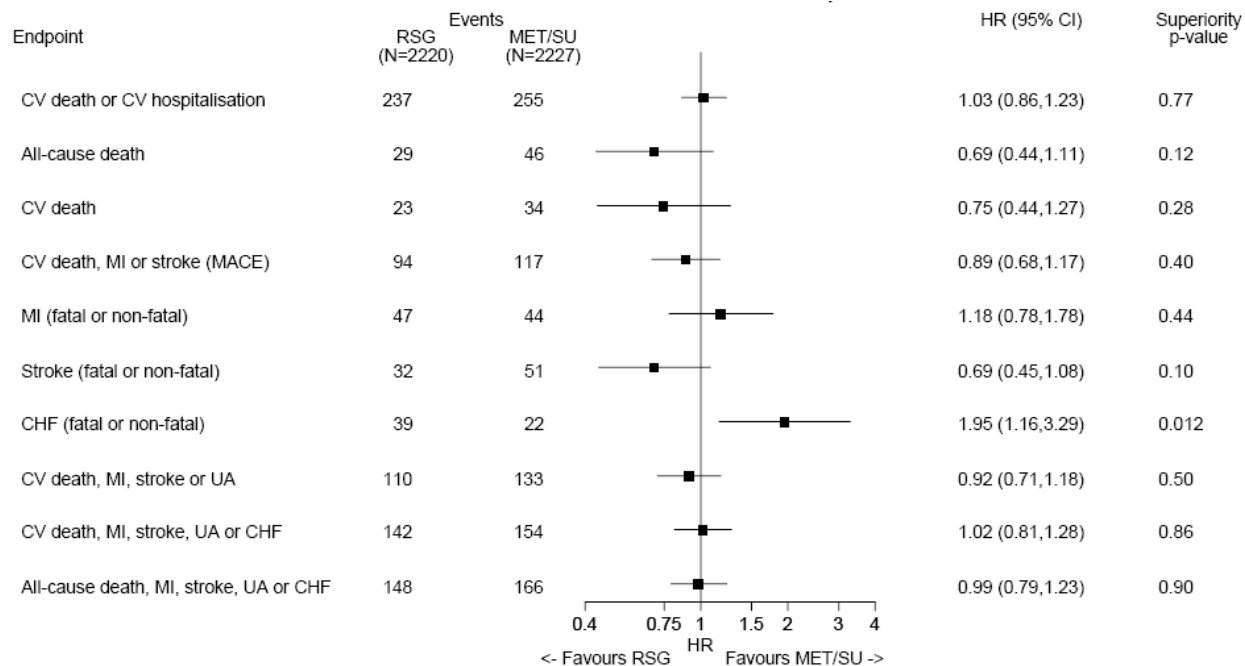
UA-unstable angina

Source: Applicant's Figure 10, pg 161, RECORD study report body

Heart failure occurred statistically significantly more commonly among rosiglitazone-treated patients than among comparator-treated patients. There were no other statistically significant differences between rosiglitazone and comparator. All other cardiovascular composites and components had point estimates <1, favoring rosiglitazone, except for myocardial infarction, which had a point estimate of 1.14, not favoring rosiglitazone, with a statistically nonsignificant result (95% CI 0.80, 1.63; p-value 0.47).

The following Forest plot displays these same cardiovascular endpoints, this time for the patient-time population of dual oral combination therapy only.

Figure II.G.2: Forest Plot of Hazard Ratios and 95% Confidence Intervals for Cardiovascular Outcomes, “Per-Protocol” Analyses (Time on Randomized Dual Oral Combination Therapy Only)



Source: Applicant's Figure 7.2.1, pg 5674, RECORD study report body

In general, the point estimates for this patient-time period were very similar to those for the ITT population, except for all-cause mortality, which favored RSG more strongly for the dual oral therapy patient-time population than for the ITT population (HR 0.69 dual vs 0.86 ITT). However, confidence intervals for this endpoint for both populations included 1. As one might expect in a population with less patient-time and therefore fewer events, confidence intervals for the dual oral therapy patient-time analyses were somewhat wider than for the ITT analyses.

For both the ITT and dual oral therapy populations, heart failure occurred statistically significantly more commonly among RSG-treated patients than among comparator-treated patients. Death attributed to heart failure occurred among 10 RSG-treated patients and among 2 add-on MET patients.

For myocardial infarction, point estimates did not favor RSG, with a statistically nonsignificant difference between RSG and comparator. There was no evidence of a statistical interaction by baseline subgroup characteristics, including by baseline history of ischemic heart disease and by baseline use of nitrates and angiotensin-converting enzyme inhibitors.

For the MACE composite, the hazard ratio favored rosiglitazone (0.93; 95% CI 0.74, 1.15). When considering only time on randomized dual oral combination therapy (a “per protocol” analysis), the point estimate was slightly lower than that for the ITT population analysis, favoring RSG, and the upper bound of the 95% confidence interval was similar (HR 0.89, 95% CI 0.68-1.17). For both the ITT and “per protocol” analyses, the 95% CI upper bounds would have met the criteria, under the new diabetes CV safety evaluation Guidance, for demonstration that a drug is not associated with an unacceptably increased risk for major adverse cardiovascular events.

Patients in the RSG group had a longer duration of time until glycemic failure, defined as two consecutive HbA1cs $\geq 8.5\%$. This was true for both strata, and particularly for RSG vs SU.

Initiation of insulin occurred more commonly among comparator-treated patients than among RSG-treated patients, but this must be considered in the context of the asymmetric study design.

Mean low-density lipoprotein cholesterol increased in the first six months of therapy for the RSG group, and then declined over time. Mean LDL declined over time throughout study for comparator group patients. Mean LDL remained higher among RSG-treated patients than among comparator-treated patients throughout study, despite a higher rate of on-study initiation of statins in the RSG group.

At the beginning of study, statin use was equal between treatment groups (18% in RSG grp, 19% in MET/SU grp). Over time, use of statins became more common among patients in the overall RSG group. At the end of cardiovascular follow-up, 50.7% of patients in the overall RSG group were taking a statin, compared to 42.2% of patients in the overall MET/SU group. This difference in statin use was apparent at Year 1, and from Year 2 on, the percentage difference in statin use remained stable over time, at approximately 7-8% at each time point.

If one assumes hypothetically that all patients who started a statin had the full 25% risk reduction that would be expected based on other studies of statins, the 8% difference in use of statins would be expected to alter the observed primary endpoint hazard ratio (0.99) by only 0.02, with no change in the statistical significance of the non-inferiority conclusion.

Although statin use was higher in the RSG group over time, levels of low density lipoprotein cholesterol remained higher in the RSG group. Therefore, the differential statin use did not convey an LDL advantage for the RSG group.

Although analyses of most categories of adverse events of special interest displayed very similar results to those in the current FPI, a difference in incidence of adverse renal events between treatment groups occurred in RECORD, and is not described in the current FPI. Renal adverse events occurred less commonly among RSG-treated patients than among comparator-treated patients (rates per 100 PY during randomized dual oral therapy RSG 0.97 [0.78, 1.19], MET/SU 1.50 [1.27, 1.76]). The 95% confidence intervals for the incidence rates of renal events did not overlap for this comparison. Events of microalbuminuria (0.9% RSG vs 1.8% MET/SU) and albuminuria (0.1% RSG vs 0.8%) occurred numerically less frequently among RSG-treated patients than among comparator-treated patients; this was also true for both strata. Events of diabetic nephropathy occurred numerically less frequently among RSG-treated patients than among comparator-treated patients (1.0% vs 1.6%); and in the background SU stratum, diabetic nephropathy occurred numerically less frequently among RSG-treated patients than among MET-treated patients (0.9% vs 2.0%).

Urinary albumin:creatinine ratio was a predefined efficacy endpoint. At most timepoints throughout study, mean alb:cr favored (i.e. was lower for) RSG-treated patients, with a statistically significant difference. This result was consistent by stratum.

Rosiglitazone was associated with slightly numerically greater declines from baseline in systolic blood pressure, diastolic blood pressure and heart rate, but standard deviations were large.

Rosiglitazone was associated with a statistically significant increase in body weight compared to both SU and MET.

Concerns which may limit the interpretability of RECORD are discussed above in Section II.F. Some issues include:

- Overall complexity of the trial design, particularly in regard to the noninferiority comparison, the open-label nature of the trial for patients and caregivers, and an asymmetric design with regard to the addition of 3rd agents for glycemic rescue

- An observation that the overall rate of myocardial infarction seemed low, and could have reflected underascertainment, although the rate reflected, at least in part, the low risk of the patient population.
- A higher rate of statin initiation among rosiglitazone group patients, although it appears that this did not confer an LDL advantage, and mathematically speaking, would not have altered the statistical conclusion of noninferiority
- Concern regarding the percentage of patients who were not taking their original randomized dual oral combination therapy at end of study. This was due in part to the protocol-specified removal of patients from their randomized groups after insulin initiation (as necessitated by the EMEA proscription against concomitant use of RSG and insulin at the time of study initiation), and was not solely due to withdrawal for adverse events or other drop-outs. Sensitivity analyses involving only the time on dual oral therapy addressed this concern somewhat, and results were similar to those for the ITT population.
- Concern regarding a possible cross-over effect of the study design. It appears that this did not occur in a large percentage of patients. This effect could have been more concerning if either of the comparators was known to have a significant effect, either positive or negative, on cardiovascular outcomes, but this is not the case.
- Concern regarding possible effects of publicity and a 2007 interim analysis on the study outcome. Patients and investigators were aware of the negative publicity regarding rosiglitazone in 2007, and some alteration in study behavior, either intentional or unintentional, was possible. Patient retention after this time was reasonable. The rate of reporting of new onset events after this time was somewhat lower than before this time, but the relative incidence between RSG and comparator was similar.

Some potential strengths of RECORD, when compared to other sources of cardiovascular safety regarding rosiglitazone, include:

- It provides a large patient-year exposure
- Since it is a single trial, randomization is preserved, and RECORD did not have the issues of statistical heterogeneity that occurred for the meta-analysis and of unmeasured confounders for observational studies
- Blinded endpoint adjudication occurred
- “Hard” cardiovascular endpoints, such as stroke and MI, were included
- More MACEs occurred in RECORD than in all trials in the 2007 FDA meta-analysis combined, and therefore estimates were more robust and not subject to change with the addition or subtraction of only a few events
- Use of an active comparator, while also discussed as a limitation, provides a comparison involving the usual choice a practitioner would be faced with in a patient who is failing monotherapy, i.e., in the clinic, one cannot add a placebo to the care of a patient who has inadequate glycemic control on a single agent
- Despite negative publicity following the 2007 NEJM meta-analysis, patients did not leave the trial in large numbers subsequent to this publication
- Subgroup analyses were generally consistent with the primary analysis and analyses for MI, and did not demonstrate a statistical interaction by most baseline characteristics
- “Per-protocol” analyses that included the “clean” time period on dual oral combination therapy were generally consistent with findings from the ITT analyses
- The upper bound of the 95% confidence interval for MACE (for both ITT and “per protocol” analyses) would meet the Agency standards for demonstration that rosiglitazone is not associated with an unacceptably increased risk of major adverse cardiovascular events
- Total mortality, which generally does not require adjudication and is associated with fewer problems with ascertainment, favored rosiglitazone

III. Briefing Document Summary

Please see Section IV of the Appendices for a discussion of information that was available at the time of the 2007 Advisory Committee meeting.

A 2007 FDA meta-analysis of 42 randomized, double-blinded, controlled trials (median duration 6 months) of rosiglitazone was consistent with an increased risk of myocardial ischemic events, most of which were angina, for rosiglitazone versus comparator. The meta-analysis did not detect a statistically significant increase in risk for myocardial infarction; for the composite of cardiovascular death, myocardial infarction or stroke (MACE); or for total mortality.

At the time of the 2007 meta-analysis, preliminary data were available from two completed longterm rosiglitazone clinical trials (DREAM and ADOPT), and interim data were available from RECORD. In 2007, the median duration of these trials was 41 months. Analyses of these trials did not detect statistically significant differences between rosiglitazone and comparator for risk of myocardial infarction, MACE, cardiovascular mortality, or total mortality. Point estimates for myocardial infarction generally exceeded 1. Point estimates for MACE, CV mortality and total mortality were <1.

At the time of the interim analysis, the event rate for RECORD had been lower than anticipated, and there was concern that the study would be uninterpretable upon completion. At study end, however, RECORD did have sufficient power for the applicant to conclude that add-on rosiglitazone was noninferior to add-on metformin or add-on sulfonylurea for risk of the primary endpoint, which was cardiovascular death or cardiovascular hospitalization. Rosiglitazone was associated with a statistically significantly greater risk of heart failure. Multiple other cardiovascular endpoints were examined, and for most of these, point estimates favored rosiglitazone, and there was not a statistically significant difference between rosiglitazone and comparator. For myocardial infarction, the point estimate was 1.14, not favoring rosiglitazone, but this difference was not statistically significant (95% CI 0.80-1.63, p-value 0.5). The results for the MACE composite (HR 0.93, 95% CI 0.74-1.15, p-value 0.5) would have met the Agency's criteria, under a Guidance for evaluation of the cardiovascular safety of diabetes drugs, for evidence that rosiglitazone is not associated with an unacceptably increased risk of major adverse cardiovascular events.

As mentioned earlier, at the time of the interim analysis, it was assumed by some that RECORD would turn out to be uninterpretable. A major question that now exists is whether it is indeed interpretable. The RECORD study has received an extraordinary degree of scrutiny, and multiple parties have identified potential limitations to interpretability of the trial. These include the study's open-label design, concerns about the number of patients who were no longer taking their randomized treatment at end of study (partly related to initiation of insulin and partly to true drop-outs), a higher rate of initiation of statins among rosiglitazone-treated patients than among comparator-treated patients, a rate of myocardial infarction that some feel is low, and other issues which are discussed further in the briefing document. The Division of Metabolism and Endocrinology Products looks forward to the Advisory Committee's discussion of the significance of the various potential limitations, and seeks their opinion regarding whether RECORD's results can be considered to be interpretable.

Please see Sections V and VI of the Appendices for discussions of additional data, apart from RECORD, that have become available since the 2007 Advisory Committee meeting.

Final review of ADOPT, and preliminary review of the final study report for DREAM, are consistent with the results described above for data available at the time of the 2007 Advisory Committee meeting.

While data from large randomized clinical trials (if properly conducted) are generally considered to be of a higher level of evidence than other types of clinical data sources, other information is expected to be included in the briefing document from an updated FDA meta-analysis, now with 52 trials of rosiglitazone;

from an FDA meta-analysis of trials of pioglitazone; from a recently conducted observational study which used a database from the Centers for Medicare and Medicaid Services; and from a summary of published observational studies for which the Agency does not have datasets for independent verification of results.

Although the results of RECORD, on their face, would have met the Agency's criteria for evidence that rosiglitazone is not associated with an unacceptably increased risk for major adverse cardiovascular events, there continue to be differences of opinion in this regard. The ongoing TIDE study is a large, randomized, double-blind, placebo- and active- controlled cardiovascular outcomes trial, the design of which does not contain many of the limitations of the RECORD study. It is double-blinded and compares the risk of add-on rosiglitazone not only to placebo, but also to pioglitazone, the only other approved thiazolidinedione. The study population has higher cardiovascular risk and is expected to have a higher event rate. The study is conservatively powered. This trial, if it continues to completion, has the potential to address the question of the cardiovascular safety of rosiglitazone more definitively. The Division of Metabolism and Endocrinology Products looks forward to discussion of the advisability of continuation of TIDE.

APPENDICES

IV. Summary of Cardiovascular Safety Information Available at the Time of the Previous (July 2007) Advisory Committee Meeting Regarding the Cardiovascular Safety of Rosiglitazone

IV.A. Meta-analysis of Myocardial Ischemic Events from 42 Clinical Trials of Rosiglitazone

The findings of this meta-analysis were the basis of the concern regarding myocardial ischemic event risk.

Dr. Joy Mele conducted a carefully constructed patient-level meta-analysis, which included numerous sensitivity analyses. The meta-analysis included all double-blind, randomized, controlled trials of RSG that were available up to the time of the meta-analysis; at that time, there were 42 trials. It did not include any large longterm trials, because these trials had not been complete at the time of the meta-analysis.

The meta-analysis included a total of 14,237 patients, and a total rosiglitazone exposure of 4,143 patient-years. Mean duration of the trials was 6 months, and 38/42 trials were ≤ 6 months in duration. Except for one study conducted in heart failure patients, the included trials were not cardiovascular outcomes studies, but rather were trials of glucose-lowering efficacy in type 2 diabetes.

The endpoint used in the meta-analysis was the same as that used by GSK in a previous pooled studies analysis of the same clinical trials. In the interest of sensitivity, GSK had used a broad endpoint of dozens of potential myocardial ischemic event terms, such as myocardial infarction, cardiac arrest, chest pain, coronary artery occlusion, angina, etc. About 2/3 of the actual events which occurred were angina events. Ms. Mele defined meta-groups by comparator agent to allow logical evaluations of rosiglitazone effect. For example, there was a meta-group of trials where rosiglitazone (RSG) plus sulfonylurea (SU) were compared to placebo (PBO) plus SU.

The primary endpoint included all terms in the broad composite of myocardial ischemic event terms, included serious and nonserious events, and included all meta-groups. There was statistical heterogeneity among trials. The overall result suggested an increased risk for RSG vs comparator. A total of 2% of RSG-treated patients had an event from the broad composite, compared to 1.5% of patients in the comparator agent groups. The odds ratio was 1.4 and the difference between RSG and comparator was statistically significant (95% CI 1.1, 1.8). As mentioned earlier, about 2/3 of the events

which contributed to the analysis were angina events, and most were nonserious by the regulatory definition. (Briefly, the regulatory definition of serious adverse events includes those events which result in death, significant disability, or hospitalization.)

Although the overall comparison, as described above, showed statistical significance, multiple comparisons of interest did not show a statistically significant difference between rosiglitazone and comparator:

- RSG versus active comparator (i.e., excluding placebo-controlled trials)
- the endpoint of myocardial infarction (MI) alone
- the endpoint of total mortality
- the MACE endpoint (cardiovascular death, MI or stroke)
- the subset of serious myocardial ischemic events from the broad composite

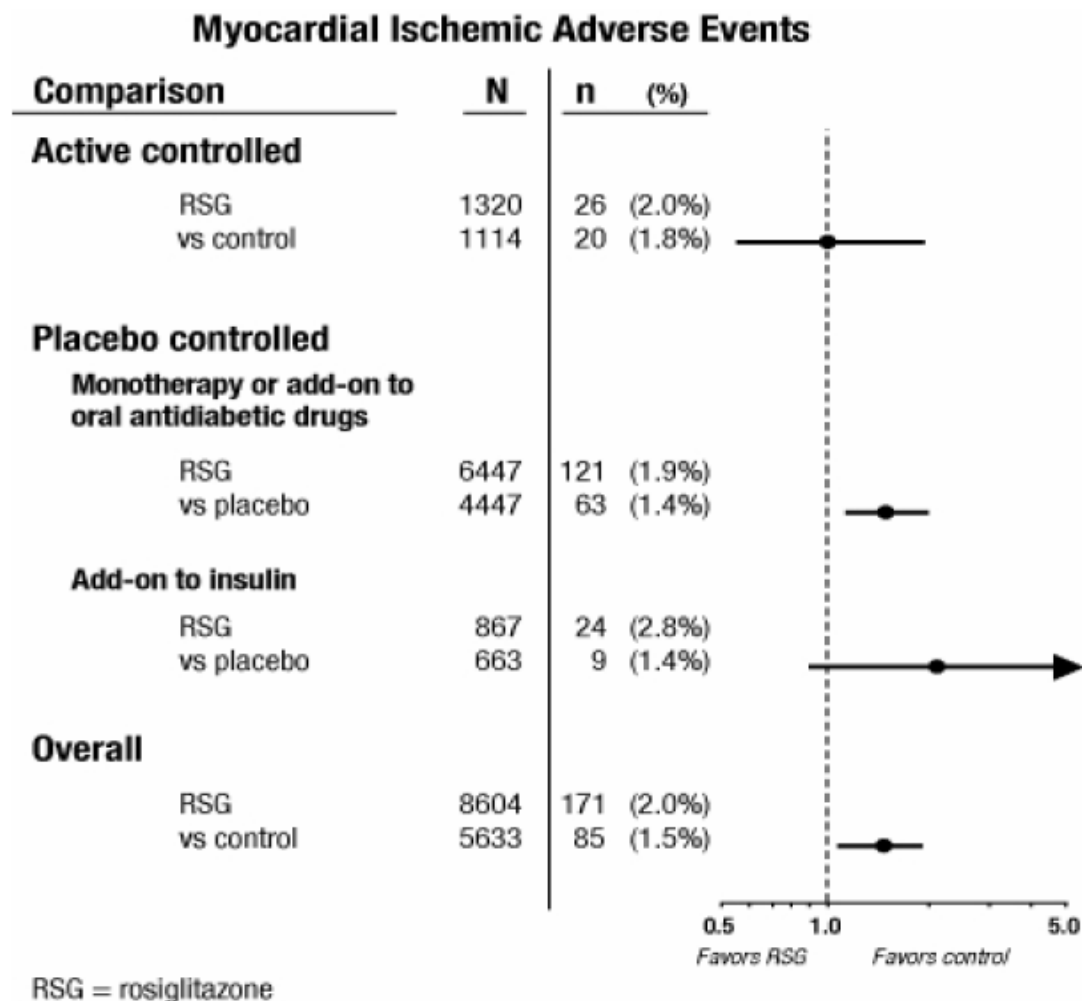
It should be noted that, for most comparisons, the overall number of events was small, and it is possible that a difference could have existed which was not detected.

When one examined only trials in which RSG was compared to placebo, e.g. when either RSG or PBO was added to another agent, the difference between RSG and comparator remained statistically significant. However, when RSG was compared to other active antidiabetic drugs, e.g. to SU, or to metformin (MET), there was not a statistically significant difference between treatment groups.

Ms. Mele looked at multiple factors to try and assess for possible higher risk subgroups. As mentioned above, Ms. Mele examined meta-groups by comparator agent. This identified a possible high-risk subgroup, namely patients for whom rosiglitazone was added to established insulin therapy. The incidence of the broad event composite among patients who had RSG added to insulin was 2.8%, while that for patients who had PBO added to insulin was 1.4% (OR 2.1, 95% CI 0.9, 5.1).

The following figure illustrates the meta-analysis findings discussed thus far:

Figure IV.A: Myocardial Ischemic Events in an FDA Meta-analysis of 42 Clinical Trials of Rosiglitazone



In addition to dividing patients into meta-groups by type of comparator, Ms. Mele also looked at many kinds of baseline characteristics, such as CV risk factors, medications, etc. For essentially all of these subgroups, there was no evidence of a statistical interaction by baseline characteristics. That is, the odds ratios generally slightly exceeded 1, but not statistically significantly so, whether the baseline characteristic was present or not. However, one baseline characteristic did make a difference, namely nitrate use. Only a small percentage (4%) of patients were taking nitrates at baseline- 361 for RSG and 244 for controls. However, this small group had an odds ratio of 2.9 (95% CI 1.4, 5.9). Taking out this small group of patients rendered the overall meta-analysis results statistically nonsignificant, although the odds ratio remained >1 (OR 1.3; 95% CI 0.9, 1.7; total number of patients not on nitrates 13,362). In a meta-analysis, it is undesirable (in terms of confidence in the robustness of the results) to see a loss of statistical significance with removal of a small subgroup of patients. The interaction by nitrate use was examined for other endpoints, and was not significant for MI, MACE, or when analyzing only serious events. One might wonder if nitrate use was simply a marker for underlying coronary heart disease. However, Ms. Mele also analyzed by baseline history of coronary heart disease, and patients with baseline coronary heart disease who were not taking nitrates did not exhibit this statistical interaction.

Ms. Mele also commented on the robustness of the overall meta-analysis data. Supporting robustness was the observation in subgroup analyses that the odds ratio point estimate was generally greater than 1.0. Robustness was not supported in other ways:

- Ms. Mele used multiple methods of analysis. Odds ratio estimates varied depending on method of analysis and endpoint used, with loss of statistical significance and/or reduction of odds ratio by other methods.
- There was statistical heterogeneity among trials.
- The exploratory endpoint used was a broad group of myocardial ischemic events of varying clinical severity, rather than a standard clinical trial major cardiovascular outcome endpoint. The majority of these events were angina, not major cardiovascular events. Results were marginally statistically significant for the broad exploratory myocardial ischemic event endpoint (including angina), but were not significant for more commonly used major cardiovascular outcome endpoints (e.g. MACE [cardiovascular mortality + myocardial infarction + stroke] or myocardial infarction alone or mortality alone).
- Results for the meta-analysis exploratory endpoint were significant only when one included nonserious events, and not when serious events from the broad composite were examined separately.
- Exclusion of a small number of high risk patients rendered the results statistically nonsignificant (e.g., with exclusion of nitrate users, who comprised only 4% of the total database).
- The overall number of events was small, rendering estimates of risk unstable.
- The magnitude of the risk effect was small, with a 95% CI upper bound of <2.
- Calculated absolute risk differences were small.

Thus, the FDA's meta-analysis was consistent with a signal of a small increase in absolute risk for myocardial ischemic events, most of which were angina events. This risk was seen only when combining serious and nonserious events, and not when serious events alone were considered. The risk appeared higher for patients who were taking insulin or nitrates at baseline. Increased risk was not observed for the endpoints of myocardial infarction alone, total mortality alone, or the MACE composite of myocardial infarction (MI) + stroke + cardiovascular (CV) death. The findings were not statistically robust.

IV.B. Data from Larger Longterm Randomized Controlled Prospective Trials of Rosiglitazone (Trial Data Available Prior to Submission of Final RECORD Study Report)

In the FDA's meta-analysis, as with many meta-analyses, heterogeneity among included trials limited the interpretability of the data. After a meta-analysis of smaller trials, it is desirable to search for larger prospective trials in which one can analyze for the signal in a larger population for whom randomization is truly preserved. After submission of the original pooled data for the 42 trials on which the meta-analysis was conducted, data from 3 larger longer-term prospective controlled clinical trials of RSG became available. These trials were analyzed separately from the meta-analysis. They included ADOPT, DREAM and interim data from RECORD (abbreviations expanded in trial descriptions below).

Together, available data from these 3 trials at the time of the RECORD interim included a total of 14,067 patients (RSG N=6,311; comparator N=7,756). Patient-year exposure to that date was 21,803 for RSG and 25,998 for comparator. Mean duration of follow-up was 41 months (>3 years in each of the 3 trials). That patient-year exposure was >5-fold that of all trials in the meta-analysis combined, and mean duration of follow-up was >6-fold that of the combined trials in the meta-analysis.

The ADOPT study (A Diabetes Outcomes Progression Trial) was a 4- to 6- year randomized, active-controlled study in patients recently diagnosed with type 2 diabetes, who were naïve to diabetes drug therapy. It was an efficacy and general safety trial that was designed to examine the durability of AVANDIA (N=1,456) as monotherapy for glycemic control in patients with type 2 diabetes, with comparator arms of sulfonylurea (SU) monotherapy (N=1,441) and metformin (MET) monotherapy

(N=1,454). Preliminary results which were discussed at the time of the 2007 AC meeting are discussed in this section; final review results are discussed in Section V.A.

The DREAM study (Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication); was a 3- to 5- year randomized, placebo-controlled study in patients with impaired glucose tolerance and/or impaired fasting glucose. It had a 2x2 factorial design, intended to evaluate the effect of RSG, and separately of ramipril (an angiotensin converting enzyme inhibitor [ACEI]), on progression to overt diabetes. In DREAM, 2,635 patients were in treatment groups containing RSG, and 2,634 were in treatment groups not containing RSG.

At the time of 2007 Advisory Committee meeting, interim results had recently been published for RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemic in Diabetes; Home 2007), which was then ongoing with an average treatment duration to that date of 3.75 years. Please see Section II.B for a more extensive description of the study design of RECORD. The RECORD study included patients with type 2 diabetes who had failed MET or SU monotherapy; those who had failed MET were randomized to receive either add-on RSG or add-on SU, and those who had failed SU were randomized to receive either add-on RSG or add-on MET. A total of 2,220 patients received add-on RSG, and 2,227 patients received one of the add-on regimens not containing RSG.

The BARI 2D trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes), sponsored by the National Institutes of Health, was designed to test whether prompt revascularization with intensive medical therapy, or intensive medical therapy alone, was superior for management of stable ischemic heart disease in patients with type 2 diabetes mellitus. The trial stratified by type of revascularization procedure (coronary artery bypass grafting vs percutaneous coronary intervention). Simultaneously, BARI 2D also evaluated whether “insulin-providing” or insulin-sensitizing medical therapy was superior. The trial included 2368 patients, and the mean duration of follow-up was 5.3 years. At the 3-year follow-up point, rosiglitazone was being administered to 55.1% of patients in the insulin-sensitizing group, and to 2.9% of patients in the insulin-providing group. The trial was not designed to evaluate individual drugs, but rather an overall strategy of insulin provision vs insulin sensitization. However, the fact that a large percentage of patients in the trial were receiving RSG, with markedly more use in the insulin-sensitizing arm, prompted the trial’s DSMB to examine the data in order to assure study subject safety after publicity regarding concerns about the cardiovascular safety of rosiglitazone.

The PROactive trial was a cardiovascular outcomes trial of pioglitazone, which had a randomized, double-blind, placebo-controlled, parallel group design. A total of 5,238 patients participated, with 2,605 in the pioglitazone treatment group, and 2,633 in the placebo group. Patients were men and women with type 2 diabetes who had a hemoglobin A1c value at entry of >6.5%. All patients had a history of macrovascular disease, which was predefined. Study treatments were added to the patients’ entry diabetes medications. Patients were randomized to the addition of pioglitazone or a matching placebo. The mean duration of treatment was 34.5 months.

For the 3 longterm trials of rosiglitazone at that point, data for minor endpoints such as nonserious angina were not available, and therefore the broad endpoint used for the meta-analysis could not be utilized. The data sources at the time of the 2007 AC were heterogeneous, and a variety of endpoints had been used to assess cardiovascular safety. In the meta-analysis of pooled short-term diabetes studies, the major endpoints used to assess myocardial ischemic event risk were retrospectively-defined groupings of a large number of adverse event terms. In DREAM, RECORD, and PROactive, there were predefined and adjudicated composite and individual endpoints, but the exact composites differed from study to study. Biometricians and clinicians, both within and outside of the FDA, suggested that use of a common composite endpoint could allow for a better perspective on the risk information provided by these data sources. There were many endpoints which could have been considered. In large cardiovascular outcome trials, composite endpoints are often used which contain individual endpoints

which are felt to be important serious events for which there is a relatively good likelihood that the assigned event term actually represents the event in question. One endpoint that is commonly used in cardiovascular outcome trials is a composite of cardiovascular death, myocardial infarction and stroke, sometimes referred to as the MACE (Major Adverse Cardiovascular Events) endpoint. After discussions with the FDA regarding the desirability of utilizing a common endpoint across data sources, GSK performed analyses using a composite of cardiovascular death, serious adverse events of myocardial infarction, and serious adverse events of stroke. FDA Biometricians also performed analyses of this composite endpoint. These analyses have significant limitations: some events were adjudicated and some were not; inclusiveness of terms in the composite was difficult to confirm and compare; and the heterogeneity of the study populations limited comparability. However, there was felt to be some value in assessing whether the estimates for cardiovascular risk generally trended in the same direction across data sources. The following table displays results of MACE analyses for trial data available at the time of the 2007 AC.

Table IV.B.1: Analyses of a Composite of Cardiovascular Death, Myocardial Infarction and Stroke ("MACE"), and Its Components, for the Rosiglitazone Pooled Studies Meta-Analysis, and for the Large Longterm Thiazolidinedione Clinical Trials that Were Available at the Time of the 2007 Advisory Committee Meeting

			HR or OR (95% CI), p-value			
Data Source	Comparison	Analysis Model	CV Mort + MI + Stroke ("MACE")	CV Mort	MI	Stroke
Meta-analyses of pooled diabetes treatment studies ¹	ALL RSG vs ALL CONTROL	GSK model	HR 1.161 (0.773, 1.744), p=0.4731	HR 1.914 (0.790, 4.635), p=0.1502	HR 1.590 (0.934, 2.706), p=0.0875	HR 0.475 (0.231, 0.976), p=0.0428
		FDA exact model (excludes studies with zero events in both arms)	OR 1.2 (0.8, 1.8), p=0.4	OR 1.7 (0.7, 5), p=0.2	OR 1.5 (0.9, 2.7), p=0.11	OR 0.6 (0.2, 1.2), p=0.10
		FDA MH model (no studies excluded)	OR 1.15 (0.8, 1.6), p>0.3			
ADOPT ²	RSG vs SU	GSK model	HR 1.188 (0.739, 1.908), p=0.4771	HR 0.582 (0.190, 1.783), p=0.3429	HR 1.518 (0.785, 2.938), p=0.2149	HR 0.944 (0.430, 2.071), p=0.8849
		FDA Model	HR 1.2 (0.7, 1.9), p=0.3	HR 0.6 (0.2, 1.9), p=0.4	HR 1.6 (0.8, 3.1), p=0.17	HR 0.9 (0.4, 2.1), p=0.9
	RSG vs MET	GSK model	HR 1.109 (0.709, 1.735), p=0.6500	HR 1.304 (0.350, 4.859), p=0.6929	HR 1.227 (0.677, 2.221), p=0.5004	HR 0.773 (0.376, 1.593), p=0.4860
		FDA model	HR 1.1 (0.7, 1.8), p=0.6	HR 1.3 (0.4, 5), p=0.7	HR 1.3 (0.7, 2.3), p=0.4	HR 0.8 (0.4, 1.6), p=0.5
DREAM ³	ALL RSG vs ALL CONTROL (RSG group + RSG+RAM group vs PBO group + RAM group)	DREAM investigators model	HR 1.39 (0.81, 2.37), p=0.2	HR 1.20 (0.52, 2.77), p=0.7	HR 1.66 (0.73, 3.80), p=0.2	HR 1.39 (0.44, 4.40), p=0.6
		FDA model	OR 1.44 (0.82, 2.58), p=0.23	OR 1.20 (0.47, 3.11), p=0.83	OR 1.78 (0.74, 4.58), p=0.23	OR 1.40 (0.38, 5.60), p=0.77
	RSG group vs PBO group	FDA model	OR 1.07 (0.48, 2.4), p=1	OR 1.00 (0.23, 4.34), p=1	OR 0.83 (0.20, 3.27), p=0.77	OR 1.66 (0.32, 10.7), p=0.73
	RSG+RAM group vs RAM group	FDA model	OR 2.02 (0.86, 5.12), p=0.09	OR 1.41 (0.38, 5.63), p=0.58	OR 3.70 (0.97, 20.7), p=0.03	OR 1.00 (0.07, 13.8), p=1
RECORD interim analysis ⁴	ALL RSG vs ALL CONTROL	GSK with only adjudicated events	HR 0.97 (0.73, 1.29), p=0.83	HR 0.83 (0.51, 1.36), p=0.46	HR 1.16 (0.75, 1.81), p=0.50	Component analysis not published
		GSK with all events (adjudicated and nonadjudicated)	HR 0.96 (0.74, 1.24), p=0.74	HR 0.80 (0.52, 1.24), p=0.32	HR 1.23 (0.81, 1.86), p=0.34	Component analysis not published
PROactive ⁵	ADD-ON PIO vs ADD-ON PBO	Takeda model	HR 0.82 (0.70, 0.97), p=0.0201	HR 0.94 (0.74, 1.20), p=0.6163	component analysis not provided	HR 0.81 (0.61, 1.07), p=0.1398

Table IV.B.1: Analyses of a Composite of Cardiovascular Death, Myocardial Infarction and Stroke ("MACE"), and Its Components, for the Rosiglitazone Pooled Studies Meta-Analysis, and for the Large Longterm Thiazolidinedione Clinical Trials that Were Available at the Time of the 2007 Advisory Committee Meeting

			HR or OR (95% CI), p-value			
Data Source	Comparison	Analysis Model	CV Mort + MI + Stroke ("MACE")	CV Mort	MI	Stroke
<p>1 N.B. Heterogeneity across the pooled studies reduces the reliability of an overall estimate. See Ms. Mele's statistical review of 3 Jul 07 for details on these analyses by meta-group.</p> <p>GSK analyses used proportional hazards model including covariate for baseline risk and term for treatment. Included CV mortality, MI serious adverse events (SAEs) and stroke SAEs. NDA 21071 sub 31 May 07, pg 5</p> <p>FDA analyses by J Mele: FDA "exact model" = exact test with conditional maximum likelihood estimates where studies with zeros in both arms are excluded; stratified by meta-groups. FDA "MH" model = Mantel-Haenszel fixed effects model with continuity correction where no trials are excluded. MI = MI SAEs, stroke = stroke SAEs.</p> <p>2 GSK analyses source NDA 21071 EDR 31 May 07, proportional hazards model with terms for treatment and number of major CV risk factors</p> <p>FDA analyses by J Mele, DFS (now DARRTS) 3 Jul 07; proportional hazards model with terms for treatment and number of major CV risk factors, and with gender as stratifier</p> <p>3 DREAM investigators model (DREAM Investigators, 2006), analyses with Cox proportional hazards model with ramipril interaction term</p> <p>FDA analyses by J Lawrence, in FDA statistical review authored by J Mele, NDA 21071, DFS (now DARRTS) 3 Jul 07. Conditional MLE of odds ratio, Fisher exact test p-value</p> <p>4 From published RECORD interim analysis (Home 2007). MI = acute myocardial infarction. Cox proportional hazards regression stratified by background medication.</p> <p>5 From PROactive study report, NDA 21073 Suppl 026, Tables 11.i (pg 87), 11.g (pg 80), 11.h (pg 81). Cox proportional hazards model with treatment as only covariate. MI in composite = nonfatal MI excluding silent MI; separate analysis of component of nonfatal MI excluding silent MI was not provided. For all nonfatal MI (including silent MI), HR = 0.83 (0.65, 1.06), p=0.1312. Stroke events in composite not specified as SAE.</p>						

There were several limitations to viewing this endpoint across data sources; some of these included:

- Between data sources, the patient populations were heterogeneous in terms of cardiovascular risk factors, duration of diabetes, and other important characteristics.
- Within the pooled studies, heterogeneity existed, and therefore pooling for an overall estimate may not be appropriate.
- Methods of ascertainment differed between data sources. There were likely differences in the precise sets of cardiovascular adverse event terms that were included within each of the components. For the pooled studies, some events were migrated from WHO terms to MedDRA (Medical Dictionary for Regulatory Activities) terms.
- Not all events were adjudicated. In ADOPT, none were adjudicated. In DREAM and PROactive, essentially all were. Results from the RECORD interim are presented in the above table by adjudication status. In GSK's pooled studies database, CV death and MI were adjudicated post hoc, but stroke was not adjudicated. Definitions used for adjudication varied across studies.
- Event rates in some data sources were low, increasing uncertainty; a few added events to one treatment group or another could change an estimate considerably.
- Duration of study varied; in the pooled studies 38/42 studies were ≤ 6 months in duration. The large prospective trials were much longer.
- Analysis models differed somewhat.

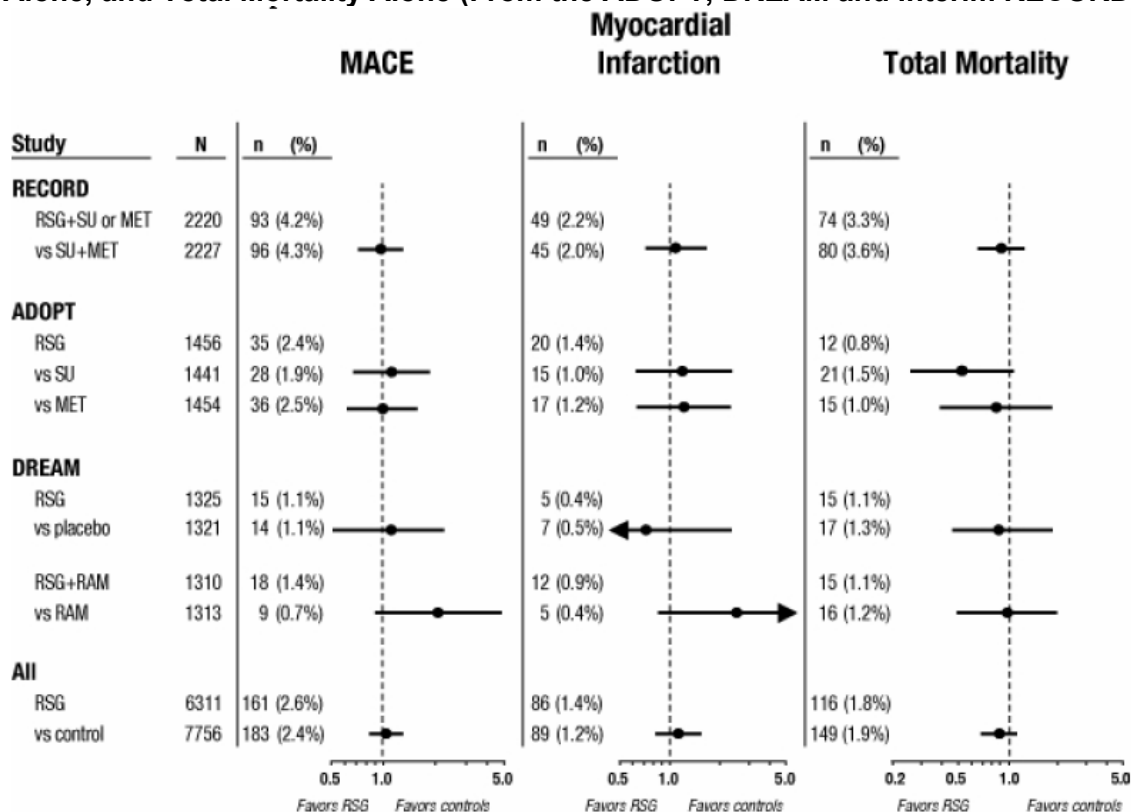
These limitations were not unique to this particular endpoint, however; virtually any endpoint one chose would have had similar concerns regarding interpretability of cardiovascular event data across data sources. The 2007 meta-analysis itself, which raised this concern of cardiovascular risk, was a retrospective identification of selected endpoints across different clinical trials with no pre-defined criteria for coding of CV events.

Because of these limitations (and possibly other weaknesses), firm conclusions from the above table were not possible. Some observations include:

- For the composite of CV death, stroke and MI, for the two sources of cardiovascular outcome data (RECORD interim for RSG and PROactive for PIO), hazard ratios were <1, and confidence intervals overlapped. For the other trial data sources, hazard ratios were generally slightly >1; statistical significance was not noted for any one analysis. There appeared to be an interaction between RSG and ramipril with regard to cardiovascular events in the DREAM study.
- For cardiovascular mortality, there was variability in the estimates, depending on the data source, and on the treatment comparison. The differences between treatment groups were not statistically significant. For the two cardiovascular outcome study data sources, hazard ratios were <1, and confidence intervals overlapped.
- For myocardial infarction, hazard ratios were generally >1, and confidence intervals generally included unity. In DREAM, there again appeared to be an interaction between RSG and ramipril. For the comparison of RSG to PBO in DREAM, the OR was <1, but when considering RSG + ramipril compared to ramipril alone, the OR was higher, and there was a significant difference between treatment groups. The PROactive study report presented the composite, but it appears that the study report did not present an analysis for the myocardial infarction component defined for the composite.
- For stroke, estimates varied across data sources, with multiple hazard ratios (HRs) <1, and multiple HRs >1.

The following figure displays the results of these analyses for the longterm trials of rosiglitazone for MACE and MI, and adds total mortality.

Figure IV.B: Hazard Ratios for Risk of MACE (MI + Stroke + CV Death), Myocardial Infarction Alone, and Total Mortality Alone (From the ADOPT, DREAM and Interim RECORD Trial Data)



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

Source: NDA 21071 label from approval letter for Supplement 31, 14 Nov 07. MI = fatal + nonfatal

In each of the large longterm trials of RSG available at that point, point estimates for total mortality favored RSG, and 95% confidence intervals included 1.

As noted in the above figure, in the DREAM trial, a question of an ACEI interaction arose due to an observation of a higher rate of CV events for patients in the RSG + ramipril (RAM) group. This finding was not noted in analyses of the ADOPT trial, or of the RECORD interim data.

Data from these trials were felt to neither confirm nor exclude an increased risk for myocardial ischemic events for RSG.

In addition to those previously discussed, some limitations of these trials included:

- ADOPT and DREAM were not designed or powered as CV outcomes trials, although DREAM did have preplanned in-stream adjudication of CV events.
- At that point, RECORD had had a lower-than-expected rate of CV events, resulting in a lower-than-expected statistical power.
- The Agency had not received the full study report for DREAM or RECORD, and therefore examination of source data for confirmatory analyses was not possible.

These trials had some strengths which were felt to be possibly useful in the overall assessment of the CV risk of RSG:

- For each trial, randomization was maintained for analyses, reducing the likelihood of unmeasured confounders. The problem of statistical heterogeneity that occurred in the meta-analysis was not present in these trials.
- These trials had far greater rosiglitazone exposure than did all the trials in the meta-analysis combined (25,998 patient-years at that point vs 4143 patient-years).
- In the case of the interim analysis of RECORD, a cardiovascular outcome study, risk estimates appeared to be neutral at that time.
- When one removed heart failure events from the longterm trial endpoints, risk estimates fell even lower; in the case of the primary endpoint for RECORD, it fell to a hazard ratio (HR) of 1.008.
- For RECORD, even at interim, more CV events had already accrued than in the entire set of 42 trials in the meta-analysis. Estimates from the RECORD interim were not fragile, in contrast to those of the meta-analysis; i.e. RECORD's results could not be swayed in one direction or another by only a few events, which was a problem with the meta-analysis.
- Total mortality was not increased in these trials; in fact, HRs were all <1.

There was a difference between the findings of the meta-analysis of the 42 trials (which had a mean duration of 6 months), and that of the 3 large trials (which had a mean duration of 41 months). The possibility was discussed that there could be a difference between outcomes at 6 months, and longterm outcomes for diabetes medications. For example, in the PROactive trial, a longterm cardiovascular outcome trial involving pioglitazone, the longterm effect of pioglitazone on the primary endpoint was statistically neutral. However, as illustrated in the following table, at 6 months, most of the components of the primary endpoint did not favor pioglitazone. This was presented not to imply that pioglitazone carries an increased CV risk, but rather to underscore that accurate assessment of CV risk requires longterm clinical trials specifically designed to assess CV outcomes.

Table IV.B.2: Results for Predefined Secondary Endpoints for PROactive (Measured at 6 Months)			
Endpoint	PIO N=2605 n (%)	PBO N=2633 n (%)	HR¹
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			

Regarding BARI 2D, after the 2007 Nissen meta-analysis publication, the Data Safety Monitoring Board examined the BARI 2D data regarding rosiglitazone, which was the most commonly used agent in the “insulin-sensitizing” arm of the study. In a press release (BARI 2D Study Group, 15 Jun 2007), the investigators stated that the DSMB “found no evidence to require discontinuing the use of rosiglitazone in the trial or to revise the study protocol”. The actual results of the DSMB analyses were not released at that time because the trial was ongoing. The trial is now complete and the rosiglitazone analyses will be discussed at the AC.

A noteworthy observation is that the incidence of all-cause mortality (which requires not adjudication) was similar between rosiglitazone and comparators in all longterm controlled trials for which such data were available at the time of the 2007 Advisory Committee meeting.

Table IV.B.3: Incidence of All-Cause Mortality in Longterm Controlled Trials of Rosiglitazone at Time of 2007 Advisory Committee Meeting		
Clinical Trial	Rosiglitazone	Control
ADOPT	2.3%	2.2% (SU) and 2.1% (MET)
DREAM	1.1%	1.3% (placebo)
RECORD (based on interim analysis)	3.3%	3.6% (MET/SU combination)

Overall, at the time of the RECORD interim, analyses of data from randomized controlled clinical trials of RSG, including those for the meta-analysis and the 3 longterm prospective trials, were considered to be inconclusive regarding the risk of myocardial ischemic events for RSG.

IV.C. Observational Data Available at Time of 2007 Advisory Committee Meeting

At the time of the 2007 Advisory Committee Meeting, the Agency had received several reports of nonrandomized observational studies, some of which suggested an increased risk of cardiovascular events with rosiglitazone, and some of which were neutral or favorable. At that time, the Office of Surveillance and Epidemiology asserted that evidence from randomized controlled clinical trials should be considered to be of higher quality than that from observational studies, and the Division of Metabolism and Endocrinology Products concurred.

V. Additional Information from Large Clinical Trials of Rosiglitazone that has Become Available Since the July 2007 Advisory Committee Meeting

On 30 Jul 2007, a joint public meeting was held of the Endocrine and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Committee members felt that the data suggested a possible increased risk of myocardial ischemic events for RSG. However, by a vote of 22 to 1, they recommended that Avandia® remain on the market. A number of suggestions were made by committee members regarding possible actions to address this risk.

On 14 Nov 2007, GSK and FDA agreed upon a revised Full Product Information and Patient Information Leaflet describing the findings of the myocardial ischemic event analyses under Supplement 31. At that time, GSK also agreed to conduct a cardiovascular outcomes study (TIDE), the protocol for which is reviewed by Dr. Irony in a separate document. The TIDE study is ongoing. On 22 Feb 2008, GSK and FDA agreed upon a Patient Medication Guide under Supplement 32. This Medication Guide replaced the Patient Information Leaflet and includes detailed information for patients at an appropriate reading level, and is to be distributed to each patient who fills a prescription for Avandia®.

Since that time, some additional information has become available from other large trials in which patients received rosiglitazone.

V.A. ADOPT (A Diabetes Outcomes Progression Trial)

At the time of the 2007 AC, the FDA review of ADOPT was ongoing. It has since been completed (DARRTS 4 Mar 2008), and a summary of the findings follows.

The ADOPT study was a randomized, active-controlled, double-blind trial conducted in patients with recently diagnosed type 2 diabetes who were naïve to diabetes drug treatment, and who were inadequately controlled with diet and exercise. It was intended to examine the effect of rosiglitazone monotherapy on slowing of progressive loss of glycemic control. A total of 4351 patients were randomized 1:1:1 to receive rosiglitazone, glyburide or metformin. Study medications were titrated to effect, up to the dose of maximum expected therapeutic effect. Initially, a four-year follow-up was planned. The primary efficacy outcome was time to monotherapy failure, defined either as a fasting plasma glucose >180 mg/dL on consecutive occasions, or as assigned by an independent adjudication committee. During study, the duration was extended to six years due to a higher-than-expected withdrawal rate and a lower-than-expected rate of monotherapy failure.

The cumulative incidence of monotherapy failure at five years of study was 15% for rosiglitazone, 34% for glyburide, and 21% for metformin; this difference between rosiglitazone and each of the other two groups was statistically significant. Rosiglitazone group patients were less likely to reach a plasma glucose of ≥140 mg/dL, and more likely to maintain a hemoglobin A1c of <7%.

A substantial percentage of patients in each treatment group discontinued treatment for reasons other than monotherapy failure. This presented challenges in the evaluation of adverse event data; techniques such as time-to-event analyses were used. The rate and pattern of withdrawal were similar for the rosiglitazone and metformin groups, but the glyburide group had a higher withdrawal rate, largely due to hypoglycemia.

Rosiglitazone-associated adverse events in the trial were generally consistent with those described in the label. Weight gain, edema and anemia occurred more commonly among rosiglitazone-treated patients than among comparator-treated patients. Heart failure occurred at equal rates between rosiglitazone- and metformin- treated patients, but at a lower rate among sulfonylurea-treated patients.

Other cardiovascular events did not occur at a higher rate among rosiglitazone-treated patients than among comparator-treated patients. Numerous individual and composite endpoints were examined. Reviews were conducted of analyses of the original adverse event terms assigned, and of an independent blinded adjudication conducted at two academic medical centers. Ascertainment and coding were examined, and no significant problems were detected. Separately, an FDA cardiologist reviewed the entire adverse event database, using multiple endpoints of clinical cardiologic relevance, and did not find evidence of miscoding or a significant imbalance in cardiovascular events.

The following table displays the results of the FDA's analyses of cardiovascular endpoints from ADOPT.

Table V.A: FDA Proportional Hazards Model Analysis Results for Ischemic et al Cardiovascular Endpoints, ADOPT		
	RSG vs SU OR (95% CI), p-value	RSG vs MET OR (95% CI), p-value
All cardiac ischemic events (serious and nonserious)	1.2 (0.9, 1.6), p=0.2	1.0 (0.8, 1.3), p=0.9
Serious cardiac ischemic events	1.2 (0.8, 1.8), p=0.3	1.0 (0.7, 1.4), p>0.9
CV death, MI or stroke	1.2 (0.7, 1.9), p=0.3	1.1 (0.7, 1.8), p=0.6
CV death	0.6 (0.2, 1.9), p=0.4	1.3 (0.4, 5.0), p=0.7
All-cause mortality	0.5 (0.3, 1.1), p=0.1	0.8 (0.4, 1.8), p=0.7
MI	1.6 (0.8, 3.1), p=0.2	1.3 (0.7, 2.3), p=0.4
Stroke	0.9 (0.4, 2.1), p=0.9	0.8 (0.4, 1.6), p=0.5
Source: Statistical review briefing document by J Mele, DFS 3 Jul 07, Table 4.1.6, pg 22		

For all these endpoints, a statistically significant difference between RSG and comparator was not established; 95% confidence intervals for all odds ratios included unity. For RSG vs SU, there was a numerically lower risk of all-cause mortality for RSG, with a p-value of 0.1. Myocardial infarction was associated with a hazard ratio of 1.6 for RSG vs SU, a 95% confidence interval including 1, and a p-value of 0.2.

Insulin use was an exclusion criterion in ADOPT, and therefore could not be examined as a risk factor for myocardial ischemic events. There was no evidence of a statistical interaction by baseline nitrate use for risk of myocardial ischemic events, but baseline use of nitrates was relatively low. As mentioned earlier, preliminary data from the DREAM ("Diabetes Reduction Assessment with Rosiglitazone and Ramipril Medication") trial had raised a concern about an increased risk of cardiovascular events with concomitant use of rosiglitazone and ramipril. Analyses of ADOPT revealed no interaction by baseline angiotensin-converting enzyme inhibitor use. There was also no evidence of an interaction for myocardial ischemic event risk by baseline presence or absence of cardiovascular disease.

There was no difference between rosiglitazone and comparator for the incidence of cardiovascular or total mortality.

In women, fractures occurred at a higher rate in rosiglitazone-treated patients than in comparator-treated patients. These fractures tended to involve the upper arm, hand and foot.

V.B. DREAM

At the time of the 2007 AC, the DREAM study report had been published, but the full study report had not been received by the Agency. The report has now been received and review is ongoing by DMEP and an FDA cardiology consultant.

The DREAM study was a placebo-controlled, randomized, double-blind clinical trial conducted by McMaster University in pre-diabetic patients. The trial was designed to determine if the use of early treatment with medication could forestall the development of overt type 2 diabetes. The study was conducted in nearly 5,300 patients who were randomized to either rosiglitazone or placebo and were followed for a mean duration of 3 years. The study also was intended to examine whether rosiglitazone and/or ramipril delayed onset of overt type 2 diabetes. Therefore the trial used a factorial design, with patients randomized to any of four treatment arms: placebo with placebo; rosiglitazone with placebo; placebo with ramipril; and rosiglitazone with ramipril. A composite of cardiovascular events was adjudicated. This study, as reported in the Lancet (DREAM Trial Investigators, 2006), showed an effect of rosiglitazone in delaying the development of type 2 diabetes (effect not found with ramipril) in these prediabetic patients. There was a statistically significant increase in heart failure events among rosiglitazone-treated patients, and this increase drove a difference in a composite of cardiovascular events which included heart failure. Without heart failure events, there was not a statistically significant difference between rosiglitazone and comparator for overall adjudicated cardiovascular events. There was also no statistically significant difference between rosiglitazone and comparator for the MACE composite (myocardial infarction, stroke or cardiovascular death) or for individual endpoints of myocardial infarction, stroke, cardiovascular death, overall mortality, new-onset angina, or revascularization. When comparing by-strata data, there appeared to be a higher event rate for the combination of rosiglitazone and ramipril when compared to ramipril alone. This difference was not seen in the comparisons of rosiglitazone to placebo.

The following table displays results of FDA analyses for cardiovascular events when comparing RSG to placebo, and when comparing RSG + ramipril to ramipril alone in DREAM. These analyses used adjudicated events as reported by McMaster University; review of ascertainment and adjudication in DREAM is ongoing and could result in some changes to the numbers of events.

Table V.B: Odds Ratios for CV Events in DREAM, FDA Analyses by Dr. John Lawrence

Event	Placebo N=1321 Rate ¹	RSG N=1325 Rate	OR ² 95% CI p-value	RAM N=1313 Rate	RSG+RAM N=1310 Rate	OR ³ 95% CI p-value	OR ⁴ 95% CI p-value
Any CV Event	33 (2.5%) 0.78	33 (2.5%) 0.77	1.00 (0.59, 1.68) 1	24 (1.8%) 0.56	45 (3.4%) 1.07	1.91 (1.13, 3.30) 0.01	1.38 (0.96, 1.98) 0.08
MACE	14 (1.1%) 0.33	15 (1.1%) 0.35	1.07 (0.48, 2.40) 1	9 (0.7%) 0.21	18 (1.4%) 0.43	2.02 (0.86, 5.12) 0.09	1.44 (0.82, 2.58) 0.23
CV Death	5 (0.4%) 0.12	5 (0.4%) 0.12	1.00 (0.23, 4.34) 1	5 (0.4%) 0.12	7 (0.5%) 0.17	1.41 (0.38, 5.63) 0.58	1.20 (0.47, 3.11) 0.83
MI	6 (0.5%) 0.14	5 (0.4%) 0.12	0.83 (0.20, 3.27) 0.77	3 (0.2%) 0.07	11 (0.8%) 0.26	3.70 (0.97, 20.7) 0.03	1.78 (0.74, 4.58) 0.23
Stroke	3 (0.2%) 0.07	5 (0.4%) 0.12	1.66 (0.32, 10.7) 0.73	2 (0.2%) 0.05	2 (0.2%) 0.05	1.00 (0.07, 13.8) 1	1.40 (0.38, 5.60) 0.77
CHF	1 (0.1%) 0.02	3 (0.2%) 0.07	2.99 (0.24, 157) 0.6247	1 (0.1%) 0.02	11 (0.8%) 0.26	11.1 (1.61, 477) 0.003	7.03 (1.61, 64) 0.004

¹ number of events per 100 patient years

² Conditional MLE of odds ratio, Fisher exact test p-value for RSG vs. Placebo

³ Comparison of RSG+RAM vs. RAM

⁴ Comparison of {RSG plus RSG+RAM} vs. {Placebo plus RAM}

Source: Briefing document by Dr. Joy Mele for 30 Jul 07 Advisory Committee mtg, Appendix 5, pg 44

Ramipril carries an indication for reduction of risk of cardiovascular events. In comparisons of RSG to PBO, RSG was not associated with a statistically significantly increased risk for CV death, MI, stroke, the composite of the former 3, or CHF. In comparisons of RSG + RAM to RAM alone, RSG was associated with a significantly increased risk of heart failure. For the comparison of RSG + RAM to RAM alone, risk of MI was higher for RSG + RAM with a p-value of 0.03, although the 95% confidence interval included 1.

V.C. VADT (Veterans Affairs Diabetes Trial)

The VADT was intended to examine the effect of intensive glucose control on cardiovascular outcomes in military veterans with longstanding diabetes (mean time since diagnosis 11.5 years) and suboptimal glycemic control at entry. The study report has been published (Duckworth 2009). Patients were not randomized to a particular medication but rather to either “intensive” or “standard” levels of diabetes control. The primary endpoint was a composite of myocardial infarction, stroke, cardiovascular death, congestive heart failure, surgery for vascular disease, inoperable coronary artery disease, or amputation for ischemic gangrene. A total of 1791 veterans were randomized, and median follow-up was 5.6 years. Median hemoglobin A1c was 8.4% in the standard therapy group, and 6.9% in the intensive treatment group. Most patients in both groups received rosiglitazone as part of their regimen, and therefore specific comparisons could not be made of rosiglitazone to another agent. However, the investigators did attempt to examine for any potential negative cardiovascular effect of rosiglitazone. At the American Diabetes Association meeting on 8 Jun 2008, Mr. Thomas Moritz, lead statistician for the study, presented several analyses using case-control and time-dependent covariate analysis methods. These analyses did not suggest a negative effect of rosiglitazone for the primary endpoint, MACE, cardiovascular death, or a composite of myocardial infarction and cardiovascular death. Mr. Moritz acknowledged the limitations of these analyses. Mr. Moritz will present analyses from VADT at the Advisory Committee meeting.

V.D. BARI 2D

The BARI 2D trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes), sponsored by the National Institutes of Health, was designed to test whether prompt revascularization with intensive medical therapy, or intensive medical therapy alone, was superior for management of stable ischemic heart disease in patients with type 2 diabetes mellitus. Results have been published (BARI 2D Study Group 2009). The trial stratified by type of revascularization procedure (coronary artery bypass grafting vs percutaneous coronary intervention). Simultaneously, BARI 2D also evaluated whether “insulin-providing” or insulin-sensitizing medical therapy was superior. The trial was not designed to evaluate individual drugs, but rather an overall strategy of insulin provision vs insulin sensitization. The trial included 2368 patients, and the mean duration of follow-up was 5.3 years. In general, there was no difference in rates of death or major adverse cardiovascular events between the revascularization group and the intensive medical therapy group, and no difference between the insulin-providing and insulin-sensitizing medical regimens. In a stratum where the revascularization procedure was coronary artery bypass grafting, the rate of major cardiovascular events was lower in the revascularization group (22.4%) than in the medical therapy group (30.5%, $p = 0.01$). By-strata comparisons revealed no differences between medical treatment approaches.

Because a large percentage of patients in the trial were taking RSG at the time of the 2007 meta-analysis of RSG, the BARI 2D Data Safety Monitoring Board (DSMB) examined event rates among patients who were and were not taking RSG, in the interest of protecting study subject safety. At that time, the DSMB reported that there was no evidence of an adverse effect of RSG on CV safety. The CV safety of RSG was also evaluated at study end. At the 3-year follow-up point, rosiglitazone was being administered to 55.1% of patients in the insulin-sensitizing group, and to 2.9% of patients in the insulin-providing group. The trial was not designed to evaluate individual drugs, but rather an overall strategy of insulin provision vs insulin sensitization. However, the lack of difference in the rate of deaths and major

cardiovascular events between medical therapy groups, in the presence of a large difference in rosiglitazone use between groups, suggested that the choice of rosiglitazone did not have a negative impact on patients in the insulin-sensitizing group. Investigators noted that similar coronary angiographic results were found for patients taking rosiglitazone vs those taking pioglitazone at baseline (Pop-Busui et al 2009).

The following post hoc analyses were reported at the American College of Cardiology Meeting in 2010.

Table V.D: Cardiovascular Event Rates in BARI 2D for Patients Treated with Rosiglitazone and Those Not Treated with a Thiazolidinedione							
Endpoint	Unadjusted Analyses				Adjusted Analyses¹		
	RSG Events/100 PY	Non-TZD Events/100 PY	RR	p-value	RR	95% CI	p-value
MACE	3.79	5.81	0.71	0.002	0.72	0.55, 0.93	0.01
MI	2.16	3.16	0.76	0.06	0.77	0.54, 1.10	0.15
All-cause mortality	1.88	2.56	0.77	0.08	0.83	0.58, 1.18	0.29
Source: American College of Cardiology 2010 annual meeting abstract 10-LBCT-15179-ACC 1 Model adjusted for baseline characteristics and use of other antidiabetes medications							

The above analyses have limitations in that they are post hoc and are not based on randomized groups. However, they do not suggest that exposure to RSG in BARI 2D was associated with increased risk of MACE, MI or death, but rather favor RSG for these endpoints.

The BARI 2D investigators will present a summary of their analyses related to RSG CV safety at the July 2010 ACC.

V.E. ACCORD

The ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) is a prospective, randomized, open-label, controlled trial which originally had a 2x2x2 factorial design, and was intended to assess the effects of controlling glycemia, lipids and blood pressure on cardiovascular outcomes in patients with type 2 diabetes. A total of 10,251 patients participated; in addition to diabetes, all had a prior history of cardiovascular disease or at least two risk factors for CVD. Mean duration of DM at entry was 10 years. In February 2008, the glycemic control portion of the trial was discontinued after interim safety analyses revealed an increase in mortality in the arm with the lower HbA1c goal (257 deaths vs 203 deaths in the "standard" glycemic goal group). Mean duration of follow-up at the time of publication of the glycemic study results was 3.5 years. Treatment goal in the intensive treatment group had been an HbA1c of <6%. Rosiglitazone was one of the treatment choices available for the trial, although patients were not randomized to a particular medication. Prior to cessation of the glycemic control arm of the trial, approximately 2,000 study patients were receiving rosiglitazone. In the press release related to cessation of the trial, the investigators reported that the Data Safety Monitoring Board specifically examined rosiglitazone, and the increase in mortality did not appear to be attributable to rosiglitazone use. This was reiterated in the publication of the results of the glycemic study (ACCORD Study Group 2008). The embedded studies examining lipid and blood pressure control continued. The press release regarding cessation of the glycemic control portion of the trial may be found at:

<http://www.nhlbi.nih.gov/health/prof/heart/other/accord/>

V.F. APPROACH

The APPROACH trial (Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes patients with Cardiovascular History) was a double-blind, randomized, active-controlled study to assess the effect of rosiglitazone on the progression of coronary atherosclerosis as determined by intravascular ultrasound (Ratner 2008). The study population was composed of patients with type 2 diabetes who are undergoing coronary angiography. The active comparator was glipizide. The composite of death, MI and stroke was a predefined secondary endpoint, and MACE events were adjudicated by a blinded endpoint committee. A total of 668 patients participated, 331 of whom were randomized to rosiglitazone. In that study, 13/331 (3.9%) of RSG-treated patients and 9/337 (2.7%) of glipizide-treated patients had a MACE. There were a total of 8 myocardial infarctions, 5 (1.5%) for RSG, and 3 (0.9%) for glipizide. This trial is included in the FDA's updated meta-analysis of RSG, and in GSK's updated Integrated Clinical Trials Analysis.

VI. Additional Cardiovascular Safety Information from Sources Other than Large Clinical Trials

VI.A. Updated Meta-Analysis of Rosiglitazone Clinical Trials

The applicant submitted an updated Integrated Clinical Trials Analysis (ICTA) which added 10 trials to the previous set of 42 trials. This ICTA used the same pooled studies approach that GSK had used in their previous ICTA, rather than a classical meta-analysis approach. The 10 trials added 2758 patients, brought the total number of trials to 52, and brought the total number of patients to 16,995. All included trials were randomized, controlled and double-blinded.

The endpoints examined by the applicant included the previously described composite of potential myocardial ischemia event terms used in the original meta-analysis, and MACE. For the myocardial ischemic events composite, most events were angina events.

The following table displays the ten additional studies, their controls, and the countries in which the trials were conducted.

Table VI.A.1: Summary of Ten Additional Trials Added to Applicant's Integrated Clinical Trials Analysis

Study ID	Control	RSG N	Control N	Country
BRL-049653/376	PBO	19	21	Global
BRL-049653/351	PBO	27	29	Global
BRL-049653/128	PBO + SU	39	38	Taiwan
AVD105248	PBO + SU	74	75	Japan
BRL-049653/374	PBO + alpha-glucosidase inhibitor	84	85	Japan
AVD102209	INS + PBO	132	131	China
AVS101946	PBO + simvastatin ¹	276	93	Global
AVD104742	PBO, PIO	159	213	Japan
AVM100264	MET + SU	294	301	Europe
AVD100521 (APPROACH)	Glipizide	331	337	Global

Source: Applicant's Table 1, pg 6, NDA 21071 subm 7 Oct 2009

¹ Eight-arm study (RSG 4 mg + PBO, RSG 8 mg + PBO, SIM 40 mg + PBO, SIM 80 mg + PBO, RSG 4 mg + SIM 40 mg, RSG 4 mg + SIM 80 mg, RSG 8 mg + SIM 40 mg, and RSG 8 mg + SIM 80 mg)

Of the 52 trials, 40 were ≤ 6 months in duration. Mean duration of treatment was 188 days.

The following table displays the number and percentage of patients who had events from the myocardial ischemia composite, and those who had MACEs, from the additional 10 trials and the combined 52 trials.

Table VI.A.2: Number and Percentage of Patients with Myocardial Ischemic Events and MACE, 10 Additional RSG RDBCTs, and Combined 52 RSG RDBCTs

Study	Myocardial Ischemic Events		MACE	
	RSG n (%)	Control n (%)	RSG n (%)	Control n (%)
BRL-049653/376	0	0	0	0
BRL-049653/351	2 (7.4)	1 (3.5)	0	0
BRL-049653/128	1 (2.6)	0	1 (2.6)	0
AVD105248	0	0	0	1 (1.3)
BRL-049653/374	1 (1.2)	0	0	0
AVD102209	0	3 (2.3)	0	1 (0.8)
AVS101946	2 (0.7)	0	1 (0.4)	0
AVD104742	0	0	0	0
AVM100264	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
AVD100521 (APPROACH)	42 (12.7)	53 (15.7)	13 (3.9)	9 (2.7)
10 New Studies Combined	50 (3.5)	59 (4.5)	17 (1.2)	13 (1.0)
52 Studies Combined	222 (2.2)	145 (2.1)	80 (0.8)	51 (0.7)

Source: Applicant's Table 2, pg , pg 8; and Table 4, pg 10; NDA 21071 subm 7 Oct 2009

The following table displays the applicant's analyses for myocardial ischemic events and MACE.

Table VI.A.3: Applicant's Updated Integrated Clinical Trial Analyses, Myocardial Ischemic Events Composite and MACE

Endpoint Composite	Studies Included	HR ¹ (95% CI)	p-value	RSG n/N (%)	Control n/N (%)	RSG PY (Rate per 100 PY)	Control PY (Rate per 100 PY)
Myocardial ischemic events	Orig 42	1.3 (1.0, 1.7)	0.047	172/8604 (2.0)	86/5633 (1.5)	4143 (4.2)	2675 (3.2)
	New 10	0.8 (0.6, 1.2)	0.307	50/1435 (3.5)	59/1323 (4.5)	978 (5.1)	964 (6.1)
	Updated 52	1.1 (0.9, 1.4)	0.383	222/10039 (2.2)	145/6956 (2.1)	5121 (4.3)	3639 (4.0)
MACE	Orig 42	1.1 (0.7, 1.6)	0.760	63/8604 (0.7)	38/5633 (0.7)	4143 (1.5)	2675 (1.4)
	New 10	1.3 (0.6, 2.7)	0.485	17/1435 (1.2)	13/1323 (1.0)	978 (1.7)	964 (1.4)
	Updated 52	1.1 (0.8, 1.6)	0.525	80/10039 (0.8)	51/6956 (0.7)	5121 (1.6)	3639 (1.4)

Source: Applicant's Table 3, pg 9; and Table 5, pg 10; NDA 21071 subm 7 Oct 2009

¹ Proportional hazards regression analysis, pooled RSG vs non-RSG, without covariates

By the applicant's analyses, addition of these 10 trials rendered the results statistically nonsignificant for the myocardial ischemic events composite. Results for the MACE composite had been statistically nonsignificant for the original group of 42 trials, and remained so for the group of 52 trials. In their submission, the applicant did not present results for myocardial infarction.

FDA biometricians are conducting their own meta-analysis of these data, using multiple endpoints and sensitivity analyses. As of 8 Jun 2010, the full meta-analysis report is pending. However, preliminary results support a statistically significantly increased risk of myocardial infarction for an overall comparison of rosiglitazone to pooled comparator across the 52 trials.

VI.B. Meta-Analysis of Pioglitazone Clinical Trials

FDA biometricians are conducting a meta-analysis of pioglitazone clinical trial data, using the same methods as they are using for an updated rosiglitazone meta-analysis. The clinical trials programs for the pioglitazone and rosiglitazone differ substantially, and cross-program comparisons between drugs are often difficult to interpret. As of 8 Jun 2010, the full meta-analysis report is pending.

VI.C. Observational Studies

Please see reviews by Drs. Kate Gelperin and David Graham from the Office of Surveillance and Epidemiology.

VII. Ongoing Clinical Trial of Rosiglitazone- the TIDE Study

The TIDE (Thiazolidinedione Interventions with Vitamin D Evaluation) is a cardiovascular outcomes trial being conducted as a postmarketing requirement specified by the U.S. Food and Drug Administration. It is a multicenter, international, randomized, double-blind, placebo-controlled, 3x2 factorial study which is designed to examine, independently, the effects of thiazolidinediones versus placebo, and vitamin D versus placebo. Please see Dr. Ilan Irony's review of the study protocol, which is included in the briefing package. The trial is being conducted by McMaster University. The objectives of the study are to evaluate the effects of the addition of rosiglitazone or pioglitazone or placebo, for up to 5.5 years, to the background diabetes care regimen of approximately 16,000 patients with type 2 diabetes and other cardiovascular risk factors. The risk for the composite of cardiovascular death, myocardial infarction or stroke is the primary outcome to be measured. A noninferiority assessment of rosiglitazone to placebo will be conducted after approximately 4.5 years of study. There will be numerous secondary cardiovascular endpoints; and secondary comparisons will also be made between rosiglitazone and pioglitazone, and between pioglitazone and placebo, and between the thiazolidinedione class and placebo. The study is powered to detect both superiority of the thiazolidinedione class versus placebo, and noninferiority of rosiglitazone versus placebo, based on a margin of 1.3 for the upper limit of the 95% confidence interval for the hazard ratio. Separately, the study will examine the effect over 10 years of vitamin D or placebo on the risk for a composite of death or serious cancer requiring hospitalization, chemotherapy or surgery.

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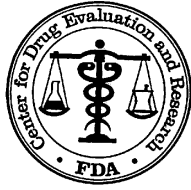
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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/s/

KAREN M MAHONEY
06/15/2010

MARY H PARKS
06/15/2010



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

CLINICAL STUDIES

NDA/Serial Number:

NDA#: 21071

Drug Name:

Avandia (The RECORD trial)

Indication(s):

Type 2 Diabetes

Applicant:

Glaxo Smith Kline

Date(s):

Review Priority:

High

Biometrics Division:

DBII

Statistical Reviewer:

David Hoberman, Ph.D.

Concurring Reviewers:

Medical Division:

Division of Metabolic and Endocrine drugs

Clinical Team:

Karen Mahoney, M.D.

Project Manager:

Jena Weber

This is a DRAFT document. Numbered tables and figures are taken from the sponsor's submission and are not meant to be in a natural order.

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Summary

The goal of the RECORD trial was to show that subjects taking Avandia as an add-on to either a sulfonyurea or metformin had no more than a 20% increased risk of suffering a cardiovascular event than subjects taking both a sulfonyurea and metformin. The sponsor reported a hazard ratio of .99 with 1.16 as the upper bound of a 95% confidence interval. However, there have been comments critical of the trial, possibly due to its open label status. Some of them include 1) the slight imbalance in the percentage subjects taking a statin during the trial favoring the Avandia arm, 2) possibly sloppy record keeping which may have underestimated the number of events on both arms, 3) the changing of medication in the event that a subject's HbA1c reached an upper threshold, and 4) the interpretation of the trial as failing to be adequate as an "inferiority" trial, i.e. one that should have amassed enough events to show that Avandia's risk is, in fact, statistically greater than the control's.

This review has found the sponsor's analytic methods to be essentially non-controversial, and that any modifications on the margin do not materially affect the results. And that is the important issue: to what extent do either alternative statistical methods or the conduct of the trial, either designed or unanticipated, affect the results in such a way as to lead to different inferences from the ones which would be drawn from the data's face value. The review addresses the issue of statins and finds that the evidence that differential statin use in the two arms substantially affects the results is weak. With regard to possible under reporting of events, as long as it occurs at random between the groups, the effect would be to make it harder to demonstrate non-inferiority if the groups' risks were the same. If "inferiority" is the focus of attention, then fewer events would depress the power to show a statistically significant difference between the groups if there were one. Medication added on to dual randomized therapy, depending upon the arm in question, can confound the intent-to-treat analysis. However, there are two mitigating factors. The first is the option to analyze only the time spent on the randomized therapy. This shows no increased risk of ischaemic events on Avandia. The second is that, in both groups, the vast majority of time was spent on the randomized therapy in both groups: 83% in the control group and 75% in the Avandia group. The influence of the add-on medications after going off dual randomized therapy is not calculable, but may be small in the intent-to-treat analysis. Finally, the review considers the possibility that the trial could have reasonably demonstrated the putative inferiority of Avandia and finds that there is evidence that RECORD could have done so.

Background

RECORD was a centrally randomized, open-label, active control trial comparing two regimens to determine the cardiovascular safety of Rosiglitazone (RSG) with respect to the non-inferiority hazard ratio of 1.2 (RSG/active control). Subjects had T2DM, age range: 40 to 75, HbA1c had to be between 7.0% and 9.0%, and BMI greater than 25.0 kg/m². Randomization was stratified within background medication, either Metformin (MET) or a Sulfonylurea (SU). Background MET subjects (N=2222) were then randomized to either RSG or SU. Background SU subjects (N=2225) were randomized to either RSG or MET. Thus a subject's identification (background/randomized treatment) could be either MET/RSG, SU/RSG, MET/SU or SU/MET. The group of MET/RSG and SU/RSG subjects constituted the "Rosiglitazone" arm (N=2220) and the group of SU/MET and MET/SU subjects constituted the (control) MET/SU arm (N=2227). Thus, the "treatment by strata interaction" would compare the effect of RSG vs MET with the effect of RSG vs SU. The study ran from April 2001 to December 2008 in 836 centers in 25 European countries (see table below). There was a two-year accrual period and a target of 6 years follow up for each subject. A "completer" was someone who attended his/her last study visit which fell between August and December of 2008.

The table below displays recruitment by country along with the hazard ratio for the primary endpoint: CV death or CV hospitalization, determined by the proportional hazard assumption.

	# subjects	#1 ^o events	% Risk	HR (RSG/cont)
Australia	52	12	23	.8
Belgium	104	15	14	.5
Bulgaria	204	18	9	1.0
Croatia	273	30	11	.6
Czech Republic	144	30	21	1.0
Denmark	57	9	16	1.2
Estonia	219	29	13	1.1
Finland	193	30	16	.5
France	86	18	21	1.3
Germany	178	34	19	1.4
Greece	135	12	9	1.0
Hungary	400	56	14	1.3
Italy	116	11	9	1.0
Latvia	173	37	21	.8
Lithuania	134	22	16	1.1
New Zealand	35	6	17	1.0
Poland	362	50	14	1.3
Romania	157	21	13	.9
Russia	149	28	19	1.8
Slovakia	325	26	8	1.4
Spain	64	9	9	1.8
Sweden	467	82	18	.9
The Netherlands	75	7	9	1.5
Ukraine	103	16	16	.4
United Kingdom	242	36	15	1.0

Individual center recruitment ranged from 1 to 73 subjects among a total of 836 centers.

The overall estimate of the Poisson rate is 2.8 events/100 person-years.

Study Phases

This initial period during which subjects were adjusted to therapy, and when the RSG group might add a third agent, was called the Randomized Treatment Phase. All patients were followed for CV endpoints during this period and thereafter. Subjects who **withdrew** from the study during this period were still followed in what was then called the CV Outcomes Phase. *It is important to note that the ‘CV Outcomes Phase’ is, in essence, nothing more than a reference to the entire length of follow up in the trial.* Those who refused to be followed for CV endpoints may have still agreed to be followed for survival status, only. Those refusing even this limited participation were later checked for survival status using Vital Status records.

Insulin Rescue

Subjects taking RSG who recorded an HbA1C of greater or equal to 8.5% on two consecutive occasions at least one month apart received the alternate background medication, thus constituting “triple oral therapy”. If further elevations of HbA1C occurred, then these patients started insulin and the RSG was dropped. Insulin was also added to MET/SU subjects who exceeded the 8.5% limit twice in two months. Either background medication could be withdrawn once a subject received insulin. During the trial, 24% of the MET/SU subjects added to insulin and 13% RSG subjects did. *Among those subjects who experienced primary events*, there were 93 subjects in the control group and 61 subjects in the RSG group who started insulin. In both groups, 78% of these subjects started insulin after the primary event occurred.

Primary Endpoint and Power

The *primary endpoint* was the composite endpoint of cardiovascular (CV) death or CV hospitalization for the following events: MI, CHF, Stroke, Unstable Angina, TIA, and selected Arterial Revascularizations. The planned total sample size of 3956 (989 X 4) subjects was based on the following assumptions: a) a composite endpoint rate of 11%/year, and b) a lost to follow-up rate of 2%/year. These numbers provide a 99.2% chance (*power*) that the upper bound of a two-sided 95% confidence interval for the hazard ratio would fall below 1.2 if the true hazard ratio were 1.0.

Considerable controversy has arisen with regard to the capacity of RECORD to demonstrate a meaningful clinical result using the primary endpoint. Much has been made of the vastly overestimated yearly event rate of 11%, when the actual event rate was more like 3%. However, the lower rate over 6 years yielded 644 primary events, enough to generate 90% power to rule out a hazard ratio of 1.3, the current FDA diabetes guidance benchmark (albeit for MACE, not RECORD’s primary composite) and just over 60% to rule out the study’s target 1.2 (assuming the true hazard ratio is 1.0).

In addition, the sponsor's unplanned interim analysis conducted in March of 2007 yielded a point estimate of 1.08 with 95% confidence interval (.89, 1.31) for the primary endpoint. At that time, the Division of Biometrics produced conditional power calculations which showed that the chances of ruling out the hazard ratio 1.2 was between 40-50% if the true hazard ratio was 1.0, and 94% for ruling out 1.3. If the true hazard was, in fact, the estimate of 1.08, then the former power decreased to 22% and latter to 80%.

For the MACE endpoint, the HR estimate was .97. If the true hazard was 1.0, the conditional power to reject 1.2 was 43% and to reject 1.3 the power was 82%.

The protocol-specified method of analysis of the primary endpoint was Cox regression with background medication (MET or SU) as a covariate. *However the eventual study report incorporates the background medications as strata in a stratified Cox regression with no covariates.*

Patient Disposition During the Trial

Table 7 Summary of Follow-up for CV Events (ITT population)

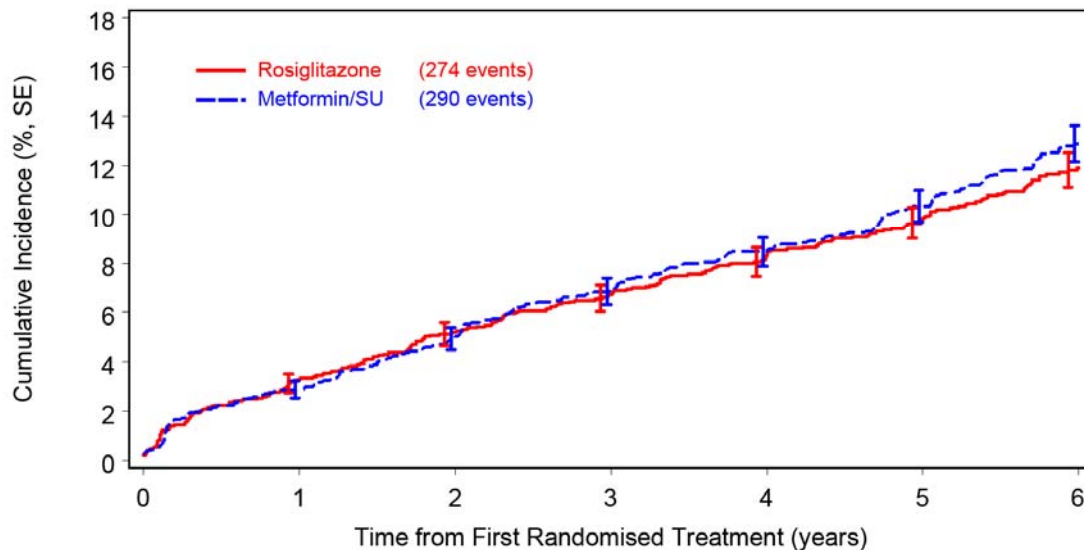
Completion Status n (%)	Treatment Group		Total (N=4447)
	Combined RSG (N=2220)	MET/SU (N=2227)	
Completion status for CV follow-up			
Completed CV follow-up to final visit ¹	1835 (82.7)	1798 (80.7)	3633 (81.7)
Died ²	111 (5.0)	139 (6.2)	250 (5.6)
Withdrew from CV follow-up	274 (12.3)	290 (13.0)	564 (12.7)
Primary endpoint	31 (1.4)	31 (1.4)	62 (1.4)
No primary endpoint	243 (10.9)	259 (11.6)	502 (11.3)
Completed follow-up for primary endpoint ³	1977 (89.1)	1968 (88.4)	3945 (88.7)
Vital status at study end for subjects withdrawn from CV follow-up			
Alive	189 (8.5)	205 (9.2)	394 (8.9)
Died	25 (1.1)	18 (0.8)	43 (1.0)
Vital status unconfirmed ⁴	60 (2.7)	67 (3.0)	127 (2.9)

Data Source: DS [Table 6.8](#) and DS [Table 6.11](#).

1. Either via main study or tracking sub-study.
2. Whilst still eligible for SAE reporting
3. Either: at least one adjudicated event; no event and completed CV follow-up to study end; no event and follow-up terminated due to non-CV death.
4. During study end window (24 Aug 2008 to 26 Dec 2008)

Over 80% of the subjects finished the trial to the final visit. The number of primary endpoints assessed after withdrawal was the same in both groups (31). **Note that Approximately 11% in both groups were truly lost to follow up with no primary endpoint assessed.** Withdrawals from CV follow up were balanced between groups. (RSG:12% vs control:13%). There was no imbalance with regard to reason for withdrawal: AE: 15 vs 19, Lost to Follow up: 54 vs 55, Survival Status, only: 59 vs 61, Own Request: 118 vs 126, and Other: 28 vs 29.

Kaplan-Meier Cumulative Incidence Curves for Time to Withdrawal from Cardiovascular Follow-up



Follow Up (FU) Time

The total follow up time to the first event was 11,500 years in each group with a median follow up on the primary endpoint of 5.7 years on each subject. These times contrast with the greater numbers (RSG: 12,346 vs control: 12,280) including time on study after the first event. *Using the latter total follow up times, the percentage of time that the control group was on randomized dual therapy was 83%, while the comparable percentage in the RSG group was 75%.*

In a commentary in the March 24/31, 2010 issue of JAMA, Dr. Steven Nissen questioned the plausibility that 88% of the follow up time in the RSG group was actually spent on RSG when 40% of the RSG subjects were not taking RSG by the end of the trial. The following table of subject numbers and person-years in the RSG group (either on dual or triple oral therapy) demonstrates that these two features of the trial are consistent.

Taking RSG at End of Follow Up?

No (N=876)		Yes (N=1344)	
Total FU time:	4169 p-y	Total FU time:	8176 p-y
Total FU time on RSG:	2685 p-y	Total FU time on RSG:	8176 p-y

Note that the two follow up times are the same for those who completed the study, and also that $876/(876 + 1344)=39.5\%$ and thus $(2685 + 8176)/(4169 + 8176)= 88\%$.

Results of Primary Composite Endpoint

Figure 4 Cumulative Incidence of Time to First Occurrence of CV Death or CV Hospitalisation (ITT population)

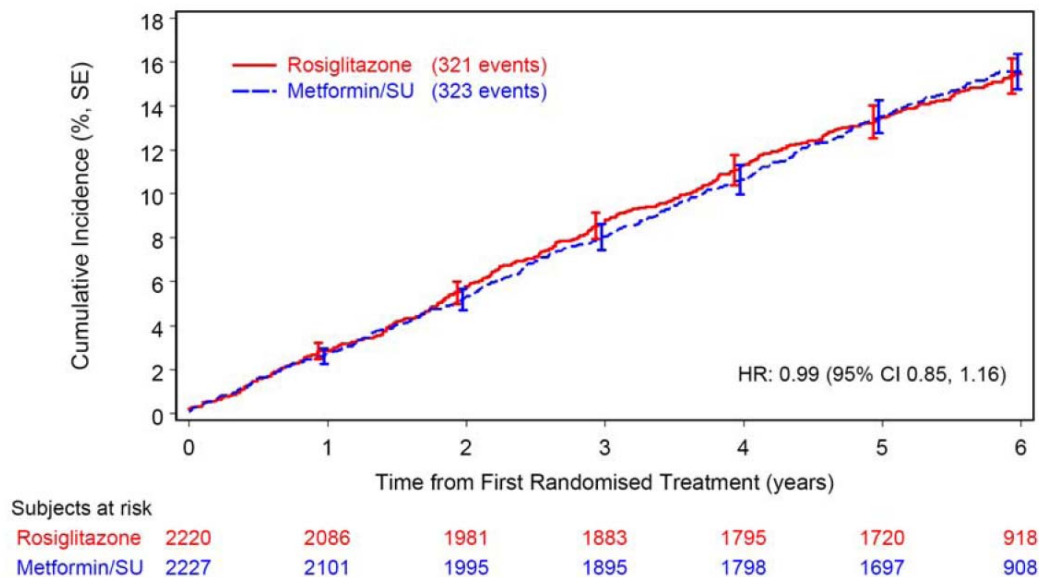


Table 49 Occurrence of CV Death or CV Hospitalisation (ITT population)

Time to First Occurrence of CV Death/Hospitalisation	Treatment Group	
	Combined RSG (N=2220)	MET/SU (N=2227)
No. (%) subjects with an event	321 (14.5)	323 (14.5)
Incidence: rate/100 PY ¹ (95% CI)	2.79 (2.49, 3.11)	2.81 (2.51, 3.13)
Hazard ratio ² , (95% CI); Non-inferiority p-value ³	0.99 (0.85, 1.16); p=0.0164	
Absolute rate difference/100PY ¹	-0.02 (-0.45, 0.41)	

The figure and table above are the sponsor's summary of the statistics for the primary composite endpoint. *The protocol-specified analysis using background medication as a covariate yielded nearly identical results.* Note that 1.16 is the upper bound of the confidence interval for the hazard ratio. There was a total of 644 primary events. Adjustment for baseline covariates (smoking status, age, blood pressure, waist circumference, alanine aminotransferase, hemoglobin, WBC, history of peripheral vascular disease and history of ischaemic heart disease) produced a hazard ratio of 1.05 with confidence interval (.88, 1.25). However, this analysis includes only 499 events due to missing covariate values on 1042 subjects. The curves cross slightly at 5 years, reversing a trend which had been favoring the control group. If the 80 events occurring after 5 years are censored, the results do not change from the primary analysis. Similarly, using time-dependent indicator variables in a Cox regression, there is no evidence of a time by treatment interaction with respect to the hazard ratio. In addition to the Cox analysis, the Mantel-Haenszel analysis stratified on centre yields an odds ratio of .98 with

upper confidence bound of 1.17. The Breslow-Day test p-value for treatment by centre interaction is .45.

Another portrait of the evolution of the primary endpoint events is the yearly epochal incidence densities by treatment group displayed below.

	<u># Events/100 person-years</u>					
Yearly Epoch:	0-1	1-2	2-3	3-4	4-5	5+
RSG:	2.9	2.8	3.3	2.9	2.5	2.2
MET/SU	2.7	2.7	2.9	2.9	3.3	2.2

Note the lower incidence rate in the RSG group between years 4 and 5 which accounts for the merging of the cumulative incidence curves and the reduction in rates after 5 years.

Table 51 Summary of First Events Contributing to CV Death or CV Hospitalisation (ITT population)

Event Contributing to Primary Endpoint n (%)	Treatment Group	
	Combined RSG (N=2220)	MET/SU (N=2227)
Subjects with event contributing to primary endpoint	321 (14.5)	323 (14.5)
CV Death	33 (1.5)	39 (1.8)
Acute MI	3 (0.1)	4 (0.2)
CHF	2 (<0.1)	0
Sudden death	8 (0.4)	8 (0.4)
Acute vascular events ¹	0	2 (<0.1)
Other CV mortality	2 (<0.1)	1 (<0.1)
Death: Presumed CV cause (insufficient data)	18 (0.8)	24 (1.1)
CV Hospitalisation	288 (13.0)	284 (12.8)
Acute MI	53 (2.4)	46 (2.1)
Unstable angina pectoris	20 (0.9)	21 (0.9)
CHF	39 (1.8)	19 (0.9)
Stroke	43 (1.9)	56 (2.5)
Transient ischaemic attack	9 (0.4)	9 (0.4)
Invasive CV procedure	24 (1.1)	25 (1.1)
Amputation of extremities	1 (<0.1)	10 (0.4)
Other CV hospitalisation ²	99 (4.5)	98 (4.4)

Primary Events Before and After the Interim Analysis (IA)

Between 75%-80% of the person-time in the trial accumulated before the publication of the IA in June of 2007. Some questions have arisen about the conduct of the trial before and after the publication. The follow up times (person-years) to the first adjudicated event and incidence densities/100 p-y for each group before and after the publication of the IA are as follows:

	Person-time		Incidence Densities	
	Before	After	Before	After
RSG	9173	2357	2.9	2.2
MET/SU	9186	2327	2.9	2.5

The rate of primary events on RSG was somewhat less than that of the MET/SU group after the IA while the rates in both groups seem to decrease.

In terms of withdrawals, recall that there were a total of 502 subjects who withdrew without having had a primary event. *After the publication of the IA*, 65 of these subjects withdrew in each group. The groups' distributions of reasons for withdrawal were similar, and there was no evidence that the rate of withdrawal without a primary event was different before vs after the IA.

A note on adjudication: This data is for adjudicated events. There are cases in which an event was *reported before* the publication but *adjudicated after* the publication. Specifically, among subjects who eventually went on to have experienced adjudicated events in the MET/SU group, there were 267 primary events that had onsets before the publication. Of the 236 of those that were reported to the CEC, 36 were adjudicated *after* the publication. In the RSG group, the respective numbers were 270, 245, and 25.

The numbers in the table above may help to explain why there might be a perception of a 'drop off' in the number of events after the interim analysis. It is true that there is a smaller percentage of events after the interim analysis than would be expected if follow-up time and number of events were exactly proportional to each other. For example, there were 435 events before and 109 events after. Thus the share of events after the IA was 16.9%, whereas the proportion of person-time was 20.3%. It is also the case that the rate of withdrawal without a primary endpoint was greater after the IA than before (1.9/100 p-y before, 2.5/ 100 p-y after). This increased rate of withdrawal after the IA may be responsible for the incidence of fewer events.

The Issue of Statins

A. Statin use and Events

In those who were *not* on a statin at baseline **and** who *eventually had a primary event*, statin use arose sometimes after a subject had suffered a primary event. Specifically, there were 510 subjects who had an event and who were *not* on a baseline statin. In the control arm, 201 subjects received a statin at the time of or *after* a primary event, while 178 did so in the RSG arm. Among those who got a statin *before* their events, 55 were in the MET/SU group and 76 in the RSG group.

There were 3114 subjects who were *not* on a baseline statin and who *did not* have a primary event, approximately 1550 subjects in each group. In the MET/SU group 492 subjects (32%) received a statin during the study while 671 (43%) in the RSG group did so.

Among the 2180 subjects who were never on a statin, there were 99 primary events on RSG (n=995) and 130 events on MET/SU (n=1185), with HR=.92 (upper confidence bound=1.20). For the MACE endpoint (CV death, MI, or stroke) in this subgroup, the hazard ratio was .74 with an upper 95% confidence bound of 1.08. Since these subjects may have been at low risk, we can also look at the 578 subjects who were taking a statin at baseline (presumably at higher risk) who never had a change in dose. Of the 320 control subjects, 13 had MACE's (4.1%) while 17 of 258 subjects (6.6%) did so in the RSG group.

Of note is the fact that the chances of having a primary event in the “never statin” subjects was 1.5 times the chance of the subjects who had a baseline statin which never changed on study.

B. Potential Bias Due to Statin Imbalance

1) Attention has been drawn to the fact that a greater proportion of subjects on RSG took statins than in the control group. According to the sponsor's report, at baseline approximately 18% of the subjects in both groups were taking statins. At the end of year 4, 48% were taking statins in the RSG group and 40% in the control group. The sponsor conducted an analysis that claims that if the assumption that a statin's effect is a 25% decrease in risk of the primary endpoint, then there would be no more than a 2% adjustment. A demonstration of this potential bias on the risk ratio scale follows:

Let s_1 = % of subjects on statins in the control group

s_2 = % of subjects on statins in the RSG group

b = background risk of the primary endpoint in subjects *not* on statins

Then the risk in the control group is $s_1 \cdot .75 \cdot b + (1 - s_1) \cdot b$.

And the risk in the RSG group is $s_2 \cdot .75 \cdot b + (1 - s_2) \cdot b$.

The risk ratio is then $(1 - .25 \cdot s_1) / (1 - .25 \cdot s_2)$ (control:RSG).

With $s_1 = .4$ and $s_2 = .48$, the Risk ratio = $(1 - .10) / (1 - .12) = 1.02$.

If the risk difference is used, the result is exact because $(.48 - .40) \cdot .25 = .02$.

Thus, the inflation factor is approximately 2% and the point estimate for the primary endpoint hazard ratio (.99) would be adjusted to $1.02 \cdot .99 = 1.01$ and the upper bound of the 95% confidence interval to 1.19. If statin use at 5 years is used, then the inflation factor is 1.027. If the risk reduction due to a statin is set at 40%, then the above ratio is 1.037. N.B.: The application of a population inflation factor to a point estimate is very dubious and is presented only for heuristic illustration.

2) Another way to search for potential bias in the use of statins is to divide all subjects into two groups: those who changed statin status during the trial and those who did not. The former consists of subjects who were not on a baseline statin but who were put on a statin during the trial, and those who were on a statin at baseline who either had the dose increased or got an additional statin during the trial ('statin changers'). The latter group consists of those who were not on a baseline statin and never got one during the trial, and those who were on a baseline statin and did not change dose or receive an additional statin.

Among 'statin changers', we compare mean (yearly) cross-sectional LDL levels of those who had a primary event with those who did not. If statin use were to have an effect on the risk of an event, one would expect the mean of those who eventually suffered an event to be greater than those who did not have an event, regardless of treatment group. More precisely, if the distributions of LDL over time of those who suffered an event were the same as the distributions of those who did not suffer events, then having an event would be independent of LDL level. Thus, there would be no importance to the differential statin use between the two groups among statin changers. This data pattern can also be interpreted as a series of time-wise logistic regressions with LDL level as the covariate. The test of association is essentially a t-test comparing the LDL means of the "event" vs "no event" groups. Since these are post-randomized subgroups, a basic caveat

is required, viz. that those at greater baseline risk (subjects with events) do not have LDL's lower than would be expected if they had not been at greater risk than those without events. This seems to be a reasonable assumption.

The groups are pooled and disjoint cohorts of subjects are generated based upon the year of their events: 1, 2, 3, 4, 5, 6+. Thus, for subjects with a primary event (excluding CHF), the calculation of the mean LDL at a particular year uses all subjects whose event occurred during that year or later. Also, we use only the events for which the statin status changed *before* the event. The table below displays the mean LDL's of those with and without primary events over time:

	<u>Mean LDL (#subj with event)</u>	<u>Mean LDL(#subj w/o event)</u>
Baseline	137 (121)	139 (1216)
Year 1	134 (112)	138 (1203)
Year 2	124 (98)	124 (1149)
Year 3	122 (70)	118 (1101)
Year 4	103 (46)	109 (1034)
Year 5	111 (22)	111 (937)

Mean LDL levels are similar, but there seems to be a trend where the mean is the same or lower in those with events rather than those without, contrary to the expectation that taking post-randomization statins might have an appreciable effect on preventing primary events.

3) Due to the guidelines for treating subjects with elevated LDL, the greater use of statins in the RSG group could be due to the larger percentage of subjects who reached an LDL of 130 mg/dL during the trial. The data set with LDL lab values accounts for 4209 subjects about of the total of 4447, 2097 in the control arm and 2112 in the RSG arm. Sixty-three percent (63%) of the control subjects exceeded 130 during the trial, while 75% did so in the RSG arm.

First, we examine the extent to which investigators followed the guidelines for treating subjects who LDL exceeded 130 sometime during the trial *among those who changed their statin status during the trial*. The fraction of control subjects who received a statin *after* reaching 130 was 86% while 85% did so in the RSG group.

Second, among the subjects who reached 130, the fraction of the RSG group who received a statin *and* did so *after* reaching 130 was 42% ,while 33% did so in the control group. The larger percentage in the RSG group could be due the higher rate of statins

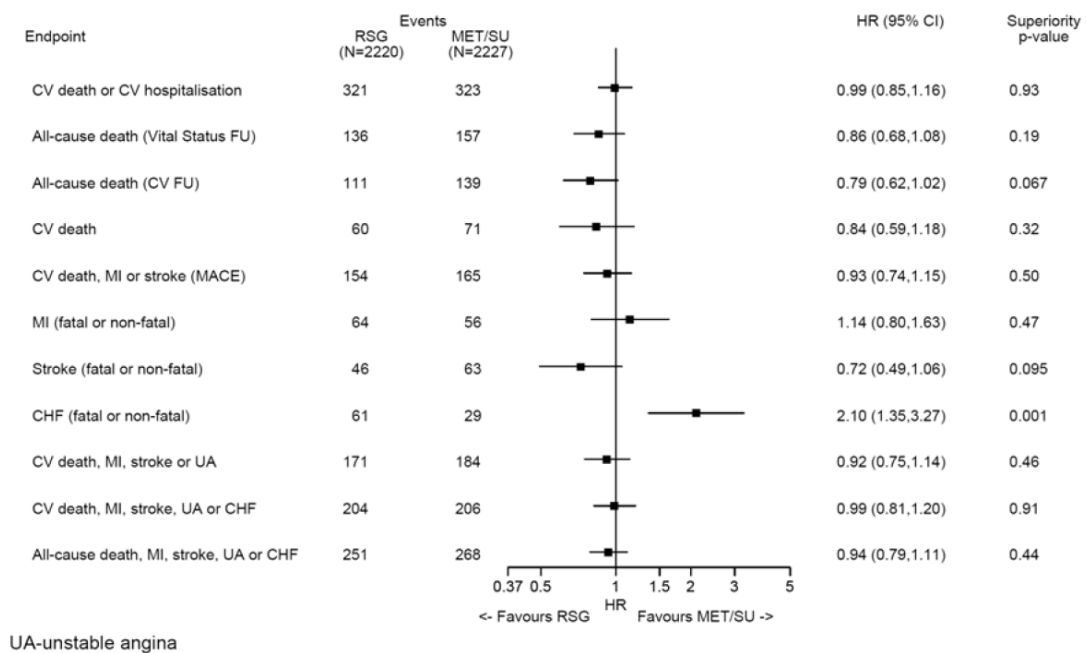
administered overall in the RSG group: 46% vs 34%.

Third, the fraction in the RSG group who received a statin but *never* reached an LDL of 130 was 31%, while 25% did so in the control group.

There is no indication that the treatment groups were treated differentially with regard to on-study administration of statins once a reaching an LDL>130.

Secondary Endpoints

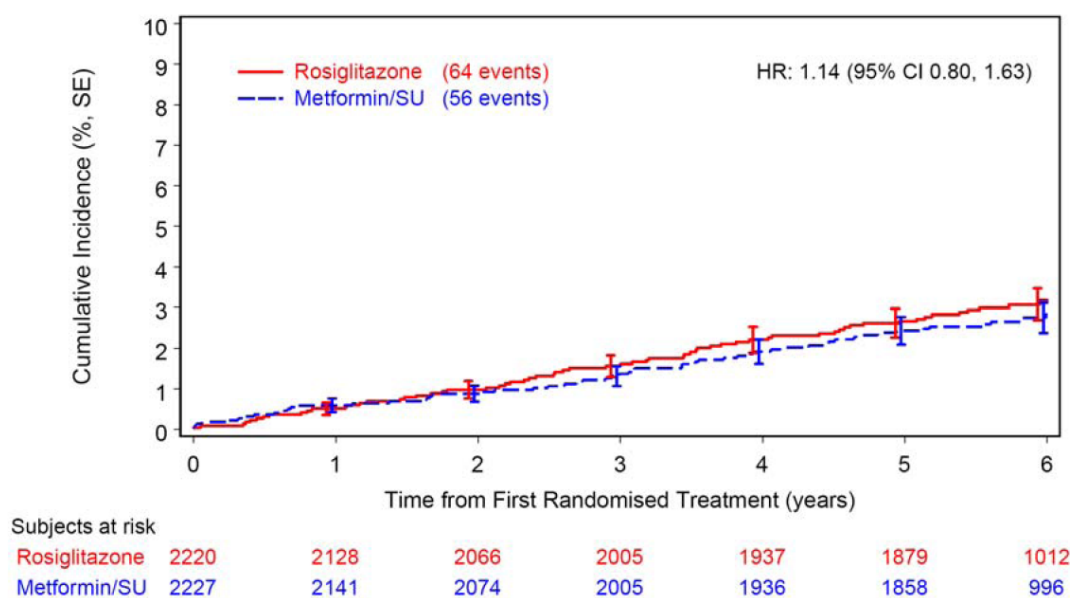
Figure 10 Forest Plot of Hazard Ratios (95% CIs) for Secondary CV Outcomes (ITT population)



The numbers in this table do not necessarily reflect first events. Thus, if someone had a stroke as a first event and then went on to have an MI, the MI is counted in the table above. Note that CHF is an expected risk when taking RSG and that there is somewhat protective effect of RSG for stroke. The confidence intervals and p-values are not adjusted for multiple comparisons. See below for a discussion of myocardial infarctions.

Myocardial Infarctions

Figure 15 Cumulative Incidence of Time to First Occurrence of Acute MI (ITT population)



The only secondary endpoints which have upper bounds above 1.2 are MI and CHF. The association between RSG and CHF is well known, so that a more relevant endpoint is MACE whose upper bound is 1.15. For MI, the overall rate was .5/100 persons per year. and there are 8 more cases of MI in the RSG group than in the control. The upper bound of 1.63 follows largely from the fact that the total number of MI's is 1/5 of the total number of primary endpoints.

The p-value for interaction between treatment and background medication was .13, which resulted from the following pattern in the subgroup of subjects with a history of ischaemic heart disease: In subjects on background MET, there were 11 MI's in the group randomized to RSG and 4 in the group randomized to SU; whereas in subjects on background SU, there were 9 MI's in the group randomized to RSG and 15 in the group randomized to MET.

As a sensitivity analysis, the 5 MI's occurring within a month of randomization were deleted. The result was a hazard ratio of 1.21 with confidence interval (.83, 1.76), 52 control MI's and 63 RSG MI's.

There are those who wish to treat RECORD as an *inferiority* trial, i.e. hold it to the standard which would have been imposed on a trial whose goal was to demonstrate that RSG was strictly inferior to the control group (the lower bound of the confidence interval

excluding 1.0). This interpretation is in response to Dr. Nissen's statement in the March 24/31 2010 issue of JAMA:

Fortunately for GSK, the steering committee was convinced to publish an interim analysis, even though the analysis was so underpowered that no conclusion could be drawn about the safety of rosiglitazone.

It is important to keep in mind the fact that power is a function, not only of the number of events, but also the true hazard ratio which is not knowable. Instead of creating various scenarios for a true hazard which lead to different powers given the number of events in the trial, it is more straightforward to look at confidence intervals as follows:

We treat Dr. Nissen's meta-analysis as evidence purporting to demonstrate the greater risk of RSG. In one of his meta-analyses, there were 158 MI's. One of his statistical methods achieved a p-value below .05, indicating "statistical significance". Using simple asymptotic results, we can compute the entire family of confidence intervals as a function of the observed hazard ratio, HR. In this case, it is:

$$(HR*.73, HR*1.38), \text{ or equivalently } HR*(.73, 1.38),$$

where the two numbers in the parentheses are reciprocals of each other. They are related to the square root of the total number of events. One can interpret this expression as separating two components: The HR is the signal not directly dependent on the number of events, and the numbers in the parentheses related to the amount of information contributing to the width of the confidence interval. We can now ask: what would the HR in Dr Nissen's study have to be in order for the lower bound of the confidence interval to exclude 1.0. Since .73 and 1.38 are reciprocals, the answer is simply 1.38, which was in fact close to the HR in his meta-analysis.

Now RECORD had 120 MI's. The corresponding family is:

$$(HR*.71, HR*1.44), \text{ or equivalently } HR*(.71, 1.44),$$

where again the numbers in the parentheses are reciprocals.

Note that there is little difference between 1.38 and 1.44, indicating little difference in the information available for constructing confidence intervals and also the HR required to exclude 1.0. For RECORD, the HR would have had to be 1.44. But the actual ratio was 1.14, 21% below the required HR. Hence there is evidence that the lack of statistical inferiority of RSG is due to a weak signal rather than the lack of 'enough' events to reach statistical significance. In fact, with 1.14 as the HR estimate, it would have taken approximately 910 MI's events to reach statistical significance at the 5% level.

There appears to be a drop off in the rate of MI's after the interim analysis (IA) in March 2007. The table below displays the incidence rates of MI before and after March 30, 2007. *Rates reflect the onsets of MI in the 120 subjects who were eventually adjudicated*

to have had MI's. After the IA, there were 18 subjects with these events: 8 in the control group and 10 in the RSG group.

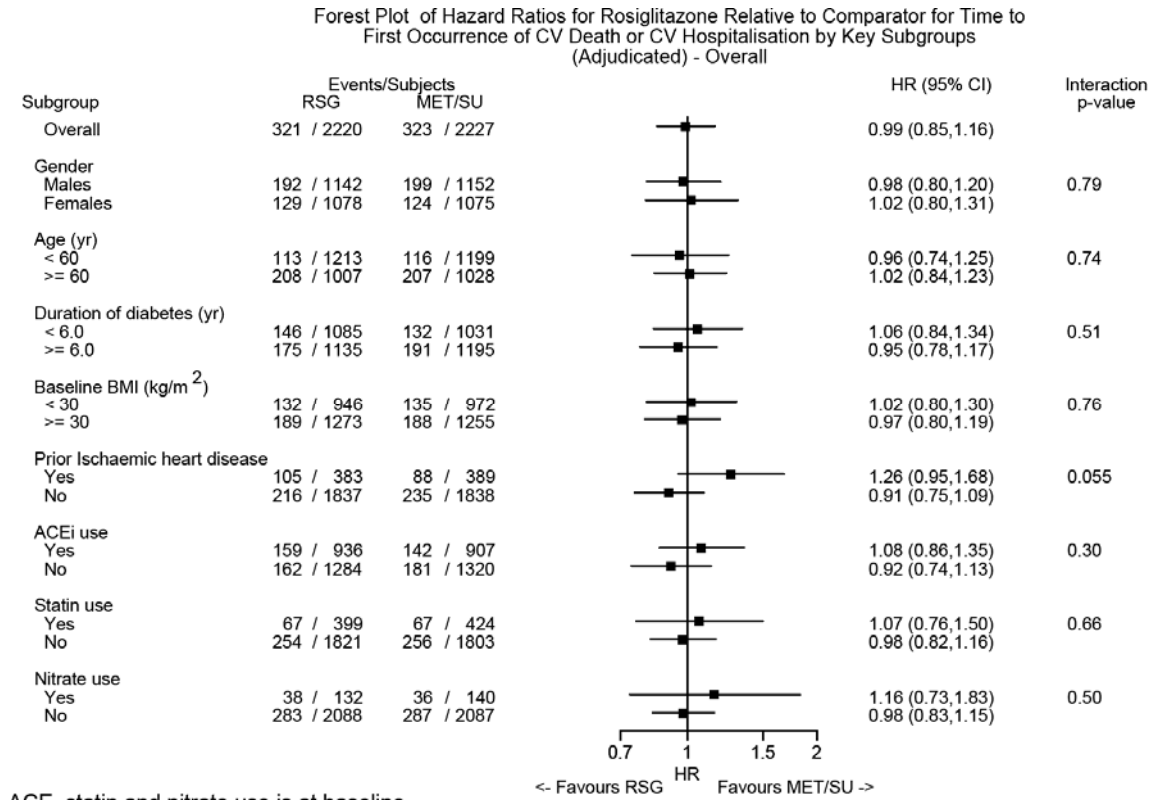
	<u>Person-time</u> (#events)		<u>Rates</u>	
	Before	After	Before	After
RSG	9240 (54)	2943 (10)	.58	.34
MET/SU	9255 (48)	2900 (8)	.52	.28

Note that there is no evidence that the difference between rates in the groups differed before vs after the IA.

Using the simplifying assumption of proportionality of person-time to events, one would expect 32 MI's after the IA rather than the 18 which occurred. According to the sponsor, there were no events reported as MI's after the IA that were later adjudicated to be non-MI's according to the Investigator-Reported Terms for MI.

With regard to MI's which might have occurred among the 502 subjects who withdrew from the trial and not followed up, there were approximately 1700 person-years lost using Oct 15, 2008 as the endpoint of the trial (the midpoint of the window for final visits between August and December 2008). Using the overall rate of .5/100 person years, we estimate that approximately 8 unknown MI's may have occurred. If all 8 are attributed to the RSG group, a chi-square test comparing the groups yields a p-value of .15.

Subgroups and Interaction



Subjects with Prior Ischaemic Heart Disease

In this subgroup, seventeen (17) more subjects in the RSG arm than in the MET/SU arm had first events included in the primary endpoint (105 vs 88). The HR of 1.26 and upper CI bound of 1.68 attracts attention as a signal of concern. The breakdown of CV events (including events that may have occurred after a first primary event) is displayed below:

Number of Events

	RSG	MET/SU
MI	20	19
Stroke	10	9
CV death	23	24
CHF	17	8

These numbers do not reflect strictly first events, but they overwhelmingly do. A subject in the table may have had more than one event, clearly if he/she died of the event. However, there were only 4 cases of non-fatal repeat events. It is clear that the reason that there is a “signal” is due to the result for CHE, an endpoint which is essentially deemed irrelevant for the purpose of comparing ischaemic risk. The other results in this subgroup do not indicate an increased risk of MACE endpoints in the RSG arm.

Experience on Dual Randomized Therapy

One of the factors advanced for the questionable interpretability of RECORD is the potential modification of the randomized treatments. Consequently, an alternative to the ITT analysis is to account for only events and person-time while on the dual randomized treatment.

In all, 48% of the subjects completed the study on dual therapy, 45% on RSG and 51% in the control group. As stated above, *the percentage of time that the control group was on randomized dual therapy was 83%, while the comparable percentage in the RSG group was 75%. The total of 492 events occurring on dual therapy represents 76% of the total of 644 ITT events. See table below.*

Summary of Adjudicated Cardiovascular Endpoints, “Per-Protocol” Analyses (Time on Randomized Dual Combination Therapy Only)				
Endpoint	Combined RSG N=2220 n (%)	Combined MET/SU N=2227 n (%)	HR (95% CI)	Absolute Rate Difference per 100 PY (95% CI)
CV death or CV hosp	237 (10.7)	255 (11.5)	1.03 (0.86, 1.23)	0.07 (-0.40, 0.54)
All-cause death	29 (1.3)	46 (2.1)	0.69 (0.44, 1.11)	-0.14 (-0.31, 0.03)
CV death	23 (1.0)	34 (1.5)	0.75 (0.44, 1.27)	-0.09 (-0.24, 0.07)
CV death, MI or stroke (“MACE”)	94 (4.2)	117 (5.3)	0.89 (0.68, 1.17)	-0.13 (-0.43, 0.17)
Myocardial infarction (fatal or nonfatal)	47 (2.1)	44 (2.0)	1.18 (0.78, 1.78)	0.08 (-0.12, 0.27)
Stroke (fatal or nonfatal)	32 (1.4)	51 (2.3)	0.69 (0.45, 1.08)	-0.16 (-0.34, 0.03)
Heart Failure (fatal or nonfatal)	39 (1.8)	22 (1.0)	1.95 (1.16, 3.29)	0.21 (0.05, 0.37)
CV death, MI, stroke or unstable angina	110 (5.0)	133 (6.0)	0.92 (0.71, 1.18)	-0.11 (-0.43, 0.21)
CV death, MI, stroke, unstable angina or HF	142 (6.4)	154 (6.9)	1.02 (0.81, 1.28)	-0.02 (-0.35, 0.32)
All-cause death, MI, stroke, unstable angina or HF	148 (6.7)	166 (7.5)	0.99 (0.79, 1.23)	-0.02 (-0.39, 0.34)

In this reduced follow up analysis, confidence intervals are wider than in the case of the ITT analysis due to fewer events but otherwise similar to the ITT results. There is only a difference of 3 MI events between the two groups, so that the upper bound of 1.78 conveys little information about the true potential risk ratio for MI.

Table 15 Reasons for Discontinuation of Randomised Dual Combination Treatment (ITT population)

Completion Status for Dual Combination Treatment, n (%)	Treatment Group		Total (N=4447)
	Combined RSG (N=2220)	MET/SU (N=2227)	
Completion Status			
Completed study to final visit on randomised (dual) treatment	1003 (45.2)	1131 (50.8)	2134 (48.0)
Prematurely discontinued ¹	1217 (54.8)	1096 (49.2)	2313 (52.0)
Subsequent CV Follow-up for Withdrawals ²			
Insulin ³ /triple therapy initiated ⁴	615 (27.8)	373 (16.7)	988 (22.2)
Moved to post-RT CV follow-up (reason other than insulin)	360 (16.2)	425 (19.1)	785 (17.7)
Withdrawn from CV follow-up	173 (7.8)	206 (9.3)	379 (8.5)
Reason for discontinuation of randomised (dual) treatment			
Insulin Initiated ³	64 (2.9)	377 (16.9)	441 (9.9)
Adverse Experience ⁵	278 (12.5)	300 (13.5)	578 (13.0)
ALT levels > 3 times the upper limit of reference range	3 (0.1)	2 (<0.1)	5 (0.1)
Continued participation presents safety risk due to medical condition	16 (0.7)	19 (0.9)	35 (0.8)
Prohibited glucose lowering medication	15 (0.7)	59 (2.6)	74 (1.7)
Subject admitted to long-term healthcare facility	5 (0.2)	3 (0.1)	8 (0.2)
Lost to follow-up	36 (1.6)	43 (1.9)	79 (1.8)
Triple-therapy initiated ⁴	553 (24.9)	0	553 (12.4)
Other	247 (11.1)	293 (13.2)	540 (12.1)
High HbA1c	6 (0.3)	48 (2.2)	54 (1.2)
High HbA1c, insulin refused	2 (<0.1)	15 (0.7)	17 (0.4)
Add-on study drug stopped for >2 weeks	8 (0.4)	6 (0.3)	14 (0.3)
Poor compliance	18 (0.8)	23 (1.0)	41 (0.9)
Subject moved	16 (0.7)	18 (0.8)	34 (0.8)
Subject withdrew at own request	150 (6.8)	137 (6.2)	287 (6.5)
Withdrawal reason not reported	14 (0.6)	14 (0.6)	28 (0.6)
Other	33 (1.5)	32 (1.4)	65 (1.5)
Death terminated randomised (dual) treatment follow-up	69 (3.1)	92 (4.1)	161 (3.6)

Data Source: DS [Table 6.24](#) and DS [Table 6.26](#)

1. This includes those where death terminated randomised dual therapy
2. Subsequent CV follow-up for Withdrawals excludes subjects known to have died
3. Insulin initiated as indicated by tick box for reason for discontinuation of randomised treatment. Randomised treatment was to be stopped on initiation of insulin therapy
4. Triple therapy initiated as indicated by the add-on study medication dosing records.
5. Includes fatal and non-fatal AEs.

Of those who discontinued dual therapy in the RSG group (n=1217), 23% did so due to adverse experiences (AE's). Twenty-seven percent (27%) did so in the MET/SU group. In the RSG group, 45% of discontinuations were due to initiation of triple oral therapy. Triple oral therapy was not available to MET/SU subjects.

Due to the different protocol provisions for subjects who needed additional therapy due to HbA1C's reaching 8.5, the control arm experienced approximately 900 more person years on dual therapy than the RSG arm. This additional time to accumulate events in the control group could have resulted in making the RSG arm look similar to or better than the control arm in terms of percentage of events. However, the percentage of total events in the RSG arm (48%) is the same as its percentage of total person-time (8834 vs 9761), suggesting an essentially null result. More explicitly, the rates were 2.7 events/100 p-y in the RSG arm and 2.6/ 100 p-y in the control arm. A stratified (on background medication) Poisson analysis yields a relative risk of 1.02 with a p-value of .76 and a 95% confidence interval of (.86, 1.23).

The Kaplan-Meier plots below display the primary endpoint results for the 4 randomized strata. The lowest curve is the RSG arm with SU as background medication, suggesting a somewhat a higher rate in one of the RSG strata. However, the overall multivariate logrank p-value is .81 and the Wilcoxon p-value is .59. The logrank test for a difference between the RSG background strata yielded p= .57.

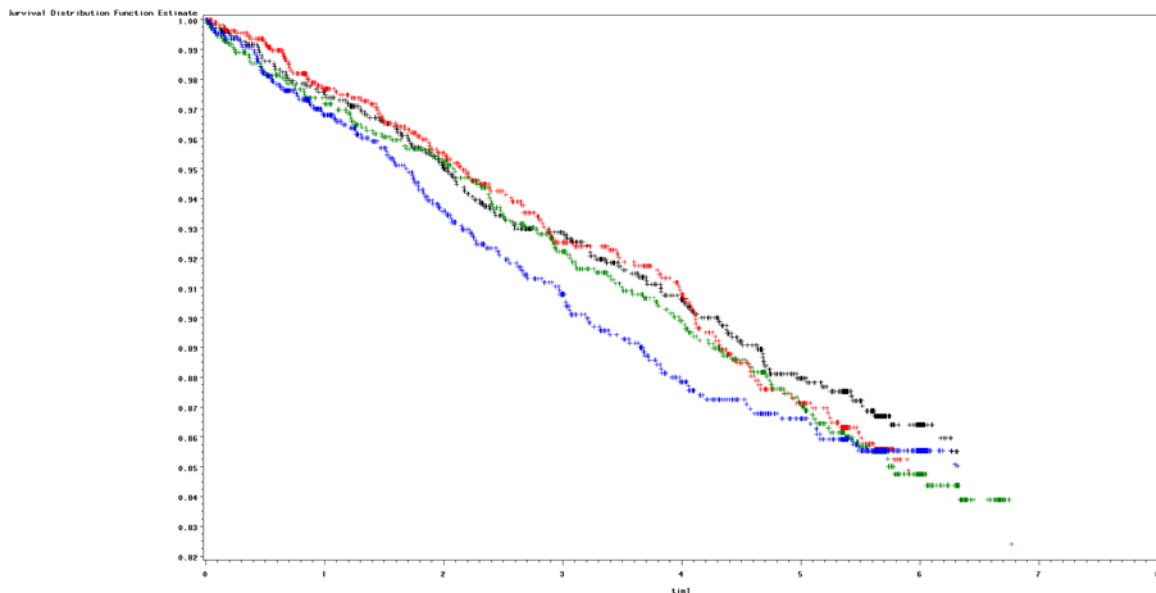


Figure 20 Cumulative Incidence of Time to Death from CV Causes (ITT population)

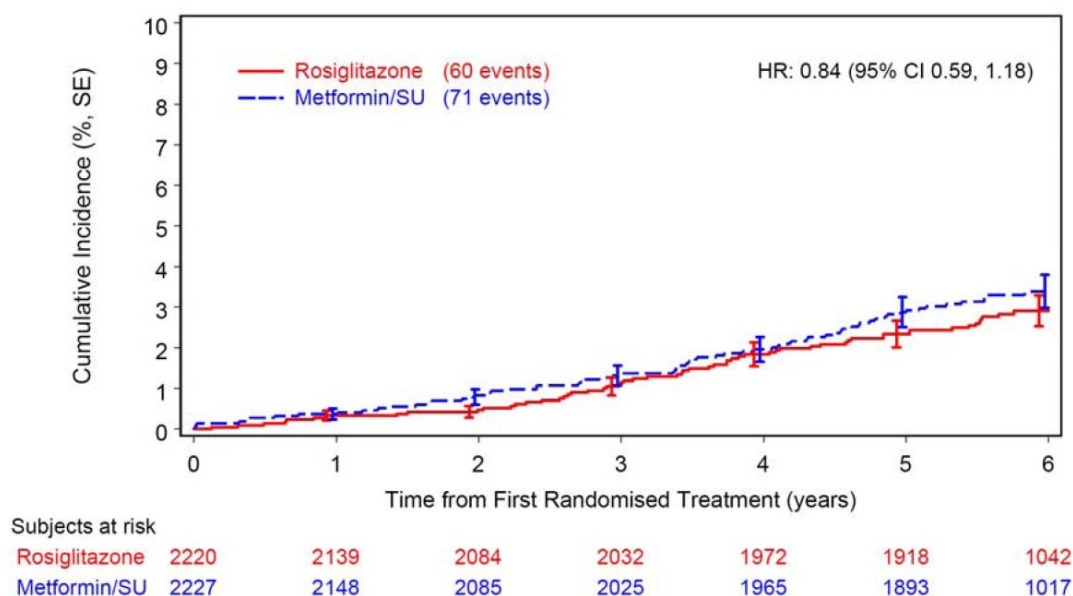


Figure 21 Cumulative Incidence of Time to Death from Any Cause (CV Follow-up) (ITT population)

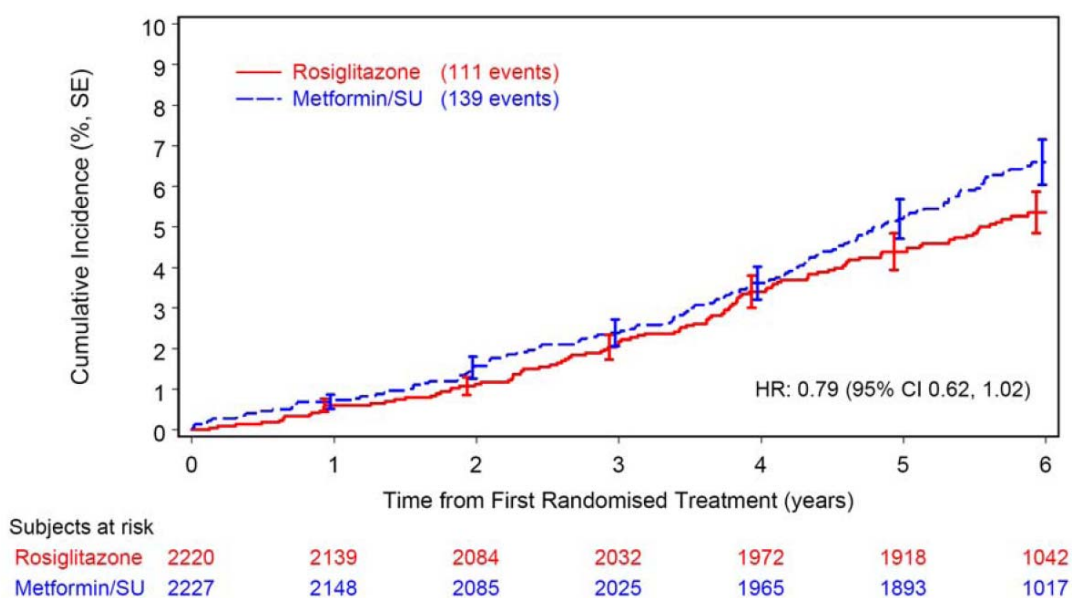
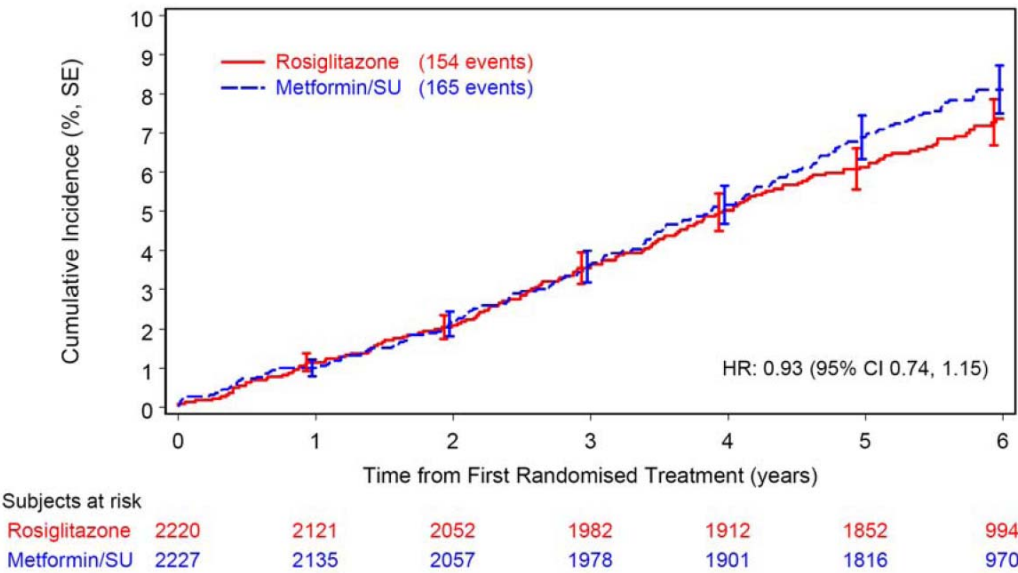


Figure 11 Cumulative Incidence of Time to First Occurrence of MACE (ITT population)



Date: June 18, 2010

From: Susan Leibenhaut, M.D., Medical Officer, GCP II

Thru: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP II

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Summary of Inspections for NDA 21-071

Division of Scientific Investigations

I. Background

Five inspections were performed in support of this NDA: three clinical sites, the sponsor GlaxoSmithKline (GSK), and Quintiles, a contract research organization (CRO). Inspections of the clinical sites, the sponsor, and CRO targeted subject records that contained entries such as adverse events and hospitalization that either were not submitted as potential endpoints, were submitted late for adjudication, or were adjudicated as not representing an endpoint. Inspections of GSK and Quintiles were conducted to assess adjudication support procedures as a result of 1) concerns regarding ascertainment and adjudication of the primary endpoints of cardiovascular (CV) hospitalizations and CV death and 2) concerns about clinical trial governance and the effect of an unplanned interim analysis in June 2007 on clinical trial conduct. It is beyond the scope of inspections and of this review to evaluate the appropriateness of the 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.

Name of CI/ Sponsor/ CRO and Location	# of Subjects enrolled (for clinical sites) or inspection goals
GlaxoSmithKline Sponsor London, UK	Sponsor inspection
Quintiles -CRO Dublin, Ireland	CRO/ Adjudication committee inspection
Zeljko Metelko Croatia	57 subjects
Lena Nicol Sweden	73 subjects
Elena Henkel Dresden, Germany	58 subjects

II. Inspections of the Clinical Sites

The review division selected three clinical sites for inspection based on high enrollment. Because of the large number of clinical sites in the trial, these 3 sites represented less than 1% of the 364 centers in 25 countries that participated in the trial. A total of 188

subjects (4%) of the 4447 subjects enrolled into the trial participated at these sites. Inspections targeted subject records containing entries such as hospitalization, adverse events or concomitant cardiovascular medications, or other entries that may have suggested potential under-reporting of cardiac events. A total of 60 subjects' records meeting these criteria were reviewed in detail at these three sites and no significant regulatory violations were detected.

Of the 60 patient records reviewed, there was only one potential endpoint (congestive heart failure in the rosiglitazone group) that more appropriately than not, should have been submitted for adjudication. This potential endpoint was not initially submitted by the inspected clinical site for adjudication. However, it was later submitted in response to a Sponsor data query requesting that the clinical investigator (CI) reconsider whether to report this event as an endpoint, most likely as part of the routine review of serious adverse event (SAE) data established to find unreported endpoints. The CI subsequently withdrew this potential endpoint from adjudication, and the rationale for withdrawal is undocumented by the clinical investigator. This episode may have been due to the lack in the protocol of a definition of "potential" endpoint to trigger referral for adjudication and the complicated requirements for potential endpoint reporting by the clinical investigative sites. While it appears that the intent of the sponsor and CRO was to set lower threshold requirements for reporting a potential endpoint than the requirements for positive adjudication of an endpoint, this was not explicitly stated in the protocol or other study documents including the endpoint CRFs. Although the protocol defined the requirements for positive adjudication of an endpoint, (e.g. myocardial infarction is defined as hospitalization plus elevation of biochemical markers plus either typical symptoms of cardiac ischemia or new pathological ECG findings; congestive heart failure is defined as hospitalization requiring a change in current medication in the context of new symptoms and signs and objective evidence of cardiac dysfunction), and the CRFs had detailed checklists, the definition of "potential" was not provided, giving the investigators the impression that they were to have the same criteria for referral to the Clinical Endpoint Committee (CEC) as the CEC had for positive adjudication. According to CEC telecon minutes of January 26, 2009, it appears that the majority of the "potential" endpoints captured in the SAE data review process mentioned above resulted in adjudication as not representing an endpoint. We cannot determine whether this specific potential endpoint would have been positively adjudicated if referred to the CEC. Another limitation of the inspection was that for many sites, subjects were treated for CV events at locations other than the study site. Adverse event reporting relied on subject reporting of events to the clinical investigator who then had to obtain records documenting the event

III. Sponsor Inspection of GlaxoSmithKline (GSK)

The inspection of GSK focused on issues concerning clinical trial governance including review of the charters and minutes of the Steering Committee (SC), CEC, and Data Safety Monitoring Board (DSMB), and interviews with chairmen of these committees. The Clinical Trial Master File including contracts, monitoring reports, and data management procedures was reviewed, and the inspection targeted subject records that had been identified by the Cardioresenal review division as indicative of possible under-

reporting of cardiac events, or identified from the CEC MS Assess Database with long intervals between the time of the event and the date of submission to CEC. Subjects' files from sites in Sweden and Australia that were monitored by GSK and from the Slovak Republic that were monitored by Quintiles were reviewed for completeness of endpoint reporting. A total of 32 subjects' records were reviewed.

Interviews with GSK staff determined that GSK set-up the clinical trial governance structure to include: a Steering Committee (SC), Data Safety Monitoring Board (DSMB), and the CEC. GSK contracted directly with each of the members of these groups. GSK and the members of these groups approved the charters that defined each of their functions. The SC consisted of seven external individuals and two sponsor representatives. Prof Phillip Home, diabetologist was the chair and Prof. Stuart Pocock, statistician, served on the SC and also as the liaison with the London School of Medicine and Hygiene, the external body responsible for performance of statistical analysis of data provided by GSK. The responsibility of the SC was to work "with the sponsor to ensure proper study conduct and conformance to the protocol." The SC was to "assess the impact of safety information provided by the DSMB or Sponsor and liaise with the DSMB and Sponsor in the event that protocol amendments or other actions are recommended on the basis of emerging safety data." Additional functions of the SC were to review and approve charters of the committees, develop patient identification strategies, review patient recruitment rates and assist the sponsor in coordination of study-related publications and presentations. A quorum, defined as a minimum of 4 of 7 non-Sponsor members was required at meetings and an absolute majority of total members (5 or more) was required for a routine proposal that did not involve suspending enrollment, eliminating a treatment arm or discontinuing the study. The SC could not exclude the Sponsor from its deliberations. GSK wrote the protocol for review by the SC. The DSMB consisted of 5 individuals: Prof. Ian Campbell, diabetologist was the chair and, Prof. Ian Ford was the statistician. The responsibility of the DSMB was to work with the SC and Sponsor to monitor the safety of patients treated with rosiglitazone. They were to review reports summarizing accumulating interim information concerning safety, including serious adverse events (SAEs), all cause mortality, and CV deaths. A simple majority of total membership (3 or more members) was required for a proposal that did not involve suspending enrollment, eliminating a treatment stratum, or discontinuing the study.

Sponsor responsibilities were contracted to Quintiles, and change in scope (CIS) documents were issued for changes in the contract that occurred over the course of the trial. Sponsor responsibilities contracted to Quintiles included initiation of clinical sites and monitoring in the majority of countries, data management, and statistical analyses for the DSMB reports and all clinical trial statistical analyses that, at the time of the initiation of the trial, were planned to be conducted. The interim CV analysis was not proposed until May 2007, thus was not covered in the scope of the contract, and was performed by GSK statisticians. Change in scope (CIS) of November 10, 2008 documents the transfer of the work on the final biostatistical analysis from Quintiles back to GSK. London School of Hygiene and Tropical Medicine was contracted to perform confirmatory analysis for the interim CV analysis and the final analysis, using datasets provided by

GSK. Quintiles had responsibility for the Clinical Event Validation and Adjudication Services (CEVA), the administrative support of the CEC. GSK collected data for post marketing safety reporting, and this was reconciled with the clinical trial databases and endpoint reporting database maintained by Quintiles. GSK and Quintiles met frequently during the conduct of the trial. In addition to the GSK representatives on the SC, additional personnel representing both GSK and Quintiles were present at SC meetings that were held every six months.

Data collection and handling tasks were shared by Quintiles and GSK. Broadly speaking, Quintiles managed the clinical study data and the adjudication process and GSK managed the pharmacovigilance for serious adverse event (SAE) reporting. The protocol required that clinical investigators (CI) report SAEs to the local clinical monitor (CRA) within 24 hours of knowledge of the SAE. The CRA forwarded the data to GSK Global Safety and Pharmacovigilance (GCSP). The protocol also required that the CI report potential endpoints within 2 weeks of knowledge of an endpoint by faxing endpoint CRFs to the CRA. The CRA forwarded the data to Quintiles CEVA. CRFs, except endpoint CRFs, were collected at the clinical study sites by the monitors, reviewed for completeness, and submitted to Quintiles Data Management. Endpoint CRFs, source documents (redacted and translated into English) and other data concerning potential endpoints were forwarded to CEVA for pre and post adjudication processing, including tracking, and compiling of dossiers, and adjudication results. Dossiers were reviewed for completeness of documentation and adequacy of redaction. Completed dossiers were sent to members of the Clinical Endpoint Committee (CEC) for adjudication. During most of the trial, dossiers were sent to 2 CEC members for adjudication. Those cases in which there was disagreement as to outcome were presented to the entire committee at CEC meetings. Dossiers were referred to the entire CEC committee for initial training sessions and near the end of the trial, when it was considered that primary full committee adjudication would be more efficient than initial two physician adjudication. Because this was an open label study, the study staff, including clinical investigators, monitors, data management, GSK GCSP, and CEVA staff had knowledge of treatment assignment.

Inspection of GSK revealed that the procedures outlined in the charters of the DSMB and SC were not followed in regard to the performance of the interim CV analysis. According to interviews with GSK during the inspection and documented in e-mails, the verbal endorsement to conduct an interim analysis was made by GSK following telephone conversations between GSK personnel and the chairs and statisticians of the SC and the DSMB, rather than consultation with the full committees; the full committees were subsequently briefed.

Inspection of the 31 subject records identified by the Cardiorenal review division for the clinical site inspections as well as additional subjects identified 13 instances concerning lack of referral for adjudication, timely processing and adjudication of potential endpoints, and lack of documents critical for adjudication. Of the 13 instances of apparent violations cited on the Form FDA 483 at GSK with respect to issues with adjudication, all but four were resolved during the inspection of Quintiles by auditing of additional documents in these subjects' records located at Quintiles. Two of these issues,

which involved late adjudication of endpoints, were not considered to have impact on data integrity. The two remaining unresolved cases did not have hospital summaries available for adjudication. The two cases with inadequate documentation were a subject hospitalized with a severe stroke and a subject hospitalized with ventricular arrhythmia who died. Both these cases were in the rosiglitazone group.

IV. CRO Inspection of Quintiles

Inspection of Quintiles was conducted to evaluate the adequacy of performance of the sponsor responsibilities contractually transferred to Quintiles. These included initiation of clinical sites and monitoring in the majority of countries, data management, and statistical analysis as described above, as well as the procedures and activities of CEVA.

Procedures for the contracted responsibilities, including monitoring, auditing, and data entry and validation were reviewed as well as audit documents. Twelve subjects' records that supported the observations cited at GSK were re-inspected and a total of 53 dossiers were inspected for quality control. The inspected records showed no evidence of quality control issues. Inspection of the subject records identified problems in four subjects regarding the adjudication process as described above. The inspection determined that adequate procedures were in place for monitoring of the clinical trial and that adequate training was provided to clinical investigators and monitors. CEVA procedures and data base tracking were reviewed. While the trial was in progress, GSK and Quintiles identified issues including possible under-reporting of endpoints by the clinical sites and difficulties with documentation of potential endpoints. In an effort to mitigate these problems, the sponsor and CRO I conducted additional procedures conducted during the trial such as endpoint sweep, quarterly endpoint reconciliation, and a final reconciliation that were designed to capture unreported endpoints. Additional study staff was hired to assist in identification and processing of endpoints. During the trial, the issue of a long lag time from reporting to adjudication of endpoints was identified as a problem by the sponsor and CRO, so additional resources were provided to the monitors and to CEVA in an attempt to decrease the time to adjudication of endpoints.

V. Summary of Inspection Results and Recommendations

The findings of the inspections of clinical sites, the sponsor, and the CRO included the following:

- Procedures, resources, and training for the conduct of the trial were adequate
- No evidence of tampering with or falsification of data
- No evidence of serious violations
- No evidence that publication of the interim CV analysis in June 2007 influenced the conduct of the trial.
- The endorsement to conduct an interim CV analysis by the 2 members of the Steering Committee and 2 members of the DSMB did not fulfill the requirements of the charters of these committees.

In general, FDA inspections at clinical sites, the sponsor, and the CRO did not identify evidence of systemic or pervasive findings that would undermine the reliability of the data; however, there were limitations in what the FDA inspections could evaluate.

Limitations of FDA inspections include the following:

1. With respect to the clinical site inspectional findings, of the 60 records reviewed, there was a single instance of an event that should more likely than not have been referred for adjudication. This appears to be isolated and unlikely to significantly impact data reliability. However, FDA only inspected less than 1% of the enrolled subjects' records. Although the inspections of clinical sites, sponsor, and CRO targeted subject records where under-reporting of endpoints may have occurred and found few instances of problems, DSI cannot comment upon additional instances where there may have been issues of reporting and documentation of potential endpoints in support of adjudication.
2. Unlike efficacy trials with discrete endpoints such as hemoglobin or blood pressure, data integrity in safety endpoint trials depends on complete reporting. In inspection of a clinical trial site, detecting an event poses challenges, including determination that an event actually occurred, and, if occurred, was reported correctly. In our inspections of this trial we attempted to mitigate this limitation by targeting subjects with certain characteristics described above who may have had an unreported event.
3. In an open-label trial, DSI cannot detect the presence of subtle bias in attribution and reporting of endpoints. It would also be difficult to detect systematic bias that may have taken place verbally or by other means that would escape detection.
4. The inspection could not determine the effort actually expended by the clinical investigators to determine if potential endpoints occurred for subjects who did not have office visits, and the effort expended to obtain the necessary documentation. DSI could only determine that the CIs were encouraged by the sponsor to obtain documentation and follow-up.
5. For those potential events that were withdrawn from consideration by the clinical investigator, the inspection could not determine whether the results of an eventual adjudication would have been positive and resulted in an additional endpoint.
6. Although the 3 cases cited above for inadequate documentation and lack of referral were all in the rosiglitazone group, because the number of these instances is small, DSI cannot determine if these cases represented bias.

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/

SUSAN LEIBENHAUT
06/18/2010

LESLIE K BALL
06/18/2010

**NDA 21-071 Avandia (rosiglitazone)
Cardiovascular adverse effects**

**Clinical Review Perspectives of FDA inspections of
GlaxoSmithKline, London, UK and Quintiles, Dublin, Ireland**

May 10 – 14, 2010	GlaxoSmithKline, Stockley Park, London, UK
May 17 – 21, 2010	Quintiles Ireland Ltd., Dublin, Ireland

MEMO TO FILE

Date: June 11, 2010

From: Khin Maung U, MD, Medical Officer, DCaRP, ODE I, OND

To: Norman Stockbridge, MD, PhD, Director, DCaRP, ODE I, OND
Stephen Grant, MD, Deputy Director, DCaRP, ODE I, OND
Thomas Marciniak, MD, Medical Team Leader, DCaRP, ODE I, OND

Cc: Leslie K. Ball, MD, Director, DSI, OC
Susan Leibenhaut, MD, Medical Officer, GCPB 2, DSI, OC
Mike M. Rashti, BIMO specialist, PHI-DO

Cc: Mary H. Parks, MD, Director, DMEP, ODE II, OND
Karen M. Mahoney, MD, Medical Officer, DMEP, ODE II, OND

Cc: Robert Temple, MD, Director, ODE I, OND
Ellis Unger, MD, Deputy Director, ODE I, OND

Reference: NDA 21-071 – Avandia (rosiglitazone): Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial

Subject: Clinical review perspectives of FDA inspections at GlaxoSmithKline, Stockley Park, London, UK and Quintiles, Fairview, Dublin, Ireland to determine the integrity of data and data handling processes in the (RECORD) trial of Avandia® (rosiglitazone) to evaluate post-marketing cardiovascular (CV) events

Applicant: GlaxoSmithKline, LLC

Drug class: Rosiglitazone is a peroxisome proliferator-activated receptor (PPAR) γ agonist.

Mission Critical Considerations

I participated as a subject matter expert and consultant to the Division of Scientific Investigations (DSI), Office of Compliance, in FDA inspections of the data archival site of the sponsor, GlaxoSmithKline (GSK) in Stockley Park, London, United Kingdom (May 10-14, 2010), and the sponsor's contract research organization (CRO) – Quintiles – in Fairview, Dublin, Ireland (May 17-21, 2010). Other FDA staff who participated in the inspections were Dr. Leslie Ball, Director, DSI (for the GSK inspection), Dr. Susan Leibenhaut, Medical officer, DSI, and Mr. Mike Rashti, BIMO specialist, Philadelphia District Office.

The purpose of my participation in the inspections was to determine (i) the integrity of data in the RECORD trial related to post-marketing cardiovascular (CV) safety of Avandia® (rosiglitazone) (approved by FDA under NDA 21-071), (ii) the roles of GSK and Quintiles in data collection and preparation of dossiers submitted to the central endpoint committee (CEC), and, (iii) whether the CEC made the adjudications according to its Charter. The inspection findings were anticipated to be discussed in an Advisory Committee meeting scheduled in July, 2010.

Background

The RECORD study was a 6-year, open-label, non-inferiority trial in which patients with type 2 diabetes who had inadequate glucose control with metformin or sulfonylurea alone were enrolled. Patients on monotherapy with either metformin or sulfonylurea and less than optimal glycemic control (hemoglobin A_{1c} (HbA_{1c}) of >7.0 – 9.0%, mean =7.9%) were randomly assigned to receive addition of rosiglitazone (n=2,220) or metformin (if already on sulfonylurea) or sulfonylurea (if already on metformin) (active control group, n=2,227). The study was open-label because of planned differences in the strategy for rescue therapy and the need to allow different

types and doses of comparator sulfonylurea therapy.

The primary endpoint was a composite of hospitalization and death from CV causes, with a hazard ratio (HR) non-inferiority margin of 1.20. Analysis was by intention to treat.

The study was conducted at 364 centers in 25 countries in Europe and Australasia. Randomization was by telephone from a dedicated center, using random permuted blocks stratified by background medication. Choice of sulfonylurea (glimepiride, gliclazide, or glibenclamide [glyburide]) was according to local investigator practice. Other glucose-lowering therapies were not permitted.

The study was monitored by a CRO (Quintiles), which also coordinated data collection.

Biochemical measurements were performed by a central laboratory (b) (4), (b). The study was overseen by a Steering Committee (SC) who was blinded to treatment.

An independent Data Safety and Monitoring Board (DSMB) reviewed conduct of the study and unblinded data at about 6-month intervals. Interim analyses were allegedly not made available to the SC, except for those required for the interim publication. Adverse-event data were allegedly made available to the sponsor's pharmacovigilance department, but not to staff involved with the study.

In 2006, GlaxoSmithKline submitted to drug regulators a combined analysis of several studies which suggested that, despite large observational studies to the contrary^{1,2}, rosiglitazone increased myocardial ischemia.³ Nissen and Wolski, using similar data sources, reported similar findings.⁴ In response to the Nissen report, the RECORD SC published in March 2007 an unplanned interim analysis of data on 4,447 patients who were randomized and followed for a mean of 3.75 years.⁵ The interim report suggested that rosiglitazone was associated with non-significant increases in the relative risk of (i) the primary composite outcome (HR, 1.08; 95% confidence interval [CI], 0.89, 1.31, and (ii) fatal or nonfatal myocardial infarction (MI) outcome (HR, 1.16; 95% CI, 0.75, 1.81).

In June 2009, the RECORD Study Team published their final report on these 4,447 patients.⁶ 321 people in the rosiglitazone group and 323 in the active control group experienced the primary outcome during a mean 5.5-year follow-up. This met the criterion of non-inferiority (HR 0.99, 95% CI, 0.85, 1.16). HR was 0.84 (95% CI, 0.59, 1.18) for CV death, 1.14 (95% CI, 0.80, 1.63) for MI, and 0.72 (95% CI, 0.49, 1.06) for stroke. Heart failure causing admission to hospital or death occurred in 61 people in the rosiglitazone group and 29 in the active control group (HR 2.10, 95% CI 1.35, 3.27, risk difference per 1000 person-years 2.6, 95% CI 1.1, 4.1). Upper and distal lower limb fracture rates were increased mainly in women randomly assigned to rosiglitazone. Mean HbA_{1c} was lower in the rosiglitazone group than in the control group at 5 years. The authors concluded that rosiglitazone does not increase the risk of overall CV mortality or CV hospitalization compared to standard glucose-lowering drugs, and that the increased risk of MI by 14% was not a conclusive finding.

¹ McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiol Drug Safety* 2007; **16**: 711–25.

² Margolis DJ, Hoffstad O, Strom BL. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. *Pharmacoepidemiol Drug Safety* 2008; **17**: 753–59.

³ GlaxoSmithKline. FDA Advisory Committee briefing document – cardiovascular safety of rosiglitazone. <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-01-sponsor-background.pdf> (accessed April 7, 2009).

⁴ Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457–2471.

⁵ Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes –an interim analysis. *N Engl J Med* 2007; **357**: 28–38.

⁶ Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJV for the 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**: 2125–35.

Comments on review issues

Use of a **non-inferiority design** in an **open-label** clinical trial to determine **post-marketing** adverse event issues gives the appearance that the trial will be likely to have biased event reporting and biased adjudication towards a finding of “no difference” between the treatment groups. CV death and CV hospitalization, the endpoints of this RECORD trial, may not be related to the effect of drugs but to the co-morbid diseases prevalent in this patient population. Apart from trying to determine if there was sloppy conduct, these issues are beyond the scope of our inspection.

Prior FDA inspections of RECORD clinical trial sites

FDA field investigators had performed GCP inspections of 3 clinical trial sites in Europe. Preliminary communications suggest that no major GCP violations were found:

- (b) (4) Inspected by Gerald N. McGirl, D.D.S. No Form FDA-483 was issued.
- (b) (4) Inspected by Laura E. Garcia. No Form FDA-483 was issued. There was one verbal discussion item related to lack of Part B Financial Disclosure Form for 5 of 13 sub-investigators.
- (b) (4) Inspected by Laura E. Garcia. There was one Form FDA-483 inspectional observation: that the investigation was not conducted in accordance with the investigational plan in that there was failure to ensure that drug dispensing and the investigational product accountability was conducted by a designated staff personnel (a study dietician was not assigned on the Site Staff Signature Sheet, Form F-MON-003, version number 1, to be part of the key authorized personnel dispensed and handled the investigational drug).

Approach to the inspection

I was assigned the role of a consult to follow the lead by DSI to investigate the issues that were identified. In preparation for the inspection I performed a brief evaluation of the submission and initiated questions to the sponsor (issued in information requests (IRs) through DSI).

At GSK, I performed a detailed audit of the CRFs to examine some of the problems found by Dr. Tom Marciniak, and then queried the sponsor to provide an explanation or documentation, if possible. I gave the sponsor every chance to explain, and if the sponsor could not, then that becomes an observation of a data integrity problem.

At Quintiles, I made a broad sweep of the problems Dr. Marciniak had identified and checked for physical evidence of the documents which Quintiles said they had in-house, including the CEC packages (source documents:- ECGs, laboratory results, etc.) physically for their existence. I reviewed these documents for data integrity and to determine whether they were processed timely and adjudicated appropriately.

I had planned to speak to one or all of the three CRAs at Quintiles who were instrumental in processing data from almost ALL of the sites and countries – (b) (6) (9 countries), (b) (6) (9 countries) and (b) (6) (7 countries). However, during the inspection at Quintiles, I found that (b) (6) and (b) (6) had left Quintiles, and that only (b) (6) continued to work there.

Special issues to address during the inspections

From the CEC MS Access Database, I identified a list of 135 endpoints where the interval between the time of onset of an event and the date of submission to the CEC for adjudication was about 2 to 5 years.

From the Quintiles Clinical Event Validation and Adjudication (CEVA) Tracking Database, I found also that the CEC took longer than 1 year from receipt of the dossiers to completion of adjudication for at least 37 patients. I raised these issues at the opening interviews, and selected the documents (CRFs, dossiers, etc.) pertaining to these patients for inspection.

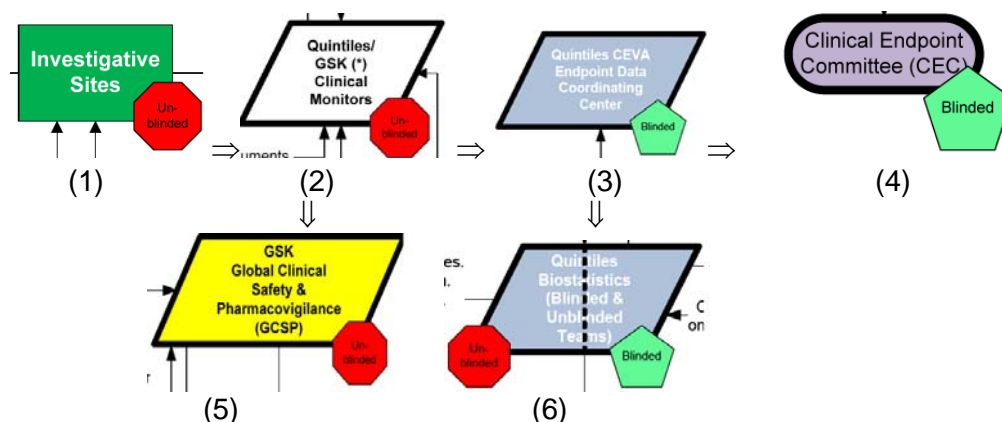
Limitations of the Inspection

This inspection is limited to the audit of Sponsor/CRO per the Compliance Manual, review of CRFs and completed endpoint dossiers submitted to the Central Endpoint Committee (CEC) for adjudication and supporting documents, Charters of the Steering Committee (SC), Data Safety Monitoring Board (DSMB) and CEC, review of Quintiles QA audit information and discussions with Quintiles QA personnel, and interviews with the CEC chairman and the Quintiles personnel involved in the RECORD trial.

It is beyond the scope of this inspection to evaluate the appropriateness of the study design, correctness of protocol-specified definitions of endpoints, timing of statistical analyses and appropriateness of the CEC adjudications, all of which are review issues.

Potential problem areas with data integrity

For the inspections, I simplified the organization of data flow in the RECORD trial into four main steps where problems with data integrity could occur as follows:



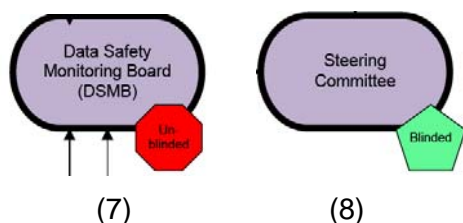
- (1) Investigative sites (where the data was *unblinded*). The unblinded investigators prepared and submitted CRFs, and faxed SAEs and Endpoint Forms to Quintiles/GSK monitors (2).
- (2) Quintiles/GSK monitors who triaged the *unblinded* data received from the investigators, and forwarded the *blinded* data to Quintiles CEVA (3), and the *unblinded* data to GSK Global Clinical Safety and Pharmacovigilance (GCSP) (5).
- (3) Quintiles CEVA staff who received the *blinded* data, and prepared the endpoint dossiers containing the *blinded* data to submit to the CEC (4), and subsequently collected the adjudicated CRFs.
- (4) The CEC adjudicated the endpoints based on the *blinded* information in the endpoint dossiers.

The other steps in data flow included the following (probably with less impact on data integrity):

- (5) GSK GCSP group, *unblinded*, who evaluated SAEs and entered them in the safety database.
- (6) Quintiles Biostatistics Team where *unblinded* statisticians inside the firewall and *blinded* statisticians allegedly outside the firewall worked together.

(7) The Data Safety Monitoring Board (DSMB) with access to the *unblinded* data.

(8) The Steering Committee (SC) who saw only the *blinded* data.



(1) Investigative sites

At the investigative sites, 7,428 patients were screened, 4,458 were randomized, 4,447 received treatment, and, at study end, 420 patients had died and 4,027 remained alive. During the course of the RECORD trial, 1,643 events were sent for adjudication.

The review perspectives of our inspection findings pertaining to data integrity at the investigative sites include the following:

- a) FDA inspections of 3 investigative sites ((b) (4)) (b) (4) did not reveal major problems.
- b) From the CEC MS Access Database, I identified 135 patients who had intervals between the time of onset of an event and the date of submission to the CEC as long as 2 to 5 years, and for 218 patients this interval was > 1 year. This observation forms the basis for our citation in FDA-483s issued to GSK of their deficiency to submit data related to clinical events to the CEC in a timely manner. During our inspections, Quintiles CEVA submitted to us with a breakdown of 128 endpoints which were received at Quintiles >2 years after the onset of the events. Examples cited in the Form FDA-483 include patients #19734, #31421 and #31507 who had 2 to 4 years between the onset of events and submission to the CEC.
- c) Quality assurance (QA) audits of RECORD study sites: Quintiles QA audited 39 clinical trial sites; there were some sites GSK QA audited (12 sites) where a Quintiles auditor was not present. In the case of 'for-cause audits,' Quintiles QA and GSK QA conducted the audits together. Five clinical sites were terminated due to non-compliance, which included:
 - (i) (b) (4) (serious non-compliance, problems with integrity of source data and inappropriate recruitment, 9 patients),
 - (ii) (b) (4) (Informed Consent Form signed by the investigator on behalf of a patient who did not meet entry criteria, 1 patient),
 - (iii) (b) (4) (loss of PK samples, IP accountability questions and inadequate source documents, 4 patients),
 - (iv) (b) (4) (research fraud including fabrication of subject data discovered by (b) (4) 11 patients), and
 - (v) (b) (4) (disagreement by investigator to record the IP storage conditions, 2 patients).
 - (vi) Another clinical trial site in (b) (4) 39 patients) was found to have source data issues for vital signs, weight/height and ECG data.

Quintiles arranged for the patients enrolled at these sites to be followed by a sub-investigator or by another investigator at a nearby site. Data from patients at these closed sites were included in the ITT analyses by default (which, I think, would favor the non-

inferiority findings). A sensitivity analysis conducted for the primary endpoint excluding these subjects allegedly did not appear to change the overall findings.

- d) Ten clinical investigative sites were audited by regulatory authorities {three sites by FDA (no major findings), two sites by Greek Regulatory Agencies (no major findings), two by German Regulatory Authorities (no major findings, these do not include (b) (4) one by French Regulatory authorities (no findings), one by British Regulatory Authorities (record keeping problems), and one by Lithuanian Regulatory Authorities (unapproved informed consent form used for 11 subjects, protocol not followed, recording keeping problems)}.
- e) From review of CRFs and endpoint dossiers, I found that unblinded investigators appeared to have made endpoint determinations on their own, without further submitting the data to CEVA, and subsequently, for appropriate adjudication by the CEC. There were examples of CRF pages that were crossed out by the investigator (for SAEs or for endpoints) with the reason that the investigator determined that the event was not an SAE or not an endpoint event. This procedure was not found frequently. While this appeared to comply with the letter of the protocol (and in some instances, the reasons given were valid), the investigators and/or monitors appeared not to realize that some of the events could be potential endpoints that required adjudication. For example, for patient #19079, a SAE and an endpoint of MI were deleted by the investigator, which resulted in this event being not adjudicated by the CEC. It is possible that due to the open-label design, the investigators were aware of the treatment assigned to their patients, and some of these investigator-determined or investigator-deleted events could have been biased. However, I found no evidence during the inspection to document this.
- f) When two events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated properly. For example, for patient #19437, the endpoint of MI was not adjudicated, only heart failure and death events were adjudicated (although there was a CK-MB fraction of 25% documented in the CRF). Again, the open-label design allowed bias on the part of the investigators to not follow up or obtain/provide complete clinical or laboratory information. However, I found no evidence during the inspection to document this.

(2) Quintiles/GSK monitors

The monitors conducted 100% source data verification vs. CRFs at visits #1 and 2, and then 10% source data verification throughout the course of the study, according to their monitoring plan. During their site monitoring visits, the monitors also made sure that consent forms were signed by all participating patients. If corrections were needed the site's staff made corrections to the CRFs, and they were documented. These monitors worked with their team leaders within the project and with line managers in the country. The monitors received training every 2 years.

- a) It is possible that due to the open-label design, unblinded monitors could have colluded with unblinded investigators to make endpoint determinations on their own, without submitting the data to CEVA, and subsequently, for appropriate adjudication by the CEC {please see (1) f) above}. However, I found no evidence during the inspection to document this.
- b) There were 135 patients who had intervals between the time of onset of an event and the date of submission to the CEC as long as 2 to 5 years, and 218 patients where this interval was > 1 year {please see (1) b) above}. I think the monitors were responsible for these delays as much as the investigators were.
- c) Before going on the inspection, I asked the sponsor to provide – by site number – a listing of patients who had CV hospitalization checked 'yes' or had event forms other than HAE forms

submitted which were not sent for adjudication (which I have compiled in Table 1).

Table 1 Listing of events which had CV hospitalization checked as Yes or had Event Forms other than HAE forms submitted that were NOT SENT FOR ADJUDICATION

Treatment arm	Total number of events	Total number of CV hospitalization checked 'yes'	Number of events forms other than HAE forms submitted
Background MET + SU	15	8	14
Background SU + MET	24	20	18
Total in MET/SU arm	39	28	32
Background MET + RSG	23	16	19
Background SU + RSG	22	17	21
Total in RSG arm	45	33	40

The number of CV hospitalizations checked 'yes' and event forms other than HAE forms submitted which were not sent for adjudication appear to be more in the rosiglitazone arm than in the metformin/sulfonylurea arm.

- d) During the course of the RECORD trial, 1,643 events were sent for adjudication. However, the monitors (i) did not forward 266 events to CEVA (which were determined by the sites as non-CV), and (ii) deleted 104 events (see Table 2). Thus, it appeared that 370 events were not captured or submitted for adjudication by the CEC.
- e) There were a number of events that were adjudicated "non-CV" because of "insufficient information." A hospital discharge summary or a current ECG or levels of cardiac biomarkers to diagnose MI were missing which the monitors appeared not to have put too much effort to obtain. This lack of crucial information could contribute to an event being adjudicated as "non-CV." There are many examples in the EIRs, some cited as FDA-483 items.
- f) These monitors triaged both the SAEs (which were processed unblinded and forwarded to GSK GCSP and entered into GSK's OCEANS database) and the endpoints (which were processed blinded and forwarded to Quintiles CEVA). When an event could be both an SAE and an endpoint (e.g., a hospitalization for chest pain), there could be errors in forwarding the information. For example, for patient #31510, the patient's discharge summaries and other documents were sent to GSK in error instead of to CEVA in Quintiles. This error did not appear to occur frequently.

(3) Quintiles CEVA

- a) Quintiles CEVA staff received the *blinded* data, and prepared the endpoint dossiers containing the *blinded* data (completed endpoint forms and source documents such as ECGs, cardiac biomarkers, hospital discharge summaries) to submit to the CEC. Subsequently, endpoints adjudicated by CEC were collected and entered into databases.

Data entry was performed as a double entry process. From 2001 to 2005, data entry was performed in Dublin, Ireland, and from 2006 to 2009, data entry was performed in Bangalore, India. The data entered included the information from each patient's entry into the study until completion of the study visits.

- b) There were four databases used by Quintiles CEVA:
 - (1) Clintrial 4.2 database: patients' CRFs and endpoint data were entered into this.
 - (2) MS Access database: to track endpoint dossiers
 - (3) Innatrax database: used by monitors, clinical team leaders and data management staff to track patients' data.
 - (4) QDUB Fortis database: scanned copy of CRF page was used as working a copy of the

CRF.

The validation reports for the above databases were checked by the FDA team during the inspection, including a working demonstration on a laptop. No deficiencies were found.

We also reviewed documents related to Quintiles' data management and endpoint processing including the following: data management plan summary, RECORD study endpoint reporting controls, training for the RECORD study, project specific endpoint processing (example used: endpoint # 49653/231), and flow diagrams of SAE processing, endpoint adjudication processing, endpoint process and accountability list, and data life cycle.

- c) Quintiles CEVA conducted quality control (QC) of the data throughout the study and prior to the database lock on 27-Mar-2009 when GSK accepted the database for BRL49653/231 – RECORD study. CEVA also performed endpoint tracking, and facilitated query resolution with the CEC. CEVA received 1,643 endpoint events, of which 1,106 (67.3%) were adjudicated as CV events (see Table 2).

Table 2 cumulative summary of CV events in CEVA database

	All Events (N=1,643) n (%)	First Events (N=4,447) n (%)
Endpoint events received	1,643 (100)	645 (14.5)
Adjudicated as CV events*	1,106 (67.3)	645 (14.5)
Adjudicated as 'NOT' CV events	537 (32.7)	
- Did not meet criteria for CV hospitalization	417 (25.4)	
- Did not meet criteria for CV death	120 (7.3)	

Source: Sponsor's Table 3.1, GSK\FSKB0565_SC\Biostatistics\Production\Tables\end-endpt-sum-FDA.sas 21May2010

*includes deaths adjudicated as 'Unknown deaths (insufficient data)'

Note: 266 non-CV events confirmed by sites were not sent for adjudication. 104 events were given the status of 'deleted.'

- d) We found that HAE forms (hospitalization endpoint forms) were not databased on the clinical data management system (CDMS) at CEVA. Thus, the hospitalization information could not be cross-checked with the data in the medical care utilization records on the CDMS. Only the SAEs were databased on the CDMS, which allowed a crosscheck between the medical care utilization record and the SAEs.
- e) Redactions of patient identifiers and study drug names were made by CEVA. In the adjudication package for Patient # 97870 submitted to the CEC (on page 21 of the endpoint package Serial #018), the information related to the antidiabetic drugs was found not redacted although the patient's identification information (patient's name) within the same paragraph was found redacted. There was this sentence in the second paragraph under **Therapy and progress**: "..... Furthermore, we also stopped treatment with metformin and rosiglitazone, and replaced these with a sulfonyl urea....." This could have caused the treatment allocation to become unblinded to the CEC reviewers.

The Quintiles personnel stated that the CEC had not told CEVA about any such unblinding problem. They explained the procedure related to redaction as follows. When the dossiers were considered complete with source documents, they were reviewed by Quality Control (QC) before they were sent to the CEC. QC evaluated the dossiers to check clinical forms for completeness and that the appropriate treatment-related and identifying information were redacted; then QC highlighted problems, where present, in the dossier sent back to the CEVA processor. After the required corrections were made by the CEVA processor, the dossier went back to QC to confirm that the treatment information necessary to be blinded were redacted. Then only was the dossier forwarded to the CEC.

- f) Our review of the QC actions in 53 randomly selected endpoint dossiers did not reveal major

problems (Table 3). It appeared that failure to redact treatment information occurred rarely.

Table 3 List of endpoint dossiers we reviewed for QC actions

Patient #	Country	Center #	End-point #	Review finding of the QC audit status
18106	Poland	386	13863-386	OK
			13870-386	OK
			13877-386	OK
18156	Germany	182	16085-182	OK
			29720-182	OK
			Pneumonia (non- EP)	OK
18282	Estonia	092	12004-092	OK
			12006-092	OK
18388	United Kingdom	498	22443-498	OK
			22444-498	OK
			22459-498	OK
18498	United Kingdom	519	21527-519	OK
			21531-519	OK
			21533-519	OK
			21534-519	OK
18735	Hungary	272	26222-272	OK
18977	Croatia	021	14330-021	OK
			28962-021	OK
			28963-021	OK
19338	Netherlands	343	13201-343	OK
			13203-343	OK
			13204-343	OK
19731	Germany	210	25270-210	OK
19825	France	135	12442-135	OK
			18505-135	OK
19870	Belgium	015	14466-015	OK
			14467-015	OK
20493	Poland	385	13512-385	OK
20554	Bulgaria	668	21481-668	OK
20839	Belgium	007	24783-007	OK
			26874-007	OK
29094	United Kingdom	485	27161-485	OK
			27162-485	OK
29200	Russia	743	22167-743	OK
30256	Sweden	830	21861-830	OK
31057	Sweden	821	23407-821	OK
31421	Sweden	823	23269-823	OK
31554	Ukraine	727	21042-727	OK
			21046-727	OK
37516	Ukraine	726	21021-726	OK
			21023-746	OK
			21024-726	OK
38383	Poland	384	25143-384	OK
			12477-384	OK
			12507-384	OK
43767	Sweden	831	20748-831	OK
97579	Estonia	093	12045-093	OK
			12050-093	OK
			12051-093	OK
97954	Finland	109	12246-109	OK
98276	Czech Republic	041	12129-041	OK
			12130-041	OK
98364	Germany	182	25248-182	OK

- g) Endpoint reconciliation: A reconciliation process between all reported SAEs which were checked against all reported endpoints was performed in the end of 2008 (Proposal made to

GSK on 24-Oct-2008). This uncovered some endpoints which were then sent to the CEC for adjudication, explaining some endpoints with onset time 2 to 5 years earlier than the adjudication time of 2008 or 2009.

- h) **Endpoint Sweep:** An endpoint sweep was performed in 2004 at 49 randomly selected sites in 6 countries in which 388 patients were contacted and interviewed regarding hospitalizations during the past 4 years and since their last visit. The endpoint sweep detected several very recent endpoints, most of which would have been detected at the next site visit by the monitors. Thus, a decision was made not to extend the sweep to other countries.

(4) **The Clinical Endpoints Committee (CEC)**

- a) From the CEVA Tracking Database, I found that the CEC took longer than 1 year from receipt to completion of adjudication for at least 37 patients. Examples include patients #18282, and #97579 for whom the CEC reviewers completed their adjudications 1.5 to 2 years after the endpoint dossiers were submitted to the CEC.
- b) In 2002-2003, a dilution of events by planned CV procedures was discovered. A “**back adjudication**” process was initiated following Amendment 1 of the CEC Charter in December 2003, which stated that only unplanned CV procedures would be considered endpoints. In early 2004, the CEC went back to adjudicate (i.e., “back adjudicate”) all events related to CV procedures. I asked the sponsor to provide a list of patients who were “back-adjudicated.” I tabulated the line listings of these back-adjudicated patients in Table 4.

Table 4 List of number of subjects who had adjudicated events “back-adjudicated”

Treatment Group	Total Back-Adjudicated events	Number of Endpoints Back-Adjudicated as:		Number of CV hospitalizations Back-Adjudicated as:		Number of CV deaths Back-Adjudicated as:	
		Yes	No	Yes	No	Yes	No
Bg MET + SU	8	6	2	6	2	0	0
Bg SU + MET	7	5	2	5	2	0	0
Total in MET/SU	15	11	4	11	4	0	0
Bg MET + RSG	1	1	0	1	0	0	0
Bg SU + RSG	3	3	0	3	0	0	0
Total in RSG	4	4	0	4	0	0	0

Yes = met endpoint criteria; No = did not meet endpoint criteria; “Back adjudicated” = the process initiated because of change of definition of invasive procedures as noted in Amendment 1 of the CEC charter.

I considered that bias would be indicated if I found more

- (a) “Yes” in the MET/SU treatment group, and
(b) “No” in the RSG treatment group.

None of the 4 back-adjudicated endpoints in the RSG group was re-classified as ‘not a CV hospitalization.’ On the other hand, 4 back-adjudicated endpoints in the MET/SU group had become re-classified as non-CV hospitalization. This does not help the RSG group appear better. Therefore, I found no reason that there was bias in the back-adjudication process.

- c) **Re-adjudications** were done for three main reasons:
- all stroke/TIA endpoints were re-adjudicated by the neurologist Prof. Lees (if he agreed with previous adjudication this was considered final; if he disagreed with the previous adjudication, then this went to the Full Committee although Prof. Lees had the final say). The majority of re-adjudications of endpoints of the same type, critical data changes, non-urgent CV procedures and arteriosclerotic events were made by the Full Committee.
 - revascularization procedures (‘back adjudication’ mentioned above), and

(iii) “sequence adjudication,” i.e., adjudication of endpoints occurring on the same day. This arose around August 2007 when the CEC was presented with binders of 10 patients who had two or more events (e.g., MI plus CHF) that occurred on the same day. The aim of the CEC was to determine which event was the cause and which was the effect (e.g., MI led to CHF or a patient with CHF was complicated by MI). Thus, the CEC decided that for cases where there was more than one event on the same day, the temporal sequence must be determined to decide which event occurred first and contributed to the primary endpoint. In the case of death, it was always considered the second event. These cases requiring sequence adjudications were discussed at face-to-face meetings of the CEC to determine which the first event was.

There were two situations which could preclude the event that occurred chronologically earlier. In the case of a planned coronary angiography followed by MI, there could be two endpoint forms, but the first – planned coronary angiography – was considered not an endpoint (because it was “planned”), and the second was considered an endpoint. In the case of a patient who experienced unstable angina, was hospitalized, then developed MI and subsequently CHF on the same day, the CEC discarded unstable angina, and the CV hospitalization was considered the primary endpoint event.

I asked the sponsor to provide a list of patients who were “re-adjudicated;” i.e., adjudication performed again because of additional information was provided or other reason. I tabulated the line listings of these re-adjudicated patients in Table 5.

Table 5 List of number of subjects who had adjudicated events “re-adjudicated”

Treatment Group	Total Re-Adjudicated events	Number of Endpoints Re-Adjudicated as:		Number of CV hospitalizations RE-Adjudicated as:		Number of CV deaths RE-Adjudicated as:	
		Yes	No	Yes	No	Yes	No
Bg MET + SU	32	22	10	21	9	1	1
Bg SU + MET	32	25	7	24	6	1	1
Total in MET/SU	64	47	17	45	15	2	2
Bg MET + RSG	21	12	9	12	9	0	0
Bg SU + RSG	28	19	9	19	9	0	0
Total in RSG	49	31	18	31	18	0	0

Yes = met endpoint criteria; No = did not meet endpoint criteria; “Re-adjudicated” =any re-adjudication performed because of additional information provided or other reason.

I considered that bias would be indicated if I found more

- (a) “Yes” in the MET/SU treatment group, and
- (b) “No” in the RSG treatment group.

18 (37%) of 49 re-adjudicated endpoints in the RSG group was re-classified as not a CV hospitalization. Relatively fewer endpoints – 17 (27%) of CV hospitalization endpoints and half of CV death endpoints – were re-adjudicated in the MET/SU group as “non-CV”. This does not help the RSG group appear better. Therefore, I found no reason that there was bias in the re-adjudication process.

- d) The CEC members and staff were hired and paid by the sponsor, GSK. Members of the CEC included six cardiologists (including the CEC chairman), one diabetologist, and, later, one neurologist, from different geographical parts of Europe. There was a possibility of conflict of interest. To determine if there were inter-reviewer variability and/or potential bias by any CEC member in adjudicating endpoints the rosiglitazone group versus the metformin/sulfonyl urea combination group, I requested a tabulation of the individual CEC reviewer’s adjudications by treatment group, and their decisions as to “Yes” or “No” for a CV event.

The table of individual CEC reviewer’s adjudications (Table 6) does not appear to suggest

individual bias on the part of any one of the CEC reviewers.

Table 6 Summary of adjudication frequencies by CEC members

CEC Member	Total Adjudications	Rosiglitazone Arm		MET/SU Arm	
		Yes	No	Yes	No
Total	4,024	1,370	610	1,437	607
Prof. Komajda	458	155 (33.8%)	77 (16.8%)	164 (35.8%)	62 (13.5%)
Prof. Gavazi	475	191 (40.2%)	59 (12.4%)	149 (31.4%)	76 (16.0%)
Prof. Syvanne	478	159 (33.3%)	64 (13.4%)	186 (38.9%)	69 (14.4%)
Prof. Ponikowski	462	145 (31.4%)	80 (17.3%)	168 (36.4%)	69 (14.9%)
Prof. Bohm	471	152 (32.3%)	71 (15.1%)	171 (36.3%)	77 (16.3%)
Prof. Marre	471	181 (38.4%)	56 (11.9%)	167 (35.5%)	67 (14.2%)
Full Committee	1045	329 (31.5%)	191 (18.3%)	348 (33.3%)	177 (16.9%)
Prof. Lees	164	58 (35.4%)	12 (7.5%)	84 (51.2%)	10 (6.1%)

Source: Sponsor's Table 1: GSK\FSKB0565_SC\Biostatistics\Production\Tables\endpt_prof_sum_fda.sas 18May2010

- e) CEC meetings: Over the course of the RECORD trial, there were 11 face-to-face meetings and 28 teleconferences of the CEC. If there were disagreements in the adjudication between the CEC reviewers, these cases were discussed at the face-to-face meetings and adjudicated by the Full Committee. Also at face-to-face meetings, additional new information which CEC members had requested and considered crucial for decision were presented and discussed for adjudication.

Of the 28 teleconferences, adjudications were discussed at 27 teleconferences; in one teleconference (which was a start up meeting) only the chairman of the CEC was in attendance. During the last few months before closure of the study in the fall of 2008, there was an accumulation of endpoints. The adjudications were made during several telecon meetings (and backup ones) in November and December of 2008 and January of 2009.

Regarding the CEC meeting minutes of 09-Feb-2009 which mentioned 6 deaths in patients who had cancer, withdrew from the study and died, for which Prof. Komajda (the CEC chairman) single-handedly adjudicated their events on behalf of the CEC (although there was no provision for such action in the CEC Charter), the explanation given was that all CEC members were in attendance at the telecon and rendered their adjudications, and that Prof. Komajda merely signed off on these adjudications.

- f) CEC work: The working document was the CEC Charter. There was an initial training period for the CEC members when all events were adjudicated by all members. Later, adjudication was made by paired members. Because special knowledge of neurological endpoints was missing, the Steering Committee (SC) decided to add a neurologist to adjudicate all strokes/TIAs. Prof. Lees of the UK was recommended by the SC Chairman in about 2004. Subsequently, all previous stroke/TIA events were re-adjudicated by Prof. Lees.
- g) CEC interactions: Prof. Komajda, the CEC chairman, said that there was no communication between the CEC and the DSMB. The only interactions of the CEC with the SC were (i) regular updates from CEC to SC of the time lines and backlog of events to adjudicate, and (ii) communications from the SC to the CEC regarding (a) the addition of the neurologist Prof. Lees as a CEC member to adjudicate stroke/TIAs and (b) the discussion of non-urgent vs. planned CV procedures as endpoints.
- h) The CEC chairman also responded to the FDA observation that when two events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately (Examples: Patients #19437 and #19731). The CEC members reviewed the discharge summary from the hospital whenever available, and doctors' notes or any hospital forms from the physician (usually a discharge summary),

because a large number of events occurred outside the hospital. To adjudicate an endpoint as MI, the documentation sought was a copy of ECG, or a rise in cardiac biomarkers or, in a few instances, the medical report which stated that the patient had a MI. For deaths, the CEC requested death certificates, medical letters from the doctor, and indirect reports from family members or witnesses. If crucial medical information was lacking, the CEC asked Quintiles to get them. The local Quintiles monitor would then try to obtain the information and reply whether they were able or unable to do so.

Conclusion: It is beyond the scope of this inspection to evaluate the appropriateness of study design, protocol-specified definitions of endpoints, and the adjudications. Our inspections of GlaxoSmithKline and Quintiles covered many issues of potential concern with data integrity which were raised by FDA reviewers. Our inspections showed that there were delays in reporting events from the time of onset to the time they reached GSK (safety data) or Quintiles (endpoint data) (by 2 to 5 years), delays at the CEC to adjudicate (by 6 months to a year), instances where documentation critical for the CEC to adjudicate were not submitted to the CEC, and when two events occurred in close temporal relationship or during the same hospitalization, one of the events was not followed up rigorously. The monitors and Quintiles staff appeared to follow the specified operation procedures, and the databases appeared reliable. I found no evidence of unblinding or bias in the adjudication process.

My clinical review perspectives which are limited to our findings during the FDA inspections of GlaxoSmithKline and Quintiles are intended to supplement the reviews of other FDA reviewers, and are not intended to replace, refute or undermine their recommendations.

Appendix I: My section of the establishment inspection report (EIR) of GlaxoSmithKline inspection conducted May 10-14, 2010 at Stockley Park, London, United Kingdom

BACKGROUND AND METHODOLOGY

I participated as a subject matter expert and consultant to the Division of Scientific Investigations (DSI), Office of Compliance, in this FDA inspection of the data archival site of GlaxoSmithKline (GSK – the sponsor) in Heathrow, London, United Kingdom.

The purpose of my participation in this inspection was to determine (a) who knew what and when, (b) the integrity of clinical data in the RECORD trial related to post-marketing cardiovascular (CV) safety of Avandia[®] (rosiglitazone) which was approved by FDA under NDA 21-071, and (c) if adjudications related to endpoints were made according to the charter of the Central Endpoint Committee (CEC). The inspection findings are anticipated to be discussed in an Advisory Committee meeting scheduled in July, 2010.

Comments on review issues

Use of a *non-inferiority design* in an *open-label* clinical trial to determine *post-marketing* adverse events gives the appearance that the RECORD trial will be likely to have biased event reporting and biased adjudication towards a finding of “no difference” between the treatment groups. Sloppiness in conduct of the RECORD trial will also contribute towards a “no difference” finding. CV death and CV hospitalization, the endpoints of this RECORD trial, may not be related to the effect of drugs but to co-morbid diseases prevalent in this patient population. Apart from trying to determine if there was sloppy conduct of the clinical trial, these review issues are beyond the scope of our inspection.

Approach to the inspection

I was assigned the role of a consultant to follow the lead by DSI for the inspectional issues they have identified.

In preparation for the inspection I performed a brief evaluation of the submission and initiated questions to the sponsor (which were issued in IRs through DSI). My review findings to the sponsor’s responses are beyond the scope of the inspection; I will present them in a separate memo submitted in DARRTS to NDA 21-071.

Methodology

I participated in the opening interview of the RECORD trial personnel, interviews of the chairmen of the SC (Dr. Philip Home) and DSMB (Dr. Ian Campbell) during which I asked the questions/issues which had been raised by the review division, and audit of trial-related documents and electronic data bases.

I reviewed the case report forms (CRFs) and associated documents (e.g., laboratory reports, ECGs, hospital discharge summaries and physician notes, where available, and explanatory notes produced by the sponsor) for 30 patients:

- (i) some of the CRFs contained the clinical problems identified by the review division,
- (ii) some CRFs were selected from the sites monitored by GSK (Sweden, Australia), and
- (iii) a sample of CRFs which had long intervals from onset of event to completion of adjudication, to determine if there were clinically relevant data integrity problems.

Limitations of the Inspection

This inspection is limited to the audit of Sponsor/CRO per the Compliance Manual, review of CRFs and related documents, Charters of the Steering Committee (SC), Data Safety Monitoring Board (DSMB) and Central Endpoint Committee (CEC), and interviews with personnel involved in the RECORD trial.

It is beyond the scope of this inspection to evaluate the appropriateness of the study design, correctness of protocol-specified definitions of endpoints, timing of statistical analyses and appropriateness of the CEC adjudications, all of which are review issues.

In a separate memo submitted in DARRTS to NDA 21-071, I will present a limited evaluation of the review issues I worked on after being given this assignment to the RECORD inspection team and including the review inferences from the findings in the inspection. My limited review comments are intended to supplement the reviews of other FDA reviewers, and not intended to replace or refute their recommendations.

Special issues to address during the inspection of GSK

From the CEC MS Access Database, I had identified a list of 135 patients where the interval between the time of onset of an event and the date of submission to the CEC for adjudication was as long as 2 to 5 years (Exhibit: KMU G-1). From the CEVA Tracking Database, I found that the CEC took longer than 1 year from receipt to completion of adjudication for at least 37 patients (Exhibit: KMU G-2, first two pages of the CEVA Tracking Database). These issues were raised at the opening interview, and evaluated during the audit. Explanations were sought from Dr. Murray Stewart, the GSK physician most responsible for the RECORD trial and his staff.

INSPECTION FINDINGS

Inspection of CRFs and associated documents

I reviewed the following CRFs and associated documents, some of which were identified as problems by the review division, some of which I identified from the CEC MS Assess Database with long intervals between the time of the event of date of submission to CEC, and some CRFs from the sites in Sweden and Australia which were monitored by GSK (other sites were monitored by Quintiles).

Patient #18106 had a hospitalization for heart failure on (b) (6) adjudicated as non-CV due to insufficient information (EP 13863-386). The adjudication dossier for this EP is not included in submission S046, the complete CRFs? Why? (The dossier is in S031.)

During the inspection, I found in the hospital notes and CRF (Exhibit: KMU G-3) that this patient was hospitalized for sudden onset of effort dyspnea, with history of hypertension and diabetes type 2, had dyspnea at rest and chest pain and pulmonary edema, had no chest X-ray or Echocardiogram done, did not receive new IV diuretics (but received oral and IV nitrates), and had no increase in total daily dose of medication. This endpoint event was adjudicated definite CHF by Prof. Komajda, non-CV hospitalization (unknown hospitalization, insufficient data) by Prof Ponikowski, and went to the Full Committee which adjudicated as non-CV hospitalization (unknown hospitalization, insufficient data). Adjudication appears to have been done appropriately. I did not cite this in the 483.

Patient #18215 was hospitalized for pulmonary edema relieved with furosemide from (b) (6) ultimately dying from "pneumonia."

- The death from pneumonia was adjudicated as a non-CV death. Why was the hospitalization for pulmonary edema not adjudicated or the reason for the pulmonary edema not explored? MI?
- There is little information in the CRFs about this 47 day in Chesterfield for which a hospital summary was not obtained. This could have contributed to the death from "pneumonia" being adjudicated as non-CV. (A letter in the adjudication package describes admission for pulmonary edema treated with furosemide.) Why were the events leading up to the "pneumonia" not documented?

I found that this patient had Myelodysplastic Syndrome (MDS) which could have caused the pneumonia leading to death (Exhibit: KMU G-4). Dr. Murray Stewart explained that pulmonary edema could be part of the respiratory complication of MDS, which appeared plausible. The investigator did not consider pulmonary edema as a SAE/AE, and wrote on the SAE page that the reason for this patient's death was pneumonia caused by MDS. There was no discharge summary, but the sponsor had surrogate documents: a hospital letter outlining what occurred during the patient's stay and a notification of inpatient death to the patient's GP. I accepted Dr. Stewart's explanation and did not cite this in the 483.

Patient #18282: The event of myocardial infarction (MI) was sent to CEC reviewers for adjudication on June 13, 2006; the review was completed on October 20, 2008. (Exhibit: KMU G-5)

The CRF showed that the event occurred on 26-Apr-2005, that it was ready for adjudication on 13-Jun-2006, but review was completed only on 20-Oct-2008. I cited this observation of delayed completion of adjudication of events by the CEC in the 483 (item a (ii)(1)).

Patient #19079 had four adjudicated endpoints on (b) (6) (stroke), (b) (6) (two: heart failure (HF) and other CV), and (b) (6) (HF death). However, he was also hospitalized on (b) (6) for a suspected stroke (ultimately diagnosed as "cervicobrachial syndrome with vertigo") and on about 11/10/05 (through 12/7/05) for HF then pulmonary embolus (b) (6), MI (b) (6), and (b) (6) (Exhibit: KMU G-6)

- a. Why was the MI not adjudicated?
- b. Why was the MI SAE dropped 18 months after the event?
- c. Why was the MI SAE dropped after other later events were adjudicated?

The sponsor explained that the SAE and the endpoint of MI were deleted by the investigator, which resulted in this endpoint being not sent to the CEC for adjudication. This information was communicated to Data Management in a Clinical Data Clarification Form. I did not cite this in the 483.

Patient #19437 was hospitalized with cough, sputum, acute heart failure, and ventricular arrhythmias and at one point had a CK-MB fraction of 25%. The clinical diagnosis included the possibility of a MI. However, the MI was not adjudicated; only the heart failure event and death event were adjudicated. (Exhibit: KMU G-7)

The hospital notes do not state any diagnosis of heart failure, and there was no current ECG available which was critical data to determine if there was a MI. I cited this observations that when two endpoint events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately in the 483 (item d (i)).

Patient #19731 was hospitalized for ventricular arrhythmias and died. A hospital discharge summary was not found. The death was adjudicated as “unknown.” The hospitalization was not adjudicated. Other problems with this patient included an AE (for which patient withdrew from the study) with a last visit on 8/17/05, although no documentation of the visit is submitted. The AEs is mentioned in a DCF as pancytopenia and the AE.XPT file lists a pancytopenia as severe and starting in 6/02 with a corresponding CRF from the month 8 visit. The patient died on (b) (6). The investigator faxed in the SAE report of the death on May 5, 2006, and Quintiles recorded the receipt date as May 5, 2005. However, there is a second SAE report fax dated February 7, 2002 (year and day likely reversed). Many other Quintile records seem to indicate this SAE was processed in 2007. Finally, there is a cryptic, “NOTE TO FILE” signed by a Quintiles Pharmacovigilance Program Manager but undated that “Please note that the patient was hospitalized and died, it states that the patient was hospitalized for ventricular arrhythmia but the patient had suffered from this for years it was not a case that it had worsened.” There is no documentation supporting this Note to File despite a DEATH2 CRF (dated February 7, 2002) claiming that a hospital death summary was enclosed. (Exhibit: KMU G-8)

A hospital discharge summary was not found which was confirmed by the investigator in a signed and dated response to a query from CEVA. The hospitalization was not reported as an endpoint allegedly because the CRA confirmed verbally in response to a query from CEVA that the ventricular arrhythmia was not worsening. I do not agree. I cited these observations for not ensuring that critical documentation for adjudication was submitted to the CEC in the 483 (item b (i)), and that when two endpoint events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately in the 483 (item d (ii)).

Patient #19734 died in (b) (6) (exact date unknown) but the site did not fax the serious adverse event (SAE) form for this event to the study monitor until February 2009, who then forwarded the event to the CEC. I asked the sponsor to explain why (i) data resolution query (DRQ) dated 03-Apr-2008 refers to two copies of tracking forms with different information, (ii) SAE form for MI which was dated 10-Feb-2008 had a fax cover sheet dated 10-Feb-2008 but amended to Feb-2009, and (iii) there was a study file note by PI Dr. Scholz, “herewith I confirm that the death of the subjects 98460 and 98463 were not related to the study drug or the study protocol – dated 10-Feb-2003.” (Exhibit: KMU G-9)

The sponsor’s explanation was that (i) the CRF page where the cause of death was recorded as MI superseded the CRF page where the cause of death was recorded as unstable angina (UA), (ii) the SAE forms appear to be unrelated to the CRF and could be misplaced from another CRF, and (iii) the study file note pertains to the survival statuses of these patients which were collected in accordance with Protocol Amendment 7 (2007), which established that both patients had died more than 30 days after being withdrawn, were not IP related and therefore documented to be not considered as SAEs.

I cited the observation of over 4 years’ delay in the receipt of the SAE by study monitor in the 483 (item a (i)(1)).

Patient #19825: This patient was hospitalized for bilateral pulmonary emboli (PE) on (b) (6) and subsequently died on (b) (6). The events ultimately appear to have been adjudicated correctly but the route to the correct and

complete adjudication appears unclear.

- a. *The death was received in QDUB on 22jun2004, adjudicated starting on 20jul2005, and finalized on 04oct2005. The hospitalization on (b) (6) was received at QDUB on 15dec2008 and adjudicated once on 26jan2009. Please explain the delay.*
- b. *CI confirmed that SAE bilateral pulmonary embolism is not a CV endpoint, but a vascular endpoint. What constitutes a “vascular” vs. “cardiovascular” endpoint?*

Dr. Murray Stewart provided the following explanation (Exhibit: KMU G-10):

- a. The hospitalization was picked up only during the SAE reconciliation carried out by Quintiles and GSK in Nov 2008, and once known, it was reported to CEVA and adjudicated.
- b. Protocol page 81, item 10.4.4 and CEC charter (amended July 10, 2008, page 17, item 1.4) defined death due to aortic dissection, aortic aneurysm, pulmonary embolism, stroke or any other vascular cause as “death due to acute vascular events.”

I accepted the above explanation and findings, and did not cite it in the 483.

Patient #20493 had a severe stroke and was hospitalized for 36 days. There was no hospital discharge summary. This event was adjudicated as a non-CV endpoint because of insufficient information. (Exhibit: KMU G-11)

A discharge summary was not available for submission to the CEC; this documentation was critical for adjudication. I cited this observation in the 483 (item b (ii)).

Patient #20839: *This patient was admitted for a GI bleed adjudicated as non-CV endpoint. After 5 days in the hospital, this patient experienced chest pain, was transferred to the ICU, and died the same day. The death was adjudicated “non-CV from unknown cause.” Cardiac biomarkers and ECG were not documented, and a death certificate and a hospital death summary were not found. The clinical investigator’s response to a data resolution query stated that myocardial infarction caused death.* (Exhibit: KMU G-12)

I found that the endpoint of death was adjudicated CV death due to MI by Prof. Komajda, non-CV death (unknown death, insufficient data) by Prof Syvanne, and it went to the Full Committee which adjudicated as non-CV death (unknown death, insufficient data). I did not find the ECG in the CRF, but found a monitor’s note that states, “no death summary or further source documents are available.” Lack of documentation critical for adjudication led to this endpoint being adjudicated as non-CV death (unknown death, insufficient data). I cited this observation in the 483 (item b (iii)).

Patient #20930 experienced a SAE of collapse on (b) (6), and was hospitalized for 18 days. This hospitalization was attributed to atrial fibrillation, but was not sent for adjudication, and a discharge summary was not available. (Exhibit: KMU G-13)

The sponsor did not ensure that all potential endpoints were submitted to the CEC for adjudication. I cited this observation in the 483 (item c).

Patient #21075 had a SAE initially recorded in CRF as a stroke but amended to “cerebral ictus (seizure),” and right hemiparesis for which the patient was hospitalized. A lab result was reported as severe thrombocytopenia. There was no hospital discharge summary. This event was adjudicated non-CV because of insufficient information. I asked the sponsor to explain why seizure with right hemiparesis (initially recorded as stroke) was not adjudicated. (Exhibit: KMU G-14)

The sponsor submitted that no SAE was reported by the investigator, there was no discharge summary, and that the sub-investigator provided a signed and dated note to file that the discharge summary was not available. After discussions with colleagues from DSI, this was not cited in the 483.

Patient #21368 was hospitalized for (a) digit amputation (b) (6), and (b) peripheral artery disease (b) (6). These hospitalizations were not sent for adjudication. (Exhibit: KMU G-15)

Dr. Murray Stewart explained that the digit amputation was not reported because it was attributed to osteomyelitis and not due to diabetes which is the reporting requirement for an amputation as stated in the protocol, section 10.9.6. The hospitalization for peripheral vascular disease was not reported as an endpoint because protocol “section 10.5.6 Hospitalization for Unscheduled (emergency) arterial revascularization or amputation of extremities,” states that the

diagnosis of peripheral vascular disease or worsening of peripheral vascular disease during the course of the study will be reported as an AE but not as an endpoint. I did not cite this in the 483.

Patient #29515 (Australia) had endpoints of hospitalization for invasive CV procedure (b) (6), hospitalization for CHF (b) (6) and CV hospitalization for angina (b) (6) adjudicated appropriately. This patient withdrew on 26-Mar-2008. (Exhibit: KMU G-16)

I did not find an inspectional observation to cite for this patient.

Patient #30187 had a stroke (left hemiparesis) on (b) (6), and was hospitalized. The event was not reported as a SAE. (Exhibit: KMU G-17)

The sponsor's explanation was that the investigator did not consider it to be a SAE, and reported it only as an AE. A subsequent hospitalization in (b) (6) followed by a right internal carotid artery resection and reimplantation, was adjudicated as a CV hospitalization for an invasive CV procedure (Exhibit: KMU G-17). I did not cite this in the 483.

Patient #30885 had a MI reported in (b) (6) and was hospitalized for 20 days. The patient was transferred from the initial hospital to another one for PTCA. The hospital discharge summary and other information, e.g., biomarkers, from the first hospital were not available. The PTCA hospitalization was adjudicated as a CV procedure. However, the initial MI hospitalization was adjudicated as "non-CV, insufficient information." (Exhibit: KMU G-18)

For the initial MI hospitalization, the investigator marked in the CRF for cardiac biomarkers and ECGs as "not done." Although there was insufficient information on which the CEC adjudicated the event as "non-CV, insufficient information," it appeared that the CEC accepted the investigator's determination. I did not cite this in the 483.

Patient #31421 (Sweden site #283) was hospitalized for an invasive CV procedure on (b) (6), but the event was not received by the study monitor until October 15, 2008. (Exhibit: KMU G-19) This patient had 5 endpoint forms for the same event: 2 endpoint forms that adjudicated yes for CV hospitalization – invasive CV procedure, and 3 endpoint forms (the first two did not agree and required a third adjudication by the Full Committee) for non CV-hospitalization.

I cited the observation of over 2 years' delay from onset of the event to receipt by the study monitor in the 483 (item a (i)(3)).

Patient #31427 had facial paralysis resulting in a 5-day hospitalization, during which a CT scan to rule out stroke and a spinal tap were performed (suggesting unusual or severe disease). This hospitalization was not sent for adjudication. (Exhibit: KMU G-20)

There was no hospitalization per the CRF and accompanying CRA notes for the facial palsy. According to a narrative, the CT scan ruled out a CV event (stroke). Hence, the investigator did not consider it to be a SAE, and reported the event as an AE that was not required to adjudicate. I did not cite this in the 483.

Patient #31507 was hospitalized for a cardiovascular (CV) procedure on (b) (6) but the event was not received by the study monitor until September 11, 2008. (Exhibit: KMU G-21)

I cited the observation of over 4 years' delay from onset of the event to receipt by the study monitor in the 483 (item a (i)(2)).

Patient #31510: Patient's discharge summaries and other documents were sent to GSK in error (instead of CEVA in Quintiles). (Exhibit: KMU G-22)

This is a probable error. I found this type of error only once. I did not cite this in the 483.

Patient #31554 was (a) hospitalized for cerebral ischemia. This event was adjudicated non-CV because of insufficient information. (b) hospitalized for angina. This event was adjudicated non-CV because of insufficient information. The discharge summary for the second hospitalization for angina mentions "Residual effects of

Stroke.” This patient did not have a history of stroke at baseline, suggesting the previous hospitalization was for a stroke. (Exhibit: KMU G-23)

Dr. Murray Stewart explained that CT and MRI scans were not done for this patient to document a stroke. The mention of “Residual effects of Stroke,” appears to be derived from the previous SAE of cerebral ischemia. I did not cite this in the 483.

Patient #38069 (Sweden) on rosiglitazone had 6 endpoints, of which 3 (2 CHF hospitalizations and 1 hospitalization for invasive CV procedure) were re-adjudicated as non-CV endpoints by the Full Committee, which appeared suspicious. (Exhibit: KMU G-24)

I found that the Full Committee adjudications were appropriate. I did not cite this in the 483.

Patient #38161 (T= rosiglitazone) had a CVA with left arm hemiparesis on (b) (6). This was not reported as a SAE (the reason was that the patient was not hospitalized for this, so it was not a SAE). (Exhibit: KMU G-25)

Dr. Murray Stewart explained that the investigator considered the event did not meet the seriousness criteria, and thus did not report it as a SAE. I did not cite this in the 483.

Patient #43697 had an SAE “cerebral hemangioma with hematoma in intracerebral left temporal region, and symptomatic epilepsy for which the patient was hospitalized. The SAE was changed to “epilepsy.” The hospitalization was not adjudicated. (Exhibit: KMU G-26)

Dr. Murray Stewart explained that the hospitalization did not go to adjudication as the endpoint was deleted by the investigator who reported on the Event Report Fax Coversheet that the event was Non-CV in origin. There was also a CRA fax dated 28-Feb-2005 confirming that this event should be deleted. I accepted Dr. Stewart’s explanation and did not cite this in the 483.

Patient #43767 was hospitalized for unstable angina and Coronary Artery Bypass Graft procedure in December 2005. The discharge summary was not available. This hospitalization was adjudicated as non-CV event because of insufficient information. (Exhibit: KMU G-27)

I found on the hospital discharge summary page a note that “ECG tracing = not done,” and that cardiac biomarkers were not done. The available ECG was from 27-Mar-2003. I cited this observation in the 483 (item b (iv)).

Patient #97579: The event for invasive CV procedure was sent to CEC reviewers for adjudication on June 27, 2007; the review was completed on November 26, 2008. Another event for “Other CV reason – atherosclerosis of extremities” was sent to CEC reviewers for adjudication on January 26, 2007; the review was completed on February 26, 2009. (Exhibit: KMU G-28)

I cited the observation of over 1 to 2 years’ delay by the CEC to complete adjudication of events in a timely manner in the 483 (item a (ii)(3)). However, I found later that the second event required to be adjudicated by the Full Committee because of disagreement between reviewers, and that it was re-adjudicated on 23-Feb-2009 by the Full Committee.

Patient #97988 had a MRI scan for visual impairment, which revealed an ischemic stroke (occipital region). This was not reported as a SAE. I asked why a stroke is not considered a SAE. (Exhibit: KMU G-29)

Dr. Stewart explained that all strokes were not considered SAEs, because the protocol (section 8.1.2) defines that “a SAE must fulfill one of the 9 criteria: (i) fatal, (ii) life threatening, (iii) disabling/ incapacitating, (iv) results in hospitalization or prolongs a hospital stay, (v) a congenital abnormality, (vi) any important medical occurrence which the investigator regards as serious based on appropriate medical judgment, (vii) cancer, (viii) overdose, and (ix) pregnancy.” This patient was not hospitalized, so it was not considered a SAE.

Patient #98216 had a chest pain SAE “which was suspected to be ischemic” with a 2-day hospitalization. This hospitalization was not sent for adjudication. This patient later developed sick sinus syndrome and heart failure. (Exhibit: KMU G-30)

Dr. Stewart explained that the Investigator had commented on the SAE form “Patient had chest pain which was suspected to be ischemic. All tests were negative. The most likely cause for the chest pain was gastroesophageal

reflux.” I accepted Dr. Stewart’s explanation and the investigator’s determination, and did not cite this in the 483.

Patient #98276: *The event for stroke was sent to CEC reviewers for adjudication on June 29, 2004; the review was completed on October 5, 2005. (Exhibit: KMU G-31)*

I cited the observation of over one years’ delay by the CEC to complete adjudication of events in a timely manner in the 483 (item a (ii)(2)). However, I found that because of disagreement between reviewers, the endpoint had to be adjudicated by the Full Committee. Later, when the neurologist Prof Lees, joined the CEC, this stroke EP was re-adjudicated by Prof Lees, and finally, again by the Full Committee. These contributed to the delay in the final adjudication date.

Patient #98364: *This patient was hospitalized for 10 days starting (b) (6) for heart insufficiency and leg edema. (Exhibit: KMU G-32)*

- a. *Why was this hospitalization not adjudicated, i.e., not in CVENDPT.XPT?*
- b. *The SAE CRF has an annotation of “EP NO: E25248-182 HK 28-NOV-2007”. We can not locate any documentation on this endpoint. What happened to it? Please provide the endpoint dossier for it.*
- c. *This patient was hospitalized from (b) (6) for heart failure. Why was this hospitalization not adjudicated?*
- d. *Please provide a translated copy of the German discharge summary in the CRFs.*

Dr. Murray Stewart provided the following explanation (all related to EP# 25248):

- (a) See (b and c).
- (b) The hospitalization was deleted per instruction from the site, with receipt of crossed-through Event Report Fax Coversheet. The following appears to have taken place: see (c).
- (c) The hospitalization for heart failure was recorded in the CRF following a telephone information that the patient had “hospitalization with edema both legs with heart insufficiency.” A CRA note (b) (4) - (b) (4) says “the patient was not hospitalized.” A subsequent note by Paul Murphy says “if patient was not hospitalized, this was not an endpoint.” Hence, the endpoint was deleted, and did not show up in the database CVENDPT.XPT (answer to a).
- (d) Hospital discharge summary in native language - a data query had a reply as “not available,” although there appears to be a hospital note in the German language.

I accepted the above explanation and findings, and did not put it in the 483.

Information obtained from interviews

The following summarizes the information I obtained from the interviews during which I raised some questions. Other aspects of the interviews in response to questions by other FDA staff will be presented in their sections of the EIR.

Opening interview

The following summarizes the information provided by Dr. Murray Stewart, the GSK physician most responsible for the RECORD trial.

In February 2000, the RECORD protocol (synopsis) was submitted to CHMP. The original endpoint was (i) all CV deaths and hospitalization, and (ii) heart failure hospitalizations. The CHMP reviewed the protocol synopsis; the full protocol was submitted to the Steering Committee (SC) thereafter.

Recruitment was slow in 2003, and was closed in 2003 after completion of enrollment. At that time, the World Health Organization (WHO) suggested evaluating myocardial ischemia in RECORD patients treated with insulin.

The interim analysis was submitted to GSL, FDA, CHMP and SC.

The EMA reviewed the final RECORD findings and approved continued marketing for 5 years.

Dr. Murray Stewart and Nigel Jones wrote the RECORD protocol, designed the CRF and ICF (informed consent form), and were involved with the RECORD trial from the start to finish. Nigel Jones also represented GSK in the SC from 2000 to present date.

Dr. Stewart nominated Prof. Philip Home as chair of the SC. Prof. Philip Home recommended Prof. Ian Campbell as chair of the data safety monitoring board (DSMB). He also suggested a neurologist (Prof. Kennedy Lees) to be

added to the CEC to adjudicate stroke and TIAs, and also a diabetologist (Prof. Michel Marre) to be included to the CEC.

The SC met every 6 months.

The charters of the SC, DSMB and CEC define the functions of these groups. The contracts for each member of these groups describe the terms of payment for services.

SAE data (unblinded) were submitted (by fax) from the Quintiles CRAs to the GSK safety group (GSK Global Clinical Safety and Pharmacovigilance – GCSP). For SAEs, the investigator was given the responsibility to decide whether a SAE should be reported.

The endpoint (EP) data (blinded) were faxed to Quintiles Clinical Event Validation and Adjudication (CEVA) Services.

The responsibility of GSK was to manage SAE (by GCSP).

GSK proposed sites for selection to Quintiles, and Quintiles chose the trial sites.

Quintiles was responsible for the operation of the trial (including training of CRAs and investigators, project management, data management, and processing endpoints).

GSK initially monitored trial sites in 3 countries: Sweden, Australia and New Zealand. In Sweden, GSK knew that (b) (4) had conducted the SOS trial, and had an established network of clinical investigators. Patient enrollment and treatment was delegated to the (b) (4); GSK performed monitoring only. Later, GSK transferred to Quintiles the monitoring function of trial sites in Australia (in 2003) and New Zealand (in 2005).

Re-adjudication activities were performed by both GSK and Quintiles.

EP Sweep: The SC requested GSK to ascertain over a 3 month period all hospitalizations and endpoint events for all patients. CRAs were encouraged to go back and check data, and uncover missed events, if any. This activity found that missed events were very low, and that most of these events would have been found at the next scheduled visit. Thus, there was no need to repeat the EP Sweep.

Statistical analyses (interim and end-of-study) were performed by GSK.

Quality assurance audits were performed by Quintiles or GSK or sometimes jointly.

Study closeout was performed over a 4-month period (because the follow up was every 4 months) from August to December 2008.

I requested Dr. Stewart to provide the following:

- (1) names and position titles of GSK and Quintiles physicians and statisticians involved with the RECORD trial, who were blinded and unblinded
- (2) Re: his statement that the SC made the decision to publish interim results without knowing the results, I requested Dr. Stewart to provide a chronological account of who knew what and when (names, dates, context of messages (phone, e-mail), communications with SC and DSMB members) from the time GSA and FDA met in April 2007 to the time of publication of the interim report in the New England Journal of Medicine, specifically the formation apart from that already in the GSK White paper.

Dr. Stewart prepared a written response and discussed with me on May 13, 2010; Dr. Ball and Dr. Leibenhaut who were present suggested that Dr. Stewart should make the written response on GSK letter head and sign and date it. I did not receive the written response from Dr. Stewart by close out. It is possible that Dr. Stewart may have submitted his written chronology to DSI later.

Interview with Prof. Philip Home, Steering Committee chairman

The questions were mainly asked by Dr. Ball and Dr. Leibenhaut. I will present Prof. Home's response to questions requested by the review division. Other information obtained during the interview by Drs. Ball and Leibenhaut will be presented in their sections of the EIR.

Q. The "Final Draft minutes 8th Steering Committee Meeting – September 03" records that "The Steering committee members were informed of the unrestricted availability of unblinded treatment code within Quintiles and GSK : no concerns raised." What is your understanding of how this question was raised? What is your

understanding of what was the availability of unblinded treatment code within Quintiles and GSK? Did you have any concerns?

- A. Prof. Home was aware that there was a need to ensure that firewalls were maintained within GSK and in Quintiles so that the blind was maintained. When some personnel from pharmacovigilance (i.e., GSK GCSP) who were unblinded to access codes were present as some of the SC meetings, Prof. Home asked these personnel to leave the room.

Q. Were you involved in the NDA submission?

- A. No.

Q. RECORD Steering Committee Meeting 3 August 2007, Stuart Pocock raised concerns about some data issues that were discovered during the recent interim analysis work. Jackie to liaise 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 about some data issues?

- A. Prof. Home replied that myocardial ischemia was a concern, and the interim analysis was prepared because of that. He was aware of an interim analysis being prepared for submission to FDA and other regulatory authorities.

Prof. Home learned about the Nissen article on a Monday, but did not focus on it much because he was preparing to go on vacation in Colorado. Then, it became obvious to have a SC meeting. He called (from Colorado) for a telecon meeting of the SC on May 24 (Thursday), because it became clear that the RECORD study was going to lose investigators and participants. Thus, even without knowing the results, the SC had to agree to publish the interim results. Prof. Home knew that FDA had the interim analysis data already, and he worried about leaks of the interim analysis to the Press. He thought that it was better to get a formal publication rather than a New York Times article.

About 16 days later, Prof. Home had a look at the data (he had not seen the data during his holiday in Colorado). Stuart Pocock and Nigel Jones volunteered to write the paper, and wrote it in 6 days and submitted to the New England Journal of Medicine. They got the referees' comments within 48 hours, revised the manuscript, and published on-line on Monday. Prof. Home thought that this publication helped with preventing loss of patients from the RECORD trial.

Q. You are likely aware of the following quote from Dr. Steve Nissen's article "Setting the RECORD Straight" in the March 24/31, 2010, issue of JAMA: "The experience with RECORD raises important questions about the conduct of industry-sponsored clinical trials. 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. Although the final RECORD articles report that external statistical confirmation was obtained, the extent and depth of these confirmatory analyses remain uncertain." Which of these two approaches is more applicable to RECORD? How would you describe "the extent and depth of these confirmatory analyses" in RECORD?

- A. Prof. Home was of the opinion that while some academic centers provide computers where data may be held, this would leave the data exposed. In the case of the RECORD trial, the database was held by Quintiles (admittedly funded by GSK), and therefore the database was more under the control of GSK than of the SC. Prof. Home never had any opportunity to have access to the data. Independent patient data was provided for the interim and final analyses to Prof. Stuart Pocock to check for data integrity. The data were transferred from Quintiles to GSK by the Quintiles statisticians. The SC would work with GSK for their analyses on the blinded data.

Prof. Home mentioned that he never saw raw data or patient level data.

Interview with Prof. Ian Campbell, chairman of Data Safety Monitoring Board

The questions were mainly asked by Dr. Ball and Dr. Leibenhaut. I will present Prof. Home's response to some of

the same questions that the review division wanted me to ask Prof Home. Other information obtained during the interview by Drs. Ball and Leibenhaut will be presented in their sections of the EIR.

Question related to unblinding: What is your understanding of what was the availability of unblinded treatment code within Quintiles and GSK? Did you have any concerns?

The DSMB Charter permitted limited contact with the SC, GSK or investigators. Prof. Campbell had no contact, and did not speak to local GSK reps over the course of the RECORD trial. CEC data were made available to the DSMB by Quintiles. Interactions with the SC or CEC were usually by letter such as advising that a neurologist to be included in the CEC, raising the question of low event rates (two cardiologists in the DSMB raised the question of low MI rates) in 2004 to the SC, and urging the CEC to speed up their process of adjudicating endpoints.

Question related to interim analysis and the Nissen article:

Prof Campbell's stated that an integrated summary of clinical trials (excluding the RECORD trial) was submitted to FDA. This information was also presented to DSMB. He realized that some of the studies in the integrated summary were of short duration, and that the RECORD trial would provide more definite information regarding CV outcome events in diabetic patients treated with rosiglitazone.

In May 24, 2007 meeting and June 2007 meeting of DSMB, Prof. Campbell was approached as DSMB chair for permission to unblind data for interim analysis. The Prof Ian Ford, the statistician in the DSMB, pointed out that the study should NOT be blinded. Finally, because there was a pressure to assure FDA and regulatory authorities (although he was not aware whether FDA asked the sponsor or not), DSMB agreed to give permission to unblind the RECORD trial data, the data for fractures, and the data for interactions of rosiglitazone with ACE-inhibitors and nitrates. Though not sure of the exact date, it was in 2007 when Prof. Campbell contacted other members of the DSMB by phone to explain the need for unblinding (over overall safety issues) and to obtain a consensus within DSMB before giving permission to unblind the data. Prof. Campbell saw the results of the interim analysis soon after giving the permission to unblind and before the publication. He thought that the data presented in the publication was quite similar to that at the interim analysis. The unblinded data analyses for fractures and for interactions of rosiglitazone with ACE-inhibitors and nitrates came later.

Appendix II: My section of the establishment inspection report (EIR) of Quintiles CRO inspection conducted May 17-21, 2010 at Fairview, Dublin, Ireland

BACKGROUND AND METHODOLOGY

I participated as a subject matter expert and consultant to the Division of Scientific Investigations (DSI), Office of Compliance, in this FDA inspection of the contract research organization (CRO) – Quintiles Ireland Limited (hereinafter referred to as “Quintiles”).

The purpose of my participation in this inspection was to determine (a) the integrity of clinical data in the RECORD trial related to post-marketing cardiovascular (CV) safety of Avandia® (rosiglitazone) which was approved by FDA under NDA 21-071, and (b) the role of Quintiles in data collection and preparation of dossiers submitted to the CEC, and (c) if adjudications related to endpoints were made according to the charter of the Central Endpoint Committee (CEC). The inspection findings are anticipated to be discussed in an Advisory Committee meeting scheduled in July, 2010.

Comments on review issues

Use of a *non-inferiority design* in an *open-label* clinical trial to determine *post-marketing* adverse events gives the appearance that the RECORD trial will be likely to have biased event reporting and biased adjudication towards a finding of “no difference” between the treatment groups. Sloppiness in conduct of the RECORD trial will also contribute towards a “no difference” finding. CV death and CV hospitalization, the endpoints of this RECORD trial, may not be related to the effect of drugs but to co-morbid diseases prevalent in this patient population. Apart from trying to determine if there was sloppy conduct of the clinical trial, these review issues are beyond the scope of our inspection.

Approach to the inspection

I was assigned the role of a consultant to follow the lead by DSI for the inspectional issues they have identified.

In preparation for the inspection I performed a brief evaluation of the submission and initiated questions to the sponsor (which were issued in IRs through DSI). My review findings to the sponsor’s responses are beyond the scope of the inspection; I will present them in a separate memo submitted in DARRTS to NDA 21-071.

Methodology

I participated in the opening interview of the Quintiles personnel involved with RECORD trial, in the interview of the chairman of the CEC (Prof. Michel Komajda) during which I asked the questions/issues which had been raised by the review division, and in the audit of trial-related documents, adjudication packages (dossiers) and electronic data bases.

I reviewed the case report forms (CRFs) and associated documents (e.g., laboratory reports, ECGs, hospital discharge summaries and physician notes, where available, and explanatory notes produced by GSK):

- (i) 12 CRFs which contained information in support of the observations cited in the FDA-483 issued previously to GSK,
- (ii) 31 of the 53 completed endpoint dossiers selected at random to review adequacy of QC (listed in table above in the section written by Mike M. Rashti), and
- (iii) a random sample of 6 problematic CRFs and corresponding completed endpoint dossiers for which there were long intervals from onset of event to completion of adjudication, to determine if there were clinically relevant data integrity problems.

I reviewed also the quality assurance (QA) audit information accrued from Quintiles QA audit of 39 sites that participated in the RECORD trial, including the 5 sites that were terminated because data integrity problems were found.

Limitations of the Inspection

This inspection is limited to the audit of Sponsor/CRO per the Compliance Manual, review of CRFs and completed endpoint dossiers submitted to the Central Endpoint Committee (CEC) for adjudication and supporting documents, Charters of the Steering Committee (SC), Data Safety Monitoring Board (DSMB) and CEC, review of Quintiles QA audit information and discussions with Quintiles QA personnel, and interviews with the CEC chairman and the

Quintiles personnel involved in the RECORD trial.

It is beyond the scope of this inspection to evaluate the appropriateness of the study design, correctness of protocol-specified definitions of endpoints, timing of statistical analyses and appropriateness of the CEC adjudications, all of which are review issues.

In a separate memo submitted in DARRTS to NDA 21-071, I will present a limited evaluation of the review issues I worked on after being given this assignment to the RECORD inspection team, including the review inferences made from the findings in the inspection. My limited review comments are intended to supplement the reviews of other FDA reviewers, and not intended to replace, refute or undermine their recommendations.

Special issues to address during the inspection of GSK

From the CEC MS Access Database, I had identified a list of 135 endpoints where the interval between the time of onset of an event and the date of submission to the CEC for adjudication was about 2 to 5 years (Exhibit: KMU Q-1). During the inspection, Quintiles CEVA also submitted a breakdown of 128 endpoints which were received at Quintiles, Dublin, > 2 years after the onset of the events (Exhibit: KMU Q-2).

From the CEVA Tracking Database, I found that the CEC took longer than 1 year from receipt to completion of adjudication for at least 37 patients (Exhibit: KMU Q-3, the first two pages of the CEVA Tracking Database). These issues were raised at the opening interview, and used for evaluation of documents (CRFs, dossiers, etc.) during the audit.

INSPECTION FINDINGS

Inspection of CRFs and associated documents

I reviewed the following CRFs and associated documents including the 12 CRFs that contained information in support of the observations cited in the FDA-483 issued to the sponsor. I review 31 of the 53 completed endpoint dossiers selected at random to review adequacy of QC. I reviewed also a random sample of CRFs which were identified as problematic by the review division, and completed endpoint dossiers which had long intervals from onset of event to completion of adjudication, to determine if there were clinically relevant data integrity problems.

Re-inspection of the 12 CRFs which supported the observations cited in the FDA-483 issued to the sponsor (GSK)

Patient #18282: *The event of myocardial infarction (MI) was sent to CEC reviewers for adjudication on June 13, 2006; the review was completed on October 20, 2008.* (Exhibit: KMU Q-4)

The CRF showed that the event occurred on (b) (6) that it was ready for adjudication on 13-Jun-2006, but review was completed only on 20-Oct-2008. I cited this observation of delayed completion of adjudication of events by the CEC in the FDA-483 {item a (i)} issued to Quintiles.

Patient #19437 *was hospitalized with cough, sputum, acute heart failure, and ventricular arrhythmias, and at one point had a CK-MB fraction of 25%. The clinical diagnosis included the possibility of a MI. However, the MI was not adjudicated; only the heart failure event and death event were adjudicated.* (Exhibit: KMU Q-5)

At the GSK inspection, I cited this observation that when two endpoint events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately in the 483 {item d (i)}. The hospital notes do not state any diagnosis of heart failure, and there was no current ECG available which was critical data to determine if there was a MI. However, at Quintiles, I obtained information that this patient had long-standing mitral incompetence, tricuspid incompetence, chronic obstructive pulmonary disease (COPD) and Cor Pulmonale. The patient was hospitalized for heart failure on (b) (6) and had to be intubated and put on a ventilator; the patient died the next day. There does not appear to be any reason to suspect that a MI occurred during that hospitalization. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Patient #19731 *was hospitalized for ventricular arrhythmias and died. A hospital discharge summary was not found. The death was adjudicated as "unknown." The hospitalization was not adjudicated. Other problems with this patient included an AE (for which patient withdrew from the study) with a last visit on 8/17/05, although no documentation of the visit is submitted. The AEs is mentioned in a DCF as pancytopenia and the AE.XPT file lists a pancytopenia as severe and starting in 6/02 with a corresponding CRF from the month 8 visit.*

The patient died on (b) (6) The investigator faxed in the SAE report of the death on May 5, 2006, and Quintiles

recorded the receipt date as May 5, 2005. However, there is a second SAE report fax dated February 7, 2002 (year and day likely reversed). Many other Quintile records seem to indicate this SAE was processed in 2007.

Finally, there is a cryptic, "NOTE TO FILE" signed by a Quintiles Pharmacovigilance Program Manager but undated that "Please note that the patient was hospitalized and died, it states that the patient was hospitalized for ventricular arrhythmia but the patient had suffered from this for years it was not a case that it had worsened." There is no documentation supporting this Note to File despite a DEATH2 CRF (dated February 7, 2002) claiming that a hospital death summary was enclosed. (Exhibit: KMU Q-6)

A hospital discharge summary was not found which was confirmed by the investigator in a signed and dated response to a query from CEVA. The hospitalization was not reported as an endpoint allegedly because the CRA confirmed verbally in response to a query from CEVA that the ventricular arrhythmia was not worsening. I do not agree. I cited these observations in the FDA-483 {item c (i)} issued to Quintiles for not ensuring that when two endpoint events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately.

Patient #19734 died in (b) (6) (exact date unknown) but the site did not fax the serious adverse event (SAE) form for this event to the study monitor until February 2009, who then forwarded the event to the CEC. I asked the sponsor to explain why (i) data resolution query (DRQ) dated 03-Apr-2008 refers to two copies of tracking forms with different information, (ii) SAE form for MI which was dated 10-Feb-2008 had a fax cover sheet dated 10-Feb-2008 but amended to Feb-2009, and (iii) there was a study file note by PI (b) (4), "herewith I confirm that the death of the subjects 98460 and 98463 were not related to the study drug or the study protocol – dated 10-Feb-2003 (Exhibit: KMU Q-7)

At GSK, I cited this observation of over 4 years' delay in the receipt of the SAE by the study monitor in the FDA-483 {item a (i)(1)}. At Quintiles, I found that this patient was withdrawn on 20-Jun-2005, and that the death was found during survival status data collection carried out in 2009. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Patient #20493 had a severe stroke and was hospitalized for 36 days. There was no hospital discharge summary. This event was adjudicated as a non-CV endpoint because of insufficient information. (Exhibit: KMU Q-8)

A discharge summary was not available for submission to the CEC; this documentation was critical for adjudication. I cited this observation in the FDA-483 {item b (i)} issued to Quintiles.

Patient #20839: *This patient was admitted for a GI bleed adjudicated as non-CV endpoint. After 5 days in the hospital, this patient experienced chest pain, was transferred to the ICU, and died the same day. The death was adjudicated "non-CV from unknown cause." Cardiac biomarkers and ECG were not documented, and a death certificate and a hospital death summary were not found. The clinical investigator's response to a data resolution query stated that myocardial infarction caused death. (Exhibit: KMU Q-9)*

I found that the endpoint of death was adjudicated CV death due to MI by Prof. Komajda, non-CV death (unknown death, insufficient data) by Prof Syvanne, and the dossier went to the Full Committee which adjudicated the event as non-CV death (unknown death, insufficient data). I did not find the ECG in the CRF, but found a monitor's note that states, "no death summary or further source documents are available." Lack of documentation critical for adjudication led to this endpoint being adjudicated as non-CV death (unknown death, insufficient data). AT the GSK inspection, I cited this observation in the 483 {item b (iii)}. During the inspection at Quintiles, I found the ECG and hospital discharge summary. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Patient #20930 experienced a SAE of collapse on (b) (6), and was hospitalized for 18 days. This hospitalization was attributed to atrial fibrillation, but was not sent for adjudication, and a discharge summary was not available. (Exhibit: KMU Q-10)

The sponsor did not ensure that all potential endpoints were submitted to the CEC for adjudication. At the GSK inspection, I cited this observation in the 483 {item c}. At Quintiles, I found a CRA note that alluded to the doctor's notes that this patient had memory loss, was disorientated (mention of Alzheimer's) and that a CT scan was awaited. The patient was withdrawn from the trial because of poor compliance. It is questionable whether there was a CV reason for hospitalization. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Patient #31421 (Sweden site #823) was hospitalized for an invasive CV procedure on (b) (6), but the event was not received by the study monitor until 15-Oct-2008. (Exhibit: KMU Q-11) This patient had 5 endpoint forms for the same event: 2 endpoint forms that adjudicated yes for CV hospitalization – invasive CV procedure, and 3 endpoint forms (the first two did not agree and required a third adjudication by the Full Committee) for non CV-hospitalization.

I cited the observation of over 2 years' delay from onset of the event to receipt by the study monitor in the FDA-483 {item a (i)(3)} issued to GSK. The study site in Sweden was monitored by GSK, not by Quintiles. Thus, I did not cite this in the FDA-483 to Quintiles.

Patient #31507 (Sweden site #821) was hospitalized for a cardiovascular (CV) procedure on (b) (6), but the event was not received by the study monitor until September 11, 2008. (Exhibit: KMU Q-12)

In the inspection at GSK, I cited the observation of over 4 years' delay from onset of the event to receipt by the study monitor in the FDA-483 {item a (i)(2)}. The study site in Sweden was monitored by GSK, not by Quintiles. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Patient #43767 was hospitalized for unstable angina and Coronary Artery Bypass Graft procedure in December 2005. The discharge summary was not available. This hospitalization was adjudicated as non-CV event because of insufficient information. (Exhibit: KMU Q-13)

I found on the hospital discharge summary page a note that "ECG tracing = not done," and that cardiac biomarkers were not done. The available ECG was from (b) (6). At the GSK inspection, I cited this observation in the FDA-483 {item b (iv)}. At Quintiles, I found the ECG in the CEC dossier: the ECG shows no acute ischemic changes or MI. It appears that this endpoint was adjudicated appropriately based of adequate information as non-CV. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Patient #97579: The event for invasive CV procedure was sent to CEC reviewers for adjudication on June 27, 2007; the review was completed on November 26, 2008. Another event for "Other CV reason – atherosclerosis of extremities" was sent to CEC reviewers for adjudication on January 26, 2007; the review was completed on February 26, 2009. (Exhibit: KMU Q-14)

At the GSK inspection, I cited the observation of over 1 to 2 years' delay by the CEC to complete the adjudication of the above two events in a timely manner in the FDA-483 {item a (ii)(3)}. At Quintiles, I found that for the second event there was disagreement between reviewers which required the Full Committee to re-adjudicate on 23-Feb-2009. I cited the first observation in the FDA-483 {item a (ii)} issued to Quintiles.

Patient #98276: The event for stroke was sent to CEC reviewers for adjudication on June 29, 2004; the review was completed on October 5, 2005. (Exhibit: KMU Q-15)

At the GSK inspection, I cited the observation of over one years' delay by the CEC to complete adjudication of events in a timely manner in the FDA-483 {item a (ii)(2)}. However, I found that because of disagreement between reviewers, the endpoint had to be adjudicated by the Full Committee. Later, when the neurologist Prof Lees, joined the CEC, this stroke EP was re-adjudicated by Prof. Lees, and finally, again by the Full Committee. These contributed to the delay in the final adjudication date. Thus, I did not cite this in the FDA-483 issued to Quintiles.

Inspection of 31 of the 53 completed endpoint dossiers selected at random to review adequacy of QC

The list of 53 completed endpoint dossiers we randomly selected and reviewed for adequacy of QC during the inspection at Quintiles are tabulated in the section written by Mike M. Rashti (reproduced below). I reviewed 31 of these dossiers for QC (Mike Rashti and Susan Leibenhaut reviewed the other 22 endpoint dossiers) and did not find any problems in the QC process of these 31 endpoint dossiers.

Patient #	Country	Center #	End-point #	Review finding of the QC audit status
18106	Poland	386	13863-386	OK
			13870-386	OK

			13877-386	OK
18156	Germany	182	16085-182	OK
			29720-182	OK
			Pneumonia (non EP)	OK
18282	Estonia	092	12004-092	OK
			12006-092	OK
18388	United Kingdom	498	22443-498	OK
			22444-498	OK
			22459-498	OK
18498	United Kingdom	519	21527-519	OK
			21531-519	OK
			21533-519	OK
			21534-519	OK
18735	Hungary	272	26222-272	OK
18977	Croatia	021	14330-021	OK
			28962-021	OK
			28963-021	OK
19338	Netherlands	343	13201-343	OK
			13203-343	OK
			13204-343	OK
19731	Germany	210	25270-210	OK
19825	France	135	12442-135	OK
			18505-135	OK
19870	Belgium	015	14466-015	OK
			14467-015	OK
20493	Poland	385	13512-385	OK
20554	Bulgaria	668	21481-668	OK
20839	Belgium	007	24783-007	OK
			26874-007	OK
29094	United Kingdom	485	27161-485	OK
			27162-485	OK
29200	Russia	743	22167-743	OK
30256	Sweden	830	21861-830	OK
31057	Sweden	821	23407-821	OK
31421	Sweden	823	23269-823	OK
31554	Ukraine	727	21042-727	OK
			21046-727	OK
37516	Ukraine	726	21021-726	OK
			21023-746	OK
			21024-726	OK
38383	Poland	384	25143-384	OK
			12477-384	OK
			12507-384	OK
43767	Sweden	831	20748-831	OK
97579	Estonia	093	12045-093	OK
			12050-093	OK
			12051-093	OK
97954	Finland	109	12246-109	OK
98276	Czech Republic	041	12129-041	OK
			12130-041	OK
98364	Germany	182	25248-182	OK

Inspection of a random sample of CRFs endpoint dossiers which had long intervals from onset of event to completion of adjudication

Patient #18388 had a “collapse” and was hospitalized with an angio showing severe 3 vessel disease in (b) (6). The patient subsequently died in (b) (6).

- d. Why was the hospitalization with collapse not adjudicated as CV? Some CRFs indicate that a hospital discharge summary was enclosed but the dossier appears to include only an op note for a CABG from Aug. Why was this not checked?
- e. Why was more information not obtained about the death at (b) (6) hospital in 2008?

This patient was not on study meds (metformin) since August, 2006. During the hospitalization on (b) (6) for a collapse (with an angiogram showing severe 3 vessel disease), a laparotomy (page 268 of CRF) revealed a bleeding vessel at the esophago-gastric junction, which explained the collapse (Exhibit: KMU Q-16). Thus, I thought that this event was appropriately adjudicated non-CV. This patient’s death on (b) (6) was found at third party survival status collection during Oct to Dec, 2008. I did not cite this in the FDA-483 issued to Quintiles.

Patient #18498 was hospitalized on in (b) (6) for chest pain/cholecystitis (adjudicated as non-CV) and then again on (b) (6) for acute coronary syndrome ultimately leading to his death. (Exhibit: KMU Q-17)

- a. The SAE CRF remarks for the cholecystitis hospitalization has in the Remarks section “Developed arrhythmia & given IV amiodarone + diuretics. Resolved.” Why was the type of arrhythmia not elicited? One adjudication form records atrial fibrillation. Note: We believe that “arrhythmia” is being used as a synonym for atrial fibrillation at some of the RECORD sites. However, arrhythmia in the US is a nonspecific term and atrial fibrillation is a specific term in MedDRA.
- b. In the Adjudication Package tab for this Endpoint 21527-519 in submission S046 the identities of the diabetic drugs are given on multiple forms. Please explain. Do you have any estimate how often diabetic drug identities were revealed in the dossiers sent to CEC committee members?
- c. The Adjudication Package tab for Endpoint 21531-519 contains a file note regarding “Missing Original Endpoint Forms” stating that “Original Documents were never received for case E21531-519 pt 18498. Please find fax copies in the Master binder.” The tab includes at least two sets of very slightly different endpoint forms. Who generated these endpoint forms? When? What endpoint forms did the CEC members review? Did you provide us with Adjudication Packages identical to those reviewed by the CEC?
- d. CVENDPT.XPT for Endpoint 21531-519 has three records, one each for reviewers adjudicating MI and unstable angina and a third for the full committee adjudicating unstable angina. We could only find adjudication forms in Submission S046 for the two reviewers. Please explain how the full committee adjudications are documented and provide the documentation.

- a. The medical notes related to cholecystitis were by a surgeon who mentioned only that the patient “... developed an arrhythmia...” The CRF SAE pages also mentioned only arrhythmia, and a narrative mentions “... the subject developed palpitations and attended a cardiology clinic.” In all these situations, the patient was treated with oral amiodarone, which suggests atrial fibrillation, but does not confirm it. An accompanying ECG (no date on it) showed sinus rhythm with ventricular extrasystoles.
- b. The identities of antidiabetic drugs are on forms prior to the QC. After the QC, and in the dossier sent to the CEC, these were blacked out.
- c. The slightly different forms are found during our review of QC. For this patient, there were two QC checks done by Paul Murphy (first and second level QC related to endpoint 21533-519 and 21534-519); the QC auditor would highlight corrections to be made on the forms, which were faxed to the CRA, who then faxed back the corrected forms; thus, some dossiers contain a set of forms before and after QC, which could be slightly different.
- d. The full committee adjudication for endpoint 21533-519 in on page 166 of the CRF, included as part of (Exhibit: KMU Q-17). Similarly, the full committee adjudication for endpoint 21527-519 is included as part of this exhibit.

I did not cite this in the FDA-483 issued to Quintiles.

Patient #18977 was hospitalized from (b) (6) for “coronarography due to unstable angina pectoris” (UA). He

did have an initial episode of UA in (b) (6)

- a. Why was this hospitalization not adjudicated?
- b. Why was the date of unstable angina not established? How was it determined that this was not a new episode, when the SAE is noted as ongoing, constant, and moderate? If new, why was a MIUA1 form not completed?
- c. Why was the UA SAE deleted one year later?
- d. Please provide documentation supporting all of these answers.

For this endpoint, first recorded on the CRF, was later struck out {in . (Exhibit: KMU Q-18)} by the investigator. A DRQ (dated 21-Mar-2007) showed that coronarography due to unstable angina pectoris is not an endpoint as it was a planned procedure, and the investigator wrote "Please delete" (and signed and dated it 21-Mar-2007). It appears that these actions were carried out strictly following the letter of the protocol. I did not cite this in the FDA-483 issued to Quintiles.

Patient #20554 had an other CV endpoint for an angina hospitalization in (b) (6) adjudicated as atrial fibrillation. (Exhibit: KMU Q-19)

- a. The discharge summary clearly describes the AFib starting intermittently in (b) (6) with a stroke occurring during one of the attacks. It does not describe a neuro exam but does state that exercise testing could not be done due to the post-stroke condition. Why were details on the stroke not sought?
- b. Only one hospitalization is reported. Why was a query regarding a stroke hospitalization not done?

By the time of the hospitalization that was adjudicated on (b) (6) for AFib, the patient already had a stroke (ischemic stroke in region of left middle cerebral artery in (b) (6)). It appeared that this hospitalization in (b) (6) was for paroxysmal AFib. There is no information whether the earlier stroke resulted in a hospitalization. I did not cite this in the FDA-483 issued to Quintiles.

(Note: In response to the DRQ on 03-May-2007, the investigator wrote that this patient "withdrew his consent and was lost to follow-up.")

Patient #29094 died at home suddenly after complaining of chest pain. The death was called an MI but no autopsy was done. (Exhibit: KMU Q-20)

- a. One CEC reviewer called this an MI death and another called it a sudden death. However, the full committee allegedly called it an "other CV death" "cardiac arrest". Please explain how "cardiac arrest" differs from "sudden death". Please provide the minutes of the full committee meeting at which this death was adjudicated.

Per the RECORD protocol, Sudden Death was defined as due to one of the following reasons:

- 1) within one hour after onset of new symptoms
- 2) witnessed death, without new symptoms occurring within 72 hours preceding death
- 3) cardiac arrest followed by death within 30 days even if temporarily recovered
- 4) unwitnessed death in the absence of new symptoms (i.e., the patient did not have any signs or symptoms 24 hours before the death occurred)

Otherwise it will constitute a death of unknown cause. (Exhibit: KMU Q-20)

A death certificate states that this patient died at home at 00:12 hr whilst lying in bed, wife and son present. There was no mention of chest pain, shortness of breath or other symptoms of a MI or heart failure. His death did not fit in with one of the four categories defined as sudden death in the protocol. Thus, I think the Full Committee adjudicated appropriately as Other CV death (and specified as cardiac arrest, which appeared plausible). I did not cite this in the FDA-483 issued to Quintiles.

Patient #97954 died by drowning confirmed by autopsy.

- a. The autopsy results are reported on a DRQ dated 20-Dec-2006. Were these results provided to the CEC? If so, where are they documented?
- b. The EP adj form for one of the CEC reviewers specifically mentions the autopsy report. Why was this annotation not followed up?

I found several DRQs by CRAs and responses by the investigator related to the autopsy report (Exhibit: KMU Q-21). The investigator later wrote it "... 'pending autopsy.' It is uncertain if I will be informed of the results.

However, it is true that the patient drowned and died.....” On 20-Dec-2006, the investigator responded to Certified Cause of Death as “death by drowning,” and the “post mortem findings” were summarized by the investigator as “Death by drowning. Hypertension was marked as contributory factor. Hypertension is mentioned in medical History. All drug concentrations were within therapeutic ranges. Mild generalized atherosclerosis was seen in coronary arteries, aorta and cerebral arteries. Hypercholesterolemia is mentioned in medical history. There changes were not marked as contributory.” This information was entered in Form D of the CRF. I think there was adequate follow up of the autopsy report. I did not cite this in the FDA-483 issued to Quintiles.

Information obtained from interviews

The following summarizes the information I obtained from the interviews during which I raised some questions that the review division wanted information about. Other aspects of the interviews in response to questions by other FDA staff will be presented in their sections of the EIR.

Opening interview

The following information was provided by Catherine A. Tyner, Paul Murphy and Dr. Juris Nikitins:

Regarding our query about cross checking hospitalization information between the endpoint report forms and the medical care utilization records on the clinical data management system (CDMS), Ms. Tyner replied that endpoint reporting forms (e.g. HAE forms) were not databased on the CDMS, and therefore no cross checks were performed (Exhibit: KMU Q-22). There was a check performed between the medical care utilization record on the CDMS and SAEs (also databased on the CDMS).

The CEC members and staff were hired and paid by the sponsor, GSK. CEC reviewers were paired differently at different times to account for potential variability. To determine if there were inter-reviewer variability and/or potential bias in the adjudication of endpoints of patients on rosiglitazone versus metformin/sulfonyl urea combination, I requested a tabulation of the individual CEC reviewer’s adjudications broken down by treatment group, and their decisions as to “Yes” or “No” for a CV event. The table of individual CEC reviewer’s adjudications (Exhibit: KMU Q-23) does not appear to suggest individual bias on the part of the CEC reviewers.

Over the course of the RECORD trial, there were 11 face-to-face meetings and 28 teleconferences of the CEC (Exhibit: KMU Q-24). If there were disagreements in the adjudication between the CEC reviewers, these cases were discussed at the face-to-face meetings and adjudicated by the Full Committee. Of the 28 teleconferences, adjudications were discussed at 27 teleconferences; in one teleconference (which was a start up meeting) only the chairman of the CEC was in attendance.

Regarding re-adjudications (Exhibit: KMU Q-25), the majority were reviewed by the Full Committee as follows:

- endpoints adjudicated as the same type, critical data changes, non-urgent CV procedures and arteriosclerotic events were re-adjudicated by the Full Committee;
- all stroke/TIA endpoints were re-adjudicated by the neurologist Prof. Lees (if he agreed with previous adjudication this was considered final; if he disagreed with the previous adjudication, then this went to the Full Committee although Prof. Lees had the final say).

In response to my question regarding the CEC meeting minutes of 09-Feb-2009 which mentioned 6 deaths in patients who had cancer, withdrew from the study and died, for which Prof. Komajda (the CEC chairman) single-handedly adjudicated their events on behalf of the CEC (although there was no provision for such action in the CEC Charter), the explanation given was that all CEC members were in attendance at the telecon and rendered their adjudications, and that Prof. Komajda merely signed off on these adjudications.

I asked about the redaction of treatment-related information to maintain blinding of treatment group to CEC members. The redactions were made by CEVA services at Quintiles. I showed an example in the adjudication package for Patient # 97870 submitted to the CEC, in which the information related to the antidiabetic drugs was not redacted although the patient’s identification information (patient’s name) within the same paragraph was found redacted. On page 21 of the endpoint package Serial # 018 (Exhibit: KMU Q-26), there was this sentence in the second paragraph under **Therapy and progress**: “..... Furthermore, we also stopped treatment with metformin and rosiglitazone, and replaced these with a sulfonyl urea.....” This could have caused the treatment allocation to become unblinded to the CEC reviewers.

The Quintiles personnel said that the CEC had not told CEVA about any such unblinding situation. They explained

the procedure related to redaction as follows. When the dossiers were considered complete with source documents, they were reviewed by Quality Control (QC) before they were sent to the CEC. QC evaluated the dossiers to check clinical forms for completeness and that the appropriate treatment-related and identifying information were redacted; then QC highlighted problems, where present, in the dossier sent back to the CEVA processor. After the required corrections were made by the CEVA processor, the dossier went back to QC to confirm that the treatment information necessary to be blinded were redacted. Then only was the dossier forwarded to the CEC. Our review of the QC actions in 53 randomly selected endpoint dossiers did not reveal any major problems. It appeared that failure to redact treatment information occurred rarely.

Interview with Prof. Michel Komajda, Central Endpoint Committee Chairman

The questions were asked mainly by Dr. Leibenhaut. I will present Prof. Komajda's response to questions that the review division wanted me to ask him. Other information obtained during the interview by Dr. Leibenhaut will be presented in the section of the EIR written by Dr. Leibenhaut.

Prof. Komajda said that he was contacted by GSK due to his CV background, and the recommendation by the French Research and Development Team. Other members of the CEC included five cardiologists, one diabetologist, and, later, one neurologist, from different geographical parts of Europe.

The working document was the CEC Charter. The CEC members reviewed the discharge summary from the hospital whenever available, and doctors' notes or any forms from the physician (usually a discharge summary), because a large number of events occurred outside the hospital. For deaths, the CEC requested death certificates, medical letter from the doctor, and indirect reports from the family member or witnesses. If crucial medical information was lacking, CEC asked Quintiles to get them. The local Quintiles CRA would then try to obtain the information and reply whether they were able or unable to do so.

There was an initial training period for the CEC members when all events were adjudicated by all members. Later, adjudication was made by paired members. Because special knowledge of neurological endpoints was missing, the Steering Committee (SC) decided to add a neurologist to adjudicate all strokes/TIAs. Prof. Lees of the UK was recommended by the SC Chairman in about 2004. Subsequently, all previous stroke/TIA events were re-adjudicated by Prof. Lees.

Prof. Komajda explained the "back adjudication" process as follows: A dilution of events by planned CV procedures was discovered. He said that the CEC did not change the definition of the endpoint, but changed its interpretation, and considered only unplanned CV procedures as endpoints. Following Amendment 1 of the CEC Charter in December 2003, the CEC went back to adjudicate (i.e., "back adjudicate") all events related to CV procedures in early 2004.

At face-to-face meetings of the Full Committee of CEC, additional new information which CEC members had requested and considered crucial for decision were presented and discussed for adjudication.

Prof. Komajda also explained the process of "sequence adjudication," i.e., adjudication of endpoints occurring on the same day. This arose around August 2007 when the CEC was presented with binders of 10 patients who had two or more events (e.g., MI plus CHF) that occurred on the same day. The aim of the CEC was to determine which event was the cause and which was the effect (e.g., MI led to CHF or a patient with CHF was complicated by MI). Thus, the CEC decided that for cases where there was more than one event on the same day, the temporal sequence must be determined to decide which event occurred first and hence contributed to the primary endpoint. In the cases where death was one of the events, death was always considered the second event. These cases requiring sequence adjudications were discussed at face-to-face meetings of the CEC to determine which was the first event.

Prof. Komajda mentioned two examples which could preclude the event that occurred chronologically earlier. In the case of a planned coronary angiography followed by MI, there could be two endpoint forms, but the first – planned coronary angiography – was considered not an endpoint (because it was "planned"), and the second was considered an endpoint. In the case of a patient who experienced unstable angina, was hospitalized, then developed MI and subsequently CHF on the same day, the CEC discarded unstable angina, and the CV hospitalization was considered the primary endpoint event.

Prof. Komajda said that re-adjudications were done for three main reasons: (i) stroke/TIA (by the neurologist, Prof. Lees), (ii) revascularization procedures (mentioned above), and (iii) sequence endpoints that occurred on the same day.

There was a period of slow adjudication of endpoints, partly attributable to the re-adjudications (above). There was a time when Prof. Komajda was warned by Quintiles and GSK that one CEC member was not doing timely adjudications, and Prof. Komajda said he had had to communicate with that member by phone and letter to improve his adjudication.

Prof. Komajda said that there was no communication between the CEC and the DSMB.

The only interactions of the CEC with the SC were (i) regular updates from CEC to SC of the time lines and backlog of events to adjudicate, and (ii) communications from the SC to the CEC regarding (a) the addition of the neurologist Prof. Lees as a CEC member to adjudicate stroke/TIAs and (b) the discussion of non-urgent vs. planned CV procedures as endpoints.

In response to my question regarding a failure to redact information related to study drug(s) in documents submitted in the dossiers, Prof. Komajda said that he believed the CEC members were totally unblinded. He had no memory of a case of a failure to redact and the treatment becoming unblinded.

Regarding financial conflict of interest, Prof. Komajda said that he joined the CEC in 1999, and did not remember if he was requested to disclose.

To adjudicate an endpoint as MI, the documentation sought was a copy of ECG, or a rise in cardiac biomarkers or, in a few instances, the medical report which stated that the patient had a MI.

During the last few months before closure of the study in the fall of 2008, there was an accumulation of endpoints. Thus, instead of face-to-face meetings, the adjudications were made during several telecon meetings (and backup ones) in November and December of 2008 and January of 2009.

Discussions with Martial Verschoot, Executive Director, Quality Assurance (QA) and Barry Ryan, Associate Director, QA

I had a discussion with Martial Verschoot and Barry Ryan regarding QA audits of study sites that participated in the RECORD trial.

Mr. Verschoot explained that the selection of sites for QA audits were based on intelligence obtained about the site (e.g., from project managers and team leaders), detection of safety issues or data quality issues, when new offices or new countries were recruited to participate, and the audit plan.

The timing of QA audits was planned for a site after an accrual of about 33% of the planned enrollment had occurred. If data quality issues were identified at a site, Quintiles QA department would wait till at least 3 patients had been enrolled at that site before performing a QA audit.

Quintiles QA audited 39 clinical trial sites; there are some sites GSK QA audited (12 sites) where a Quintiles auditor was not present. In the case of for-cause audits, Quintiles QA and GSK QA conducted the audits together. Mr. Verschoot provided a list of QA audits carried out at investigator sites, and a listing of top line finding categories at these QA audits. (Exhibit: KMU Q-27)

Five clinical sites were terminated due to non-compliance. Mr. Verschoot provided a list of the sites with the reasons for closure, which included:

- (i) serious non-compliance, problems with integrity of source data and inappropriate recruitment (b) (6) (b) (4) 9 patients),
- (ii) Informed Consent Form signed by the investigator on behalf of a patient who did not meet entry criteria (b) (6) (b) (4) 1 patient),
- (iii) loss of PK samples, IP accountability questions and inadequate source documents (b) (6), 4 patients),
- (iv) research fraud including fabrication of subject data discovered by (b) (6). (b) (4) 11 patients) and
- (v) disagreement by investigator to record the IP storage conditions (b) (4) 2 patients) (Exhibit: KMU Q-28).

Another clinical trial site in (b) (4) 39 patients) was found to have source data issues for vital signs, weight/height and ECG data (Exhibit: KMU Q-29).

Quintiles arranged for patients at these above sites to be followed by another investigator at a nearby site or by a sub-investigator. Following discovery of data integrity problems, a Kappa Plan was put in place which included reporting the findings to the local ethics committees and the local regulatory authorities as required by ICH 5.20 compliance, retraining the site staff (9 CRAs were retrained), discussing the lessons learned, and setting up a data trend analysis which would aid the detection of research fraud.

Data from patients at these closed sites were included in the ITT analyses by default (which, I think, would favor the non-inferiority findings). A sensitivity analysis conducted for the primary endpoint excluding these subjects allegedly did not appear to change the overall findings.

Nine clinical investigator sites were audited by regulatory authorities {two sites by FDA (a third site recently audited by FDA was not in their system yet), two sites by Greek Regulatory Agencies, two by German Regulatory Authorities, one by French Regulatory authorities, one by British Regulatory Authorities, and one by Lithuanian Regulatory Authorities} Their findings were provided. (Exhibit: KMU Q-30)

Mr. Verschoot also informed us that Quintiles QA had performed QA audits of GSK's CEVA in 2003, 2004, 2005 and 2006. Another QA audit was planned for the 4th Quarter of 2009, but was postponed to 2010, and had not been performed yet.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-37	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/

KHIN M U
06/11/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER 10903 New Hampshire Avenue Building 51, Room 5357 Silver Spring, MD 20993-0002	(301) 796-3150	DATE(S) OF INSPECTION 5/10-14/10
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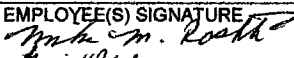



TO: Murray Stewart, M.D., Clinical Head of Biopharm Unit

FIRM NAME GlaxoSmithKline	STREET ADDRESS Stockley Park West
CITY, STATE AND ZIP CODE Uxbridge, Middlesex, UB11 1BT Great Britain	TYPE OF ESTABLISHMENT INSPECTED Sponsor/Monitor

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DURING AN INSPECTION OF YOUR FIRM, (I) (WE) OBSERVED:

1. For Protocol Number BRL-049653/231 (RECORD Trial), there was evidence that you did not ensure that the research conformed to good clinical practice (GCP) [21 CFR 312.120]. Specifically,
 - a. You did not always ensure the timely processing and adjudication of events.
 - i. You did not ensure that the Clinical Endpoint Committee (CEC) received potential endpoints for adjudication in a timely manner from the clinical trial sites. For example,
 - 1) Patient #19734 died in Jan (b) (6) (act date unknown) but the site did not fax the serious adverse event (SAE) form for this event to the study monitor until February 2009, who then forwarded the event to the CEC.
 - 2) Patient #31507 was hospitalized for a cardiovascular (CV) procedure on (b) (6) if the event was not received by the study monitor until September 11, 2008.
 - 3) Patient #31421 was hospitalized for an invasive CV procedure on (b) (6) if the event was not received by the study monitor until October 15, 2008.
 - ii. You did not ensure that the CEC completed adjudication of events in a timely manner. For example,
 - 1) Patient #18282: The event of myocardial infarction (MI) was sent to CEC reviewers for adjudication on August 15, 2006; the review was completed on October 28, 2008.
 - 2) Patient #98276: The event for stroke was sent to CEC reviewers for adjudication on June 29, 2004; the review was completed on October 5, 2005.
 - 3) Patient #97579: The event for invasive CV procedure was sent to CEC reviewers for adjudication on June 27, 2007; the review was completed on November 26, 2008. Another event for "Other CV reason - atherosclerosis of extremities" was sent to CEC reviewers for adjudication on January 26, 2007; the review was completed on February 26, 2009.
 - b. You did not always ensure that documentation which was critical for adjudication (such as ECGs, cardiac biomarkers, hospital discharge summaries, etc.) was submitted to the CEC. For example,
 - i. Patient #19731 died while hospitalized for ventricular arrhythmias. There was no hospital discharge summary. The death was adjudicated as "unknown".
 - ii. Patient #20493 had a severe stroke and was hospitalized for 36 days. There was no hospital discharge summary. This event was adjudicated as a non-CV endpoint because of insufficient information.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE    	EMPLOYEE(S) NAME AND TITLE (Print or Type) Mike M. Rashti/Investigator Leslie K. Ball, M.D./Director, DSI Susan Leibenhaut, M.D./Medical Officer, DSI Khin Maung U, M.D./Medical Officer, DCaRP	DATE ISSUED 5/14/10
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

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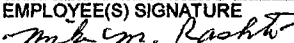
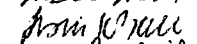

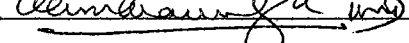
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- iii. Patient #20839 was hospitalized ~~on~~ for a GI bleed adjudicated as non-CV endpoint. After 5 days in the hospital, this patient experienced chest pain, was transferred to the ICU, and died the same day. The death was adjudicated "non-CV from unknown cause". Cardiac biomarkers and ECG were not documented, and a death certificate and a hospital death summary were not found. The clinical investigator's response to a data resolution query stated that myocardial infarction caused death.
- iv. Patient #43767 was hospitalized for unstable angina and Coronary Artery Bypass Graft procedure in (b) (6) 2005. This hospitalization was adjudicated as non-CV event because of insufficient information.
- c. You did not always ensure that all potential endpoints were submitted to CEC for adjudication. For example, patient #20930 experienced a SAE of collapse on (b) (6) and was hospitalized for 18 days. This hospitalization was attributed to atrial fibrillation, but was not sent for adjudication.
- d. When two events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately. For example,
 - i. Patient #19437 was hospitalized with cough, sputum, acute heart failure, and ventricular arrhythmias and at one point had a CK-MB fraction of 25%. The clinical diagnosis included the possibility of a MI. However, the MI was not adjudicated; only the heart failure event and death event were adjudicated.
 - ii. Patient #19731 was hospitalized for ventricular arrhythmias. A hospital summary was not found. The death was adjudicated as unknown. The hospitalization was not adjudicated.

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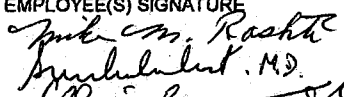
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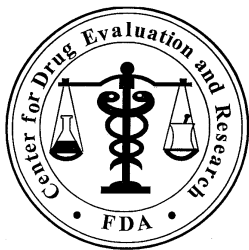
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CITY, STATE AND ZIP CODE Dublin 3 Ireland	TYPE OF ESTABLISHMENT INSPECTED Sponsors, Contract Research Organizations and Monitors

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1. For Protocol Number BRL-049653/231 (RECORD Trial), there was evidence that you did not ensure that the research conformed to good clinical practice (GCP) [21 CFR 312.120]. Specifically,
 - a. You did not always ensure the timely processing and adjudication of events. In particular, you did not ensure that the Clinical Endpoint Committee (CEC) completed adjudication of events in a timely manner. For example,
 - i. Patient #18282: The event of myocardial infarction (MI) was sent to CEC reviewers for adjudication on June 13, 2006; the review was completed on October 20, 2008.
 - ii. Patient #97579: The event for invasive cardiovascular (CV) procedure was sent to CEC reviewers for adjudication on June 27, 2007; the review was completed on November 26, 2008.
 - b. You did not always ensure that documentation which was critical for adjudication (such as ECGs, cardiac biomarkers, hospital discharge summaries, etc.) was submitted to the CEC. For example,
 - i. Patient #20493 had a severe stroke and was hospitalized for 36 days. There was no hospital discharge summary. This event was adjudicated as a non-CV endpoint because of insufficient information.
 - c. When two events occurred in close temporal relationship or during the same hospitalization, one of the events was not always followed up and adjudicated appropriately. For example,
 - i. Patient #19731 was hospitalized for ventricular arrhythmia and died. A hospital summary was not found. The death was adjudicated as unknown. The hospitalization was not adjudicated.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE  <i>Mike M. Rashti, M.D.</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Mike M. Rashti/Investigator Susan Leibenhaut, M.D./Medical Officer, DSI Khin Maung U, M.D./Medical Officer, DCaRP	DATE ISSUED 5/21/10
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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: June 15, 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.
Division of Epidemiology / OSE
David J. Graham, M.D., M.P.H.
Associate Director for Science and Medicine
Immediate Office / OSE

Subject: 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 rosiglitazone⁶ and pioglitazone⁷ 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 Diabetes⁸ 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 relative risk of 40% may seem like a modest signal from an epidemiological point of view, the public health

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.

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 which were 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 includes published controlled epidemiologic studies with a cohort or case-control design for which a full manuscript is available. Studies available as an abstract only were not included. Cross-sectional studies, case-series, and studies based on a single institution's experience were excluded. Experimental and nonclinical studies were excluded.

3.1.2 Types of data

The review includes observational studies of cardiovascular endpoints in patients treated with rosiglitazone or pioglitazone. Individual patient-level data was not available for this review.

3.1.3 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 (e.g. myocardial infarction, acute coronary syndrome, coronary revascularization, cardiovascular mortality, total mortality, heart failure, or stroke).

3.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

3.2.1 Time period

Searches of electronic databases were conducted covering the time period up to March 30, 2010.

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.

3.2.2 Electronic database searches

Sources utilized for the identification of studies included:

- 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 was used for EMBASE, Web of Science, and the Cochrane Library. Search terms were compiled from the names of individual drugs, the therapeutic class, cardiovascular endpoint terms, and study design terms. Two independent electronic database searches were conducted by two individuals, one epidemiologist and one FDA Bioscience librarian. Search results from the two separate searches were combined for the review. Searches were repeated using additional search terms identified from articles considered relevant to the review, as appropriate. Searches were limited to publications in English language only. Reviewers conducted additional hand searches from reference lists, review articles, peer-reviewed journals, and conference proceedings as appropriate.

3.3 DATA COLLECTION AND ANALYSIS

3.3.1 Selection of studies

Assessment of identified abstracts was performed independently by two reviewers from the Division of Epidemiology, with resolution of any discrepancies by a third reviewer (a senior medical epidemiologist). While it would have been desirable to conduct the study selection process in a blinded fashion, it was not feasible for this current project; however, study selection was done in a fully transparent fashion, with complete 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.

Reasons for exclusion of abstracts were 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 (e.g. from a single institution only)

Individual abstracts and studies often met multiple criteria for exclusion; however, identification of a single criterion by one or both reviewers was sufficient reason for exclusion from further analysis in this review.

3.3.2 Data extraction and management

For studies that fulfilled inclusion criteria, data extraction was performed by an epidemiologist (EZ) independently. Results were checked for accuracy by another epidemiologist (KG). Discrepancies or questions were resolved as needed by a consensus process with a third reviewer (a senior medical epidemiologist, DJG).

Study characteristics and results were 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 epidemiologists assessed each included study independently. Possible disagreement or questions were resolved by a consensus process with consultation of a third reviewer (senior medical epidemiologist). The Newcastle Ottawa scale¹⁰ (see Appendices 2 and 3) was used for this review as a measure of study quality. In addition, a separate analysis of included studies was conducted by a statistical reviewer from the FDA CDER Office of Biostatistics (see Appendix 4).

3.3.4 Data synthesis

The summary of this systematic review is qualitative. The totality of evidence has been summarized using scientific judgment. No quantitative meta-analysis to produce a consensus value was planned or conducted for this review. Summary results of cardiovascular endpoints for the individual studies are displayed using tables and forest plots. The primary summary measure for the individual studies is the 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. When a study provided the inverse of the desired comparison, reciprocal values were calculated when

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.

appropriate. The final selected studies were reviewed by a statistician to summarize and assess the statistical methodology. No re-analysis of the individual study data was performed.

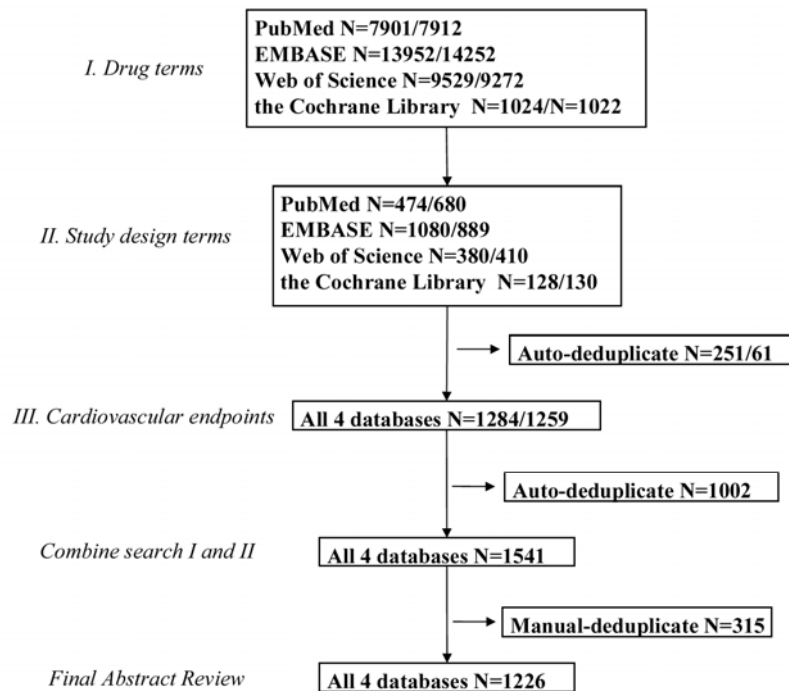
4 RESULTS

4.1 DESCRIPTION OF STUDIES

4.1.1 Results of the search

After elimination of duplicate studies, the combined initial electronic library searches identified 1226 records (see Figure 1) for which titles and abstracts were evaluated independently by two epidemiology reviewers.

Figure 1. Results of two independent searches and screening of potentially relevant abstracts



4.1.2 Excluded studies

Of these 1226 records, 57 abstracts were identified for which full published articles were obtained for further in-depth review. A second round of independent evaluation was conducted by two epidemiology reviewers, with final consensus adjudication completed with a third senior epidemiologist.

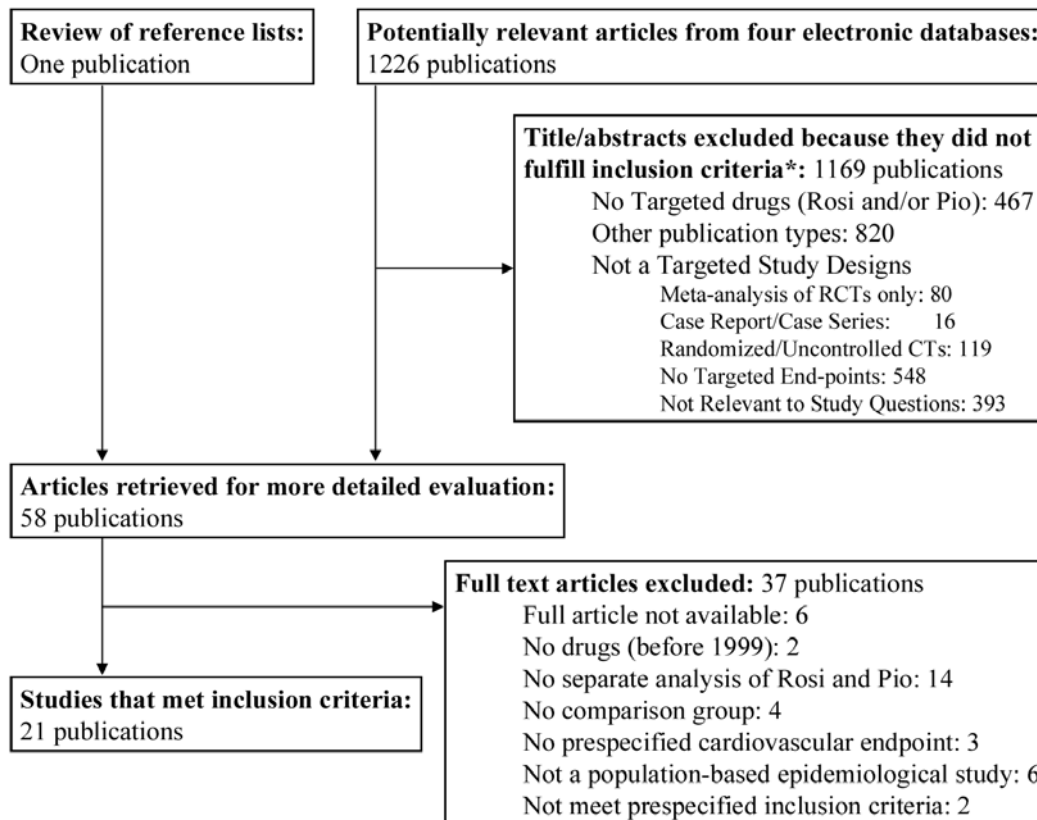
After the second round of reviews, 23 studies were considered to meet inclusion criteria; however, on closer inspection an additional two articles were excluded: 1) one study¹¹ presented

¹¹ Pantalone, K.M.; Kattan, M.W.; Yu, C.; Wells, B.J.; Arrigain, S.; Jain, A.; Atreja, A.; Zimmerman, R.S. 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 Diabetologica* 2009; 46: 145-154.

data from a single institution; 2) the other excluded study¹² stated that complete information about antidiabetic drug treatment was missing in nearly half of the patients included in the analysis.

The most common reasons for exclusion of abstracts or titles were “no targeted drugs” (i.e. neither rosiglitazone nor pioglitazone were included in the article), “other publication types (i.e., review articles, commentaries, letters to the editor), and “not a targeted study design” (i.e., not a controlled epidemiologic study). Reasons for exclusion of abstracts, and of full published articles are tabulated in Figure 2 below:

Figure 2. Flow chart of study selection and reasons for exclusion¹³



4.1.3 Included studies

After completion of in-depth screening of identified published studies, a total of 21 studies (seven nested case-control studies, and 14 cohort studies) met the final inclusion criteria, and were included in this systematic review. Section 7 of this review provides a complete list of references for each of the included studies. Section 8 of this review provides tabular summaries of the key

¹² Ramirez, S.P.B.; Albert, J.M.; Blayney, M.J.; Tentori, F.; Goodkin, D.A.; Wolfe, R.A.; Young, E.W.; Bailie, G.R.; Pisoni, R.L.; Port, F.K. Rosiglitazone is associated with mortality in chronic hemodialysis patients. *J Am Soc Nephrol* 2009; 20: 1094–1101.

¹³ Note: each abstract and full article may have multiple reasons for exclusion

characteristics of the included studies including methods, population details, covariates, data source, comparisons and outcome measures.

4.1.4 Characteristics of included studies

4.1.4.1 Design

Among the 21 published observational studies that were reviewed, there were two types of study designs: nested case-control (seven studies) or cohort (14 studies). All cohort studies were retrospective in design. Among the nested case-control studies, defined cohorts were first selected from established health care databases; cases were identified and individually matched with controls based on specific covariates. Exposure to antidiabetic agents was then determined for both cases and controls. Among the retrospective cohort studies, exposed and unexposed patients were first identified in the databases followed by identification of outcome of interest among all exposed and unexposed patients in the cohort.¹⁴

4.1.4.2 Setting

A variety of databases were used representing patient experience in the United States, Canada, UK, and Taiwan. Table 1 below, excerpted from the statistical review (see Appendix 4) provides an overview (studies are referenced by consecutive numbers from 1 to 21 which match the list of references in section 7 of this review):

Table 1: Summary of Observational Epidemiology Databases Studied¹⁵

Country of Study	Database (Publication Number)
1. United States	
National	Integrated Health Information Services (13); PharMetrics Patient-Centric (15 and 21)
Regional	Medicaid Analytic Extract database in states CA, FL, NY, OH, and IL (3); Vertically integrated Health System in SE MI (5); MD Medicaid (8); Prescription Solutions in states CA, TX, OK, OR, and WA (9); i3 Drug Safety from 25 states (12); NJPAAD and PPACE in NJ and PA (16); Kaiser Permanente in Northern CA (20)
Unspecified	Partners Healthcare System (1); Ingenix Research Database (17 and 19)
2. Canada	PharmaNet in British Columbia (4); Ontario Public Drug Benefit Program (7); Quebec databases (11); Ontario health care databases (18)
3. United Kingdom	General Practitioner Research Database (2 and 10); The Health Information Network in United Kingdom (14)
4. Taiwan	National Health Insurance database (6)

CA=California; FL=Florida; NY=New York; OH=Ohio; IL=Illinois; MI=Michigan; MD=Maryland; TX=Texas; OK=Oklahoma; OR=Oregon; WA=Washington; NJ=New Jersey; PA=Pennsylvania; SE=Southeast
 NJPAAD=New Jersey Pharmaceutical Assistance for the Aged and Disabled; PPACE=Pharmaceutical Assistance Contract for the Elderly

¹⁴ Excerpted from FDA Statistical Review page 3 (Appendix 4).

¹⁵ Reproduced from FDA Statistical Review page 6 (Appendix 4).

4.1.4.3 Methods¹⁶

The primary statistical methods varied among the 21 published studies and included logistic regression (7 studies), Cox proportional hazards (PH) regression (14 studies), and Poisson generalized linear model (GLM) in one study. These methods differ in the type of estimates they provide and underlying assumptions. In logistic regression, the adjusted odds ratio (OR) of one therapy group relative to another is estimated for a dichotomous outcome. The Cox PH model is used to model time to event or outcome and estimates the hazard ratio (HR) associated with one therapy group relative to another. A major assumption of the Cox PH model is the proportionality of hazard functions in the compared treatment groups over time, i.e. the ratio of hazard remains constant between treatment groups over time. The Poisson GLM is used to model outcome counts per unit of time and to estimate rate ratios. A common problem with Poisson GLM is overdispersion i.e. the variance of the data is much larger than the mean, which violates the assumption that the mean is equal to the variance for a Poisson distribution.

All nested case-control studies used covariate matching and the analysis was performed using conditional logistic regression (CLR) models. The covariates used in matching cases and controls were generally different across studies. For example, publication 2 matched by age (within 2 year interval), sex, date of cohort entry, and duration of follow-up while publication 3 matched cases to controls by age and state of residence. In addition, some studies used similar covariates for matching cases to controls; however, there were differences in the matching criteria. For example, publication 2 matched cases to controls by age within 2 years while publication 13 matched by age within 5 years. Therefore, given that the nested case-control studies used different matching criteria, the results from the statistical analyses are not considered comparable. That is, cross-study comparisons of crude or adjusted estimates are inappropriate given variations in matching strategies.

All retrospective cohort studies except two (publications 1 and 8) used the Cox PH model in the analysis. Publication 1 used Poisson GLM while publication 8 used logistic regression. There were six retrospective studies that used the Cox PH model along with propensity score (PS) either for matching (publications 12, 19, and 21) or stratification (publications 5, 8, and 15). None of the publications except (publications 10 and 20) checked the proportionality hazards assumption in the Cox PH model or reported results from testing the assumption. Cox PH model estimates and conclusions from all the publications that either did not check this assumption or checked but did not report the results should be interpreted with some caution. The quality of the Cox PH model fit is highly dependent on a true proportionality assumption.

All nested case-control and retrospective cohort studies adjusted for various patient-level covariates. However, the covariates that were used for adjustment markedly varied from one study to another. Even if some studies were similar in some aspects (e.g. they were all cohort studies), it is still difficult to compare results because of the differing covariates that were adjusted for in the statistical models. Therefore, cross-study comparisons of adjusted estimates from studies with similar designs are inappropriate.

For a complete description of methods, see Appendix 4 (statistical review).

4.1.4.4 Outcomes¹⁷

The outcomes studied were congestive heart failure (CHF), acute myocardial infarction (AMI), stroke, mortality, coronary artery disease (CAD), heart failure (HF), angina pectoris (AP),

¹⁶ Excerpted from FDA Statistical Review, pages 3 and 4 (Appendix 4).

¹⁷ Excerpted from FDA Statistical Review, page 7 (Appendix 4).

transient ischemic attack (TIA), cerebrovascular accidents (CVA), coronary heart disease (CHD), coronary revascularization (CR), unstable angina (UA), cardiac death (CD), and coronary artery reperfusion procedures (CARP). The publications studied either one or at least one of these outcomes. The outcomes were identified using ICD-9 or ICD-10 codes. Publications 2, 5, 10, 14, 15, 16, and 21 identified outcomes using non-ICD codes which were generally dependent on the types of databases used. For example, in publications 2 and 10, Read codes were used for the GPRD database.

In several published studies, the main outcome of interest was based on primary reason for hospitalization (ICD-9 or ICD-10 code). This definition does not account for patients who might have experienced an event and who were not later hospitalized (e.g. had event and subsequently died before reaching hospitalization) and patients that had the listed code as a secondary reason for hospitalization. Patient deaths were not described in several publications and therefore it is unclear if these patients were counted among the outcome of interest.

4.1.5 Risk of bias in included studies

Of the 21 studies included in this review, nine (43%) included authors with stated affiliations with the manufacturers of rosiglitazone (7 studies) or pioglitazone (2 studies). It is not known whether such affiliations introduced bias which might tend to understate the association of study drug with an adverse outcome of interest. A recently published analysis¹⁸ from researchers at the Mayo Clinic suggested concerns with this issue generally.

Study quality was assessed independently by two epidemiology reviewers, with questions or discrepancies resolved by a consensus process with a third senior epidemiology reviewer. The Newcastle-Ottawa Scale¹⁹ was utilized for convenience based on its description in the Cochrane handbook.²⁰ Specific study criteria which were assessed by this instrument are described in Appendix 2 (case-control studies) and Appendix 3 (cohort studies). All of the 21 studies included in this review received a final consensus score of either 8 or 9 points, with nine being the maximum possible score for this instrument.

4.2 EFFECTS OF INTERVENTIONS ON CARDIOVASCULAR OUTCOMES

4.2.1 Summary estimates of relative risk

Formal data synthesis was not conducted for this review due to potential methodologic diversity among the observational studies, such as potential differences in criteria of selecting case/control or cohort formation; capturing outcomes; defining exposure; or lack of sufficient numbers of studies to combine. The non-randomized studies included in this systematic review may not be considered sufficiently homogeneous to combine in a meta-analysis, based on concerns raised by the FDA statistical reviewer (see Appendix 4).

¹⁸ Wang AT, McCoy CP, Murad MH, Montori VM. Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. *BMJ*. 2010 Mar 18; 340.

¹⁹ Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed 11 June 2010).

²⁰ Reeves BC, Deeks JJ, Higgins JPT, et al. 2008. *op.cit.* page 418.

However, as recommended in the Cochrane Handbook chapter which deals with synthesis of data from non-randomized studies,²¹ non-randomized study results can be displayed for ease of visual inspection in forest plots, with pooled estimates suppressed.

For outcomes of interest for which two or more relevant results were identified, forest plots were prepared which visually present the association of outcomes and treatment between rosiglitazone exposure versus pioglitazone exposure; as well as between rosiglitazone or pioglitazone exposures versus other anti-diabetic agents (ADAs).

Studies were grouped for visual inspection of results of interest using the following rules:

- 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.
- The outcomes of interest for which forest plots were prepared include:
 - Acute myocardial infarction (AMI)
 - Heart failure (CHF)
 - All-cause death
 - Stroke (CVA)
- A separate forest plot was prepared for comparisons limited to rosiglitazone and pioglitazone monotherapy only.
- Most studies included comparisons of patients treated with rosiglitazone or pioglitazone in combination with various other antidiabetic agents.
- If a study included results for various drug exposure duration periods (e.g., current/recent/remote), the most current exposure period result was chosen.
- If a study included comparisons of rosiglitazone or pioglitazone with both metformin (MET) and sulfonylurea (SU), the MET comparison was chosen for display in the forest plot.

4.2.2 Direct comparisons between rosiglitazone and pioglitazone

Nine published observational studies were identified for this review which reported results of direct comparisons of rosiglitazone versus pioglitazone.^{22 23 24 25 26 27 28 29 30} For convenience of

²¹ Reeves BC, Deeks JJ, Higgins JPT, et al. 2008. *op.cit.* page 423.

²² [1] 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.

²³ [4] 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.

²⁴ [6] 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.

²⁵ [7] 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.

Section 9.3.1 presents forest plots which show study results for direct comparisons of rosiglitazone and pioglitazone and cardiovascular risk outcomes including acute myocardial infarction, congestive heart failure, all-cause death, and stroke.

No studies were identified which compared rosiglitazone and pioglitazone to each other, or to other antidiabetic agents, specifically for the outcome cardiovascular death. However, in diabetic patients, all-cause death may be a reasonable indicator of cardiovascular death trends, since cardiovascular causes of death predominate in diabetic patients.³¹

In addition, several studies were identified (with separate comparisons of rosiglitazone or pioglitazone to other antidiabetic agents) for which estimated unadjusted odds ratios could be calculated for comparisons of rosiglitazone versus pioglitazone from data available in the published report. These results are also displayed with corresponding footnotes identifying them as calculated estimates in Section 9.3.1.

A separate forest plot (Section 9.3.1.5) presents data comparing rosiglitazone and pioglitazone monotherapy for the outcome acute myocardial infarction.

4.2.3 Comparisons of rosiglitazone or pioglitazone versus other antidiabetic agents

Section 9.3.2 presents forest plots which show study results for comparisons of rosiglitazone or pioglitazone and other antidiabetic agents and cardiovascular risk outcomes including acute myocardial infarction, congestive heart failure, all-cause death, and stroke.

4.2.4 Studies in older populations

Three studies^{32 33 34} included in this review were specifically limited to patient populations older than 65 or 66 years of age.

²⁶ [9] 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.

²⁷ [12] 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.

²⁸ [15] 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.

²⁹ [16] Winkelmayr, 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.

³⁰ [17] 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.

³¹ 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.

³² [7] Juurlink et al, 2009, *op.cit.*

³³ [16] Winkelmayr et al, 2008, *op.cit.*

5 DISCUSSION

5.1 SUMMARY OF MAIN RESULTS

Results of this review are presented in a series of nine forest plots in Section 9.3. Overall, comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, congestive heart failure and all-cause mortality tended to favor pioglitazone. No studies were identified in this review with results suggesting a protective cardiovascular effect of rosiglitazone compared to pioglitazone.

5.2 AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

These findings are consistent with results of the recently completed FDA Rosiglitazone and Pioglitazone Meta-Analyses of randomized clinical trials.³⁵ The rosiglitazone meta-analysis had 52 trials with 16995 patients, 10039 (59%) randomized to rosiglitazone and 6956 (41%) to the comparator. The pioglitazone meta-analysis had 29 trials with 11774 patients, 6132 (52%) randomized to pioglitazone and 5642 (48%) to the comparator. The FDA statistical reviewer stated the following conclusion:

Overall, across all trials for rosiglitazone, the estimated risk of MACE (major adverse cardiovascular event, defined as cardiovascular death, stroke, or myocardial infarction) was higher for rosiglitazone compared to control and nearly statistically significant (OR=1.44; 95% CI=[0.95, 2.20]). Overall, across all trials for pioglitazone, the estimated MACE risk was lower for pioglitazone compared to control (OR=0.83; 95% CI= [0.56, 1.21]). Overall, for congestive heart failure, the estimated risk was consistently higher and statistically significant for both drugs than control.

6 AUTHORS' CONCLUSIONS

Results of a systematic review of observational studies of cardiovascular risk with rosiglitazone and pioglitazone are consistent with results of FDA's recently completed comprehensive meta-analyses of randomized clinical trials with these drugs. It is highly likely that rosiglitazone therapy is associated with increased risk of adverse cardiovascular outcomes in patients with diabetes, compared to other available antidiabetic agents.

In the absence of any data from randomized cardiovascular outcomes trials comparing rosiglitazone and pioglitazone, it is reasonable to rely on the available body of evidence from well-designed controlled epidemiologic studies for clinical decision-making. Comparisons of rosiglitazone with pioglitazone consistently show a clinically meaningful increased risk of adverse cardiovascular outcomes, especially acute myocardial infarction, with rosiglitazone. A signal for increased all-cause mortality with rosiglitazone in older patients (>65 years of age), which was demonstrated in three well-designed observational studies, may be a reflection of the increased cardiovascular risk with rosiglitazone.

³⁴ [18] 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.

³⁵ Statistics Review. Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting. July 13 -14, 2010. Division of Biostatistics VII, Office of Biostatistics, FDA/CDER. DRAFT June 11, 2010.

7 STUDIES INCLUDED IN THIS REVIEW

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8 CHARACTERISTICS OF INCLUDED STUDIES

8.1 CASE-CONTROL STUDIES - CHARACTERISTICS

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Cases/ Controls	Population Details	Statistical Method	Model Estimate
[2] Azoulay et al., 2009	Stroke	Rosi, Pio, Sulfonylurea, Biguanines, Acarbose, Prandial Glucose Regulator	UK General Practice Research Database	1/1/88-6/30/08	2,417/ 23,987	DM2 patients ≥ 40 yrs old; UK patients; currently exposed within 90 days of index date	CLR	Odds Ratio
[3] Dore et al., 2009	AMI; ICD-9 code 410.xx	Rosi, Pio	Medicaid Analytic Extract database	2001-2002	320/1316 (Rosi), 268/1052 (Pio)	Diabetes patients used both metformin and sulfonylurea; data from CA, FL, NY, OH, and IL; exposure within 180 days of index date.	CLR	Odds Ratio
[4] Dormuth et al., 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
[9] Stockl et al., 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
[11] Vanasse et al., 2009	All-cause death or CV death (ICD-10 codes I-20-I25, I44-I52), acute MI (ICD-9 410), CHF (ICD-9 428), stroke (ICD-9 430-438)	Rosi, Pio, Metformin, Sulfonylureas, Insulin	Quebec databases (provincial hospital discharge register and provincial demographic database)	1/01-12/02	18,554/370,866 (all-cause death); 4,455/89,037 (CVD death); 4,274/85,480 (acute MI); 4,274/85,480 (CHF); 4,711/94,209 (stroke)	Diabetes patients (ICD-9 code 250) in Quebec ≥ 65 yrs old.	CLR	Odds Ratio
[13] Koro et al., 2008	MI (ICD-9 code 410.xx)	Rosi, Pio,	Integrated Healthcare Information Services healthcare claims database	99-06	9,870/ 29,610	DM2 patients; at least 1 yr enrollment.	CLR	Odds Ratio
[18] Lipscombe et al., 2007	CHF (primary; ICD-10 code I50), acute MI (ICD-10 codes I21,I24 and I25.4), all-cause mortality	Rosi, Pio, Metformin, Sulfonylureas, other oral agents	Ontario health care databases	4/1/02-3/31/05	12,491/61,827 (CHF); 12,578/62,651 (acute MI); 30,265/150,650 (all-cause mortality)	DM2 Ontario patients ≥ 66 yrs old	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								

8.2 COHORT STUDIES - CHARACTERISTICS

Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Model Estimate
[1] Brownstein et al., 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
[5] Habib et al., 2009	Fatal and non-fatal acute MI (primary), hospitalization for CHF, fatal and non-fatal CVA, TIA, CHD, all-cause mortality	Rosi, Pio	Vertically integrated health system in Southeast Michigan	1/1/00-12/1/06	1,056 (Rosi), 3,217 (Pio), 307 (Rosi and Pio)	Diabetes (ICD-9 code 250.xx) patients in SE Michigan >18 yrs; at least 1 yr enrollment.; 6-months exposure	<ul style="list-style-type: none"> • PS stratification • Cox PH model 	Hazard Ratio
[6] Hsiao et al., 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.	<ul style="list-style-type: none"> • Survival via KM method • Cox PH model 	Hazard Ratio
[7] Juurlink et al., 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	<ul style="list-style-type: none"> • Survival via KM method • Cox PH model 	Hazard Ratio
[8] Shaya et al., 2009	Acute MI (ICD-9 410-411), stroke (ICD-9 430-438), and revenue (emergency department) codes 450-459 for MI	Rosi, Pio, Other	Maryland Medicaid	1/1/01-6/30/06	Rosi and Pio not given	DM2 patients; 51% African-Americans	<ul style="list-style-type: none"> • PS stratification • Logistic Regression 	Hazard Ratio
[10] Tzoulaki et al., 2009	MI, CHF, mortality	Rosi, Pio, Metformin, Sulfonylurea, Other.	UK General Practice Research Database	90-05	6,053 (1 st Gen Sul), 58,095 (2 nd Gen Sul), 8,442 (Rosi), 9,640 (Rosi combo), 3,816 (Pio mono/combo), 37,253 (Other), 68,181 (Met)	Diabetes patients 35-90 yrs old.	Cox PH model	Hazard Ratio
[12] Ziyadeh et al., 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.	<ul style="list-style-type: none"> • PS matching • Cox PH model • Survival via KM method • Log-rank test 	Hazard Ratio

Cohort Studies (continued)								
Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/Unexposed	Population Details	Statistical Method(s)	
[14] Margolis et al., 2008	MI, unstable angina, cardiac death, CARP	Rosi, Pio, Metformin, Sulfonylureas, Meglitinides, Insulin	The Health Information Network	1/02-1/06		Diabetes patients ≥ 40 yrs.	Cox PH model	Hazard Ratio
[15] Walker et al., 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
[16] Winkelmaye et al., 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
[17] Gerrits et al., 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
[19] McAfee et al., 2007	MI (ICD-9 code 410.x), CR (ICDP 36.xx, CPT 33500-33572, CPT 92980-92984 and 92995-92996)	Rosi, Metformin, Sulfonylurea, Insulin	Ingenix Research Database	7/1/00-12/31/04	8,977 (in each triplet for mono), 1,362 (in each triplet for dual), 1,173 (in each pair for combo)	Diabetes patients ≥ 18 yrs; ≥ 6 months of plan membership.	<ul style="list-style-type: none"> • PS matching • Cox PH model • Survival via KM method 	Hazard Ratio
[20] Karter et al., 2005	CHF (ICD-9-CM codes 401.91, 402.xx, 404.xx, 428.xx, 4251, 4254, 4255, 4257)	Pio, Metformin, Sulfonylurea, and Insulin	Kaiser Permanente Northern California Diabetes Registry	10/99-11/01	3,556 (Pio), 5,921 (Sul), 11,937 (Met), 2,026 (Insulin)	DM2 patients in Northern California.	Cox PH model	Hazard Ratio
[21] Rajagopalan et al., 2004	CHF	Pio, Insulin	PharMetrics Patient-Centric Database	1/99-12/01	1668 (Rosi)/1668 (Pio)	DM2 (ICD-9-CM codes 250.x0, 250.x2) US patients ≥ 18 yrs old.	<ul style="list-style-type: none"> • PS matching • Logistic regression • 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=combined 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								

8.3 CASE-CONTROL STUDIES - COVARIATES

Case-control Studies			
Study / Funding	Outcomes Evaluated	Covariates	Population Details
[2] Azoulay (2009)/ research grants from Astra-Zeneca, Wyeth, GSK, and Organon	Stroke	obesity (BMI 30), smoking, alcohol abuse, acute coronary syndrome, atrial fibrillation, CABG, CHF, hyperlipidemia, hypertension, MI, peripheral vascular disease, renal failure, transient ischemic attacks, cerebral aneurysm, cancer, aspirin use, and NSAIDs use.	The cohort comprised 75 717 patients over the age of 40 who were prescribed a first OHA, of whom 2417 had a stroke during follow-up. Up to 10 controls were matched to each case on age, sex, date of cohort entry, and duration of follow-up. Subjects who initiated their treatment with insulin were excluded. Mean age for cases and controls 74.1 and 73.8 years, respectively.
[3] Dore (2009) / Brown Medical School, Pfizer Inc., and i3 Drug Safety	AMI; ICD-9 code 410.xx	age, sex, race; previous diagnosis of CV related confounding factors; Charlson comorbidity index; and systemic use of certain drugs before the index date	Base cohort of 307,121 patients from 5 states Medicaid claims, making source population 95,332 individuals who used MET plus SU. For 2316 cases, 9700 controls were randomly selected matched with age- and state of residence. More than 40% of participants were aged 70 years or older.
[4] Dormuth (2009)/ Grant to Therapeutics Initiative from the British Columbia Ministry of Health.	AMI; ICD-9 code 410	Patients were matched on age, sex, number of family members, supplemental health coverage, and family income. Covariates: duration of diabetes; within 5 years: CHF, angiography, CABG, PTCA, ischemic, transient ischemic, angina, prior AMI, renal disease; within one year of the index date: Romano comorbidity score, exposure to nitrates, statins, ACE inhibitors, thiazide diuretics, calcium channel blockers, beta blockers, clopidogrel, digoxin, warfarin, insulin, and past use of metformin, glitazones and sulfonylureas, and total number of distinct drugs taken.	158,578 patients with Type 2 diabetes who used metformin as first-line drug treatment; 2,244 AMI cases and 8,903 matched controls. Mean age for cases and controls 70 years.
[9] Stockl (2009)/ Prescription Solutions, Clinical Analytics, CA, USA	AMI (ICD-9 code 410.xx)	Age, cardiovascular risk score, non-cardiovascular acute hospitalization, non-cardiovascular emergency department visit, diagnosis of severe COPD, and use of estrogen replacement therapy, during the pre-index period.	Risk of AMI with RSG or Pio exposure compared to no TZD exposure; base cohort of 230,858 patients with OHA or exenatide prescription in a large US PBM. Total 1681 AMI cases were identified and matched with 6653 controls. Mean age for cases and controls were both 73 years.
[11] Vanasse (2009)/ Network of Centers of Excellence GEOIDE and the Fonds de Recherche en Santé du Québec.	All-cause or CV death (ICD-10 codes I-20-I25, I44-I52), acute MI (ICD-9 410), CHF (ICD-9 428), stroke (ICD-9 430-438)	age, gender, time of cohort entry, comorbidities and exposure to metformin, sulphonylureas, insulin, aspirin, ACE inhibitors and statins	All diabetic patients aged 65 years or older living in the province of Québec between January 2001 and December 2002. Mean age for cases and controls = 75.6 and 75.1 years.
[13] Koro (2008)/ GSK	MI (ICD-9 code 410.xx)	Cases were matched to three controls on age, gender, and year of first diabetes diagnosis. Risk factors adjusted for are age, ACE inhibitors, b-blockers, diuretics, nitrates, diagnosis of hyperlipidemia, and hypertension and CAD.	IHCIS contains total of 891,901 base diabetic non-elderly, insurance-carrying population in the USA, mean age was 63 years for the cases and controls.
[18] Lipscombe (2007)/ Ontario Ministry of Health and Long-Term Care	CHF (primary; ICD-10 code I50), acute MI (ICD-10 codes I21,I24 and I25.4), all-cause mortality	Exposure to other hypoglycemic drugs, past TZD use, and potential confounders such as sociodemographic factors, well-known risk factors for each outcome, concomitant use of cardiovascular medications, previous use of oral hypoglycemic agents, and Charlson index and the number of distinct drugs dispensed. Individuals with missing data were given a separate “missing” classification for those variables for inclusion in adjusted models.	Ontarians aged 66 years or older with diabetes as identified in the Ontario Diabetes Database and who were dispensed at least 1 oral hypoglycemic agent. For each case, up to 5 controls were randomly selected and matched on age (± 1 year), sex, diabetes duration (2 years, 2-5 years, or 5 years), and history of CVD within 5 years of cohort entry. In the CHF and AMI analyses, controls were also matched on history of an event (within 1 year of cohort entry and within 1-5 years). For different outcomes, mean age for cases and controls were 76.5-78.6 and 76.4-78.7 years.

8.4 COHORT STUDIES - COVARIATES

Cohort Studies			
Study / Funding	Outcomes Evaluated	Covariates	Population Details
[1] Brownstein (2010)/ NIH National Center for Biomedical Computing grant	Acute MI; ICD-9 code 410	Model I: age, gender, previous cardiovascular disease (CAD, MI, angina, CHF, cerebrovascular accident, percutaneous coronary intervention, CABG), any use of hypertensive/ lipid-lowering medications, and insulin use, age-adjusted Charlson score; Model II: race/ethnicity, insurance coverage, HbA1c, and creatinine.	34,252 diabetic patients treated with at least one of the four diabetic medications. Mean age were 64.0 and 63.7 for Rosi and Pio cohorts, respectively.
[5] Habib (2009)/ National Heart Lung and Blood Institute and Digestive and Kidney Diseases, NIH.	Fatal and non-fatal acute MI (primary), hospitalization for CHF, fatal and non-fatal CVA, TIA, CHD, all-cause mortality	Age, sex, and race, income; Lab: HbA1c, LDL, HDL, triglyceride levels, serum creatinine, and liver transaminases. Baseline clinical status: CHD, CHF, CVA and TIA, PVOD, CKD, and ESRD, Charlson co-morbidity index. Other classes of oral diabetes medication, antihypertensive medications, lipid lowering agents, and insulin.	All patients had prescription coverage, >18 years; at least one clinical encounter with a coded diagnosis of diabetes and at least one prescription of an oral diabetes medication; at least 12 months of continuous enrollment in the HMO prior to the index date, and at least 6 months of follow-up after the index date. Mean age was 58 years for the cohort; 59 and 57 for Rosi and Pio cohorts, respectively.
[6] Hsiao (2009)/ research grant by Taiwan's National Science Council	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	Age, sex; cardiovascular events (MI, CHF, stroke, angina pectoris and TIA) and procedures, preexisting medical conditions (hypertension, hyperlipidaemia, and chronic kidney diseases), 12 months prior to the index date; and prior history of drug use (e.g. low-dose aspirin, anticoagulants, ACE inhibitors/angiotensin RA, b-adrenergic receptor antagonists, other antihypertensive agents and lipid-lowering agents).	Newly diagnosed patients with T2DM (ICD-9: 250.xx) and were prescribed oral antihyperglycaemic agents (sulfonylurea, metformin and/or a TZD) at least three times between 03/01/2001 and 12/31/2005 (n = 473 483). None of these patients had records showing a diagnosis of diabetes during the year before the index date. Mean age were 61.2 and 60.8 for Rosi and Pio cohorts, respectively.
[7] Juurlink (2009)/ Ontario Ministry of Health and Long Term Care	Composite of death or hospital admission for acute MI (ICD-10 I20-I22) or HF (I50)	age; sex; duration of diabetes; residence in long term care facility; socioeconomic status; year of cohort entry; Charlson comorbidity index; number of distinct drugs in year before cohort entry; history in previous five years of renal disease or hospital admission for AMI, angina, CHF, coronary angiography, CABG, or percutaneous coronary intervention; and receipt in year preceding cohort entry of ACE inhibitors, or RA, β adrenergic antagonists, aspirin, other antiplatelet drugs, nitrates, calcium channel antagonists, thiazide diuretics, spironolactone, other diuretics, statins, digoxin, non-steroidal anti-inflammatory drugs, metformin, sulphonylureas, acarbose, or meglitinides.	Patient characteristics, proportion of prior cardiovascular admissions and procedures, history of medications were highly similar for the two drug groups; patients aged 66 years or older; 69.1% and 68.7% patients 66-75 years for Rosi and Pio cohorts, respectively.
[8] Shaya (2009)/ university	Acute MI (ICD-9 410-411), stroke (ICD-9 430-438), and revenue (emergency department) codes 450-459 for MI	Age, race, city residency, and sex; hypertension; hyperlipidemia; heart conditions; obesity; and alcohol, tobacco, or drug or substance abuse.	More than 14,000 patients with T2DM initially were prescribed a TZD or another OAD during the study period. Only patients who had both medical and pharmacy claims during the study period were included; those who were treated with insulin alone and who were dually eligible for both Medicaid and Medicare were excluded. Mean age was 51 years for the cohort.

Cohort Studies (cont'd)			
Study / Funding	Outcomes Evaluated	Covariates	Population Details
[10] Tzoulaki (2009)/ Imperial College London	MI, CHF, mortality	Age and calendar year; sex and duration of diabetes (1); plus previous: complications from diabetes, peripheral artery disease, CVD, and coprescribed drugs (2); plus BMI, cholesterol/ creatinine/ albumin concentration, systolic BP, HbA1c, and smoking status (model 3)	Patients aged 35-90 years identified oral antidiabetes treatments of individual patients from prescription records. Mean age was 65 years for the cohort; 64.5 and 64.8 for Rosi and Pio cohorts, respectively.
[12] Ziyadeh (2009)/ i3 Drug Safety, GSK	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)	Age, gender, Year of drug initiation, geographic region, previous CVD, any use of hypertensive/ lipid-lowering medications, and insulin use.	i3 Drug Safety has access to a proprietary integrated research database of health insurance plan members who have both medical and prescription drug benefits. There were 57.6% and 57.3% patients younger than 55 years for Rosi and Pio cohorts, respectively.
[14] Margolis (2008)/ Takeda Pharmaceutical through the Trustees of the University of Pennsylvania	MI, unstable angina, cardiac death, CARP	age; sex; BMI; hemoglobin A1c; cigarette use; eGFR; mean arterial blood pressure (MAP); prior history of MI, unstable angina, or a cardiac procedure consistent with atherosclerotic vascular cardiac disease; and atherosclerosis of the lower extremity.	All subjects enrolled in this study were required to have at least two records for diabetes between January 2002 and 2006 and ≥ 40 years old. The database diagnosis of diabetes was previously validated. First study, all diabetics could have been diagnosed with diabetes at any time since they had been enrolled. An individual could have had drug exposures or an outcome before 2002, but not contribute to our study. Second study, a smaller sub-cohort, patients' first THIN diagnosis for diabetes and first drug treatment for diabetes must both have occurred after January 2002. There were 35% and 41% patients aged 70 years and older for all diabetics and new onset diabetics, respectively.
[15] Walker (2008)/ supported by a research contract between GSK and Ingenix, Inc	MI, CR	Demographics, calendar time, use of antidiabetic drugs other than insulin, medical history (MI, CR, angina, acute coronary syndrome, CHD, CHF, hyperlipidemia, Hypertension, Obesity, Smoking), Dispensing of Nitrates, Anti-platelet agents, Beta-blockers, Calcium channel blockers, Diuretics, ACE inhibitors and angiotensin receptor blockers, Statins, Fibrates	All users of rosiglitazone, pioglitazone, metformin, and a sulfonylurea for whom the first recorded dispensing; followed (1) ≥ 6 months membership; and (2) ≥ 18 year-old. Patients were required to have medical and pharmacy benefits. Little information on persons over the age of 65. Regimens involving rosiglitazone and pioglitazone were more similar to one another in patient characteristics than were other regimens, although pioglitazone-using groups in general had a higher prevalence of baseline dyslipidemia than did rosiglitazone-using groups.
[16] Winkelmayer (2008)/ American Heart Association; Satellite Healthcare, Inc; Amgen, Fresenius Medical Care, and GSK	All-cause mortality (primary), MI, stroke, CHF	age, gender, race; Diabetes medications and Diabetes complications; Prior cardiovascular diagnoses, procedures, and medications; Other comorbid conditions, Year of index prescription	New rosiglitazone or pioglitazone users (≥ 6 months) of US Medicare beneficiaries older than 65 years (N=28,361). Patient characteristics, proportion of prior cardiovascular procedures and medications are comparable for the two drug groups. Mean age were 76.3 for both Rosi and Pio cohorts.

Cohort Studies (cont'd)			
Study / Funding	Outcomes Evaluated	Covariates	Population Details
[17] Gerrits (2007)/ Takeda Global Research and Development, Inc.	Acute MI (ICD-9 code 410.xx), CR (ICD-9 code 36.xx)	Age, gender, duration of diabetes, year of index drug initiation, medical conditions, and procedures (i.e., hypertension; prior MI, CR, angina, unstable angina, CHD, CHF, hyperlipidemia, smoking, obesity, arrhythmias, stroke), as well as dispensed drugs (i.e., antidiabetic agents: metformin, sulfonylurea, meglitinides, insulin, others, nondiabetic drugs: nitrates, beta-blockers, calcium-channel blockers, diuretics, ACE-inhibitors and ARBs, statins, fibrates, NSAIDs, antiplatelet agents, and anticoagulants.	All patients with a diagnostic code [ICD-9: 250.xx] were initially extracted. Exclusion criteria: dispensed both pioglitazone and rosiglitazone, unknown gender, gaps in their insurance coverage; younger than 45 years of age, had less than 6 months of history in the database, and had been dispensed less than two prescriptions of the index TZD within 6 months after the index date were excluded. Mean age were 58 for both Rosi and Pio cohorts.
[19] McAfee (2007)/ supported by a contract between i3 Drug Safety and GSK	MI (ICD-9 code 410.x), CR (ICDP 36.xx, CPT 33500-33572, CPT 92980-92984 and 92995-92996)	demographics, calendar time, use of antidiabetic drugs other than insulin, medical history of MI, CR, angina, unstable angina, CHD, CHF, hypertension, hyperlipidemia and hypercholesterolemia, obesity, smoking, and the dispensing of any nitrates, anti-platelet agents, beta-blockers, calcium channel blockers, and diuretics were derived.	All initiators of rosiglitazone, metformin, and sulfonylurea for whom the first recorded dispensing followed 1) at least six months' membership; and 2) the member's 18th birthday. Patients were required to have medical and pharmacy benefits. Three study groups: monotherapy and dual-therapy, and combination with insulin. Mean age were 51-52 years for Rosi, or Met, or Sulf, either monotherapy, or dual-therapy groups, or combination-with-insulin group.
[20] Karter (2005)/ American Diabetes Association	CHF (ICD-9-CM codes 401.91, 402.xx, 404.xx, 428.xx, 4251, 4254, 4255, 4257)	Model 1: maintained therapies, age and sex (crude). Model 2: other maintained therapies, age, sex, IHD, non-HDL cholesterol levels, HbA1c, urinary albumin excretion, serum creatinine, hypertension, other medication use (beta adrenergic blocker, diuretic, ACE, ARB, calcium channel blocker, other anti-hypertensives or anti-lipemics), oral diabetes medication refill adherence, self-monitoring of blood glucose, inpatient and outpatient risk adjuster score.	All patients in the Kaiser Permanente Medical Care Program with Type 2 diabetes (23,440) between Oct 1999 and Nov 2001. Only patients initiating single new therapies were included. Mean age was 59 years for the cohort; 60 and 59 for Pio and Met cohorts, respectively.
[21] Rajagopalan (2004)	CHF	Demographic characteristics, days of follow-up, year of drug initiation, previous treatment with medications indicated for CVD, selected comorbidities, diabetes complications, Charlson Comorbidity Index, and total health care costs during the pretreatment period, and patients who received insulin treatment. Patients who received insulin treatment were matched 1:1 with patients who received pioglitazone treatment based on a difference in estimated propensity score of no greater than +0.01.	Patients aged >18 years with a diagnosis of type 2 diabetes and/or evidence of use of antidiabetic medications who began receiving pioglitazone or insulin. Exclusion criteria: patients who had a prior diagnosis of CHF or used digoxin, who used troglitazone at any time, or who used any oral antidiabetic drug other than metformin or a sulfonylurea during the final 6 months of the preindex period. Patients who had facility or provider claims with a diagnosis of CHF at any time during the preindex period and those who were not eligible for health and pharmacy benefits during the entire pretreatment and follow-up periods were also excluded. No. of patients before matching for pioglitazone and Insulin are 3870 and 2577. Mean age was 51 years for the cohort; 51 for both Pio and Insulin cohorts.
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=combined coronary heart disease; CR=coronary revascularization; CARP=coronary artery reperfusion procedures			

9 DATA AND ANALYSES

9.1 RESULTS TABLE FOR CASE-CONTROL STUDIES (N = 7)

First author / year of publication	Cases	Controls	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Notes
Vanasse (2009) ³⁶	Comparison groups: current Rosi user vs. non-TZD user					
	219 vs. 18,335	11,526 vs. 359,340	All-cause death	0.37 (NR)	0.87 (0.76-0.99)	
	72 vs. 4,383	2,789 vs. 86,248	CV death	0.51 (NR)	0.88 (0.69-1.12)	
	189 vs. 4,085	3,046 vs. 82,434	Hosp AMI	1.26 (NR)	1.41 (1.21-1.65)	
	335 vs. 5,972	4,321 vs. 121,817	Hosp CHF	1.59 (NR)	1.94 (1.71-2.19)	
	171 vs. 4,540	3,280 vs. 90,929	Hosp stroke	1.04 (NR)	1.14 (0.97-1.34)	
Stockl (2009)	Comparison groups: any Rosi exposure compared with any PIO exposure					
	194 vs. 48	604 vs. 180	AMI	1.19 (0.82-1.73)	1.26 (0.79-2.00)	
	Comparison groups: current Rosi exposure compared with current PIO exposure					
	103 vs. 23	311 vs. 81	AMI	1.23 (0.72-2.08)	1.50 (0.77–2.92)	
	Comparison groups: PIO and Rosi exposure proximity vs. no TZD exposure					
	26 vs. 1410	114 vs. 5591	AMI	0.86 (0.55-1.33)	0.74 (0.46 – 1.18)	PIO current exposure
	13 vs. 1410	55 vs. 5591		0.94 (0.51-1.73)	1.18 (0.61 – 2.28)	PIO recent exposure
	13 vs. 1410	73 vs. 5591		0.70 (0.38-1.26)	0.58 (0.30 – 1.11)	PIO remote exposure
	116 vs. 1410	477 vs. 5591		0.91 (0.72-1.16)	0.93 (0.72 – 1.21)	Rosi current exposure
	52 vs. 1410	141 vs. 5591		1.45 (1.05-2.00)	1.69 (1.18 – 2.44)	Rosi recent exposure
	51 vs. 1410	202 vs. 5591		1.00 (0.73-1.37)	1.00 (0.70 – 1.41)	Rosi remote exposure

³⁶ Probable typo in published results table – query pending

First author / year of publication	Cases	Controls	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Notes
Dormuth (2009)	Comparison groups: 1-6 months Rosi exposure compared with PIO exposure					
	NR	NR	AMI	1.39 (0.76-2.52)	1.41 (0.74 – 2.66)	
	Comparison groups: >24 months Rosi exposure compared with PIO exposure					
	NR	NR	AMI	0.88 (0.41-1.89)	0.93 (0.41 – 2.11)	
	Comparison groups: Overall Rosi exposure compared with PIO exposure					
	NR	NR	AMI	0.97 (0.67-1.40)	1.00 (0.67 – 1.49)	
Dore (2009)	Comparison groups: Start of Rosi (add-on) vs. prevalent MET+SU					
	80 vs. 1529	300 vs. 5809	AMI	0.99 (0.76-1.28)	1.00 (0.72 – 1.39)	Rosi started within 180 days before index date
	54 vs. 1529	150 vs. 5809	AMI	1.32 (0.96-1.83)	1.29 (0.85 – 1.94)	Rosi started within 90 days before index date
	Comparison groups: Start of PIO (add-on) vs. prevalent MET+SU					
	70 vs. 1529	269 vs. 5809	AMI	1.00 (0.76-1.32)	1.04 (0.74 – 1.45)	PIO started within 180 days before index date
	37 vs. 1529	130 vs. 5809	AMI	1.10 (0.76-1.59)	1.15 (0.73 – 1.81)	PIO started within 90 days before index date
Azoulay (2009)	Comparison groups: Current TZD monotherapy vs. current non-TZD monotherapy					
	16 vs. 299	145 vs. 3082	First stroke	1.14 (0.67-1.94)	1.17 (0.69 – 2.01)	TZD = Rosi
	9 vs. 299	76 vs. 3082		1.20 (0.59-2.43)	1.25 (0.61 – 2.53)	TZD = PIO
	Comparison groups: Current TZD combination therapy vs. current non-TZD combination therapy					
	50 vs. 299	612 vs. 3082	First stroke	0.84 (0.61-1.15)	0.81 (0.59 – 1.12)	TZD = Rosi
	14 vs. 299	204 vs. 3082		0.71 (0.41-1.24)	0.68 (0.38 – 1.19)	TZD = PIO

First author / year of publication	Cases	Controls	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Notes
Koro (2008)	Comparison groups: Rosi (mono or combination) exposure vs. other ADAs (oral and/or insulin)					
	1149 vs. 5644	2690 vs. 13,702	AMI	1.04 (0.96-1.12)	1.03 (0.93 – 1.12)	3 month exposure
	1383 vs. 5948	3963 vs. 16,177		0.88 (0.78-0.99)	0.88 (0.77 – 1.01)	<6 mos exposure
	1180 vs. 5948	3417 vs. 16,177		0.93 (0.83-1.05)	0.92 (0.80 – 1.05)	6 – 12 mos exposure
	2256 vs. 5948	6510 vs. 16,177		1.11 (1.01-1.21)	1.15 (1.04 – 1.27)	>12 mos exposure
	Comparison groups: PIO (mono or combination) exposure vs. other ADAs (oral and/or insulin)					
	910 vs. 5644	2433 vs. 13,702	AMI	0.91 (0.84-0.99)	0.92 (0.83 – 1.01)	3 month exposure
	1094 vs. 5948	3475 vs. 16,177		0.83 (0.73-0.95)	0.85 (0.73 – 0.98)	<6 mos exposure
	930 vs. 5948	3054 vs. 16,177		0.82 (0.73-0.93)	0.79 (0.69 – 0.91)	6 – 12 mos exposure
	1848 vs. 5948	5637 vs. 16,177		1.15 (1.04-1.26)	1.13 (1.02 – 1.26)	>12 mos exposure
Lipscombe (2007)	Comparison groups: Current TZD monotherapy vs. current other OHA combination therapies					
	62 vs. 3478	151 vs. 18,045	CHF	2.14 (1.59-2.89)	1.98 (1.44 – 2.72)	TZD = Rosi
	16 vs. 3478	86 vs. 18,045		0.96 (0.56-1.64)	0.91 (0.52 – 1.59)	TZD = PIO
	53 vs. 3695	147 vs. 18,351	AMI	1.80 (1.31-2.46)	1.76 (1.27 – 2.44)	TZD = Rosi
	12 vs. 3695	81 vs. 18,351		0.74 (0.41-1.37)	0.73 (0.40 – 1.36)	TZD = PIO
	76 vs. 5529	255 vs. 18,835	All-cause mortality	0.99 (0.76-1.29)	1.47 (1.12 – 1.93)	TZD = Rosi
	26 vs. 5529	137 vs. 18,835		0.60 (0.39-0.91)	0.94 (0.61 – 1.45)	TZD = PIO
	Comparison groups: Current TZD combination exposure vs. current other OHA combination therapies					
	364 vs. 3478	1330 vs. 18,045	CHF	1.45 (1.28-1.63)	1.43 (1.25 – 1.63)	TZD = Rosi
	144 vs. 3478	683 vs. 18,045		1.12 (0.93-1.35)	1.09 (0.90 – 1.32)	TZD = PIO
	282 vs. 3695	1404 vs. 18,351	AMI	1.00 (0.88-1.15)	1.00 (0.87 – 1.16)	TZD = Rosi
	122 vs. 3695	705 vs. 18,351		0.87 (0.72-1.06)	0.87 (0.71 – 1.06)	TZD = PIO
	358 vs. 5529	1027 vs. 18,835	All-cause mortality	1.18 (1.04-1.34)	1.26 (1.10 – 1.44)	TZD = Rosi
	139 vs. 5529	413 vs. 18,835		1.15 (0.94-1.40)	1.20 (0.98 – 1.47)	TZD = PIO

9.2 RESULTS TABLE FOR COHORT STUDIES (N = 14)

First author / year of publication	Number of patients / drug therapy	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Comments
Tzoulaki (2010)	47,695 (Rosi-mono) vs. 1,049,709 (MET) *	MI	0.94 (0.62 – 1.43)	0.79 (0.41 – 1.53)	* intervals of drug treatment (instead of patients) were used as the unit of observation for this study Note: model 1 as crude OR; model 3 as adjusted OR in this table
		CHF	1.00 (0.72 – 1.38)	0.61 (0.33 – 1.15)	
		All-cause mortality	1.00 (0.78 – 1.28)	1.07 (0.77 – 1.49)	
	92,387 (Rosi-comb) vs. 1,049,709 (MET) *	MI	1.08 (0.86 – 1.35)	0.82 (0.56 – 1.20)	
		CHF	1.31 (1.09 – 1.58)	1.21 (0.91 – 1.63)	
		All-cause mortality	0.80 (0.70 – 0.93)	0.88 (0.71 – 1.09)	
	45,807 (PIO-mono & comb) vs. 1,049,709 (MET) *	MI	0.78 (0.52 – 1.17)	0.71 (0.39 – 1.30)	
		CHF	1.18 (0.88 – 1.57)	1.17 (0.77 – 1.77)	
		All-cause mortality	0.61 (0.47 – 0.80)	0.69 (0.49 – 0.98)	
Brownstein (2010)	4,274 (Rosi-comb) vs. 1,800 (PIO-comb)	AMI	1.7 (1.3 – 2.1)	2.0 (1.0 – 4.2)	
	4,274 (Rosi-comb) vs. 17,157 (SU-comb)		1.2 (1.0 – 1.3)	1.4 (1.0 – 1.9)	
	4,274 (Rosi-comb) vs. 18,162 (MET-comb)		3.3 (2.9 – 3.6)	2.4 (1.0 – 4.2)	
	1,879 (Rosi-mono) vs. 806 (PIO-mono)		1.9 (1.4 – 2.5)	2.2 (1.5 – 3.4)	
	1,879 (Rosi-mono) vs. 11,200 (SU-mono)		1.1 (1.0 – 1.3)	1.3 (1.1 – 1.6)	
	1,879 (Rosi-mono) vs. 12,490 (MET-mono)		3.5 (3.1 – 3.9)	2.2 (1.6 – 3.1)	
Ziyadeh (2009)	Rosi vs. PIO (47,501 propensity score matched pairs)	MI	NR	1.35 (1.12 – 1.62)	Regimen switch = addition of any ADA
		CR		1.08 (0.95 – 1.22)	
		MI, CR		1.10 (0.98 – 1.23)	
		MI, CR, SD		1.09 (0.97 – 1.22)	
		MI		1.41 (1.13 – 1.75)	Regimen stop = d/c of any ADA
		CR		1.12 (0.98 – 1.29)	
		MI, CR		1.12 (0.99 – 1.28)	
		MI, CR, SD		1.12 (0.98 – 1.27)	
Shaya (2009)	TZDs (n=5,712) vs. other OADs (n=8,911)	Adverse CV Events	1.20 (1.08 – 1.33)	1.12 (1.01 – 1.25)	TZD = Rosi
			NR	1.03 (0.90 – 1.18)	TZD = PIO

First author / year of publication	Number of patients / drug therapy	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Comments
Juurlink (2009)	PIO (n=16,951) vs. Rosi (n=22,785)	AMI	0.91 (0.78 – 1.06)	0.95 (0.81-1.11)	<i>Note: reciprocal value (R vs. P) used in forest plot; results favor PIO</i>
		CHF	0.75 (0.67 – 0.84)	0.77 (0.69-0.87)	
		1° outcome: CV hosp or death	0.81 (0.74 – 0.87)	0.83 (0.76-0.90)	
		All-cause mortality	0.82 (0.73 – 0.94)	0.86 (0.75-0.98)	
Hsiao (2009)	Monotherapy				
	Rosi (2093) vs. SU (97,651)	Any CV event	NR	1.54 (1.29 – 1.85)	Survival analysis: HR (95% CI) of CV events with Rosi or PIO
		MI		1.49 (0.99 – 2.24)	
		CHF		1.22 (0.86 – 1.74)	
		Stroke		1.45 (0.69 – 3.05)	
		Angina pectoris		1.46 (1.15 – 1.85)	
		TIA		1.90 (1.02 – 3.57)	
	PIO (495) vs. SU (97,651)	Any CV event		1.03 (0.65 – 1.65)	
		MI		0.72 (0.19 – 2.77)	
		CHF		1.37 (0.58 – 3.20)	
		Stroke		0.59 (0.06 – 6.03)	
		Angina pectoris		0.91 (0.47 – 1.74)	
		TIA		1.28 (0.34 – 4.86)	
	Rosi (2093) vs. MET (46,444)	Any CV event		1.89 (1.57 – 2.28)	
		MI		2.09 (1.36 – 3.24)	
		CHF		1.30 (0.89 – 1.89)	
		Stroke		1.61 (0.72 – 3.62)	
		Angina pectoris		1.79 (1.39 – 2.30)	
		TIA		2.57 (1.33 – 4.96)	
	PIO (495) vs. MET (46,444)	Any CV event		1.29 (0.81 – 2.07)	
		MI		1.00 (0.26 – 3.89)	
		CHF		1.54 (0.65 – 3.64)	
		Stroke		0.61 (0.06 – 6.25)	
		Angina pectoris		1.15 (0.60 – 2.21)	
		TIA		1.67 (0.44 – 6.41)	
	Combination therapy (SU-based)				
	SU+PIO (1231) vs. SU+Rosi (5141)	Any CV event	NR	0.84 (0.59 – 1.21)	
		MI		0.69 (0.30 – 1.55)	
		CHF		0.78 (0.36 – 1.69)	
		Stroke		1.49 (0.25 – 8.94)	
		Angina pectoris		1.11 (0.72 – 1.72)	
		TIA		0.73 (0.23 – 2.30)	

First author / year of publication	Number of patients / drug therapy	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Comments
Hsiao (2009) cont'd	Combination therapy (MET-based)				
	MET+PIO (774) vs. MET+Rosi (2,408)	Any CV event	NR	0.89 (0.51 – 1.56)	
		MI		6.34 (1.80 -22.31)	
		CHF		0.63 (0.14 – 2.82)	
		Stroke		0.01 (0.00 - >100)	
		Angina pectoris		0.79 (0.39 – 1.61)	
		TIA		2.31 (0.59 – 9.03)	
	Combination therapy (SU+MET –based)				
	SU/MET+ PIO (9,510) vs. SU/MET+ Rosi (39,982)	Any CV event	NR	0.94 (0.80 – 1.11)	
		MI		1.04 (0.73 – 1.47)	
		CHF		1.06 (0.78 – 1.44)	
		Stroke		0.65 (0.32 – 1.33)	
		Angina pectoris		1.07 (0.86 – 1.31)	
		TIA		0.62 (0.38 – 1.02)	
Hab b (2009)	Rosi (1056) vs. no TZD use (14,591)	AMI		1.00 (0.64 – 1.58)	
		CHF hosp		1.66 (1.28 – 2.15)	
		CVA or TIA		1.20 (0.82 – 1.77)	
		Combined CHD		1.22 (0.89 – 1.67)	
		All-cause mortality		0.87 (0.54 – 1.39)	
	PIO (3217) vs. no TZD use (14,591)	AMI		0.90 (0.69 – 1.18)	
		CHF hosp		1.13 (0.95 – 1.34)	
		CVA or TIA		0.91 (0.71 – 1.17)	
		Combined CHD		0.84 (0.69 – 1.04)	
		All-cause mortality		0.63 (0.45 – 0.87)	
Winkelmayer (2008)	On-Drug Exposure Models				
	Rosi (n=14,260) vs. PIO (n=14,101) <i>*except as noted</i>	All-cause mortality	1.17 (1.06 – 1.28)	1.15 (1.05-1.26)	
		MI	1.10 (0.95 – 1.27)	1.08 (0.93-1.25)	
		MI (no prior CAD)*	1.11 (0.85 – 1.45)	1.17 (0.89-1.53)	*Rosi (8313) vs. PIO (8665)
		Stroke	1.09 (0.95 – 1.25)	1.07 (0.93-1.23)	
		Stroke (no prior CVD)*	1.00 (0.82 – 1.21)	1.00 (0.82-1.21)	*Rosi (11,766) vs. PIO (12,003)
		CHF hosp	1.12 (1.00 – 1.25)	1.13 (1.01-1.26)	
		CHF (no prior CHF)*	1.19 (1.02 – 1.40)	1.21 (1.03-1.42)	*Rosi (10,938) vs. PIO (11,251)

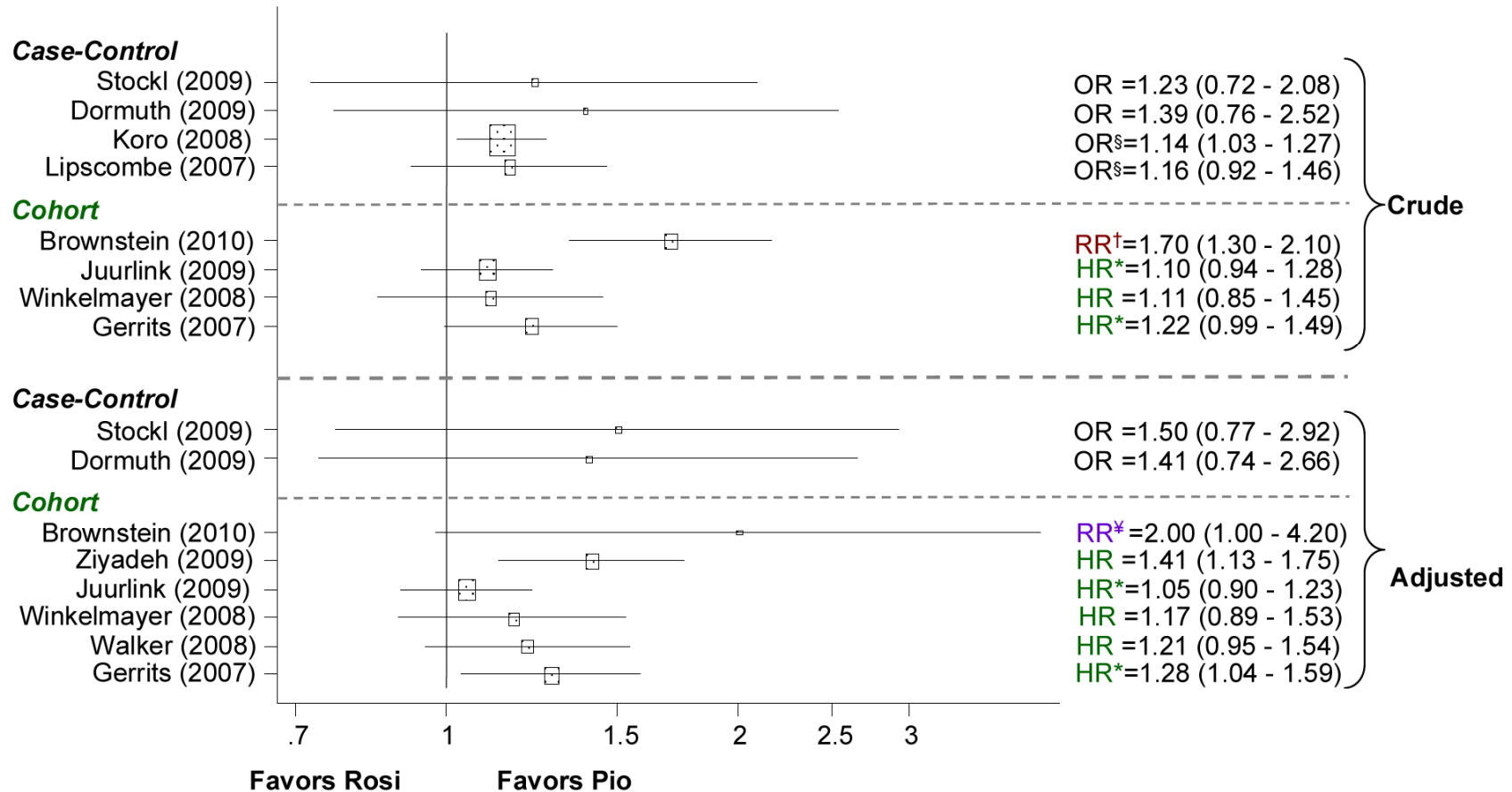
First author / year of publication	Number of patients / drug therapy	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Comments
Walker (2008)	On treatment (total follow-up time in years)				
	Rosi (8481) vs. PIO (11,453)	MI	NR	0.820 (0.491-1.370)	Monotherapy
	Rosi (25,650) vs. PIO (17,210)			1.326 (0.945-1.861)	Dual therapy
	Rosi (6028) vs. PIO (6277)			1.412 (0.876-2.274)	Combination w/ insulin
	Rosi (40,159) vs. PIO (34,940)			1.210 (0.949-1.543)	Summary
	Rosi (8481) vs. PIO (11,453)	CR		1.085 (0.832-1.415)	Monotherapy
	Rosi (25,650) vs. PIO (17,210)			1.010 (0.842-1.211)	Dual therapy
	Rosi (6028) vs. PIO (6277)			1.063 (0.816-1.385)	Combination w/ insulin
	Rosi (40,159) vs. PIO (34,940)			1.040 (0.913-1.185)	Summary
	Rosi (8481) vs. PIO (11,453)	combined outcome		1.056 (0.816-1.367)	Monotherapy
	Rosi (25,650) vs. PIO (17,210)			0.997 (0.838-1.186)	Dual therapy
	Rosi (6028) vs. PIO (6277)			1.150 (0.894-1.481)	Combination w/ insulin
	Rosi (40,159) vs. PIO (34,940)			1.047 (0.924-1.186)	Summary
	Total cohort follow-up (total follow-up time in years)				
	Rosi (14,054) vs. PIO (18,065)	MI	NR	0.783 (0.519-1.180)	Monotherapy
	Rosi (42,672) vs. PIO (28,807)			1.226 (0.955-1.573)	Dual therapy
	Rosi (12,058) vs. PIO (12,183)			1.020 (0.747-1.393)	Combination w/ insulin
	Rosi (68,784) vs. PIO (59,055)			1.065 (0.893-1.270)	Summary
	Rosi (14,054) vs. PIO (18,065)	CR		0.973 (0.776-1.221)	Monotherapy
	Rosi (42,672) vs. PIO (28,807)			1.048 (0.904-1.215)	Dual therapy
	Rosi (12,058) vs. PIO (12,183)			1.034 (0.848-1.261)	Combination w/ insulin
	Rosi (68,784) vs. PIO (59,055)			1.028 (0.925-1.141)	Summary
	Rosi (14,054) vs. PIO (18,065)	combined outcome		0.966 (0.777-1.201)	Monotherapy
	Rosi (42,672) vs. PIO (28,807)			1.047 (0.910-1.204)	Dual therapy
	Rosi (12,058) vs. PIO (12,183)			1.069 (0.887-1.289)	Combination w/ insulin
	Rosi (68,784) vs. PIO (59,055)			1.036 (0.937-1.144)	Summary
Margolis 2008	Comparison Rosi exposure vs. all other non-Rosi exposure				
	517 vs. 27,780	serious ASVD	0.8 (0.6 – 1.2)	0.9 (0.7 – 1.3)	1–5 mos
	342 vs. 27,780		0.6 (0.4 – 1.0)	0.6 (0.4 – 1.1)	6–11 mos
	288 vs. 27,780		0.7 (0.4 – 1.1)	0.7 (0.6 – 1.3)	≥ 12 mos
	Comparison PIO exposure vs. all other non-PIO exposure				
	204 vs. 13,082	serious ASVD	0.9 (0.5 – 1.6)	0.9 (0.5 – 1.7)	1–5 mos
	123 vs. 13,082		0.6 (0.2 – 1.5)	0.6 (0.2 – 1.7)	6–11 mos
	167 vs. 13,082		0.8 (0.6 – 1.9)	0.8 (0.7 – 1.1)	≥ 12 mos
	Comparison Rosi vs. PIO				
	7282 vs. 2244	serious ASVD	1.0 (0.8 – 1.3)	1.0 (0.8 – 1.3)	All diabetics
1691 vs. 494	1.1 (0.7 – 1.8)		1.1 (0.7 – 1.7)	New onset	

First author / year of publication	Number of patients / drug therapy	Outcomes	Crude estimate (95% CI)	Adjusted estimate (95% CI)	Comments
McAfee 2007	Monotherapy				
	8977 vs. 8977	MI	NR	1.19 (0.84 – 1.68)	Rosi vs. MET
	8977 vs. 8977			0.79 (0.58 – 1.07)	Rosi vs. SU
	8977 vs. 8977	CR		1.04 (0.82 – 1.33)	Rosi vs. MET
	8977 vs. 8977			0.87 (0.69 – 1.10)	Rosi vs. SU
	Dual-therapy				
	1362 vs. 1362	MI	NR	0.41 (0.16 – 1.04)	Rosi+MET vs. MET+SU
	1362 vs. 1362			1.45 (0.76 – 2.75)	Rosi+S vs. MET+SU
	1362 vs. 1362	CR		0.93 (0.53 – 1.63)	Rosi+M vs. MET+SU
	1362 vs. 1362			1.50 (0.91 – 2.46)	Rosi+SU vs. MET+SU
	Insulin Therapy				
	1173 vs. 1173	MI	NR	0.79 (0.46 – 1.36)	Rosi vs. other
	1173 vs. 1173	CR		0.70 (0.44 – 1.13)	Rosi vs. other
	Combined Therapies				
12,874 vs. 20,489	MI	NR	0.92 (0.73 – 1.16)	Rosi vs. non-Rosi	
12,874 vs. 20,489	CR		0.94 (0.79 – 1.12)	Rosi vs. non-Rosi	
Gerrits 2007	PIO (14,807) vs. Rosi (15,104)	AMI hosp	0.82 (0.67 – 1.01)	0.78 (0.63 – 0.96)	<i>Note: reciprocal value (R vs P) used in forest plot; results favor PIO</i>
	PIO (14,807) vs. Rosi (15,104)	AMI + CR	NR	0.85 (0.75 – 0.98)	
Karter 2005	PIO (3556) vs. SU (5921)	CHF hosp	1.41 (0.94 – 2.11)	1.28 (0.85 – 1.92)	
	INS (2026) vs. SU (5921)		2.23 (1.44 – 3.46)	1.56 (1.00 – 2.45)	
	MET (11,937) vs. SU (5921)		0.56 (0.40 – 0.80)	0.70 (0.49 – 0.99)	
Rajagopalan 2004	Comparison pioglitazone versus insulin				
	1668 vs. 1668	CHF	NR	0.501 (0.331 0.758)	Combination therapy
	863 vs. 863			0.452 (0.239 0.852)	Monotherapy
	1668 vs. 1668	CHF hosp		0.263 (0.135 0.51 I)	Combination therapy
	863 vs. 863			0.305 (0.111 0.835)	Monotherapy
Abbreviations: CI=confidence interval; Rosi=rosiglitazone; PIO=pioglitazone; TZD=thiazolidinedione; CV=cardiovascular; AMI=acute myocardial infarction; CHF=congestive heart failure; MET=metformin; SU=sulfonylurea; ADA=anti-diabetic agent; OHA=oral hypoglycemic agent; mono=monotherapy; comb=combination therapy; OR=odds ratio; CR=coronary revascularization; SD=sudden death; OAD=oral anti-diabetic drug; NR=not reported; hosp=hospital admission; TIA=transient ischemic attack; CVA=cerebrovascular accident (stroke); CAD=coronary artery disease; CHD=coronary heart disease; CVD=cerebrovascular disease; ASVD=atherosclerotic vascular disease of the heart;					

9.3 FOREST PLOTS

9.3.1 Comparison: rosiglitazone vs. pioglitazone (including combination therapy)[‡]

9.3.1.1 Outcome: acute myocardial infarction – rosiglitazone vs. pioglitazone



Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

[‡] See Appendix 4 for information about study specific approaches to defining exposure to TZD mono- or combination therapy.

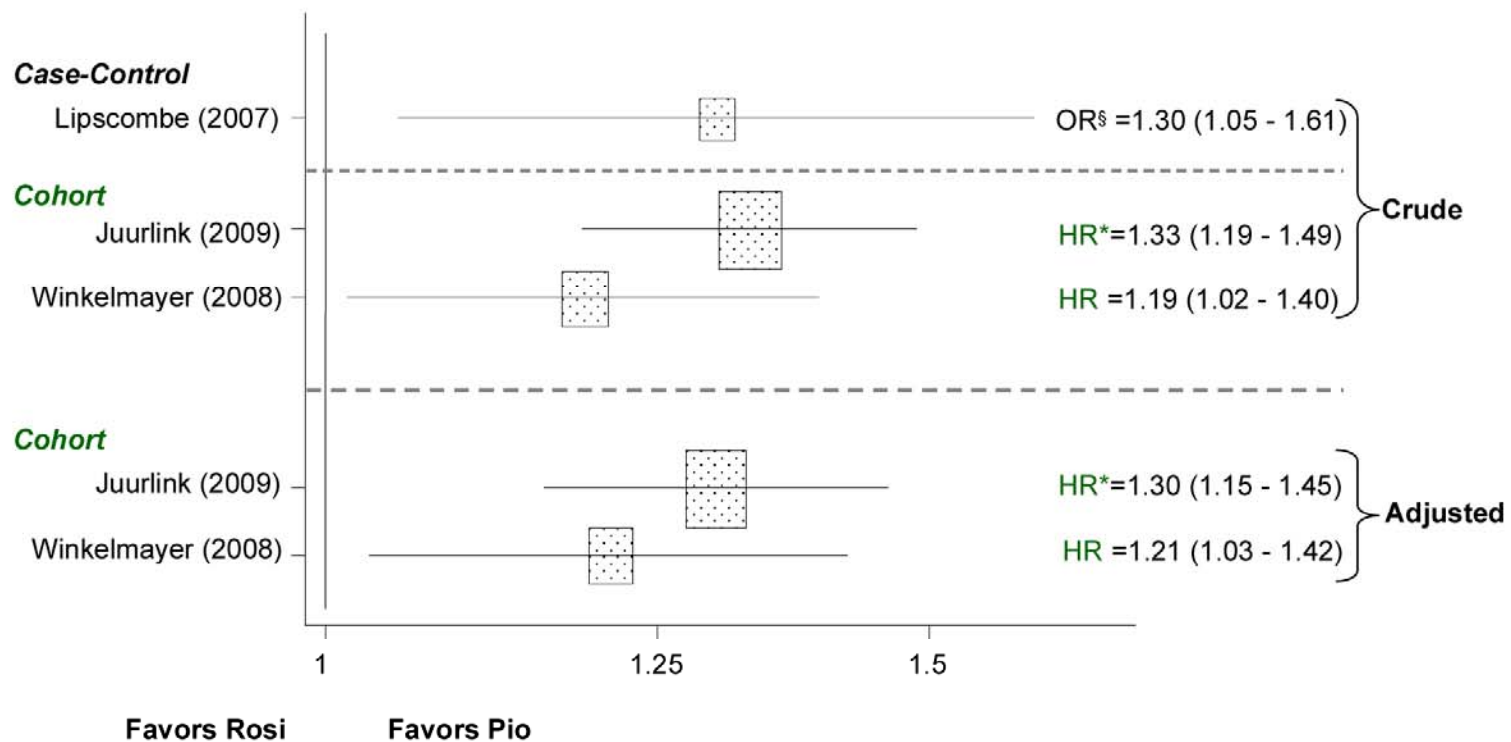
[§] Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

[†] Rate Ratio

^{*} Relative Risk

^{*} HR=reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

9.3.1.2 Outcome: congestive heart failure – rosiglitazone vs. pioglitazone

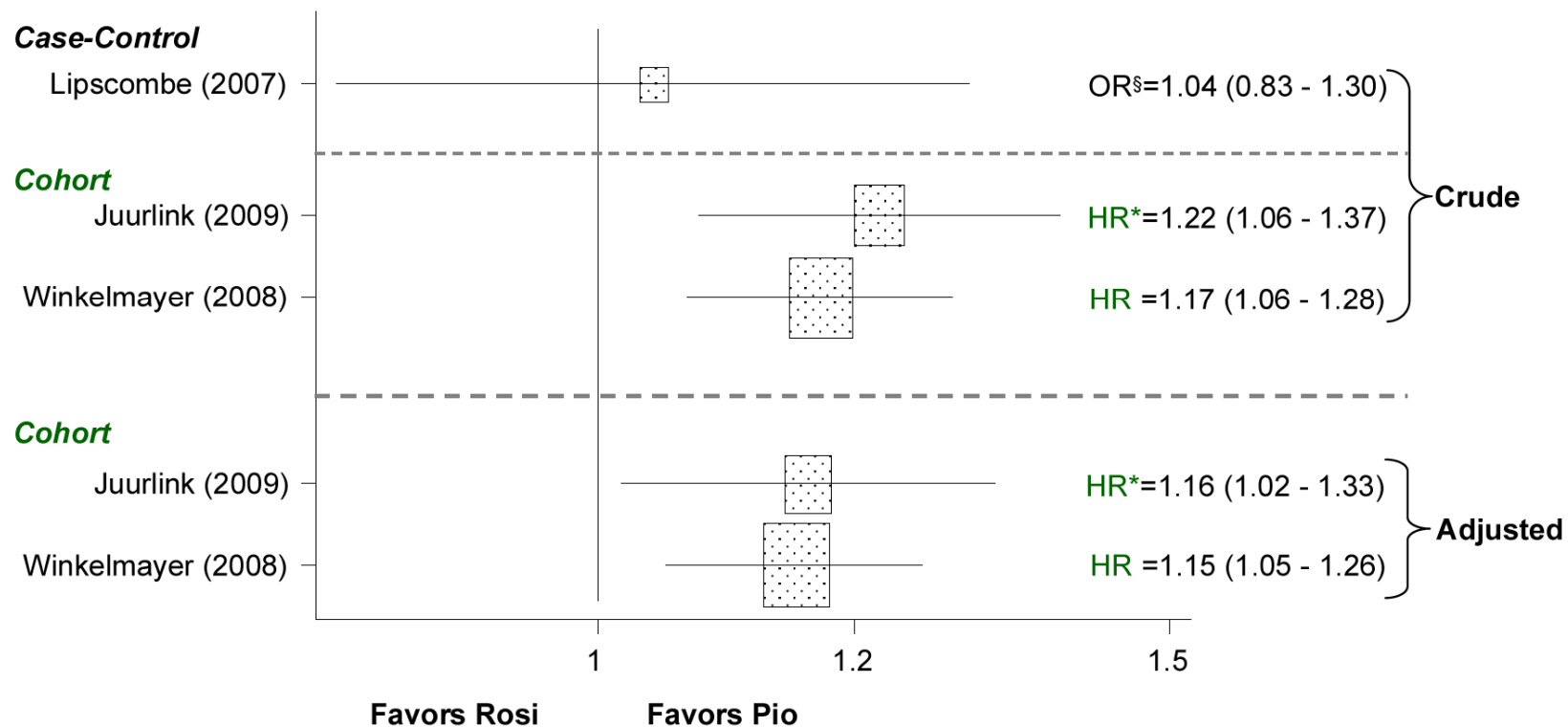


Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

[§] Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

* HR=reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

9.3.1.3 Outcome: all-cause mortality – rosiglitazone vs. pioglitazone

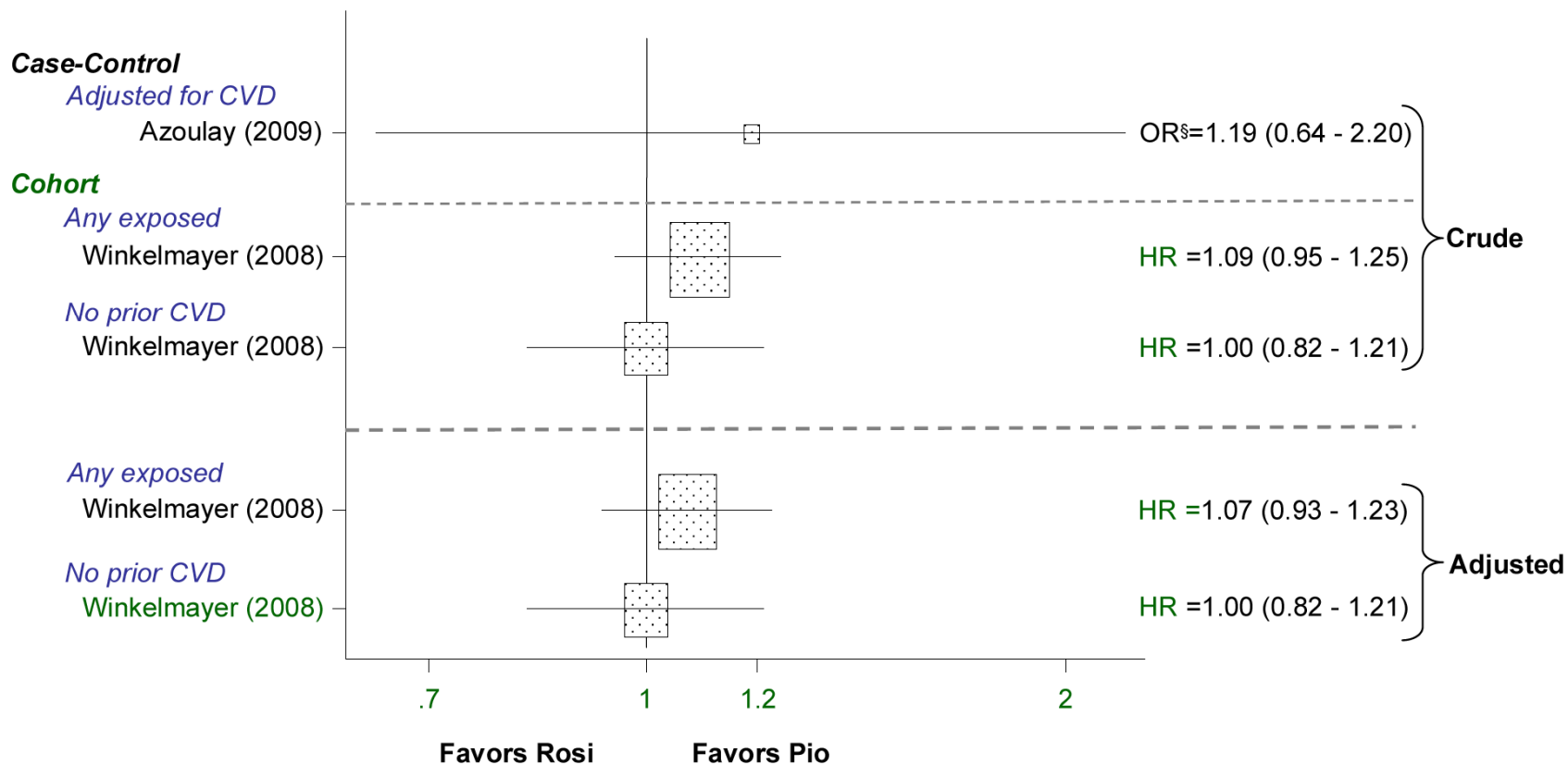


Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

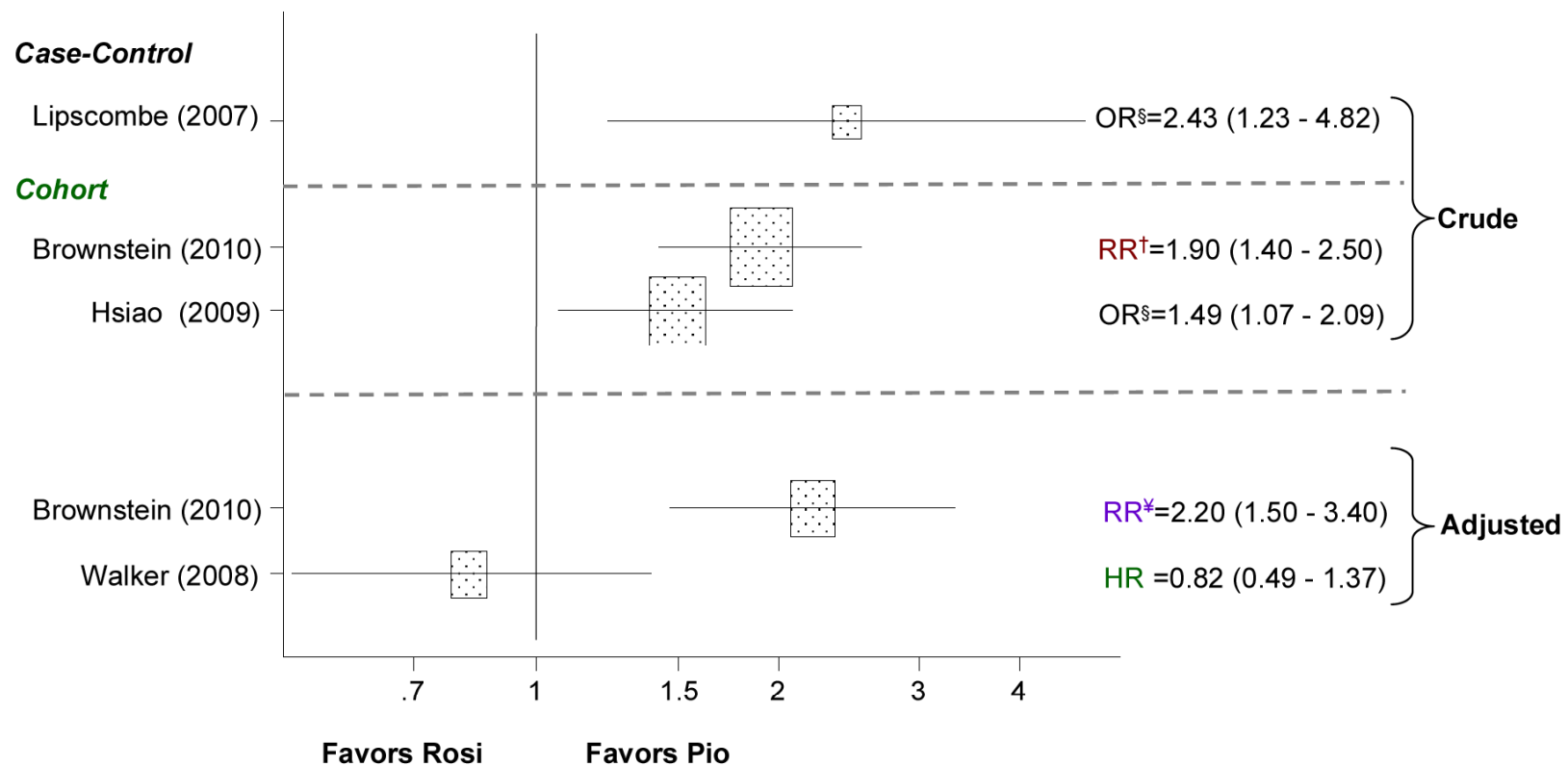
§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

* HR=reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

9.3.1.4 Outcome: stroke – rosiglitazone vs. pioglitazone



9.3.1.5 Outcome: acute myocardial infarction – rosiglitazone vs. pioglitazone monotherapy only



Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

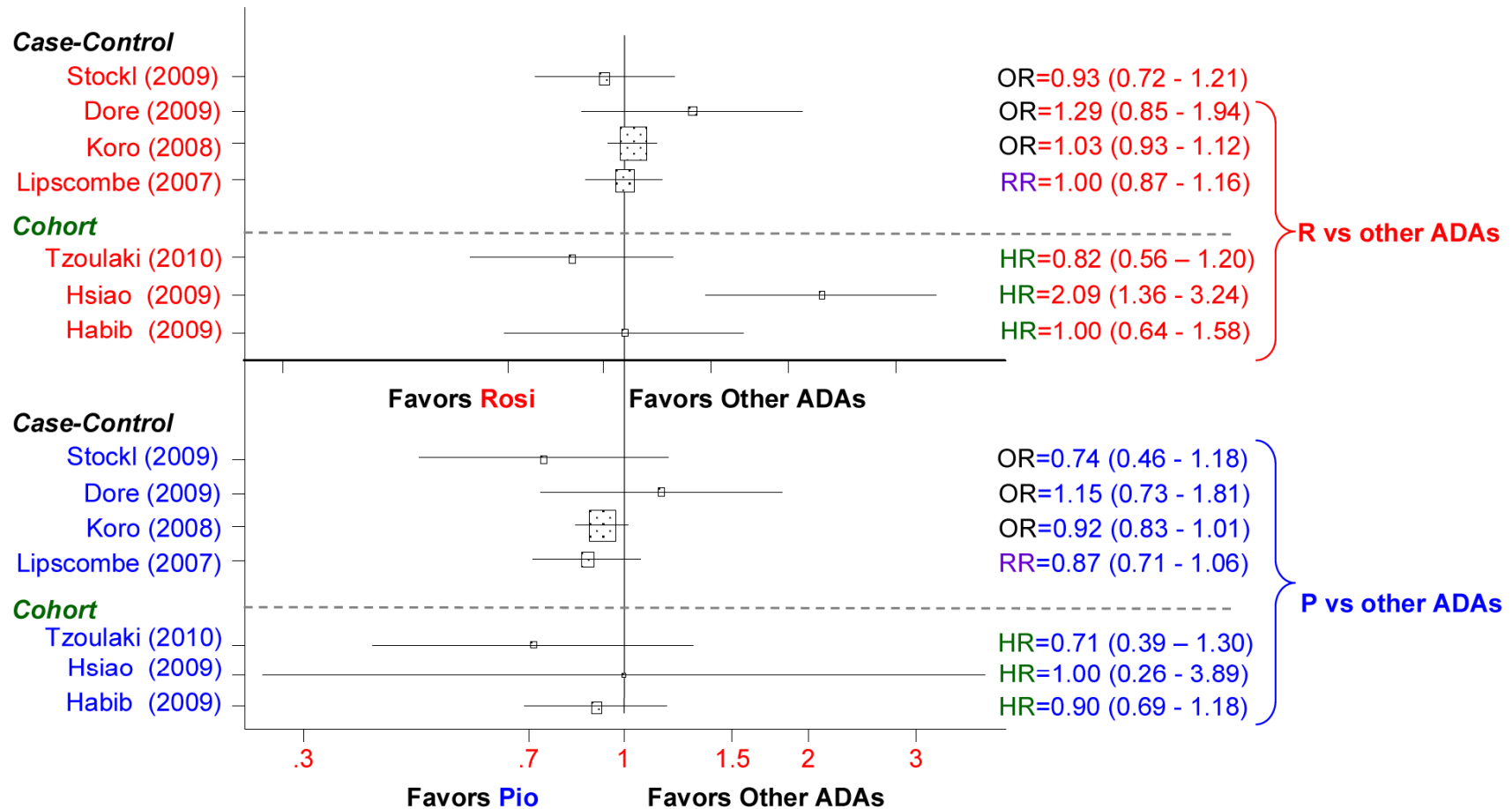
§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

† Rate Ratio

‡ Relative Risk

9.3.2 Comparison: rosiglitazone or pioglitazone vs. other ADAs* (including combination therapy) †

9.3.2.1 Outcome: acute myocardial infarction – rosiglitazone or pioglitazone vs. other ADAs



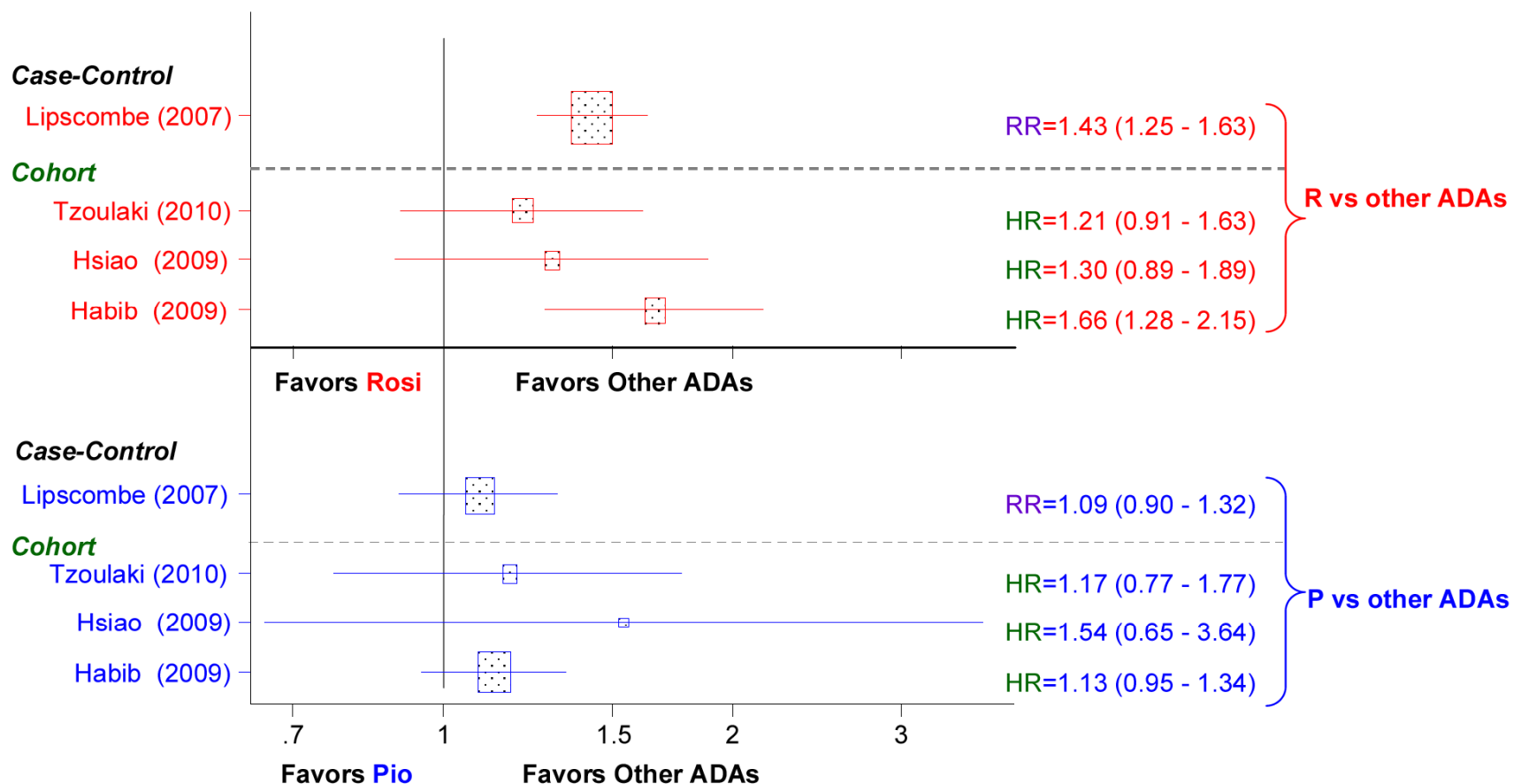
Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

† Adjusted estimates only are displayed in forest plots 9.3.2.1 - 9.3.2.4.

* Drugs included in the category "other ADAs" may differ across studies (see Appendix 4).

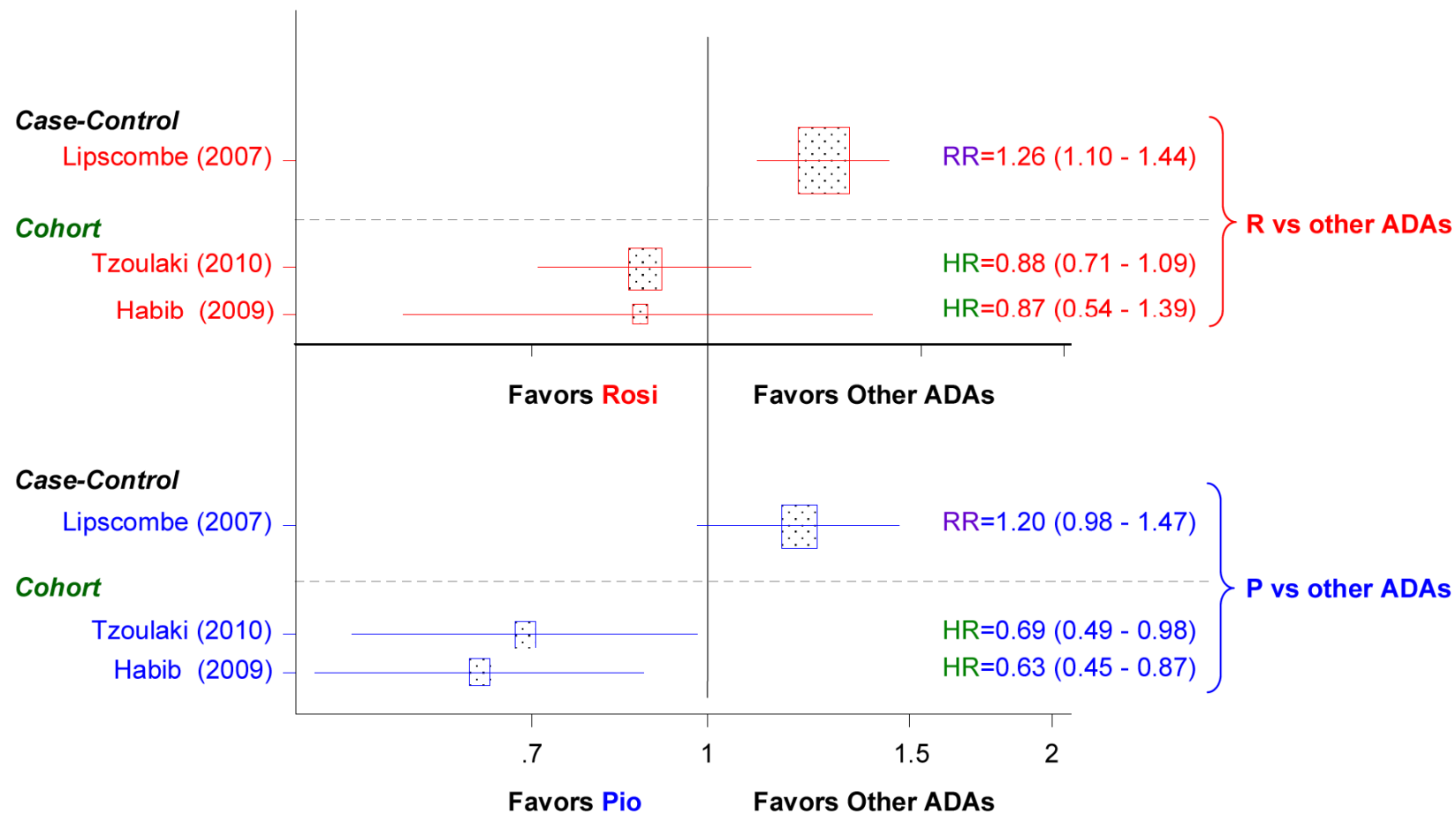
‡ See Appendix 4 for information about study specific approaches to defining exposure to TZD mono- or combination therapy.

9.3.2.2 Outcome: congestive heart failure – rosiglitazone or pioglitazone vs. other ADAs



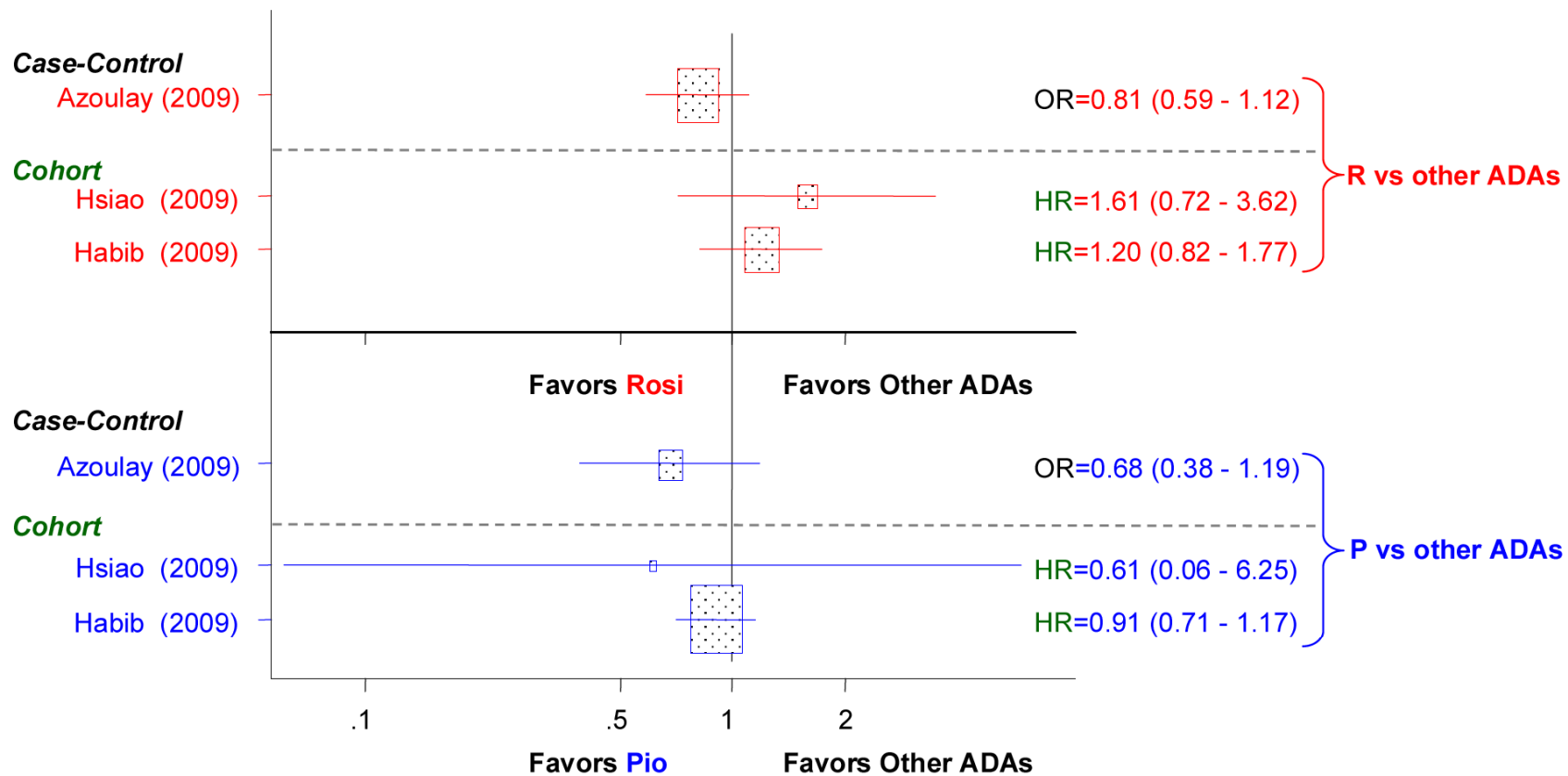
Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

9.3.2.3 Outcome: all-cause mortality – rosiglitazone or pioglitazone vs. other ADAs



Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

9.3.2.4 Outcome: stroke – rosiglitazone or pioglitazone vs. other antidiabetic agents



Boxes indicate individual study point estimates. The box size denotes the size of the study. The width of the horizontal lines represents the 95% CI for each point estimate.

10 APPENDICES

10.1 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

10.2 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 ³⁷ ★
- 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 ³⁸ ★
- b) hospital controls
- c) no description

4) Definition of Controls

- a) no history of disease (endpoint) ³⁹ ★
- b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

- a) study controls for _____ ⁴⁰ _____ (Select the most important factor.) ★

³⁷ 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.

³⁸ 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.

³⁹ 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)

⁴⁰ Age and gender

b) study controls for any additional factor ⁴¹✱ (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)⁴² ✱
- 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 ⁴³ ✱
- b) non respondents described
- c) rate different and no designation

⁴¹ Other cardiovascular risk factors

⁴² Administrative or computer pharmacy records will qualify for a star

⁴³ If study design precludes the possibility of differential non-response, a star will be given

10.3 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 _____⁴⁴ _____ (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)⁴⁵ ✱
- 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 ⁴⁶ ✱
- b) no

⁴⁴ 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.

⁴⁵ Administrative claims or electronic medical records will qualify for a star

⁴⁶ 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 ⁴⁷ _____ (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.) ⁴⁸

Outcome

1) Assessment of outcome

- a) independent blind assessment *
- b) record linkage ⁴⁹ *
- 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) ⁵⁰ *
- b) no

3) Adequacy of follow up of cohorts ⁵¹

- a) complete follow up - all subjects accounted for ⁵² *
- 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

⁴⁷ Age and gender

⁴⁸ Other cardiovascular risk factors

⁴⁹ 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.

⁵⁰ Three (3) months or longer follow up period will qualify for a star

⁵¹ 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.

⁵² If censoring criteria are specified and all patients are accounted for a star can be given

10.4 APPENDIX 4: 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

CLINICAL STUDIES

NDA/Serial Number: 21-071/35 and 21-073

Drug Name: Avandia (rosiglitazone) and Actos (pioglitazone)

Indication(s): Treatment of Type 2 Diabetes Mellitus

Applicant: GlaxoSmithKline and Takeda

Date(s): Observational Studies Received from OSE on April 28, 2010;
Review Completed on June 14, 2010

Review Priority: Standard

Biometrics Division: Division of Biometrics 7 (DB7)

Statistical Reviewer: John Stephen Yap, PhD

Concurring Reviewers: LaRee Tracy, MA, PhD (DB7 Team Leader, Acting)
Mark Levenson, PhD (DB7 Deputy Director, Acting)

Medical Division: Division of Epidemiology, Office of Surveillance and Epidemiology

Clinical Team: Kate Gelperin, MD, MPH; Esther Zhou, MD, PhD

Project Manager: N/A

Keywords: Thiazolidinedione, TZD, Avandia, Actos, Rosiglitazone, Pioglitazone, Diabetes, Observational Study, Systematic Review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The 21 observational studies reviewed were largely dissimilar (Tables 1 and 2). The main differences were as follows:

1. Varied study designs (case-control vs. retrospective cohort).
2. Multiple endpoints or outcomes considered and the way these were assessed (ICD-9 coding, other coding).
3. Various antidiabetic agents studied, including whether they were considered as single or combination therapies.
4. Variable durations of antidiabetic agent exposure and the study periods.
5. Variable ranges of patient ages included in study cohorts or populations.
6. Study populations varied by locations of study and by race/ethnicity.
7. Various statistical methods utilized (conditional logistic regression, Cox proportional hazards regression, or Poisson regression) including the estimates obtained from these methods (i.e. odds ratios versus hazard ratios); the way model assumptions (e.g. proportionality of hazards in the Cox model) and model adequacy (e.g. linearity of covariates in Cox or conditional logistic regression model) were diagnosed or assessed.
8. Variability in the types and numbers of covariates used for model adjustment.
9. Different criteria for matching (for nested case-control studies).
10. Variable amounts of missing exposure, outcome and covariate data.
11. Various comparisons among different treatment groups, including whether comparisons were made between monotherapies or combination therapies, or a combination of these; and reference groups.

These study differences strongly suggest that estimates of association from studies should not be pooled into a single meta-analytic estimate. In addition, 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. The hazard ratio is a measure of risk over time whereas the odds ratio is a ratio of probabilities that does not account for event times. The interpretation and underlying statistical assumptions of these two measures of effect are different.

The strength of observational studies generally depends on the quality and reliability of the databases used, the assessment methods used to identify exposures and outcomes, the appropriateness of the data sources to address the study aims, the statistical methodologies used to adjust for covariate imbalances, the amount of available data including covariates, the treatment of missing data, and the implementation and diagnostics of the statistical methods. In this review:

- The databases studied in each of the 21 publications vary from well known and previously studied (e.g. GPRD, Kaiser Permanente and Medicaid) databases to ones for which no, or limited, details were provided (e.g. Vertically integrated health system in Southeast Michigan from publication 5).

- Many studies identified diabetes patients and outcomes of interest using ICD codes (see item 2 above and item 8 of Section 1.3 Statistical Issues and Findings) which are considered standard in providing reliable assessments for this population and for specific outcomes (e.g. acute myocardial infarction). However, only publication 1 performed a validation of acute myocardial infarction using a random sample of the patient population. In addition, some studies used diagnostic codes other than ICD codes.
- Studies vary in the numbers and types of covariates that were used for model adjustment (see item 3 of Section 1.3 Statistical Issues and Findings). Due to lack of randomization, observational studies are prone to biases including those due to confounders that may have been unaccounted for in the statistical models. Thus, the reviewed studies may be limited in part by not being able to account for the same or similar covariates and also unable to account for unmeasured covariates in the statistical models.
- Many studies do not discuss missing covariate data and/or describe the approach used to handle missing covariate data (see item 3 of Section 1.3 Statistical Issues and Findings).
- There were two statistical models commonly used across most of the studies (conditional logistic regression and Cox proportional hazards regression). However, as stated in item 2 of Section 1.3 Statistical Issues and Findings, most of the studies that used the Cox model did not check the proportionality of hazards assumption. Moreover, none of the publications provided results from diagnostics for model fit. Thus, without checks for model adequacy, the results of the statistical analyses may be incorrect.

This review is limited by the information provided in each publication. Therefore, some of the comments by the statistical reviewer may arise from unclear and/or incomplete understanding of each of the studies. These concerns and the inability to verify results from the studies using subject-level data prevent the statistical reviewer from providing general qualitative assessments of the overall results across all studies.

1.2 Brief Overview of Clinical Studies

The following two tables, Tables 1 and 2, include a summary of the 21 case-control and cohort studies that were assessed as part of OSE's systematic review.

Case-Control Studies									
Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Cases/ Controls	Population Details	Statistical Method	Model Estimate	Comparison Groups
[2] Azoulay et al., 2009	Stroke	Rosi, Pio, Sulfonylurea, Biguanines, Acarbose, Prandial Glucose Regulator	UK General Practice Research Database	1/1/88-6/30/08	2,417/23,987	DM2 UK patients ≥ 40 yrs old; currently exposed within 90 days of index date.	CLR	Odds Ratio	Mono, Combo, with Reference
[3] Dore et al., 2009	AMI; ICD-9 code 410.xx	Rosi, Pio	Medicaid Analytic Extract database	2001-2002	320/1316 (Rosi), 268/1052 (Pio)	Diabetes patients used both metformin and sulfonylurea; data from CA, FL, NY, OH, and IL; exposure within 180 days of index date.	CLR	Odds Ratio	Mono, Combo, with Reference
[4] Dormuth et al., 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	Combo
[9] Stockl et al., 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 from CA, TX, OK, OR, WA.	CLR	Odds Ratio	Mono, Combo
[11] Vanasse et al., 2009	All-cause death or CV death (ICD-10 codes I-20-I25, I44-I52), acute MI (ICD-9 410), CHF (ICD-9 428), stroke (ICD-9 430-438)	Rosi, Pio, Metformin, Sulfonylureas, Insulin	Quebec databases (provincial hospital discharge register and provincial demographic database)	1/01-12/02	18,554/370,866 (all-cause death); 4,455/89,037 (CVD death); 4,274/85,480 (acute MI); 4,274/85,480 (CHF); 4,711/94,209 (stroke)	Diabetes patients (ICD-9 code 250) from Quebec ≥ 65 yrs old.	CLR	Odds Ratio	Mono with Reference
[13] Koro et al., 2008	MI (ICD-9 code 410.xx)	Rosi, Pio,	Integrated Healthcare Information Services healthcare claims database	1999-2006	9,870/29,610	DM2 patients.	CLR	Odds Ratio	Mono, Combo, with Reference
[18] Lipscombe et al., 2007	CHF (primary; ICD-10 code I50), acute MI (ICD-10 codes I21, I24 and I25.4), all-cause mortality	Rosi, Pio, Metformin, Sulfonylureas, other oral agents	Ontario health care databases	4/1/02-3/31/05	12,491/61,827 (CHF); 12,578/62,651 (acute MI); 30,265/150,650 (all-cause mortality)	DM2 Ontario patients ≥ 66 yrs old.	CLR	Odds Ratio	Mono, Combo, with Reference

CHF=congestive heart failure; AMI=acute myocardial infarction; CVD=cardiovascular disease
PS=propensity score; CLR=conditional logistic regression
DM2=diabetes mellitus 2
UK=United Kingdom
Pio=pioglitazone (Actos); Rosi=rosiglitazone (Avandia)
Mono=monotherapy; Combo=combination therapy; Adj.=adjusted non-TZD use in statistical model; Summary=combined monotherapy and combination therapy estimates

CHF=congestive heart failure; AMI=acute myocardial infarction; CVD=cardiovascular disease

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Pio=pioglitazone (Actos); Rosi=rosiglitazone (Avandia)

Mono=monotherapy; Combo=combination therapy; Adj.=adjusted non-TZD use in statistical model; Summary=combined monotherapy and combination therapy estimates

Table 2: Summary of Cohort Studies

Cohort Studies									
Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Model Estimate	Comparison Groups
[1] Brownstein et al., 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 old; ICD9 code DM 250.XX or an AIC>6% and ≥1 record of prescription.	Poisson GLM	Rate Ratio	Mono, Combo (not explicit)
[5] Habib et al., 2009	Fatal and non-fatal acute MI (primary), hospitalization for CHF, fatal and non-fatal CVA, TIA, CHD, all-cause mortality	Rosi, Pio	Vertically integrated health system in Southeast Michigan	1/1/00-12/1/06	1,056 (Rosi), 3,217 (Pio), 307 (Rosi and Pio)	Diabetes (ICD-9 code 250.xx) patients in SE Michigan >18 yrs old; 6-months exposure.	<ul style="list-style-type: none"> • PS stratification • Cox PH model 	Hazard Ratio	Mono, with Reference
[6] Hsiao et al., 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.	<ul style="list-style-type: none"> • Survival via KM method • Cox PH model 	Hazard Ratio	Mono, Combo
[7] Juurlink et al., 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 old; no insulin use.	<ul style="list-style-type: none"> • Survival via KM method • Cox PH model 	Hazard Ratio	Combo (Adj)
[8] Shaya et al., 2009	Acute MI (ICD-9 410-411), stroke (ICD-9 430-438), and revenue (emergency department) codes 450-459 for MI	Rosi, Pio, Other	Maryland Medicaid	1/1/01-6/30/06	Rosi and Pio not given	DM2 patients; 51% African-Americans.	<ul style="list-style-type: none"> • PS stratification • Logistic Regression 	Hazard Ratio	Unclear
[10] Tzoulaki et al., 2009	MI, CHF, mortality	Rosi, Pio, Metformin, Sulfonylurea, etc.	UK General Practice Research Database	1990-2005	6,053 (1 st Gen Sul), 58,095 (2 nd Gen Sul), 8,442 (Rosi), 9,640 (Rosi combo), 3,816 (Pio mono/combo), 37,253 (Other), 68,181 (Met)	Diabetes patients 35-90 yrs old.	Cox PH model	Hazard Ratio	Mono, Combo, with Reference
[12] Ziyadeh et al., 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 old; from 25 states.	<ul style="list-style-type: none"> • PS matching • Cox PH model • Survival via KM method • Log-rank test 	Hazard Ratio	Mono, Combo (Stratified)

Cohort Studies (continued)									
Study	Outcomes Evaluated	Antidiabetic Drugs Evaluated	Data Source	Exposure Period	No. Exposed/ Unexposed	Population Details	Statistical Method(s)	Model Estimate	Comparison Groups
[14] Margolis et al., 2008	MI, unstable angina, cardiac death, CARP	Rosi, Pio, Metformin, Sulfonylureas, Meglitinides, Insulin	The Health Information Network	1/02-1/06		Diabetes patients ≥ 40 yrs old.	Cox PH model	Hazard Ratio	Mono
[15] Walker et al., 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	Mono, Combo, Summary
[16] Winkelmaye r et al., 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	Unclear
[17] Gerrits et al., 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	Combo (Adj.)
[19] McAfee et al., 2007	MI (ICD-9 code 410.x), CR (ICDP 36.xx, CPT 33500-33572, CPT 92980-92984 and 92995-92996)	Rosi, Metformin, Sulfonylurea, Insulin	Ingenix Research Database	7/1/00-12/31/04	8,977 (in each triplet for mono), 1,362 (in each triplet for dual), 1,173 (in each pair for combo)	Diabetes patients ≥ 18 yrs old; ≥ 6 months of plan membership.	<ul style="list-style-type: none"> • PS matching • Cox PH model • Survival via KM method 	Hazard Ratio	Mono, Combo, Summary
[20] Karter et al., 2005	CHF (ICD-9-CM codes 401.91, 402.xx, 404.xx, 428.xx, 4251, 4254, 4255, 4257)	Pio, Metformin, Slufonylurea, and Insulin	Kaiser Permanente Northern California Diabetes Registry	10/99-11/01	3,556 (Pio), 5,921 (Sul), 11,937 (Met), 2,026 (Insulin)	DM2 patients in Northern California.	Cox PH model	Hazard Ratio	Combo (Adj.)
[21] Rajagopalan et al., 2004	CHF	Pio, Insulin	PharMetrics Patient-Centric Database	1/99-12/01	1668 (Rosi)/1668 (Pio)	DM2 (ICD-9-CM codes 250.x0, 250.x2) US patients ≥ 18 yrs old.	<ul style="list-style-type: none"> • PS matching • Logistic regression • Cox PH model 	Hazard Ratio	Mono, Combo
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=combined 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 (Actos); Rosi=rosiglitazone (Avandia) Mono=monotherapy; Combo=combination therapy; Adj.=adjusted non-TZD use in statistical model; Summary=combined monotherapy and combination therapy estimates									

1.3 Statistical Issues and Findings

The following are the specific statistical issues and findings identified in the review:

1. Among the 21 published observational studies that were reviewed, there were two types of study designs: nested case-control (publications 2-4, 9, 11, 13, and 18) or cohort (publications 1, 5-8, 10, 12, 14-17, 19-21). All cohort studies were retrospective in design. Among the nested case-control studies, defined cohorts were first selected from established health care databases; cases were identified and individually matched with controls based on specific covariates. Exposure to antidiabetic agents was then determined for both cases and controls. Among the retrospective cohort studies, exposed and unexposed patients were first identified in the databases followed by identification of outcome of interest among all exposed and unexposed patients in the cohort.
2. The primary statistical methods varied across the 21 published studies and included conditional logistic regression, Cox proportional hazards (PH) regression, and Poisson generalized linear model (GLM). These methods differ in the type of estimates they produce and underlying assumptions. In conditional logistic regression, the adjusted odds ratio (OR) of one therapy group relative to another is estimated for a dichotomous outcome. Conditional logistic regression accounts for the matching of cases and controls under some covariates in a matched case-control study. The Cox PH model is used to model time to event or outcome and estimates the hazard ratio (HR) associated with one therapy group relative to another. A major assumption of the Cox PH model is the proportionality of hazard functions in the compared treatment groups over time, i.e. the ratio of hazard remains constant between treatment groups over time. The Poisson GLM is used to model outcome counts per unit of time and to estimate rate ratios. The Poisson distribution assumes that the variance is equal to the mean; however, this requirement is often not met leading to overdispersion (i.e. when the variance of the data is much larger than the mean).
 - All nested case-control studies used covariate matching and the analysis was performed using conditional logistic regression (CLR) models. The covariates used in matching cases and controls generally varied across studies. For example, publication 3 matched cases to controls by age and state of residence while publication 4 matched cases to controls by age (in 5-year categories), sex, number of family members, enrollment in supplemental health coverage, etc. In addition, some studies used similar covariates for matching cases to controls; however, there were differences in the matching criteria. For example, publication 9 matched cases to controls by age within 2 years while publication 13 matched by age within 5 years. Therefore, given that the analysis of nested case-control studies included different matching criteria, the results from the statistical analyses across studies are not considered comparable. That is, cross-study comparisons of crude or adjusted estimates are inappropriate given variations in matching strategies.
 - All retrospective cohort studies except two (publications 1 and 8) used the Cox PH model in the analysis. Publication 1 used Poisson GLM while publication 8 used logistic regression. There were six retrospective studies that used the Cox PH model

along with propensity score (PS) either for matching (publications 12, 19, and 21) or stratification (publications 5, 8, and 15). None of the publications except publications 10 and 20 checked the proportionality hazards assumption in the Cox PH model or reported results from testing the assumption. Since the quality of the Cox PH model fit is highly dependent on a true proportionality assumption, estimates and conclusions from the publications that either did not check this assumption or checked but did not report the results should be interpreted with some caution.

3. The following are general issues that were identified in the review of the 21 publications:

- All nested case-control and retrospective cohort studies adjusted for various patient-level covariates. However, the covariates that were used for adjustment markedly varied from one study to another and the numbers of covariates included in the statistical models were different across studies. Even if some studies were similar in some aspects (e.g. they were all cohort studies), it is still difficult to compare results because of the differing covariates that were adjusted for in the statistical models. Therefore, cross-study comparisons of adjusted estimates from studies with similar designs are inappropriate.
- None of the 21 publications discussed diagnostic testing approaches used for model fitting. For example, in the cohort studies that used the Cox PH model, there was no discussion of the adequacy of the linearity between the log-hazards and the covariates. Similarly, among nested case-control studies using CLR models, the publications did not include results from diagnostic tests.
- Publications 1-4, 6-9, 11-17, 19, and 21 do not mention whether there were any missing covariate data and the amount of missing data. The adequacy of an adjusted statistical model depends on the available covariate data and the results depend on how missing data is handled. Given that the adjusted model omits patients with missing covariate data, estimates from these models are less precise.
- Many studies presented multiple comparisons for various antidiabetic agents (publications 1-6, 9, 10, 13, 15, and 18-20) or assessed multiple outcomes (publications 6, 8, 10-12, 14, 16, and 19). However, none of these studies, except publication 9, provide multiplicity adjustments. Publication 9 states that multiplicity was adjusted using the Hochberg method. Without multiplicity adjustment there is a risk of an inflated Type I error, i.e. falsely concluding a difference exists. Multiple comparisons should be accounted for in all statistical estimates (e.g. p-value, confidence interval) regardless of outcome (e.g. safety, efficacy) assessed.

4. Results from the following comparisons were provided:

- Rosiglitazone versus pioglitazone (direct comparison): publications 1, 4, 6, 7, 9, 12, and 15-17
- Rosiglitazone or pioglitazone versus a reference antidiabetic agent group (generally different among studies): publications 2, 3, 5, 10, 13, and 18
- Rosiglitazone or pioglitazone alone versus other groups of antidiabetic agents: publications 11, 19, 20, and 21

- Other: publications 8, 14

Not all studies directly compared rosiglitazone to pioglitazone, which is the main comparison of interest in the OSE systematic review of observational studies. For studies that did not directly compare rosiglitazone to pioglitazone, unadjusted risk estimates of odds ratios can generally be calculated for rosiglitazone versus pioglitazone using summary-level data. ***However, unadjusted risk estimates of hazard ratios or any adjusted risk estimate cannot be calculated without subject level data.***

In studies that directly compared rosiglitazone versus pioglitazone (publications 5, 7, 17 and 20), the treatment groups consisted of combination therapies including a TZD, and the non-TZDs were used as covariate adjustments in the statistical model.

In studies comparing rosiglitazone or pioglitazone versus a reference antidiabetic agent group, it should be noted that the reference group may be different from one study to another. That is, in one study, the reference group might be a single non-TZD agent, and in another study, it could be a combination of non-TZD agents.

5. The following publications included authors affiliated with the manufacturer of rosiglitazone (GSK) or pioglitazone (Takeda):

- GSK: publications 2, 10, 12, 13, 15, 16, and 19
- Takeda: publications 14 and 17

As indicated in the review of each of these publications (section 3.2), the affiliations of the authors with the drug manufacturers may introduce a possible publication bias. In this review, publication bias refers to under- or over-reporting of study results whether or not an association was found in the study.

6. The published studies each used different databases as summarized in Table 3 below. There were some published studies that were based on the same database as described below:

- Publications 2 and 10 were nested case-control and retrospective cohort studies respectively that used the United Kingdom (UK) General Practitioners Research Database (GPRD) from 1988-2008/1990-2005 to study the association of stroke/myocardial infarction (MI), congestive heart failure (CHF), mortality with the use of rosiglitazone, pioglitazone and other agents in patients who were at least 35 years old.
- Publications 15 and 21 were nested case-control and retrospective cohort studies, respectively, that used the PharMetrics database (a national database in the United States) from 1999-2001 and 2000-2007, respectively, to study the association of CHF /MI, coronary revascularization (CR) with the use of pioglitazone versus insulin/rosiglitazone, pioglitazone, metformin, sulfonylurea in patients ≥ 18 years old.

- Publications 17 and 19 were both retrospective cohort studies that used the Ingenix Research Database (United States database with unspecified region of coverage) from 2000-2004 and 2003-2006, respectively, to study the association of MI, CR/acute MI, CR with the use of rosiglitazone, metformin, sulfonylurea, insulin/rosiglitazone, pioglitazone in patients ≥ 18 /unspecified years old.

Table 3: Summary of Observational Epidemiology Databases Studied

Country of Study	Database (Publication Number)
1. United States	
National	Integrated Health Information Services (13); PharMetrics Patient-Centric (15 and 21)
Regional	Medicaid Analytic Extract database in states CA, FL, NY, OH, and IL (3); Vertically integrated Health System in SE MI (5); MD Medicaid (8); Prescription Solutions in states CA, TX, OK, OR, and WA (9); i3 Drug Safety from 25 states (12); NJPAAD and PPACE in NJ and PA (16); Kaiser Permanente in Northern CA (20)
Unspecified	Partners Healthcare System (1); Ingenix Research Database (17 and 19)
2. Canada	PharmaNet in British Columbia (4); Ontario Public Drug Benefit Program (7); Quebec databases (11); Ontario health care databases (18)
3. United Kingdom	General Practitioner Research Database (2 and 10); The Health Information Network in United Kingdom (14)
4. Taiwan	National Health Insurance database (6)

CA=California; FL=Florida; NY=New York; OH=Ohio; IL=Illinois; MI=Michigan; MD=Maryland; TX=Texas; OK=Oklahoma; OR=Oregon; WA=Washington; NJ=New Jersey; PA=Pennsylvania; SE=Southeast
 NJPAAD=New Jersey Pharmaceutical Assistance for the Aged and Disabled; PPACE=Pharmaceutical Assistance Contract for the Elderly

- Diabetes patients were generally identified in databases according to prescription use and/or International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 250 (Diabetes Mellitus). Some studies (publications 2, 4, 6-8, 13, 18, and 20-21) considered only type 2 diabetes mellitus while other studies considered general diabetes i.e. studies did not explicitly differentiate between types 1 and 2 diabetes mellitus. The type of diabetes may have been implied from the medication(s) taken by the patients; however, in some studies the diabetes type was not clear.
- Among all 21 studies, there were differences in time periods studied, ages of patients included, outcomes assessed, drugs/drug groupings and comparisons, and duration of exposure. Specifically,
 - The study observation periods ranged from 2-20 years. All studies except two (2 and 10) considered a period from 1998 and later. Publications 2 and 10 considered the periods from 1988-2008 and 1990-2005, respectively. The TZD class of drugs was introduced in the late 1990s and Avandia and Actos were not approved in the US until 1999. Therefore, data prior to 1999 would be insufficient to measure an association between exposure to either Avandia or Actos and an outcome of interest.

- The ages of patients included in the studies varied: ≥ 18 yrs (publications 1, 5, 9, 12, 15, 19, and 21); ≥ 35 or 40 yrs (publications 2, 10, 14); ≥ 65 or 66 yrs (publications 7, 11, 16, and 18); unspecified (publications 3, 4, 6, 8, 13, 17, and 20).
- The outcomes studied in all studies were congestive heart failure (CHF), acute myocardial infarction (AMI), stroke, mortality, coronary artery disease (CAD), heart failure (HF), angina pectoris (AP), transient ischemic attack (TIA), cerebrovascular accidents (CVA), coronary heart disease (CHD), coronary revascularization (CR), unstable angina (UA), cardiac death (CD), and coronary artery reperfusion procedures (CARP). The publications studied either one or at least one of these outcomes. The outcomes were identified using ICD-9 or ICD-10 codes. Publications 2, 5, 10, 14, 15, 16, and 21 identified outcomes using non-ICD codes which were generally dependent on the types of databases used. For example, in publications 2 and 10, Read codes were used for the GPRD database.
- In several published studies, the main outcome of interest was based on primary reason for hospitalization (ICD-9 or ICD-10 code). This definition does not account for patients who might have experienced an event and who were not later hospitalized (e.g. had event and subsequently died before reaching hospitalization) and patients that had the listed code as a secondary reason for hospitalization.
- Patient deaths were not described in several publications and therefore it is unclear if these patients were counted among the outcome of interest.
- The antidiabetic agents studied in all 21 published studies were rosiglitazone, pioglitazone, metformin, sulfonylurea, insulin and other agents. Studies generally group the agents according to monotherapy (drug of interest only), dual therapy (drug of interest plus at least one other agent), or combination therapy (combination of more than two agents) and comparisons are performed within one or more of these groupings. The results of the combined assessments should take into consideration the comparisons that are made. For example, the risk estimates obtained by comparing monotherapies may have different interpretations from those obtained by comparing dual or combination therapies. Publications 5, 7, 17 and 20 compare combination therapies but adjust for non-TZD use in the statistical models while in publication 12, the risk estimates are based on a stratification of treatment in the Cox statistical model. The risk estimates in these studies have different interpretations from risk estimates in studies that compare mono- or combination therapies. Finally, publications 15 and 19 show risk estimates for mono-, dual, and combination with insulin therapy, and includes summary risk estimates based on these three groups. The summary risk estimates also have different interpretations from risk estimates based on mono- or combination therapies.
- The length of drug exposures was generally not reported. However, studies that did provide some details regarding the exposure times (publications 2, 3, 4, 9, 13, 17, and 18) varied, i.e. exposure within 3, 6, 12 or > 12 months of the outcome date.
- The definition of current antidiabetic agent (e.g. TZD) exposure from index date varied across studies, e.g. within 90 days, 180 days, etc.

2. INTRODUCTION

2.1 Overview

A signal for increased cardiovascular risk in patients treated with rosiglitazone (Avandia; GlaxoSmithKline (GSK)) has been identified in previous pooled analyses of randomized controlled trials. Avandia and Actos (pioglitazone; Takeda) are both oral antidiabetic agents belonging to the thiazolidinedione (TZD) class of drugs. Both were FDA approved in 1999 and are the only currently approved TZD drugs for the treatment of type 2 diabetes mellitus. Another TZD drug, troglitazone, was approved by the FDA in 1997, but was removed from the market in 2000 due to an increased incidence of hepatotoxicity. TZDs primarily act by decreasing insulin resistance.

In April 2010, the Office of Surveillance and Epidemiology (OSE) requested that Division of Biometrics 7 (DB7) in the Office of Biostatistics (OB) conduct an independent statistical review of the methodology described in each of the 21 published observational studies that evaluated cardiovascular risks associated with TZDs in patients with diabetes mellitus. Findings from this statistical review are to be referenced in a final OSE systematic review of all the 21 publications, which will include a summary of all the findings and conclusions. The 21 publications were chosen by OSE reviewers following two rounds of evaluation using pre-determined selection criteria as specified in a systematic review study protocol. Among more than one thousand available published publications that were selected using very general search criteria, the first selection round yielded 57 publications. This number was further reduced to 23 after the second selection round. Finally, two publications were excluded because one did not satisfy the second round selection criteria and the other was deemed to be too poor quality. See the OSE review for more details regarding the systematic review.

This document contains the statistical review of each of the 21 publications referenced above. The purpose of this statistical review is to summarize and comment on the methodology described in each of the 21 selected observational studies. This review does not include an assessment or interpretation of individual study results and conclusions. Since this review is based on information provided in each publication, and not on subject-level data, the available information is limited.

2.2 Data Sources

Only published manuscripts were provided for this review. No subject-level data were available for this review.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This review focuses only on safety.

3.2 Evaluation of Safety

The following is a detailed summary of the statistical review of each of the 21 observational studies. The studies are arranged according to the year of publication and by last name of the first author. Each publication review includes a brief summary of the study and comments by the statistical reviewer.

1. Brownstein et al., Rapid Identification of Myocardial Infarction Risk Associated With Diabetes Medications Using Electronic Medical Records. Diabetes Care, vol 33, no. 3; 2010

This was a retrospective cohort study of the association between acute myocardial infarction (AMI) with the use of rosiglitazone, pioglitazone, metformin and sulfonylurea in diabetes patients. The study used the Partners Healthcare System to identify a cohort of patients who had new prescriptions for diabetes medications and the Research Patient Data Registry for clinical data (demographic information, dates of service, medications, diagnoses, laboratory results, and discharge summaries). Data for this study spanned the period from January 1, 2000 to December 31, 2006 and included patients who were more than 18 years old.

Diabetes patients were identified using ICD-9 code 250.XX or who had an A1C of >6.0% and at least one record of a prescription for an oral diabetes medication as an outpatient or dispensation as an inpatient. The antidiabetic therapy groups considered were rosiglitazone, pioglitazone, metformin, and sulfonylurea. Insulin use was included as a covariate in the statistical model and used for stratification analysis. The study population did not necessarily receive health care exclusively within the Partners system so that some patients may have had incomplete records. Health care encounters (inpatient or outpatient) were used as proxies for receipt of care at Partners over a specific observation period. Fourteen six-month intervals within the study period were investigated. Patients receiving multiple medications under consideration were excluded.

The main study endpoint for each patient was first hospitalization for AMI, which was assessed using ICD-9 code 410.

The relative risk of AMI associated with antidiabetic therapy was calculated for rosiglitazone versus metformin, sulfonylureas, or pioglitazone. The crude and adjusted rate ratios and 95% confidence intervals were estimated using a generalized linear model, assuming a Poisson distribution for the response and 6-month intervals as the offset. Extra-Poisson variability was modeled and incorporated into the estimates of standard errors to account for overdispersion. Parameter estimates were converted into rate ratios. Adjustments were made for potential risk factors or covariates. Additional analysis was performed by considering cumulative temporal effects when iteratively aggregating the 6-month intervals.

Reviewer's Comments:

- ***The use of 6-month intervals may or may not be restrictive. No justification was provided for this approach to analyzing the data.***

- *The publication states that one limitation of the study was it did not have complete longitudinal prescription data for all individuals and the patients may not have taken the medication that was prescribed.*
- *There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
- *The publication does not mention whether there were any missing covariate data and the amount of missing data related to exposure.*
- *Patients did not exclusively receive health care through the Partners system. Therefore, it is possible that outcomes were missed among patients receiving care elsewhere, which could bias the overall measure of effect.*

2. Azoulay et al., Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiology and Drug Safety, 2009

This was a nested case-control study of the association between incident stroke and the use of rosiglitazone and pioglitazone relative to other oral antidiabetic agents in type 2 diabetes patients. The study cohort was comprised from the United Kingdom (UK) General Practice Research Database (GPRD), which contains primary care medical records for more than 6 million people in the United Kingdom (UK). The study cohort comprised all subjects who were prescribed at least one antidiabetic agent between January 1, 1988 and June 30, 2008 and who were at least 40 years of age at time of their first antidiabetic agent prescription (time of prescription defined as start date into cohort). Patients who initiated treatment with insulin, with less than 1 year of up-to-standard medical history (not defined) prior to cohort entry, had a history of stroke, cerebral aneurysm or cancer were excluded. Patients in the cohort were followed until the occurrence of a first stroke, death, end of registration, or study end (June 30, 2008).

Cases were all subjects who experienced a first stroke (index date based on calendar date) during the follow-up. Cases were matched to at most ten controls based on age, sex, date of cohort entry, and duration of follow-up. Eight mutually exclusive exposure (determined via prescription record) groups were considered in the analysis: currently exposed to (1) TZD monotherapy (either pioglitazone or rosiglitazone alone), (2) TZD combination therapy, (3) non-TZD monotherapy, (4) non-TZD combination therapy, (5) insulin monotherapy, (6) insulin in combination with other agents, (7) not currently exposed to any agents, and (8) no exposure in the year prior to the index date. Current exposure was defined as last recorded prescription in 90 days prior to the index date. Adjusted (for matching variables and several listed covariates) rate ratios and 95% confidence intervals were derived using conditional logistic models.

Reviewer's Comments:

- *Although additional power can be gained by increasing the number of controls, including more than four controls for each case generally does not substantially increase the power. Efficiency can be gained when increasing the number of control in situations where the probability of exposure in the control group is small. Given that the probability of exposure is not expected to be small in this study, the*

1:10 matching of cases to control was probably unnecessary likely not leading to an increase in power.

- *The publication does not mention whether there were any missing covariate data and the amount of missing data related to exposure.*
- *The publication states the following study limitations: (1) The statistical power to detect an association between rosiglitazone and pioglitazone and stroke was lacking because these drugs were not commonly used in the UK during the study period. This raises concerns regarding the applicability of these findings to a current population in which the TZDs are more frequently prescribed. Given that the TZDs were made available in the later 1990s, it is unclear why the authors choose to include data from as early as 1988 in the study. (2) Exposure was determined based on record of written prescriptions by a general practitioner. It is unknown whether these prescriptions were actually filled at the pharmacy and if patients fully complied with the prescribed treatment regimen. This may be one cause for bias in the study results.*
- *The publication does not describe the number of subjects in the cohort who died with or without previously experiencing a stroke. Therefore, it is unclear if deaths were included among the cases and how deaths were treated among the controls.*
- *While the GPRD database captures information for a large number of subjects, the generalizability of these data to the US population might be difficult given varying prescribing practices, risk factors, and medical practices.*
- *The publication does not describe how the outcome of stroke was identified in the GPRD and if the criteria used to identify stroke are validated.*
- *There were multiple comparisons performed among the eight groups without adjustments for multiplicity.*
- *The statistical conditional logistic regression method is appropriate for analysis of matched case-control data; however, the issues and limitations stated above weaken the overall study results and conclusions.*
- *The last author, received research grants from GSK, the manufacturer of Avandia. The potential for publication bias exists, though it can not be verified based on the publication alone.*

3. Dore et al., Association Between Extent of Thiazolidinedione Exposure and Risk of Acute Myocardial Infarction. Pharmacotherapy. 29(7):775-783; 2009

This was a nested case-control study of the association between acute myocardial infarction (AMI) and the use of rosiglitazone and pioglitazone (each relative to the use of metformin and sulfonylurea) in type 2 diabetes patients using the Medicaid Analytic Extract (MAX) database. The database includes patient-specific information on dispensed outpatient drugs, outpatient services, hospital utilization, long-term care residence and other services from California, Florida, New York, Ohio and Illinois. Data from calendar years 2001-2002 were considered. The cohort included individuals who had enrolled in fee-for-service Medicaid coverage for at least 180 days who used both metformin plus a sulfonylurea during the Medicaid enrollment, and who had least one

inpatient claim. Cohort eligibility required two or more claims for Medicaid service and began on date of the first claim and ended on the date of the last claim.

Cases were defined as patients who had a primary discharge diagnosis of AMI (ICD-9-CM 410.xx) excluding any patient without 180 days of eligibility before their first AMI.

Up to five controls were chosen randomly and matched by age and state of residence using risk-set sampling. Controls were required to have 180 days of eligibility before the matched case index date.

For the primary analysis, drug exposure (based on prescription use) to rosiglitazone or pioglitazone considered persons exposed if they started taking either drug in the 180 days prior to the index date.

The primary analysis considered exposure within 180 days prior to the index date (date of AMI). Secondary analysis was also performed using exposure durations of 0-90 or 91-180 days prior to the index date. Adjusted odds ratios were derived using a conditional logistic model adjusting for covariates. To adjust for confounding, nonparsimonious modeling including variables that were considered a priori to be potential confounders was performed.

Reviewer's Comments:

- *Cohort eligibility required that a patient have at least one inpatient claim. This led to a huge reduction in cohort size from approximately 307,000 individuals to approximately 95,000. In addition, the cohort was restricted to patients receiving Medicaid services. Findings from this restrictive cohort might not be generalizable to the intended population.*
- *The publication does not mention whether there were any missing covariate data or the amount of missing data on drug exposure.*
- *Data from patients who used both pioglitazone and rosiglitazone during the 180 days prior to the index date were excluded from the primary estimates. The publication does not state how many these patients were excluded.*
- *The sample sizes were relatively low when considering TZD use within 180 days prior to the index date. There may not be enough power to detect an association between exposure and outcome, especially when adjusting for several covariates.*
- *The study makes a comparison of TZD use with or without metformin plus a sulfonylurea within 180 days before index date relative to combined use of metformin and a sulfonylurea. This comparison may be biased because the distribution of metformin and sulfonylurea use within each group may be very different from each other. That is, there may be fewer users of metformin and sulfonylurea in the TZD group compared to the metformin and sulfonylurea group.*
- *Insulin use, which might confound any relationship between exposure and outcome, was not adjusted for in the conditional logistic regression model.*
- *The authors comment that there were appreciable differences in the baseline prevalence of risk factors for AMI between cases and controls but that the crude and adjusted odds ratios were similar. They concluded that this level of*

confounding was low because some characteristics were rare and others were not substantially associated with exposure status. While this might be true for measured covariates that are infrequent in both cases and controls, the possibility of confounding due to differences in unmeasured covariates remains.

- There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
- The diabetes population studied comprises mostly older and generally sicker patients thus raising concerns of generalizability of results to healthier and younger diabetic populations.*
- Crude and adjusted odds ratios for each pioglitazone and rosiglitazone are compared to a reference group of metformin and sulfonylurea. Therefore, adjusted odds ratios for rosiglitazone versus pioglitazone can not be estimated without patient-level data to include adjusted covariates. This is a major limitation given that adjusted estimates are generally less biased estimates.*

4. Dormuth et al., Rosiglitazone and Myocardial Infarction in Patients Previously Prescribed Metformin. PLoS One, vol 4(6), e6080; 2009

This was a nested case-control study of the association between acute myocardial infarction (AMI) and the use of rosiglitazone, pioglitazone, sulfonylurea, and glyburide in patients with type 2 diabetes patients previously prescribed metformin. The source population consisted of all residents of British Columbia (BC) at any time between January 1997 and March 2007 who were registered for medical coverage for at least one year. The primary data was the PharmaNet database, which captures information on prescription use and the BC Ministry of Health databases for information on hospitalizations and medical services registration. The study period covered data from May 1, 2003 to March 31, 2007. The cohort included patients from the source population who started metformin between January 1, 1997 and March 31, 2007 and who did not receive any other oral antidiabetic medication or insulin during the past 365 days.

Patients who were admitted to the hospital with AMI (based on ICD-9 code 410) recorded as the primary reason for the admission were defined as cases. Controls were chosen among persons in the cohort who contributed the same person-time at risk of the AMI as their matching case. Each case was matched by age, sex, number of family members, family income, and supplemental health coverage to up to four controls.

Exposure to the TZDs and the sulfonylureas was based on prescription before the event date (cases) or index date (controls). There were five exposure groups considered: rosiglitazone, pioglitazone, either rosiglitazone or pioglitazone, any sulfonylurea, and glyburide. Exposure duration was divided into predefined categories (1 to 6, 7 to 12, 13 to 24, and > 24 months of current cumulative exposure) and the exposure categories were modeled using conditional logistic regression.

The publication stated that 2,100 AMI cases and 8,400 controls would be needed to observe an odds ratio of 1.40 with 80% power, Type-1 error of 0.05, and an exposure prevalence of 3.5%.

Conditional logistic regression models were used to estimate the matched odds ratios for AMI. The models were adjusted for matching covariates as well as several other covariates including duration of diabetes (based on earliest diagnoses date or initiation of metformin).

Reviewer's Comments:

- *Cases were defined as patients who were admitted to the hospital for primary reason for AMI. This definition does not account for persons who might have had AMI and subsequently died prior to hospitalization or patients who had an AMI but whose primary reason for hospitalization was not AMI. Therefore the definition of a case might lead to an under-estimation of the true AMI event rate.*
- *The publication does not mention whether there were any missing covariate data and the amount of missing exposure data.*
- *The publication states that the completeness of the PharmaNet database has not been studied before raising some concern regarding the validity of this database.*
- *The study excludes patients who received other oral antidiabetic medications or insulin within 365 days before starting metformin. The publication does not report how many patients were excluded based on this criterion.*
- *No references were provided for the assumed exposure prevalence of 3.5% in the sample size calculation. Due to differing prescribing practices in BC compared to the US, the estimated exposure prevalence might be different in the US.*
- *There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
- *The sample sizes were relatively low when comparing groups within predefined categories. Therefore, there might be a lack of power to detect the treatment effects, especially when adjusting for several covariates.*
- *The study was based on a single database of approximately 200,000 users in BC. When attempting to generalize the results to other populations, one should consider that there might be different prescribing practices and patient characteristics in a US population compared to the population studied.*

5. Habib et al., Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. *Pharmacoepidemiology and Drug Safety*, 18:437-447; 2009

This was a retrospective cohort study of the association between fatal and non-fatal acute myocardial infarction (primary outcome) and the use of rosiglitazone and pioglitazone in diabetes patients more than 18 years old using a vertically integrated health system in southeast Michigan. Secondary outcomes included hospitalization for congestive heart failure (CHF), fatal and non-fatal cerebrovascular accidents (CVA) and transient ischaemic attacks (TIA), combined coronary heart disease (CHD) events, and all-cause mortality. The study period was from January 1, 2000 to December 1, 2006.

The cohort comprised patients who were at least 18 years of age, had at least one clinical encounter with a coded diagnosis of diabetes (ICD-9 code 250.xx) during the study period, and at least one prescription of an oral diabetes medication during the study period. The index date was the first date during the study period that the patient had a clinical encounter coded as diabetes or a fill of an oral diabetes medication. At least 12 months of continuous health care plan enrollment prior to the index date and at least 6 months follow-up after index date was also required. The latest observation date was May 31, 2007.

The exposure groups considered were any TZD (rosiglitazone or pioglitazone) use, rosiglitazone use, pioglitazone use, and other oral diabetes medications use. Exposure was calculated as the number of days of supply of medication dispensed in a 6-month time block divided by the number of days. Exposure was determined using pharmacy claims data.

Cardiovascular endpoints were identified from electronically maintained claims data. Cardiovascular outcomes were based on inpatient codes while baseline cardiovascular status was derived from both inpatient and outpatient codes. Death information was obtained by comparing patient lists with records from the Division of Vital Records and Health Statistics, Michigan Department of Community Health.

Propensity scores stratification to adjust for measured covariates for each exposure or comparison group was used in the analysis. The propensity scores were included in Cox proportional hazards models along with selected covariates to estimate the hazard ratios. Additional analyses were performed by repeating the previous analyses using time-updated covariates. Forward and backward imputation was used for missing lab values.

Reviewer's Comments:

- *The publication does not identify the database source and only states that the database is a vertically integrated health system in southeast Michigan. Therefore the accuracy and completeness of this database is questionable.*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. Although the study stratified by the propensity scores, the proportional hazards assumption should have been checked within each stratum. Since this assumption was not checked, it is unknown whether the proportional hazards assumption was correct.*
- *The Cox model also assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified.*
- *The publication considers four groups in the statistical analysis: any TZD use, rosiglitazone use, pioglitazone use, and other oral diabetes medications use. However, other non-TZD therapies (e.g. sulfonylurea and insulin use) appeared to be included in both the exposed (rosiglitazone alone, pioglitazone alone, or both rosiglitazone and pioglitazone) and unexposed groups (other oral diabetes medications group). Although these non-TZD therapies were adjusted for as covariates, their true effects might not have been fully captured in the statistical*

- models and hence the current results reported by the publication could be biased. It might have been more appropriate to exclude them from the comparison groups.*
- *There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
 - *The non-TZD reference group comprises all other antidiabetic medications. It may be inappropriate to pool all non-TZD agents together for comparison given that each may confer a different risk or association on the outcome of interest.*
 - *Forward and backward imputation use last and first values, respectively, for missing values. This may cause bias in estimates because the true mechanism of missingness is unknown. This might have been an issue for the lipid values (LDL, HDL and triglycerides) which were each missing for at least 10% of the data and were included in the Cox models as time-updated covariates.*

6. Hsiao et al., Thiazolidinediones and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus. Drug Safety, 32(8):675-690, 2009

This was a retrospective cohort study of the association between myocardial infarction (MI), congestive heart failure (CHF), angina pectoris (AP), stroke and transient ischaemic attack (TIA), with the use of rosiglitazone, pioglitazone, sulfonylureas, and metformin in type 2 diabetes patients using the National Health Insurance database in Taiwan. The study period was from March 1, 2001 until December 31, 2005.

The cohort comprised newly diagnosed type 2 diabetes patients with their first ambulatory visits with a diagnosis of diabetes identified via ICD-9-CM codes (250.xx) and were prescribed sulfonylurea, metformin and/or a TZD at least three times during the study period. The index date was the first date that an oral antidiabetic drug was first prescribed. Five exposure groups of type 2 diabetes patients were considered based on the pattern of antidiabetic agent prescription from the index date to the end of follow-up: (1) rosiglitazone monotherapy; (2) pioglitazone monotherapy; (3) sulfonylurea-based therapy, meaning that the patients had been prescribed sulfonylurea during the study period, including those who had ever been prescribed a TZD and those who had not; (4) metformin-based therapy, meaning that the patients had been prescribed sulfonylurea during the study period, including those who had ever been prescribed a TZD and those who had not; and (5) sulfonylurea+metformin-based therapy. Patients who switched between rosiglitazone and pioglitazone therapy were excluded.

Study outcomes were identified based on diagnostic code of hospitalization as follows: 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), stroke (433.xx and 414.xx), angina pectoris (413.xx and 414.xx) and TIA (435.xx and 437.1). The outcomes were compared across the rosiglitazone, pioglitazone, metformin (no TZD), and sulfonylurea (no TZD) monotherapy groups. Additional analyses include dose-response relationship of exposure to the antihyperglycemic agents and cardiovascular events, and the risk of cardiovascular events for TZDs as add-on agents within the non-TZD groups.

The study estimated survival curves for CHF, AP, stroke and TIA using the Kaplan-Meier estimator. The risks in each medication groups were assessed by hazard

ratios using the Cox proportional hazards model (Cox model) adjusting for baseline and other covariates.

Reviewer's Comments:

- *The study excludes patients who switched between rosiglitazone and pioglitazone or had a combined use of these TZDs. The publication does not report how many patients were excluded.*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. Although the study stratified by the medication groups, the proportional hazards assumption should have still been checked within each stratum. This was not done in the study. Therefore, it is still unknown whether the proportional hazards assumption was satisfied or not.*
- *The Cox model assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified or not.*
- *The publication does not mention whether there were any missing covariate data or the amount of missing outcome data.*
- *The publication showed multiple comparisons among the different therapies but did not provide any multiplicity adjustments.*
- *The metformin-based therapy and sulfonylurea-based regimens both allowed for patients receiving both a TZD and one of these agents. Therefore, comparisons of the TZD monotherapy regimens against these combination regimens are likely biased. Findings from these comparisons are difficult to interpret given the presence of a TZD in both treatment groups.*

7. Juurlink et al., Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ 339:b2942; 2009

This was a population based retrospective cohort study of the association between a composite endpoint of death or hospital admission for either acute myocardial infarction (MI) or heart failure (HF) and the use of rosiglitazone and pioglitazone in patients with type 2 diabetes. In a secondary analysis, each outcome was examined individually. Prescription use was based on prescription drug records for patients 65 years of age or older from the Ontario Public Drug Benefit Program. Information on hospital visits were derived from the national ambulatory care reporting system database and the Canadian Institute for Health information discharge abstract database. Claims data were determined from the Ontario health insurance plan database. Time to event was based on time from first prescription to the event or time of censor. Patients receiving an insulin prescription during the same interval were excluded. Patients who switched to the other TZD or discontinued TZD were censored at time of switch. MI or HF was based on ICD-10 codes. The study period was from April 1, 2002 until March 31, 2008.

The authors performed time to event analyses using the Kaplan-Meier method and used the Cox proportional hazards model to estimate risk. The authors also performed a dose-response assessment by considering low dose pioglitazone (15 mg), high dose

pioglitazone (30 mg and 45 mg), low dose rosiglitazone (2 mg and 4 mg), and high dose rosiglitazone (8 mg). The authors stated that the proportional hazards assumption was verified using visual inspection of the estimated log(-log) survival curves and by testing the statistical significance of a covariate that allowed treatment to have a time varying effect.

Reviewer's Comments:

- *The study uses standardized differences to compare baseline characteristics between treatment groups, citing Mamdani et al., 2005 (BMJ) as reference for this method. Standardized differences are claimed to be useful in detecting clinical relevance instead of statistical significance. Mamdani et al. states that "Standardi[z]ed differences of greater than 0.1 are typically felt to be meaningful.", citing Cohen, 1988 (Academic Press). It is unclear from the cited publications how standardized differences impact results from the statistical analysis. For example, if all covariates have standardized differences below 0.1, it is unclear if covariate adjustment is necessary. Mamdani et al., however, points out that, "Both traditional significance testing and standardized differences focus only on one covariate at a time and do not provide an overall perspective on how the comparison groups differ", and suggests using propensity score methods instead. Propensity score methods involve multivariate assessment of confounders and provide an overall perspective on how the comparison groups differ.*
- *The publication states that the proportional hazards assumption was verified by using visual inspection of the estimated log(-log) survival curves and by testing the statistical significance of a covariate that allowed treatment to have a varying effect. However, the authors do not provide the results of the verification and the test. Therefore it is still unclear whether the Cox model was justified in the analysis of the data, i.e. if the proportionality assumption was true.*
- *The publication does not mention whether there were any missing covariate data and the amount of missing outcome data.*
- *The authors estimate the absolute risk of cardiovascular harm for rosiglitazone relative to pioglitazone using the proposed estimator by P. Austin (2008, Journal of Clinical Epidemiology). The cited publication does not provide theoretical justification (e.g. mathematical proof) or sufficient evidence (e.g. simulations) of the accuracy and precision of the estimator. Therefore, the absolute risk reported in the current publication may be incorrectly estimated.*
- *The publication states that patients who switched between low and high doses of the same drug were included in the cohort. Those patients who switched from one thiazolidinedione to another, as well as those who stopped receiving prescriptions for rosiglitazone or pioglitazone, were censored. The authors did not provide summary statistics for these patients, which might have been helpful in identifying any bias that could impact the results.*
- *The publication does not provide the rationale for the dose groupings. Furthermore, since there were patients who switched from low or high doses (see previous comment), this analysis might be biased.*

- *The Ontario Public Drug Benefit Program contains records of patients who are 65 years or older. The publication states that patient records during the first year of eligibility (age 65) were excluded in the analysis to avoid incomplete drug records. This raises an issue as to whether this exclusion might affect the results of the analysis.*
- *The publication states that only the first admission for a study outcome in patients who had multiple admissions during the study period was considered. An issue here is that later admissions that resulted in deaths are not captured in the analysis.*
- *The population studied included patients aged 66 and older. Therefore, the results reported cannot be generalized to a population of patients below 66 years of age.*
- *The final results presented in this paper are based on extensive adjustments for potential confounders, which lead to problems in generalizing the results to the overall population. Great caution should be exercised when attempting to draw conclusions based on the adjusted (or unadjusted) hazard ratios given the amount of adjustment performed. The authors did not address why other approaches to adjust for baseline imbalances, e.g. propensity score matching, etc. were not used.*

8. Shaya et al., Thiazolidinediones and Cardiovascular Events In High-Risk Patients with Type-2 Diabetes Mellitus, A Comparison with Other Oral Antidiabetic Agents. P&T, vol 34, no 9; 2009

This was a retrospective cohort study of the association between acute myocardial infarction (AMI) and stroke (hemorrhagic and non-hemorrhagic) with the use of antidiabetic treatments (rosiglitazone, pioglitazone and other oral antidiabetes agents) in patients with type 2 diabetes. The study used Maryland Medicaid medical encounter and prescription data from all managed care organizations in the state of Maryland. The study period was from January 1, 2001 to June 30, 2006. The cohort included patients with an ICD-9-CM code 250 during the study period who were enrolled continuously for at least 360 days with matching pharmacy and medical records. Patients with TZD or oral antidiabetic treatment before April 1, 2001 were excluded. This first three months of the study was used as the run-in period to reduce the likelihood of CV event prevalence bias. Patients treated with insulin alone during the entire study period were also excluded.

Exposure was defined as a cumulative 60 days of taking a drug (e.g. TZD) with no more than 30 days of taking another drug (e.g. other oral antidiabetic). Generic drug codes (i.e. National Drug Code) were used to identify information about medication use. Patients were identified via ICD-9 code 250 for diabetes as the primary, secondary, and tertiary diagnoses. Outcomes were identified using ICD-9 codes 410-411 for AMI, codes 430-438 for stroke, and revenue (emergency) codes 450-459 for MI. The authors excluded some outcomes that occurred within two weeks following the first TZD prescription.

The publication studied three groups of therapies: monotherapy (rosiglitazone, metformin, or sulfonylurea), dual therapy (rosiglitazone + metformin, rosiglitazone + sulfonylurea, or metformin + sulfonylurea), and combination with insulin (rosiglitazone + insulin or other oral antidiabetic agents + insulin). All therapy cohorts containing

rosiglitazone were also combined and compared with the remaining non-rosiglitazone therapy cohorts.

Propensity scoring was used to balance the covariates between the exposed and unexposed treatment groups. The final sample was divided into five quintiles and a weighted average over the strata in each treatment group was used to calculate the t-statistic in the groups. This was repeated for each stratum and each covariate until all patient characteristics were balanced. Logistic regression was then used to estimate the odds ratio for cardiovascular events using specific covariates as predictors.

Reviewer's Comments:

- *It is not clear from the publication what the comparison groups were although there were mentions of comparisons of TZD, rosiglitazone, and pioglitazone use with respect to some reference group. The publication states that, "The resultant reference group was the non-African-American male with type-2 diabetes, younger than 40 years of age, and a non-Baltimore resident with no other recorded comorbidity conditions." The publication does not give a reason for considering this reference group. This would imply that the remaining comparison groups include patients who were either male or female, younger or older than 40 years, and either residents of Baltimore or not.*
- *The publication states that outcomes that occurred less than two weeks following the first TZD prescription were excluded because they would not have been associated with drug effects because of their proximity to the first TZD drug exposure. The cut-off of two weeks was based on the authors' observation of the data. This analysis may lead to biased estimates because the drug effects may be associated with drug exposure even within a short period of time.*
- *The publication states that within each stratum of the propensity scores, difference-in-means of covariates were calculated. Furthermore, "Using a weighted average over the five strata, we conducted repeated tests of a t-statistic of difference-in-means between the treatment groups and each covariate." The more appropriate method to perform is a two-way analysis of variance (ANOVA) model which includes the main effects for propensity score quintile and exposure. The F-test in an ANOVA model can be used to assess not only the main effects but also possible two-way interaction of quintile and exposure. The weighted t-test cannot assess two-way interactions.*
- *The logistic regression analyses models used by the authors did not appropriately condition on propensity score matching.*
- *The study does not adjust for multiplicity when assessing multiple outcomes.*
- *Approximately 51% of the population was African-Americans and therefore may not fully represent the overall US population.*
- *The publication states the following limitations of the study: (1) There was not accurate information to control for severity of disease; (2) There was no accounting for changes in prescribing patterns; and (3) The study did not control for confounding by co-medication bias. As a result, the effect of the TZDs may not be estimated accurately.*

- *The study compared rosiglitazone and pioglitazone, and both as a TZD group, with other oral antidiabetic agents. Rosiglitazone was not directly compared with pioglitazone.*

9. Stockl et al., Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. *Pharmacoepidemiology and Drug Safety*, 18:166-174, 2009

This was a nested case-control study of the association between acute myocardial infarction (AMI) with the use of antidiabetic medications (rosiglitazone, pioglitazone, insulin and other unnamed drugs) in diabetes patients using electronic medical and pharmacy claims data from the Prescription Solutions which is a pharmacy benefits management organization. The study population consisted of 18-84 year old members of a commercial and Medicare Advantage managed care organization in the states of California, Texas, Oklahoma, Oregon, and Washington who received a prescription for an antidiabetic medication or exenatide between January 2002 and June 2006. These patients were followed from the date of the first fill of an oral antidiabetic agent or exenatide during the study period, until the first occurrence of one of the following events: (1) the end of the study (30 June 2006); (2) disenrollment from the health plan; or (3) occurrence of a hospitalization for AMI.

An outcome of AMI was defined as inpatient hospitalization for AMI with primary diagnosis ICD-9 codes of 410.xx. The hospitalization length of stay must have been at least 3 days if the patient was discharged alive and must not have exceeded 180 days. Patients who had the outcome during the study follow-up were considered as cases. Cases were matched with up to four controls based on age (within 2 years) on index date (outcome date), gender, health plan (commercial versus Medicare), geographical state, and diabetes therapy regimen.

Antidiabetic drugs were classified according to the number of medications that overlapped with the outcome date as follows: (1) monotherapy without insulin; (2) dual therapy without insulin; (3) three or more therapies without insulin; (4) insulin therapy; (5) no diabetes medications. Patients were classified according to TZD exposure (at least one prescription of a TZD during the pre-index date period) or no TZD exposure (no prescription of a TZD during the pre-index date period). Exposure was also classified by duration as current (days supply of the last TZD prescription overlapped with index date), recent (days supply of the last TZD prescription before the index date ended between 1 and 60 days before the index date) or remote (days supply of the last TZD prescription before the index date ended more than 60 days before the index date). The primary analysis was based on a comparison between TZD and non-TZD patients using conditional logistic regression, controlling for various covariates. Significant two-way interaction terms were included in the final models. The Hochberg method was applied to adjust for multiple comparisons performed within the final study population. A secondary analysis was performed comparing rosiglitazone and pioglitazone patients.

Reviewer's Comments:

- *The publication did not specify which antidiabetic medications comprised the group of other antidiabetic medications, i.e. other than rosiglitazone, pioglitazone, or insulin.*
- *There was no category for insulin in combination with other antidiabetic medications.*
- *The publication did not explain how the classification of antidiabetic therapies into TZD exposed and TZD unexposed was related to or how it affected the classification by monotherapy, dual therapy, etc. It is not clear whether comparisons were also made between groups of monotherapies, dual-therapies, etc.*
- *The publication stated that*

“To control for differences in cardiovascular risk among study patients, a cardiovascular risk score was determined for each patient. A cardiovascular risk score model was developed using a logistic regression analysis of multiple variables measured during the pre-index period for cases and controls who were not exposed to a TZD. A similar methodology has been used in other studies that evaluate cardiovascular risk in patients exposed to specific medications. The dependent variable was the occurrence of an inpatient hospitalization for acute MI...Regression coefficients from the model were used to calculate a risk score which represents each patient's predicted probability of a hospitalization for an acute MI.”

The publication also cited six references for this analysis method of which one was the primary source. This primary source publication did not cite any statistical references for this analysis method. Therefore, the analysis method performed in the current publication can not be verified and therefore is inappropriate or inaccurate.

- *The sample sizes were relatively low when considering rosiglitazone or pioglitazone use as current, recent or remote. There may not be enough power to detect the effects of each TZD, especially when adjusting for multiple covariates.*
- *The publication states the following limitations in the study: (1) Possible incomplete claims, errors in coding, and other unobservable factors associated with the database; (2) Other risk factors such as ethnicity, family history, etc. were not accounted for in the model; and (3) The sample sizes in the secondary analysis comparing rosiglitazone and pioglitazone may not have been large enough. Therefore, the estimates from the statistical model should be interpreted with caution in light of these limitations.*

10. Tzoulaki et al., Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ, 339: b4731; 2009

This was a retrospective cohort study of the association between myocardial infarction (MI), congestive heart failure (CHF), and all-cause mortality with the use of

antidiabetic treatments (rosiglitazone, pioglitazone, metformin, sulphonylureas, and other oral antidiabetes drugs). The study used the United Kingdom (UK) General Practice Research Database (GPRD) which contains clinical and prescribing data from approximately five million patients. Data for this study spanned the period from January 1, 1990 to December 31, 2005. The cohort comprised all patients 35-90 years old with an episode of care between January 1, 1990 and December 31, 2005 and a diagnostic (Read) code for diabetes. Records with multiple or missing date of death were omitted.

Drug exposures and the primary events of first occurrence of MI, CHF and all-cause mortality were identified using Read codes. The following antidiabetic treatment exposures were identified from prescription records: rosiglitazone monotherapy, rosiglitazone combination therapy (with other antidiabetic drugs), pioglitazone monotherapy, pioglitazone combination therapy, metformin monotherapy, monotherapy with first generation sulphonylureas (acetohexamide, chlorpropamide, tolbutamide, or tolazamide), monotherapy with second generation sulphonylureas (glipizide, glimepiride, glibenclamide, or gliclazide), other oral antidiabetes drugs (e.g., acarbose, nateglinide, repaglinide), and combination therapies excluding thiazolidinediones and insulin.

The authors used the interval of drug treatment as the unit of observation, defined as the period from onset of a drug treatment to onset of the next drug treatment, or until censored or until occurrence of the event of interest. Treatments were compared using Cox regression models with age at diagnosis and calendar year of prescription as stratification factors. The metformin treatment group was used as the reference group. The rosiglitazone and pioglitazone treatment groups were also compared with each other.

Analyses were adjusted sequentially for covariates. Missing values for covariates were imputed using the most recent values dating back to baseline.

The authors performed various sensitivity analyses including an analysis of prescriptions for second generation sulphonylureas, adjustment for cumulative past prescriptions of antidiabetic drugs prescribed from the start of the study period until the beginning of each drug interval, only drug prescriptions after introduction of TZDs into the market, patients aged more than 65 yrs or 65 yrs or less at prescription for oral antidiabetic drugs, sex specific analyses, and subgroup analyses by thirds of duration of diabetes before drug treatment. Covariate interactions in the model were also investigated.

Reviewer's Comments:

- ***The publication states that, because the pioglitazone monotherapy group was small, it was analyzed jointly with the pioglitazone combination group. This can introduce bias in the results for comparisons with pioglitazone given that the exposure effect might differ in a pioglitazone monotherapy regimen compared to a combination regimen.***
- ***The UK GPRD was also used by Azoulay et al., 2009 where they studied incident stroke from January 1, 1988 to June 30, 2008 in diabetic patients who were at least 40 years old. While the endpoints studied differ, use of the same population in more than one observational study should be considered when assessing the overall results among selected observational studies.***

- *There were 28,812 (~31%) patients that had missing values for at least one covariate used in the full model (with all covariates included) and were therefore excluded from the analysis. This is a large amount of missing data that might greatly bias the overall results.*
- *The authors assess the proportional hazards assumption for the Cox model by testing for a non-zero slope of the scaled Schoenfeld residuals and found no evidence of violation. This assessment cannot be verified without patient-level data.*
- *The Cox model assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified.*
- *Results are likely confounded by time given that the TZDs were not approved for use until 1999; however, this study evaluated data from 1990 through 2005.*
- *Read, and not ICD-9 codes, were used to identify exposures and outcomes; however, the validity of the codes is not described. It is unclear how these codes compare with existing, validated, ICD-9 codes for the same outcomes.*
- *Results based on multiple comparisons are presented in this publication with no discussion regarding multiplicity. Assessment of p-values alone is inappropriate given the number of tests performed.*
- *The interval of drug exposure approach used in this study is potentially flawed as it relied only on information from prescription records, which might lack detail necessary to differentiate repeat prescriptions for patients on a combination regimen. For example, a patient taking metformin plus sulfonylurea, which are usually not prescribed together, may have been defined as metformin or sulfonylurea monotherapy. This approach highlights one of the many limitations in obtaining drug exposure from a prescription claims database.*
- *Some of the authors have affiliations with GSK (e.g. co-funded grants, and consultancy fees), which might lead to potential publication bias.*

11. Vanasse et al., Stroke and cardiovascular morbidity and mortality associated with rosiglitazone use in elderly diabetic patients. Diabetes & Vascular Disease Research, 6(2) 87-93; 2009

This was a nested case-control study of the association between death, acute myocardial infarction (AMI), congestive heart failure (CHF) and stroke with the use of antidiabetic medications (rosiglitazone, pioglitazone, metformin, sulfonylureas, and insulin) in diabetes patients using Quebec databases (provincial hospital discharge register (MED-ECHO) and provincial demographic database). The databases were linked using unique encrypted identifiers.

The study population included diabetes patients 65 years or older living in Quebec between January 2001 and December 2002. Diabetes patients were identified in administrative data records as individuals who were hospitalized with a diagnosis of diabetes (ICD-9 code 250) with either one of the 16 diabetes-related diagnosis codes (MED-ECHO register) or had at least two physician claims within two years with the diagnostic code of diabetes. Patients who died during hospitalization were excluded from

the cohort. Data were collected out to 2004 to allow for a 2-year follow-up to collect data and causes of hospitalizations.

The outcomes were all-cause death, cardiovascular death (ICD-10 codes I20-I25, I44-I52), hospitalization for acute MI (ICD-9 code 410), hospitalization for CHF (ICD-9 code 428), and hospitalization for stroke (ICD-9 codes 430-438) occurring anytime within two years after cohort entry. For each outcome, patients who had the outcome during the study follow-up were considered as cases. Cases were matched with twenty controls based on age (within 5 years), gender and date of cohort entry (within 30 days).

The study considered patients who claimed a prescription at a pharmacy to be exposed to the drug for the length of time of the prescription.

The risks of the outcomes were assessed using conditional logistic regression, adjusting for covariates. Co-morbidities were identified as the presence or absence of a hospitalization with a diagnosis based on ICD-9 code. Comparisons of risks were made between rosiglitazone versus non-TZD (neither rosiglitazone nor pioglitazone). Exposure to pioglitazone, metformin, sulfonylureas and insulin were used as covariates in the statistical model.

Reviewer's Comments:

- *Although additional power can be gained by increasing the number of controls, including more than four controls for each case does not substantially increase the power. Therefore, a 1:20 matching of cases to controls does not provide additional statistical efficiency.*
- *The publication states that, "We used a retrospective population-based cohort study with a nested case-control analysis". This is more generally considered a retrospective nested cases-control study.*
- *The publication states that that a conditional logistic regression model was used to estimate the hazard ratios for the outcome events associated with the current use of rosiglitazone. It is unclear what was meant by the authors since the conditional logistic regression estimates the odds ratio and not the hazard ratio.*
- *The study states that the comparison was with current use of rosiglitazone as compared with non-TZD (neither rosiglitazone nor pioglitazone) users during follow-up and that all models were adjusted for co-morbidities and exposure to pioglitazone, metformin, sulfonylureas, insulin, ACE inhibitors and statins. It is not clear why the study adjusted for metformin, sulfonylureas, and insulin when these antidiabetic agents were all included in the assessment of exposure (the non-TZDs). The methods used in the analyses seem incorrect; however, without more information it is impossible to verify which variables were used in the models.*
- *The study does not distinguish between patients who may or may not have used multiple antidiabetic therapies during the study period.*
- *The study does not adjust for multiplicity when assessing multiple outcomes.*
- *The study does not directly compare rosiglitazone to pioglitazone, therefore adjusted estimates can not be determined based on the information provided.*
- *The population studied comprises patients aged 65 or older residing in Quebec, Canada. Therefore, the results reported in the publication cannot be generalized to a population of patients below 65 years of age. In addition, results might not be*

fully generalizable to non-Canadian population given varying baseline characteristics and differences in access to care.

- *The publication states that a limitation of the study was the assumption that patients were compliant to rosiglitazone for the time specified by the prescription. This is a major assumption given that compliance is a function of pill burden, patient characteristics, tolerability, etc., which were not considered in this assumption.*
- *All co-morbidities considered as variables in the models were assessed via hospitalization ICD-9 code. Therefore, it is possible that some co-morbid conditions, not included in discharge coding, were missed.*
- *All comparisons are TZD v. non-TZD where the non-TZD consists of various other antidiabetic agents and cardio-protective drugs such as aspirin, ACE inhibitors and statins. This pooling of all non-TZD agents of various types is inappropriate since it creates a heterogeneous comparison group for which results are uninterpretable.*

12. Ziyadeh et al., 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

This was a retrospective cohort study of the association between myocardial infarction (MI) and coronary revascularization (CR) with the use of rosiglitazone, and pioglitazone in diabetes patients. The study used a proprietary integrated research database of health insurance plan members who have both medical and prescription drug benefits. Data for this study spanned the period from July 1, 2000 to March 31, 2007 and included complete health services utilization information on approximately 14 million people in 25 states across the US. The study cohort comprised initiators of rosiglitazone or pioglitazone from July 1, 2000 through March 31, 2007, for whom the first dispensing record followed ≥ 6 months of health plan membership and who were at least 18 years of age. Patients who received troglitazone before either rosiglitazone or pioglitazone were excluded. The follow-up period started on the first day that the TZD was dispensed and ended either at the end of study (March 31, 2007), termination of healthcare plan, or modification or discontinuation of specific treatment regimen.

Outcomes were compared within three treatment regimen groups of antidiabetic agent initiators: monotherapy (rosiglitazone or pioglitazone), dual therapy (rosiglitazone or pioglitazone plus metformin, sulfonylurea, acarbose, miglitol, repaglinide, nateglinide, pramlintide, exenatide, or sitagliptin within 30 days of one another), and therapy with concomitant insulin (rosiglitazone or pioglitazone plus insulin).

The outcomes assessed were MI, CR and sudden death. For each cohort member, the earliest occurrence of each outcome of interest during follow-up was determined. MI cases were identified as primary hospital discharge diagnosis of acute MI using ICD-9 codes (410.xx). CR cases were identified as hospitalizations during which there was an ICD-9 code (36.xx) for "coronary revascularization". Death was identified in patients who met all of the following conditions: (1) a diagnosis code of MI or sudden death or a service code for ambulance services, intubation, or resuscitation; (2) no claims for medical services > 3 days after the date of the latest claim; and (3) in the absence of

diagnostic codes for sudden death or MI, there were no diagnoses for other potentially fatal non-cardiac conditions within the 30 days before presumed death. Composite outcomes of MI or CR and MI or CR or death were assessed.

The authors employed a 1:1 propensity score matching of rosiglitazone and pioglitazone users within each of the three treatment regimen groups (monotherapy, dual therapy, and therapy with insulin). The propensity scores were estimated using a logistic regression model, adjusting for potential confounders and interactions with calendar era (2000-2002, 2003-2004, and 2005-2007). Individuals were matched using a greedy matching algorithm, matching within a pre-specified maximum caliper of 0.1. The Cox proportional hazards model (Cox model) was used to estimate the risks for the outcomes among rosiglitazone versus pioglitazone users, with therapeutic regimen as stratification factor and rosiglitazone (versus pioglitazone) as predictor. The regimen switch (addition of any antidiabetic agent) and stop dates were the censoring dates. Kaplan-Meier curves were obtained for the outcomes MI and MI/CR and were compared using the log-rank test.

Reviewer's Comments:

- *The publication states that the proprietary database used in the study was accessed by i3 Drug Safety (Waltham, MA). Four of the five authors of the publication are affiliated with i3 Drug Safety. The credibility and validity of the database is unknown to the reviewer.*
- *In the dual therapy treatment regimen group, the agents were rosiglitazone or pioglitazone plus one of nine other non-TZD agents. The effects of each treatment regimen (e.g. rosiglitazone+metformin versus pioglitazone+sulfonylurea) may be different and hence the comparisons may be inappropriate.*
- *The publication states that the conditions used in the definition for sudden death were based on previous research in which the results of a National Death Index search were compared with insurance claims data citing Enger et al., 2002 as a reference. However, these conditions do not appear to have been previously validated.*
- *The publication reports that a total of 56,186 eligible rosiglitazone initiators and 51,109 pioglitazone initiators were identified and 47,501 users of each TZD were selected and grouped into matched cohorts based on propensity scores. However, the publication does not explain the exclusion of those patients not counted among the 47,501 for each TZD group.*
- *The authors claim that the cohorts generated by the propensity score matching process were balanced in terms of the patient demographic characteristics, frequencies of cardiovascular disease diagnoses, and prescription drug use during the baseline period. However, the publication does not provide the results of statistical comparisons between cohorts such as t-test for continuous covariates and/or chi-square test for categorical covariates, which is generally presented to support matching on propensity scores. The conclusion that matched data were balanced is not supported by statistical evidence.*

- *The publication states that, “Almost 76% of the TZD initiators received the drug as monotherapy, either as a switch from other oral antidiabetic agents or as the first antidiabetic drug”. The publication does not report summary statistics for the number of initiators who switched from other oral antidiabetes agents to TZDs or the number of first time TZD initiators. Therefore, it is unknown whether the rosiglitazone and pioglitazone cohorts were balanced with respect to prior therapy or first therapy. Furthermore, for the initiators who switched from other oral antidiabetes agents to TZDs, the study does not account for exposure duration of the non-TZD agents. This could be a source of bias in the study results.*
- *The study does not explain why a caliper of 0.1 was used over other numerical values. The recommended caliper is a quarter of the standard deviation of the logit of the propensity score. It is not clear if the standard deviation of the logit was considered in the choice of 0.1.*
- *The publication states the following study limitations: (1) The actual consumption of medication by the patient had to be inferred from the data available (2) There was no attempt to verify claims for diagnoses and procedures. Both limitations greatly decrease the overall validity of any findings of association since both pertain directly to assessment of exposure and outcome respectively.*
- *Several comparisons were performed in this publication for several endpoints; however the authors do not address the issues of increased type-I error, i.e. no adjustments for multiplicity were performed.*
- *One of the authors is an employee of GSK and holds GSK stock shares. This relationship might introduce publication bias.*

13. Koro et al., An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiology and Drug Safety, 17:989-996; 2008

This was a nested case-control study of the association between myocardial infarction (MI) with the use of rosiglitazone, pioglitazone, and other antidiabetic medications in type 2 diabetes patients using the Integrated Healthcare Information Services (IHCIS) healthcare claims database. This database contains inpatient and outpatient and pharmacy claims, lab results, and enrollment information on over 41.5 million patients from over 35 different healthcare plans from 1997 to 2006 and is representative of the non-elderly, insurance-carrying population in the US.

The study population included type 2 diabetes patients with at least one prescription claim and at least one year of enrollment in the healthcare plan during their follow-up time available in the database. Subjects with a history of MI prior to their diabetes diagnosis were excluded from the analysis but those with heart failure or ischemic heart disease (other than MI e.g. angina, chest pain) were not excluded.

Incidence cases were defined by ICD-9 code (410.xx) for MI hospitalization at least three months after diabetes diagnosis. Index date was defined as date of MI hospitalization. Cases were matched to three controls based on age (± 5 years), gender, and year of first diabetes diagnosis.

Patients were classified according to their antidiabetic drug exposure, based on pharmacy claims, in the past three months prior to the index date. Other exposures windows of <6 months, 6-12 months, and >12 months were also assessed. Antidiabetic drugs were categorized according to: all antidiabetic therapy (oral and/or insulin) excluding all TZDs, rosiglitazone (as mono-therapy or in combination with other antidiabetic drugs), pioglitazone (as mono-therapy or in combination with other antidiabetic drugs), rosiglitazone and pioglitazone, and no antidiabetic therapy.

Total follow-up time for cases was defined as the length of time between subject's diabetes diagnosis and the MI diagnosis date (index date). Follow-up time for controls was the time between the subject's diabetes diagnosis and the index date to the case in which the control was matched. Unadjusted incidence rates for MI were calculated as the number of patients who developed MI divided by the total person-year of follow-up. Comparisons were made between drug categories with antidiabetic therapy excluding all TZDs as the reference group. The effect of antidiabetic drug use on the risk of MI was modeled using conditional logistic regression, adjusting for various risk factors/covariates including the matching variables.

Reviewer's Comments:

- *The study only considers MI cases occurring at least three months after diabetes diagnosis and does not provide a reason for justification for this time minimum. Diagnosis of diabetes might vary depending on access to care and other factors. Therefore, this arbitrary cut-off might excluded cases artificially thus biasing the results.*
- *Although the conditional logistic regression model adjusted for coronary artery disease (unstable angina, coronary revascularization, coronary heart disease, and congestive heart failure) as a covariate, it is not clear if heart failure or ischemic heart disease were included in definition of CAD. If not included, then these two diseases were not adjusted for in the model.*
- *The rosiglitazone and pioglitazone groups used in the comparison against reference included mono-therapy or combination therapies. A separate analysis or breakdown by monotherapy and combination therapy was not provided. It is therefore difficult to interpret the odds ratio estimates comparing rosiglitazone and pioglitazone to reference since the groups consists of different combinations of regimens.*
- *The publication does not mention whether there were any missing covariate data and the amount of missing exposure data.*
- *There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
- *The publication states the following study limitations: (1) Antidiabetic drug exposure was inferred from prescription claims. While the medication was dispensed, it is not possible to determine whether patients actually consumed the prescribed medication. (2) Other important predictors of MI such as BMI, smoking status, and duration of diabetes were not adjusted for in the statistical model as they were not available in the database. Both limitations weaken any claims of*

association between exposure and outcome given uncertainties in amount of exposure and lack of controlling for key confounders.

- *The analysis fails to account for patients who died prior to having an MI that led to hospitalization.*
- *For subjects who received rosiglitazone or pioglitazone, odds ratios of MI were presented by different exposure categories (i.e. <6 months, 6-12 months, >12 months) where exposure is categorized based on time prior to index date. There are two issues with this analysis. First, a patient could be a case in one category (e.g. <6 months) and not a case in another (e.g. 6-12 months). Therefore, the categories are not mutually exclusive and thus it is inappropriate to consider trends within a drug group. Second, only exposure in the TZD group, and not the reference group, were categorized into these three groups. A three-month window was used to assess exposure in the non-TZD; however, longer exposures were considered in the TZD groups. Therefore, it is possible that there is a bias against the TZD group due to longer exposure times considered for these groups compared to reference.*
- *All authors are employees of GSK, which could lead to potential publication bias.*

14. Margolis et al., Association between serious ischemic cardiac outcomes and medications used to treat diabetes. *Pharmacoepidemiology and Drug Safety*, 17:753-759; 2008

This was a retrospective cohort study of the association between serious atherosclerotic vascular disease of the heart (myocardial infarction (MI), unstable angina, cardiac death, and coronary reperfusion procedures (CARP)) with the use of antidiabetic treatments (rosiglitazone, pioglitazone, metformin, sulfonylureas, and meglitinides). The study used The Health Information Network (THIN) database which contains medical diagnoses and prescription medication information for approximately 2.3 million active patients in approximately 300 United Kingdom (UK) practices. Data for this study spanned the period from January 1, 2002 to 2006. The study population comprised patients with at least two records for diabetes during the study period and who were at least 40 years old.

The primary exposure variable was a British National Formulary (BNF) code for rosiglitazone, pioglitazone, metformin, sulfonylureas (chlorpropamide, glipizide, tolbutamine, etc.), meglitinides (nateglinide and rapaglinide) or insulin.

The primary outcome was the onset of any serious atherosclerotic vascular disease of the heart (MI, unstable angina, cardiac death, and CARP) after the first date of exposure to each of the medications of interest between January 2002 and 2006. CARP included closed (e.g. angioplasty) and open (e.g. coronary artery bypass) procedures. Outcomes were evaluated based on the length of exposure to each therapy. A sub-analysis was also performed with MI as the only outcome.

There were two cohorts considered in the analysis: (1) All diabetes patients, including those who may have been diagnosed with diabetes at any time since they had been enrolled and followed by the general practitioners, including before 2002 and (2) All diabetes patients who were diagnosed and treated after January 2002.

Each drug group was compared with a reference group (those who did not use the drug of interest) with respect to the outcome using proportional hazards regression. A direct comparison between rosiglitazone and pioglitazone was also performed. The fit of the models were assessed using visual inspection of the Cox-Snell residuals and the graphical display of hazard rates over time. The estimates were confirmed using Poisson regression. Confounding variables were included in the model to yield adjusted estimates of risks.

Reviewer's Comments:

- *No justification was provided for the minimum age cut-off of 40 years.*
- *The publication lacks in providing details regarding outcome assessment. As such, the validity of the outcomes is questionable.*
- *In this publication, an individual may have had exposure to more than one medication. Thus, individuals may have appeared in more than one drug group and therefore were included in more than one comparison. This likely lead to bias in the analysis as some patients possibly had cumulative treatment effects due to prior drug therapies. In addition, since the same patient might have appeared in more than one comparison group, assessments across comparisons should be done with caution.*
- *In the comparisons of drug groups versus the respective groups without the drug of interest, the latter groups included other antidiabetic agents other than the drug of interest. A concern with this approach is that the latter groups may have varying distributions of other antidiabetic agents. There is no common reference group in this study because each group without the drug of interest in each comparison varies from one comparison to another. It is therefore impossible to make relative comparisons of rosiglitazone versus pioglitazone.*
- *Although the publication claims to have assessed the fit of the models including a confirmation of the estimates using Poisson regression, the results of the diagnostics were not reported. It is therefore still unclear whether the model was a good fit of the data.*
- *The study does not adjust for multiplicity when assessing multiple outcomes.*
- *The publication does not mention whether there were any missing covariate data and the amount of missing data on outcome assessment.*
- *Read, and not ICD-9, codes were used to assess exposure and outcome. It is unclear how these codes compare with existing, validated, ICD-9 codes for the same outcomes.*
- *There were seven groups of drugs considered resulting in seven different comparisons of a drug group vs. all others without any adjustments for multiple comparisons. Results should be interpreted with caution as there was not pre-specified primary comparison but rather all possible comparisons were considered.*
- *One of the authors is involved in a sponsored research agreement with Takeda Pharmaceutical through the trustees of the University of Pennsylvania. This may introduce potential for publication bias.*
- *The primary outcome included any atherosclerotic vascular disease of the heart after the first date of exposure to the medication of interest. This definition does*

not require a minimum duration of exposure and therefore may overestimate the true event rate by capturing events that occurred early and likely unrelated to exposure. That is, the presence of confounding by indication might exist given this definition for outcome.

15. Walker et al., Coronary heart disease outcomes in patients receiving antidiabetic agents in the Pharmedics database 2000-2007. *Pharmacoepidemiology and Drug Safety*, 17:760-768; 2008

This was a retrospective cohort study of the association between myocardial infarction (MI) and coronary revascularization (CR) and the use of rosiglitazone, pioglitazone, metformin and sulfonylurea in diabetes patients. The study used the PharMetrics database which contains insurance claims information from over 80 US health plans. Available data include paid claims for medical services, drugs and facility costs, linked by common patient identifiers and spanned the period from July 2000 to March 2007.

All users of rosiglitazone, pioglitazone, metformin and sulfonylurea for whom the first recorded dispensed followed at least six months membership in a plan and the member's 18th birthday were identified.

Outcomes were compared within three study groups of antidiabetic agent initiators: monotherapy (rosiglitazone, pioglitazone, metformin, or a sulfonylurea), dual therapy (rosiglitazone plus metformin, rosiglitazone plus sulfonylurea, pioglitazone plus metformin, pioglitazone plus sulfonylurea, or metformin plus sulfonylurea), and therapy combined with insulin (rosiglitazone, pioglitazone, metformin, sulfonylurea, or other antidiabetic drugs in combination with insulin). New cases of MI were identified as hospitalizations with a primary discharge diagnosis (position one on the UB-92 hospitalization record) of MI and new events of CR as hospitalizations bearing procedure codes for CR (coronary artery bypass grafts and percutaneous coronary intervention, whether elective or emergent).

The main comparisons of interest were rosiglitazone versus pioglitazone given as monotherapy, dual therapy with either metformin or sulfonylurea or in combination with insulin. For each group in the comparisons, the individual propensity scores were estimated via logistic regression models adjusting for predictor variables (calendar era of therapy initiation, baseline covariates, and two-way interactions between calendar time and baseline covariates). The propensity scores were sorted and the middle 90% were divided into ten equal size strata. The ten strata were then used in stratified proportional hazards regression models with drug regimen as the only predictor and MI, CR, composite of MI and CR as outcomes. The models were performed for on-treatment time, which was censored at the earliest time of an outcome or end of treatment, and for total observation time, which was censored at the earliest time of an outcome or end of cohort follow-up. Summaries for rosiglitazone versus pioglitazone comparisons were given within dual therapy and then overall across the three treatment groups (monotherapy, dual therapy and in combination with insulin).

Reviewer's Comments:

- *The PharMetrics database was also studied by Rajagopalan et al., 2004 (Item 1 above). The differences between Rajagopalan et al., 2004 (R) and Walker et al., 2008 (W) studies are as follows: (1) R studied congestive heart failure (CHF) while W studied MI and CR (2) R studied pioglitazone versus insulin use while W studied rosiglitazone, pioglitazone, metformin and sulfonylurea, in monotherapy, dual therapy, and therapy combined with insulin (3) R considered the exposure period from 1/99-12/01 while W considered 7/00-3/07. Thus, there is a one-year overlap between the populations in the two studies (4) R was a case-control study while W was a cohort study.*
- *Non-study oral antidiabetic medications (acarbose, repaglinide, miglitol, nateglinide, pramlintide acetate, and exenatide) were included in the baseline covariates for the mono- and dual-therapy study groups and were included in the cohort definitions for the combination with insulin study group. The publication did not provide summary statistics for these non-study oral antidiabetic medications which could potentially lead to an imbalance between the treatment groups within the combination with insulin study group.*
- *The publication states that in the combination-with-insulin study group, the starting point of observation for this cohort was the day following the initiation of insulin if patients were already using an oral antidiabetic agent. Patients on prior insulin therapy were included as of the day following the date that an oral agent was added. The two groups of patients described are different and should be analyzed separately. It may matter which drug was administered first and the exposure durations to the first therapy administered is unknown.*
- *The publication states that after the individual propensity scores were sorted, only the middle 90% were used in the stratified analysis and the upper and lower 5% were set aside. The publication does not include a justification for the exclusion of these propensity scores. Therefore, the results of the analysis may be biased due to the omission of data. In addition, the methods included dividing the middle 90% of propensity scores into 10 equally sized strata. This level of stratification is not justified in the publication. Note: A more common approach is to group propensity scores into quartiles. Furthermore, the study does not perform a two-way analysis of variance analysis to determine whether balance was achieved after stratification of propensity score for each covariate over each comparison exposure group.*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. The publication does not provide a discussion on whether this assumption was met.*
- *The Cox model also assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified.*
- *The publication states that the summaries across the treatment groups were weighted averages of the estimated regression coefficients, the weights being the inverse of the variance of the estimates. The variance of the weighted average was the inverse of the sum of the weights. The publication does not cite any references*

or provide any rationale for this statistical procedure. The summary comparisons provided in Table 4 of the publication are therefore difficult to interpret. In addition, these summary comparisons provide no information specific to comparison between specific treatment regimens.

- The publication does not mention whether there were any missing covariate data and the amount of missing outcome data.*
- The validity of the approach used to identify the MI outcome based on the UB-92 hospitalization record was not described and the authors note that no attempts to verify the claims diagnoses were made. Similarly, it is not clear if the approach used to identify new events of CR based on procedure codes is valid. Use of non-validated approaches for outcome identification might lead to under or over-estimates of the association between exposure and outcome.*
- The PharMetrics database comprises data mostly from patients less than 65 years of age and therefore generalizing these findings to an older population is not feasible.*
- Several comparisons were performed in this publication for various endpoints; however the authors do not address the issues of increased type-I error, i.e. no adjustments for multiplicity were performed.*
- The publication states that, "This work was supported by a research contract between GlaxoSmithKline and Ingenix., Inc." Furthermore, one of the authors, Alexander Walker, was a former employee of i3 Drug Safety and another author, Carol Koro, is an employee of GSK. There may be a potential publication bias associated with these relationships and funding source.*

16. Winkelmayr et al., Comparison of Cardiovascular Outcomes in Elderly Patients With Diabetes Who Initiated Rosiglitazone vs Pioglitazone Therapy. Arch Intern Med, 168(21): 2368-2375; 2008

This was a retrospective cohort study of the association between all-cause mortality (primary outcome), myocardial infarction (MI), stroke (ischemic or hemorrhagic), and hospitalization for congestive heart failure (CHF), and the use of rosiglitazone and pioglitazone in patients with type 2 diabetes. The primary data source was medical claims from the New Jersey Pharmaceutical Assistance for the Aged and Disabled program and the Pennsylvania Pharmaceutical Assistance Contract for the Elderly program. Data from January 1, 1999 through December 31, 2005 were used in the analyses.

Prescription data were used to identify all patients who filled a prescription for any TZD. The index prescription claim was identified based on the earlier TZD claims requiring that at least one claim for any prescription be present both in the 6 months prior to and in more than 6 months prior to that index claim to ensure that the index claim represented new TZD use. Patients with prior use of other antidiabetic medications were included; however, prior use with troglitazone and subjects who initiated TZD using a fixed-dose combination with metformin were excluded. Patients 65 years or younger on the index date were excluded. The main analysis considered patients to be exposed until 60 days after the date on which the supply from their most recently filled prescription

expired or until a prescription for the other TZD indicated exposure crossover at which point patients were censored.

Secondary endpoints of MI, stroke, and hospitalization for CHF were each obtained from Medicare claims based on previously validated algorithms.

The authors performed time-to-event analyses for all outcomes evaluated using the Cox proportional hazards model (Cox model) adjusting for baseline covariates. Crude and adjusted incidence rate ratios and 95% confidence intervals were obtained from the models that blocked for state and calendar year.

Reviewer's Comments:

- *It is not very clear from the publication whether the rosiglitazone and pioglitazone groups were considered in mono or combination regimens. If other antidiabetic agents were also administered, then the comparison may be biased because the distribution of these agents may not necessarily be the same in the two groups.*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. The authors claimed to have searched for violations in the proportionality assumptions by testing for significance of interaction terms with time. However, the authors do not provide the results of the search and the test. Therefore it is still unclear if the Cox model was justified in the analysis of the data.*
- *The Cox model also assumes linearity of the log hazard function and the covariates. The publication does not discuss if the functional form was correctly specified.*
- *The publication does not mention whether there were any missing covariate data or the amount of missing outcome data.*
- *The population studied comprised patients aged 65 and older receiving Medicare service in either New Jersey or Pennsylvania. Therefore, the results cannot be generalized to a population of patients below 65 years of age. Also, the population studied may not entirely represent all persons over 65 years in the United States.*
- *Multiple comparisons for several endpoints were performed without adjustments for multiplicity. Therefore, some caution should be used when interpreting individual 95% confidence intervals.*
- *The first author received a grant from GSK and the last author received salary support from GSK in the past 3 years (from 2008). These relationships might lead to potential publication bias.*
- *The authors report a greater rate of mortality and CHF among patients who initiated therapy with rosiglitazone compared to pioglitazone after adjustment for a large number of covariates. The fact that many variables are included in these models must be accounted for when interpreting the overall findings.*

17. Gerrits et al., A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. *Pharmacoepidemiology and Drug Safety*, 16:1065-1071; 2007

This was a retrospective cohort study of the association between acute myocardial infarction (AMI) (primary outcome) and coronary revascularization (CR) with the use of rosiglitazone and pioglitazone. The study used the Ingenix Research Database, a research repository of healthcare claims including insurance eligibility, pharmacy claims, medical claims, hospital claims, laboratory encounters and laboratory results. The database was extracted from the operating systems of a large US health plan covering subscribers from across 50 states capturing information for approximately 25 million lives. Data for this study spanned the period from 2003 to 2006 and included patients with an ICD-9 diagnostic code of 250.xx for diabetes and who initiated therapy with pioglitazone or rosiglitazone between 2003 and 2006. Index date was based on first dispensing of either TZD. The follow-up period began at the index date and ended upon disenrollment from the health care plan (including death), occurrence of a hospitalization for the endpoints of interest or end of study, whichever came first.

The primary outcome of interest, AMI, was identified by ICD-9 codes for hospitalization for acute MI. CR was also identified by ICD-9 codes and used together with acute MI as a composite endpoint in a secondary analysis. Rosiglitazone therapy was compared with pioglitazone using a multivariate Cox proportional hazards regression model, adjusting for various covariates.

Reviewer's Comments:

- *The publication states that patients who were dispensed both rosiglitazone and pioglitazone during the follow-up period were excluded from the study cohort. However, the publication does not mention the number of patients excluded. A sensitivity analysis could have been done by including these patients in the study cohort but considering only the follow-up from the initial prescription of the first drug up until the prescription of the second drug.*
- *The study also excluded 15,397 patients with gaps in their insurance coverage between the index date (first dispensing of rosiglitazone or pioglitazone) and end of the observation period. It is not clear what the publication means by gaps in insurance coverage.*
- *The Ingenix Research Database was also studied by McAfee et al. (2007) in a retrospective cohort study of the risk of MI and CR associated with the use of rosiglitazone, metformin, sulfonylureas and insulin from July 1, 2000 to December 31, 2004. The overlap in study period and assessment of the same outcome (i.e. MI) must be accounted for when summarizing results across studies as these studies do not consist of mutually exclusive data.*
- *Although exposure to other non-TZD drugs (e.g. metformin, sulfonylureas) were adjusted for in the Cox model, individuals may have had varying degrees and duration of exposure to multiple antidiabetic therapies. The inability to account for duration of concomitant therapy may lead to failure to control for these confounders. .*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. The publication does not provide a discussion if this assumption was violated.*

- *The Cox model also assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified.*
- *The publication does not mention whether there were any missing covariate data or the amount of missing outcome data.*
- *Mortality by treatment groups was not presented in the paper. Therefore, it is unclear if these patients were censored or treated as outcomes in the analyses.*
- *All the authors were employees of Takeda at the completion of the study. This might lead to potential publication bias.*

18. Lipscombe et al., Thiazolidinediones and Cardiovascular Outcomes in Older Patients With Diabetes. JAMA, vol 298, no 22; 2007

This was a nested case-control study of the association between congestive heart failure (CHF) (primary outcome), acute myocardial infarction (AMI), and all-cause mortality with the use of antidiabetic medications (rosiglitazone, pioglitazone, metformin, sulfonylureas, and other oral agents (meglitinides or acarbose)) in diabetes patients using Ontario healthcare databases (Ontario Drug Benefit, National Ambulatory Care Reporting System, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan, Registered Persons Database, Ontario Diabetes Database). The databases were linked anonymously using encrypted health card numbers.

The study population included diabetes patients 66 years or older who were identified from the Ontario Diabetes Database and who were dispensed at least one oral hypoglycemic drug between April 1, 2002 to March 31, 2005. Entry into the cohort was based on first prescription for the oral antidiabetic agent. Patients who received insulin in the year preceding cohort entry were omitted to attempt to exclude more advance diabetic patients and type I diabetic patients. Patients who later initiated insulin after cohort entry remained in the cohort.

The primary outcome was a first hospital visit for CHF, defined as either an emergency department visit for CHF or a hospital admission with a discharge diagnosis of CHF (ICD-10 code 150). The secondary outcomes were hospital visit for AMI (defined as either an emergency department visit for acute MI or hospitalization with a discharge diagnosis of AMI (ICD-10 codes 121, 124, and 125.4)) and all-cause mortality (identified using the Registered Persons Database and the hospital discharge abstract database). For each outcome (CHF, AMI, and all-cause mortality), cases were defined as all individuals from the cohort who had an event during their follow-up period. The follow-up period was from date of cohort entry until the event was reached, a last health service contact in Ontario (for those losing contact for more than 6 months) or March 31, 2006, whichever came first.

For each case, up to five controls were randomly matched based on age (± 1 year), sex, diabetes duration (< 2 years, 2-5 years, or ≥ 5 years), and history of cardiovascular disease within five years of cohort entry. In the CHF and AMI analyses, controls were also matched on history of an event (within 1 year of cohort entry and within 1-5 years).

Antidiabetic drugs were identified from the Ontario Drug Benefit program and were classified into six mutually exclusive groups: (1) TZD monotherapy (subdivided into rosiglitazone and pioglitazone); (2) other oral hypoglycemic monotherapy (metformin, sulfonylurea, acarbose, or a meglitinide); (3) TZD combination therapy (TZD and at least one other agent); (4) other oral hypoglycemic agent combination (two or more non-TZD agents); (5) insulin monotherapy; and (6) insulin combination therapy. Thiazolidinedione monotherapy was considered the primary exposure of interest while other oral hypoglycemic agent combination therapy was considered the reference group.

In the primary analysis, using the most proximate prescription before the index date, patients were characterized as current users if use encompassed the index date, past user if the last prescription ended in the 15 to 365 days prior to the index date, or non-users if there were no hypoglycemic prescriptions in the year preceding the index date. The risks of the outcomes were assessed using conditional logistic regression, adjusting for covariates.

Reviewer's Comments:

- *The publication states that, “We conducted a population-based, retrospective cohort study that was analyzed using a nested case-control approach”. This is more generally considered a retrospective nested case-control study.*
- *The publication defines past users as those whose last prescription ended in the 15 to 365 days preceding their index date (time of outcome). The publication does not provide a rationale for using 15 days as a cut-off.*
- *The TZD combination therapy group includes TZD and at least 1 other agent. Because the distribution of the other agents in each of the rosiglitazone and pioglitazone groups are likely different, a comparison of these groups to a reference group (Other OHA Combination Therapies) may be biased.*
- *The publication states the following in calculating the estimated absolute risk:*

“To estimate the absolute risk associated with TZDs for CHF, AMI, and death, we first calculated the event rates over four years for all cohort patients who were alive and remained in Ontario until the end of the study period. We applied the RR estimates for TZD treatment from the nested case-control analysis to the baseline event rates in the cohort population to estimate the number needed to harm for AMI, CHF, and death. Although these RRs were calculated based on comparison with the non-TZD combination therapy users, we assumed that their event rates were at least as high as for the entire cohort.”

The assumption that the event rates for the non-TZD combination therapy users were as high as for the entire cohort is a strong assumption that could significantly effect the estimate for number needed to harm, especially because the latter is very sensitive to round-off error. Furthermore, the estimates for the confidence intervals cannot be calculated directly in the same way as estimation of the point estimate. Therefore, the study's estimate for number needed to harm may be inaccurate.

- *Tables 3 and 4 show that the numbers of pioglitazone cases for current TZD monotherapy were 16 and 12, respectively. These numbers are very small and may result in the statistical model not having sufficient power to detect the true odds ratios.*
- *The population studied comprises patients aged 66 or older in Ontario, Canada. Therefore, the results reported in the publication cannot be generalized to a population of patients below 66 years of age. In addition, results might not be fully generalizable to non-Canadian population given varying baseline characteristics and differences in access to care.*
- *There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
- *It does not appear that the variables used to match controls to cases were included in adjusted models.*

19. McAfee et al., Coronary heart disease outcomes in patients receiving antidiabetic agents. *Pharmacoepidemiology and Drug Safety*, 16:711-725; 2007

This was a retrospective cohort study of the association between myocardial infarction (MI) and coronary revascularization (CR) with the use of antidiabetic treatments (rosiglitazone, metformin, sulfonylureas, other oral antidiabetes drugs and insulin). The study used the Ingenix Research Database, a proprietary research database of commercial enrollees who have both medical and prescription benefit coverage in a US managed care organization. Data for this study spanned the period from July 1, 2000 to December 31, 2004 and included patients 18 years or older who have at least six months membership in a participating plan prior to the first recorded antidiabetic drug dispensing.

The study considered three groups of therapies: monotherapy (rosiglitazone, metformin, or sulfonylurea), dual therapy (rosiglitazone + metformin, rosiglitazone + sulfonylurea, or metformin + sulfonylurea), and combination with insulin (rosiglitazone + insulin or other oral antidiabetic agents + insulin). All therapy groups containing rosiglitazone were also combined and compared with the remaining non-rosiglitazone therapy groups. The follow-up period began on the day following dispensing of the qualifying drug and ended on the occurrence of dispensing of a different study drug or insulin for the monotherapy or dual-therapy groups (at which time the subject became eligible for another drug group), June 30, 2005, termination of health plan, or date of the outcome of interest. Cessation of study drug alone was not sufficient to end follow-up.

Outcomes were identified using primary discharge diagnosis for hospitalization (ICD-9 code 410.xx) for MI and hospitalization bearing procedure codes for CR. A composite outcome (MI and/or CR) was also studied. The date of hospitalization for the first outcome was set as the date of the outcome.

The authors used propensity score matching to attempt to balance the known baseline predictors. Matched triplets were created for the monotherapy and dual-therapy groups. The matched triplets for the single drug cohorts were defined by separately modeling the probability of dispensing for metformin and sulfonylureas among initiators of those drugs plus initiators of rosiglitazone, and matching subjects whose propensities

on both dimensions (metformin and sulfonylureas) lay within a caliper on 0.01 of one another. Other triplets were formed analogously. Matched pairs were formed for the combination-with-insulin group.

Kaplan-Meier curves were used to model the outcomes in each cohort in the three study groups. The risks of the outcomes associated with exposure were assessed using Cox proportional hazards models, adjusted for baseline covariates.

Reviewer's Comments:

- *The publication states that the starting point of observation for the combination-with-insulin study group was initiation of insulin if patients were already using rosiglitazone or other oral antidiabetic agents (excluding TZDs). Patients on prior insulin therapy were included as of the date that any additional oral agent was added. These two groups of patients described might be different and should be analyzed separately. It likely matters which drug was administered first and the exposure durations to the first therapy administered was not collected.*
- *The publication does not provide a justification for combining all the groups containing rosiglitazone. The treatment groups are different from one another and any pooled analysis may result in biased estimates.*
- *There was an inconsistency in the application of the propensity score matching in the monotherapy and dual therapy groups and the comparisons that were made in the analyses. For example, in calculating the propensity scores and forming the triplets for the monotherapy group, metformin and sulfonylureas were considered as one cohort and rosiglitazone was another cohort. However, when comparing the cohorts, rosiglitazone was compared to each of metformin and sulfonylureas. A consistent comparison would have compared rosiglitazone to metformin and sulfonylureas as one cohort. Therefore, the analyses in the monotherapy and dual-therapy groups may be inaccurate.*
- *Among 11,227 initiators of monotherapy with rosiglitazone, only 8,977 (80%) were matched. Among 2,075 initiators of rosiglitazone and sulfonylurea, only 1,362 (66%) were matched. Among 1,236 initiators of rosiglitazone and insulin, only 1,173 (95%) were matched. The publication does not explain why other initiators were excluded in the matching.*
- *The publication claims that the baseline prevalence of all of the factors used in the propensity score matching process was very well balanced following propensity score matching. However, the publication does not provide any statistical test results (e.g. t-test or chi-square test) to show whether the factors were balanced. Moreover, the publication does not provide any statistical results to show that there was an imbalance among the covariates prior to the propensity score matching. Therefore, it is not clear whether propensity score matching was necessary or useful in balancing the known covariates.*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. The publication does not provide a discussion on whether this assumption was valid.*

- *The Cox model also assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified.*
- *The publication states the following limitations of the study: (1) The statistical power of the study was limited by the rarity of the outcome, particularly in the combination with insulin cohorts (2) The population has relatively few elderly patients (3) Because exposure was determined from pharmacy dispensing records, there was no documentation of actual compliance with prescribed therapy and (4) There were confounders that were not accounted for. Limitations 1, 3 and 4 raise concern regarding any estimates provided, conclusions based on these estimates, and the overall study design. Limitations 2 should be considered when attempting to extrapolate results to other populations.*
- *Infrequent usage of pioglitazone in the Ingenix Research Database during the study period prohibited an assessment specific to pioglitazone use. This raises concerns regarding the appropriateness of this database and time period studied for assessing for an association between pioglitazone exposure and outcome.*
- *The outcome date for CR was based on date of hospitalization and not based on the event date. This can lead to biased estimates (e.g. time bias) if the procedure was not performed on date of hospitalization.*
- *The publication does not account for death that occurred during hospitalization.*
- *There were three endpoints considered in several comparisons; however, no adjustments for multiplicity were included.*
- *The study was supported by a contract/grant sponsored by i3 Drug Safety and GSK. This might have influenced the authors and led to potential publication bias.*

20. Karter et al., Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabetic Medicine*, 22, 986-993; 2005

This was a retrospective cohort study of the association between congestive heart failure (CHF) with the use of antidiabetic treatments (pioglitazone, sulphonylurea, metformin, and insulin). The study used the Kaiser Permanente Northern California Diabetes Registry which is part of the Kaiser Permanente Medical Care Program, a fully integrated, non-profit, group practice, prepaid health plan that provides comprehensive medical services to over 2.9 million members (as of January 2000) throughout Northern California (including the San Francisco Bay and Sacramento metropolitan areas). Data for this study spanned the period from October 1999 to November 2001. The cohort consisted of patients who maintained continuous health-plan membership for one year prior to baseline (defined as date of drug initiation), diagnoses with type 2 diabetes prior to 1999, initiated a single-index therapy after the introduction of pioglitazone onto the drug formulary and before one month prior to study end date, and who maintained adequate pill supply.

Exposure to diabetes medications were ascertained using a computerized pharmacy database. The study restricted the cohort to patients who were initiating therapy (“new user” design) and compared four groups of “index therapies”: pioglitazone, sulphonylurea, metformin or insulin. The study however, also considered

“maintained therapies”, defined as those diabetes medications that were used (i) prior to the initiation of the index therapies and (ii) throughout the period from baseline to the end of the period of observation. Thus, a patient with an index therapy may have also had a maintained therapy of at least one other antidiabetic agent. Other antidiabetic agents such as acarbose, repaglinide, miglitol and rosiglitazone were rarely used during the study period and their exposure data were excluded because of insufficient sample size to support statistical analysis. Patients with CHF within five years from baseline, with type 1 diabetes, who were diagnosed with type 2 diabetes prior to 1999, who initiated multiple-index therapies (2%), or members not covered by a pharmacy benefit (4.2%) were excluded from the study cohort.

CHF outcomes were identified using ICD-9 codes from Kaiser Permanente hospitals via discharge automated records. Events occurring in non-Kaiser Permanente hospitals were captured through a claims database for all outside medical services. To minimize misclassification, the study excluded outpatient diagnoses of CHF because these often represent clinical suspicion or “rule-out CHF” work-up, rather than actual CHF events.

The risks of the outcomes associated with exposure were assessed using Cox proportional hazards models, adjusted for baseline covariates. The sulphonylurea group was chosen as the reference group. Maintained therapies (58% of patient cohort) were adjusted for in the model.

Reviewer’s Comments:

- *The study compared index therapy groups by adjusting maintained therapies as covariates. Although this approach is acceptable, it may not be optimal because some index groups have varying numbers of antidiabetic agents in their maintenance therapies. For example, the pioglitazone index group has a majority of at least one or two additional maintenance drugs whereas the sulfonylurea index group is mainly monotherapy. This imbalance may not be fully accounted for with covariate adjustment. A better approach might be to do comparisons across index therapies with the same number of antidiabetic agents in their maintenance therapies.*
- *The Cox model assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified or not.*
- *There were multiple comparisons performed among the different medication groups without adjustments for multiplicity.*
- *The publication states the following limitations of the study: (1) There may have been confounding by indication as it was observed that there was substantially elevated prevalence of several markers of disease severity, particularly poor glycemic control, relative to ongoing users; (2) Imbalances in disease risk as pioglitazone initiators were found to be sicker than patients who initiated other therapies; (3) Bias in metformin therapy because it was contraindicated for patients with CHF at the time of the study; and (4) The follow-up period was relatively short. All of these limitations greatly impact the overall findings and should be considered.*

21. Rajagopalan et al., Association Between Congestive Heart Failure and Hospitalization in Patients with Type 2 Diabetes Mellitus Receiving Treatment with Insulin or Pioglitazone: A Retrospective Data Analysis. Clinical Therapeutics, 26:9; 2004

This was a retrospective cohort study of the association between congestive heart failure (CHF) with the use of pioglitazone compared to insulin, each given as either monotherapy or in combination (with metformin or a sulfonylurea) therapy in adults patients with type 2 diabetes. This study used the PharMetrics Patient-Centric Database, which is a national claims database comprising data from over 36 million users. Data for this study spanned the period from January 1, 1998, to March 31, 2002. The cohort comprised patients who were at least 18 years of age with a diagnosis of type 2 diabetes based on ICD-9-CM codes 250.x0 or 250.x2, and/or evidence of use of antidiabetic medications who initiated treatment with pioglitazone or insulin between January 1999 and December 2001 were identified. The index date was based on the first prescription for pioglitazone or insulin. The follow-up period was the period beginning with the day after the index date and ending with the date of a change in therapy, or the date of the health plan disenrollment, or date in which claims for the outcome were available, whichever came first, a minimum of 90 days after the index date.

The primary measure of interest was incidence of CHF, based on either one or more provider or facility claim with a primary or secondary diagnosis of CHF or one more hospital inpatient claim with a diagnosis of CHF within the follow-up period.

The authors employed a 1:1 propensity score matching to balance various measured covariates between therapy groups (pioglitazone vs. insulin). The propensity scores were estimated using a conditional logistic regression model controlling for the covariates. Patients who received insulin treatment were matched 1:1 with patients who received pioglitazone treatment based on a difference in estimated propensity score of no greater than ± 0.01 . Univariate tests (chi-square and t) showed that balance was achieved after propensity score matching (since p-values > 0.05).

The risk for CHF was assessed using the hazard ratio estimated from the Cox proportional hazards model (Cox model) with age and pre-index health care costs as explanatory variables. CHF was based on ≥ 1 provider or facility claim with a primary or secondary diagnosis of CHF or ≥ 1 hospital inpatient claim with a diagnosis of CHF within the follow-up period.

Reviewer's Comments:

- *When using propensity score matching to achieve balance among measured covariates between therapy groups, univariate tests results are usually reported each before and after matching is done. Univariate tests results reported prior to propensity score matching will show the degree of imbalance among the covariates whereas results reported after matching will show whether balance was achieved. The publication does not show nor describe whether there was an imbalance in the covariates between treatment groups prior to propensity score matching. Thus, it is not clear whether propensity score matching resulted in a significant improvement in the covariate imbalance.*

- *The publication does not mention whether there were any missing covariate data or the amount of missing exposure data. The amount or degree of missing data may affect the validity of the propensity score matching.*
- *The authors describe selection bias due to unobservable characteristics such as disease severity and inadequate response to therapy as one limitation of the study and state that propensity score matching was used to diminish the effect of such bias. However, these unobservable characteristics were not accounted for in the propensity score model.*
- *The Cox model assesses covariate effects on the risk of an event over time. An important assumption of this model is that the hazard functions in the two treatment groups are proportional over time. The publication does not provide a discussion on whether this assumption was valid.*
- *The Cox model also assumes linearity of the log hazard function and the covariates. The publication does not discuss whether this functional form was correctly specified.*
- *It is not clear if the diagnosis used for CHF has been previously validated since the specific claims codes used are not provided. The inability to verify how the outcome was assessed is a significant limitation leading to uninterpretable findings.*
- *In addition to selection bias, the publication mentions errors due to billing and coding, and the unverifiable diagnoses of the various cardiac diseases, as two other limitations of the study. These limitations, along with concerns that the primary outcome of CHF may not be validated, should be considered when interpreting the results of the statistical analysis.*
- *The publication reports a total of 1,668 matched pairs with a mean [SE] age of 51.2 [0.2] years. It is not clear whether SE represents standard deviation because the number 0.2 seem incorrect for SE, given that patients were at least 18 years of age.*
- *The comparisons between pioglitazone and insulin combination therapies do not indicate if the same therapy, i.e. metformin or a sulfonylurea, was used in the combination for each regimen.*
- *This study does not include a regimen of rosiglitazone therapy, therefore a comparison between the two target thiazolidinediones; rosiglitazone and pioglitazone cannot be performed.*

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No special/subgroup populations were investigated in this review.

4.1 Gender, Race and Age

4.2 Other Special/Subgroup Populations

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- All publications were either nested case-control or retrospective cohort studies.
- The primary statistical methods used for the studies were conditional logistic regression, Cox proportional hazards regression, and Poisson regression. These methods estimate the odds of an event, time to an event, and event count, respectively. These methods also estimate the odd ratio, hazard ratio, and rate ratio, respectively, which have different meanings and interpretations. The statistical methods have different underlying assumptions which should be checked prior to fitting the data.
- All statistical models adjusted for different types and numbers of covariates.
- None of the studies provided diagnostic tests to assess model fit to the data.
- Most studies did not mention whether there were any missing covariate data and the amount of missing data. In addition, few studies accounted for death in the outcome assessment.
- Many studies showed multiple comparisons for various antidiabetic agents or assessed multiple outcomes. However, these studies did not provide any adjustment for multiplicity which could result in inflated type-1 errors.
- There were only 9 out of the 21 publications which directly compared rosiglitazone to pioglitazone. Other comparisons were either with reference groups of antidiabetic drugs which were not uniform across studies or groups of antidiabetic drugs that cannot be classified as reference groups.
- For studies that did not directly compare rosiglitazone to pioglitazone, unadjusted risk estimates of odds ratios can generally be calculated for rosiglitazone versus pioglitazone using summary-level data. However, unadjusted risk estimates of hazard ratios or any adjusted risk estimate cannot be calculated without subject level data.
- There were seven publications whose authors were affiliated with the manufacturer of rosiglitazone and two publications whose authors were affiliated with the manufacturer of pioglitazone.
- The databases across all studies varied by geographic locations: United States, Canada, United Kingdom, and Taiwan. For US databases, the locations were either national, regional (certain states only), or unspecified. There were studies that used the same databases: Two studies used the GPRD, two studies used the PharMetrics, and two studies used the Ingenix Research Database.
- Diabetes patients and outcomes were generally identified by the International Classification of Diseases (ICD) codes or codes that were dependent on the types of databases used. Studies considered at least one outcome.
- Studies considered population ages ≥ 18 , ≥ 35 , 40 or 65 years.
- The antidiabetic agents studied were rosiglitazone, pioglitazone, metformin, sulfonylurea, insulin, and other medications. These were classified as either monotherapy or combination therapy. Comparisons were done within each type of therapy groups. In some studies, combination therapies were compared but adjusted for non-TZD medications in the model. There were some studies where the risk estimates were derived from mono- and combination therapies.

- The lengths of drug exposures were generally not reported. However, for studies that did, the lengths or durations of exposures were varied across the studies.

5.2 Conclusions and Recommendations

The 21 observational studies reviewed were largely dissimilar (Tables 1 and 2). The main differences were as follows:

1. Varied study designs (case-control vs. retrospective cohort).
2. Multiple endpoints or outcomes considered and the way these were assessed (ICD-9 coding, other coding).
3. Various antidiabetic agents studied, including whether they were considered as single or combination therapies
4. Variable durations of antidiabetic agent exposure and the study periods.
5. Variable ranges of patient ages included in study cohorts or populations.
6. Study populations varied by locations of study and by race/ethnicity.
7. Various statistical methods utilized (conditional logistic regression, Cox proportional hazards regression, or Poisson regression) including the estimates obtained from these methods (i.e. odds ratios versus hazard ratios); the way model assumptions (e.g. proportionality of hazards in the Cox model) and model adequacy (e.g. linearity of covariates in Cox or conditional logistic regression model) were diagnosed or assessed.
8. Variability in the types and numbers of covariates used for model adjustment.
9. Different criteria for matching (for nested case-control studies).
10. Variable amounts of missing exposure, outcome and covariate data.
11. Various comparisons among different treatment groups, including whether comparisons were made between monotherapies or combination therapies, or a combination of these; and reference groups.

These study differences strongly suggest that estimates of association from studies should not be pooled into a single meta-analytic estimate. In addition, 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. The hazard ratio is a measure of risk over time whereas the odds ratio is a ratio of probabilities that does not account for event times. The interpretation and underlying statistical assumptions of these two measures of effect are different.

The strength of observational studies generally depends on the quality and reliability of the databases used, the assessment methods used to identify exposures and outcomes, the appropriateness of the data sources to address the study aims, the statistical methodologies used to adjust for covariate imbalances, the amount of available data including covariates, the treatment of missing data, and the implementation and diagnostics of the statistical methods. In this review:

- The databases studied in each of the 21 publications vary from well known and previously studied (e.g. GPRD, Kaiser Permanente and Medicaid) databases to ones for which no, or limited, details were provided (e.g. Vertically integrated health system in Southeast Michigan from publication 5).

- Many studies identified diabetes patients and outcomes of interest using ICD codes (see item 2 above and item 8 of Section 1.3 Statistical Issues and Findings) which are considered standard in providing reliable assessments for this population and for specific outcomes (e.g. acute myocardial infarction). However, only publication 1 performed a validation of acute myocardial infarction using a random sample of the patient population. In addition, some studies use diagnostic codes other than ICD codes.
- Studies vary in the numbers and types of covariates that were used for model adjustment (see item 3 of Section 1.3 Statistical Issues and Findings). Due to lack of randomization, observational studies are prone to biases including those due to confounders that may have been unaccounted for in the statistical models. Thus, the reviewed studies may be limited in part by not being able to account for the same or similar covariates and also unable to account for unmeasured covariates in the statistical models.
- Many studies do not discuss missing covariate data and/or describe the approach used to handle missing covariate data (see item 3 of Section 1.3 Statistical Issues and Findings).
- There were two statistical models commonly used across most of the studies (conditional logistic regression and Cox proportional hazards regression). However, as stated in item 2 of Section 1.3 Statistical Issues and Findings, most of the studies that used the Cox model did not check the proportionality of hazards assumption. Moreover, none of the publications provided results from diagnostics for model fit. Thus, without checks for model adequacy, the results of the statistical analyses may be incorrect.

This review is limited by the information provided in each publication. Therefore, some of the comments by the statistical reviewer may arise from unclear and/or incomplete understanding of each of the studies. These concerns and the inability to verify each results from study using subject-level data prevent the statistical reviewer from providing general qualitative assessments of the overall results across all studies.

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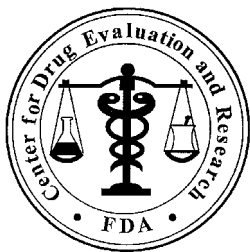
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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 15, 2010

To: Mary Parks, MD, Director
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Rita Ouellet-Hellstrom, PhD
Division of Epidemiology (DEpi)

Subject: Risk of acute myocardial infarction, stroke, heart failure, and death
in elderly Medicare patients treated with rosiglitazone or
pioglitazone: A retrospective observational cohort study

Drug Name(s): Rosiglitazone (AVANDIA[®], GlaxoSmithKline, IND 43,468, NDA
21-071)
Pioglitazone (ACTOS[®], Takeda, NDA 21-073)

Submission Number:

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Applicant/sponsor: GlaxoSmithKline (GSK)

OSE RCM #: 2007-1945, 2008-278, 2010-1274

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EXECUTIVE SUMMARY

Meta-analyses or randomized trials and an increasing number of observational studies comparing rosiglitazone with pioglitazone have suggested that the use of rosiglitazone is associated with an increased risk of serious cardiovascular events, compared either to other treatments for type 2 diabetes or to treatment with pioglitazone. We evaluated the risk of serious cardiovascular harm (acute myocardial infarction (AMI), stroke, hospitalized heart failure (HF), all-cause mortality, and the composite endpoints of AMI or death, AMI, stroke, or death, and AMI, stroke, HF, or death) in elderly persons enrolled in Medicare.

We performed a nationwide, observational, retrospective, inception cohort study of Medicare beneficiaries age 65 years or older who initiated treatment with rosiglitazone or pioglitazone through a Medicare Part D prescription drug plan between July 2006 and June 2009. Patients were included in a cohort if on the date of their first thiazolidinedione (TZD) prescription, they had at least 12 months of prior continuous enrollment in Medicare Parts A and B (inpatient and outpatient health care encounters), had at least 6 months of prior continuous enrollment in Medicare Part D (prescription drug plan), were 65 years of age or older, and were not resident in a hospital or extended care facility or enrolled in hospice care on the date the TZD prescription was filled. Baseline characteristics and potential confounding factors were collected during the 12 month period (medical conditions) and during the 6 month period (prescription drug use) preceding the first TZD prescription.

New users of rosiglitazone and pioglitazone were followed from cohort entry until the earliest occurrence of a study endpoint, a gap in continuous thiazolidinedione treatment exceeding seven days, a prescription fill for a different thiazolidinedione, a non-endpoint hospitalization, or end of the study period (June 30, 2009). To guard against bias arising from informative censoring, most importantly by events leading to death, any endpoint events occurring within 14 days following a gap in continuous treatment or admission to hospital were counted in the analysis. This 14-day period of extended follow-up was not applied to thiazolidinedione switching because it would not be possible to distinguish effects due to rosiglitazone from those due to pioglitazone, nor was it applied to censoring at the end of the study window because no data were collected after that date.

During the three-year study period, 227571 patients with a mean age of 74.4 years entered the study, with mean follow-up of 162 days and a median follow-up 105 days (range 1-1093). A total of 8667 endpoint events were observed. The attributable risk (incidence rate difference) was increased for rosiglitazone compared with pioglitazone for all endpoints, although the excess for AMI was not statistically significant. For the composite of AMI, stroke, HF, or death, the attributable risk was 1.68 (95% CI 1.27-2.08) excess events per 100 patients treated for one year. The associated number needed to harm was 60 (95% CI 48-79) persons treated for one year with rosiglitazone to produce one excess composite event. Kaplan-Meier cumulative incidence plots showed statistically significant increases in the risk of stroke, HF, all-cause mortality, and each of the composite endpoints, with clear separation of event curves within 1-2 months of starting a TZD. For AMI, the curve for rosiglitazone was greater than that for pioglitazone, but the difference was not statistically significant (logrank p value=0.18).

Cox proportional hazards regression was performed using a base model stratified for history of cancer or prior cardiovascular endpoint, and adjusted for all covariates for which data were collected. The adjusted hazard ratios (95% CI) (pioglitazone as reference) were: AMI 1.06 (0.96-1.18); stroke 1.27 (1.12-1.45); HF 1.25 (1.16-1.34); death 1.14 (1.05-1.24); AMI, or death: 1.11 (1.04-1.19); AMI, stroke, or death 1.15 (1.08-1.22), and AMI, stroke, HF, or death 1.18 (1.12-1.23). A test to assess whether the proportional hazards assumption was met for each regression suggested that the assumption was not met for the endpoint of death or the composite endpoints that included death. Several unplanned *post hoc* analyses were performed to evaluate the non-proportionality suggested by this test. We restricted the cohorts to the 110950 patients who entered the study prior to publication of the rosiglitazone meta-

analysis by Nissen and Wolski on May 21, 2007. Nearly identical results were obtained to those of the main analysis and the proportional hazards assumption was now also met for death and AMI or death. An analysis restricted to patients who entered the study after the May 2007 publication date produced results similar to the pre-publication period. Of note, there were only 15009 rosiglitazone patients during this latter period who contributed 5400 person-years of exposed observation time, compared with 101612 pioglitazone patients followed for 40400 person-years. We also partitioned follow-up time into three periods and repeated the main analysis for death-related endpoints using the entire (pre- and post-publication) study population. The hazard ratios for death, AMI or death, AMI, stroke, or death, and AMI, stroke, HF, or death were increased with rosiglitazone compared with pioglitazone during the first interval (0-2 months), were somewhat lower but still increased during the second interval (2-4 months) for death and AMI or death, but remained comparably elevated for the other composites, and were increased to a greater degree in the third interval (> 4 months) than during the first for all death-related endpoints. The proportional hazards assumption was met during each follow-up interval for all death-related endpoints and the hazard ratios for rosiglitazone compared with pioglitazone were statistically significantly increased during the third and final interval (all-cause mortality: 1.21 (1.05-1.39); AMI or death: 1.13 (1.01-1.27); AMI, stroke, or death: 1.19 (1.08-1.32); and AMI, stroke, HF, or death: 1.23 (1.14-1.34)).

During the analysis, we noted that entry into the rosiglitazone cohort dropped off substantially following publication of the rosiglitazone meta-analysis published by Nissen and Wolski on May 21, 2007. We compared the baseline characteristics of patients entering the study before or after this date. Prior to the publication, patients entering the rosiglitazone and pioglitazone cohorts were similar with respect to measured covariates. Post-publication, patients entering each cohort remained similar. At 6-, 12-, 18-, and 24-months of follow-up, the two cohorts remained virtually indistinguishable with respect to measured characteristics.

The population impact of an excess risk of various cardiovascular endpoints associated with the use of rosiglitazone rather than pioglitazone was estimated for the period 1999 (start of marketing) through 2009 using estimates of the number needed to harm. A total of 82.5 million prescriptions for rosiglitazone, representing 2.84 million person-years of usage, were dispensed to US patients age 65 years or older during this period. With an estimated number needed to harm of 60, we estimate that about 48000 excess cases of AMI, stroke, HF, or death were attributable to the use of rosiglitazone rather than pioglitazone from 1999-2009.

1 BACKGROUND

1.1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects over 20 million Americans, representing 7% of the US population.¹ It is an important risk factor for cardiovascular disease, particularly acute myocardial infarction (AMI).¹⁻³ The risk of cardiovascular disease is increased 2-4-fold in patients with T2DM, and accounts for 65% of deaths in this group.¹⁻³

While a primary goal of therapy for T2DM is the prevention of vascular complications,⁴ careful control of blood glucose levels has not been shown to reduce the occurrence of cardiovascular disease or mortality. The UK Prospective Diabetes Study (UKPDS) randomized 3867 patients with newly diagnosed T2DM to intensive therapy with sulfonylureas or insulin, or conventional therapy (diet + oral therapy as needed to maintain fasting plasma glucose below 15 mmol/L), and followed them for up to 10 years for the occurrence of a variety of macro- and microvascular outcomes.⁵ The relative risk (RR) of AMI in the intensively-treated group was 0.84 (95% CI 0.71-1.00, p=0.052); for stroke 1.11 (95% CI 0.81-1.51); for diabetes-related death 0.90 (95% CI 0.73-1.11); and for all-cause mortality 0.94 (95% CI

0.80-1.10).⁵ For microvascular complications (retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or nonfatal kidney failure), the relative risk was 0.75 (95% CI 0.60-0.93, $p=0.01$). Within a subgroup of 753 overweight patients enrolled in the UKPDS, intensive therapy with metformin ($n=342$) vs. conventional therapy ($n=411$) was evaluated.⁶ In this patient population, metformin reduced the risk of AMI (RR=0.61; 95% CI 0.41-0.89), diabetes-related death (RR=0.58; 95% CI 0.37-0.91), and all-cause mortality (RR=0.64; 95% CI 0.45-0.91).⁶ However, in overweight patients treated with metformin + sulfonylurea, the risk of diabetes-related death was increased (RR=1.96; 95% CI 1.02-3.75) compared with sulfonylurea alone. No subsequent clinical trials have been performed that demonstrate a protective effect of oral therapy, particularly metformin, on the risk of major cardiovascular events or cardiovascular or all-cause mortality. Recently, the intensive treatment arm (HbA1c < 6.0%) of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was prematurely terminated due to an increase in all-cause and cardiovascular mortality compared to patients treated less intensively.⁷

1.2 THIAZOLIDINEDIONE HISTORY

The first thiazolidinedione (TZD) to be marketed in the US, troglitazone, was withdrawn from the market as an “outmoded” drug in 2000, after two newer TZDs, rosiglitazone and pioglitazone, were found to not increase the risk of acute liver failure, based on analysis of spontaneously reported cases to FDA.^{8,9} Since then, both of these newer TZDs have been shown to increase the risk of new-onset heart failure and to worsen pre-existing heart failure.¹⁰⁻¹⁴ A meta-analysis of randomized clinical trials found that while both TZDs increased the risk of heart failure, rosiglitazone (RR= 2.18; 95% CI 1.44-3.32) appeared to have a higher risk than pioglitazone (RR=1.32; 95% CI 1.04-1.68; p -value for heterogeneity = 0.01), although no head-to head studies between the two TZDs had been performed to contribute to this analysis.¹⁵

In early 2007, a study-level meta-analysis of clinical trials of rosiglitazone found a 43% increase in risk of AMI and a 64% increase in risk of cardiovascular death with rosiglitazone compared to comparator therapy.¹⁶ The FDA performed a patient-level meta-analysis of rosiglitazone clinical trials and found that rosiglitazone was associated with a 40% increase in ischemic myocardial events.¹⁷

In July 2007, an FDA advisory committee voted 20-3 that rosiglitazone increased acute myocardial ischemic events, but also voted 22-1 to keep rosiglitazone on the market.¹⁸ Subsequently, myocardial ischemia was added as a boxed warning to the rosiglitazone label.¹⁹ The manufacturer, GlaxoSmithKline, was also asked to perform a cardiovascular outcomes trial of rosiglitazone vs. other oral therapies, with a secondary analysis of rosiglitazone vs. pioglitazone. This study, named TIDE (Thiazolidinedione Intervention with vitamin-D Evaluation) was reviewed by Drs. David Graham and Kate Gelperin of OSE in 2008. They concluded that this study was unethical and exploitative of human subjects, representing what bioethicists have called a “bad deal” trial.²⁰ In addition, Dr. Gelperin concluded that if it were somehow ethical to conduct such a study, the primary analysis should be rosiglitazone vs. pioglitazone because this was the choice that prescribing physicians and patients were faced with once the decision to use a TZD had been made.²¹

1.3 SUMMARY OF EXISTING STUDIES OF CARDIOVASCULAR RISK WITH THIAZOLIDINEDIONES

Rosiglitazone and pioglitazone are the only currently marketed thiazolidinediones (TZDs) in the US. They are peroxisome-proliferator-activated receptor gamma agonists, which modulate the transcription of various genes and act to increase insulin receptor sensitivity in adipose tissue, thereby reducing blood glucose levels in patients with type 2 diabetes.²² In mid-2007, a meta-analysis of 42 randomized controlled trials involving rosiglitazone reported a 1.4-fold increase in risk of acute myocardial infarction (AMI) compared to other therapies.¹⁶ Subsequently, a meta-analysis of 19 randomized controlled trials with pioglitazone found a statistically significant reduction in the composite outcome of non-fatal AMI, stroke, and all-cause mortality and a nearly statistically significant reduction

in non-fatal AMI by itself,²³ thereby suggesting a potential difference in cardiovascular risk between the two TZDs.

No randomized controlled trials have been completed that directly compare rosiglitazone to pioglitazone for the occurrence of AMI or other cardiovascular endpoints. In each of three large trials comparing rosiglitazone to either placebo or non-TZD therapies, AMI risk was non-significantly increased by rosiglitazone.²⁴⁻²⁷ Two of these trials were conducted in pre- or newly diagnosed diabetic patients, presumably at low risk for cardiovascular events.^{24,25} The third was open-label in design, captured fewer than half the expected number of AMI or heart failure events, and concerns about its scientific integrity have been raised by others.²⁶⁻³⁰ One large cardiovascular risk trial conducted with pioglitazone reported a non-statistically significant reduction in the composite outcome of all-cause mortality, non-fatal AMI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle.³¹ A secondary analysis was statistically significant for a reduction in the composite of all-cause mortality, non-fatal AMI, and stroke.³¹

A number of observational studies have compared the cardiovascular risks of rosiglitazone and pioglitazone against non-TZD therapies³²⁻⁴³ or against each other.⁴⁴⁻⁵² In seven studies where both rosiglitazone and pioglitazone were individually compared to non-TZD therapies but not directly to each other,³⁷⁻⁴³ rosiglitazone increased AMI risk in two,^{38,43} and in one study each, rosiglitazone increased the risk of stroke, heart failure (HF), and all-cause mortality,^{38,43} while in the same studies, pioglitazone did not increase cardiovascular risk. In one other study, pioglitazone reduced the risk of death while rosiglitazone did not.⁴²

In nine observational studies, rosiglitazone was compared directly to pioglitazone for the occurrence of a variety of cardiovascular outcomes.⁴⁴⁻⁵² Rosiglitazone increased AMI risk in seven,^{44-47,49-51} statistically significantly so in three.^{24,50,51} Stroke risk was examined in two studies, both of which reported a non-statistically significant increase with rosiglitazone.^{46,48} The risk of HF was statistically significantly increased with rosiglitazone in three of four studies,^{46,48,49} with a non-significant increase in one other.⁵² Finally, the risk of all-cause mortality was statistically significantly increased with rosiglitazone in two studies where a direct comparison to pioglitazone was made.^{46,49}

The availability of prescription drug data for Medicare beneficiaries beginning in January 2006, with introduction of the Part D benefit, provided an opportunity to investigate whether rosiglitazone increases cardiovascular and mortality risks using a large, nationally representative population of elderly patients with type 2 diabetes newly treated with a TZD.

2 METHODS

2.1 MEDICARE DATA

Medicare is the largest health insurance program in the US, providing coverage to persons age 65 years and older, as well as to persons under age 65 who have end-stage renal disease or are disabled.^{53,54} Eligibility for Medicare Part A, which covers hospitalization expenses, occurs automatically at age 65 while coverage for outpatient medical care (Part B) and prescription drugs (Part D) must be purchased.^{54,55} Computerized data for Parts A and B are available from the 1990s while data for Part D are available since January 2006, when the Medicare prescription drug benefit took effect.

In 2008, there were about 45 million Medicare beneficiaries, of whom 35 million (77%) were in traditional fee-for-service (FFS) arrangements and 10 million were enrolled in Medicare Advantage, where Medicare pays a capitated fee to participating health maintenance organizations and private health plans, which then provide comprehensive medical care to enrolled beneficiaries. Data on individual healthcare encounters are not systematically captured by Medicare Advantage so data from these patients are not available for research purposes.^{56,57}

Also in 2008, about 58% of beneficiaries (26 million) were enrolled in Part D, of which 8.6 million were enrolled in Medicare Advantage and 17.4 million were enrolled in Medicare Part A FFS and in a stand-alone prescription drug plan. Of these, about 85% (nearly 15 million) were age 65 years or older.^{56,57}

Claims for Parts A, B, and D are evaluated for data quality by Medicare and entered into an analyzable database where they are linked with the Medicare Enrollment Database. Together, these provide information about demographic and enrollment characteristics, diagnoses, procedures, prescription drugs, and medical equipment use for each beneficiary. Prescription claims include days of supply and quantities dispensed, and are mapped against reference databases to identify drug name and strength using the National Drug Code number.

We restricted the Medicare population to persons enrolled in Parts A and B fee-for-service, and Part D, since claims from these sources provide the data needed for research purposes. We linked these claims across all settings of care for each beneficiary, using a unique identifier to create a longitudinal record of each patient's healthcare utilization and related diagnoses.

2.2 STUDY DESIGN

A new user, inception cohort design was employed. Patients with at least six months of continuous Part D enrollment and at least 12 months of continuous Parts A and B enrollment prior to the date of their first TZD prescription (t_0) and who were 65 years of age or older on that date were identified, and those not resident in a hospital, long-term care facility, or receiving hospice care formed the rosiglitazone and pioglitazone inception cohorts.

During the year prior to TZD initiation, data were collected for each cohort member on the presence of cardiovascular or cerebrovascular disease, diabetes-related complications, lipid disorders, and other chronic medical conditions. The Charlson comorbidity score was calculated using claims from inpatient hospitalizations.^{58,59} Data on use of medications prescribed for the treatment of cardiovascular disease, diabetes, and other chronic medical conditions were collected for the six month period preceding t_0 . For purposes of analysis, these baseline variables were separated into two categories: core variables (variables frequently included in analyses of cardiovascular endpoints, see tables 1 and 2 for list) and additional variables (variables more indicative of general health or that represent medical conditions already captured by prescription drug use included as core variables, see table 3 for list).

Table 1. Baseline characteristics of cohort members at initiation of thiazolidinedione therapy.

Background characteristics		
Gender	Race/ethnicity	Charlson score
Age	Asian	0
65-69	Black	1
70-74	Hispanic	2
75-79	White, non-Hispanic	3+
80+	Other	Medication classes
	Low income subsidy	1-6
	Extended care [†]	7-9
		10+

[†] Nursing home or skilled nursing facility residence during year before cohort entry

Table 2. Core cardiovascular medical conditions and medications used among cohort members during the 12-month (medical conditions) or 6-month (medications) period preceding initiation of thiazolidinedione therapy.

Core variables		
Cardiovascular disease	Cardiovascular medications	Diabetes-related medications
Acute myocardial infarction [†]	ACE inhibitors and ARBs	Insulin
Coronary revascularization	Antiarrhythmics	Oral
Heart failure [†]	Anti-coagulants	Metformin
Other ischemic heart disease	Anti-platelets	Sulfonylureas
Stroke [†]	Beta-blockers	Other
Diabetes-related disorders	Calcium channel blockers	Lipid lowering
Microvascular disease	Digoxin	Fibrates
Peripheral vascular disease	Diuretics	Statins
	Loop	
	Potassium sparing	
	Thiazide	
	Nitrates	

[†]Hospitalized events only

Table 3. Additional medical conditions and medications used among cohort members during the 12-month (medical conditions) and 6-month (medications) period preceding initiation of thiazolidinedione therapy.

Additional variables	
Medical conditions	Medications
Alcohol abuse	Antidepressants
Chronic liver disease	Biphosphonates
COPD	Estrogen replacement
Dementia	H2-antagonists
Gout	NSAIDs
Hypercholesterolemia	Proton pump inhibitors
Hypertension	Thyroid replacement
Hypertriglyceridemia	
Hypothyroidism	
Inflammatory arthritis	
Kidney failure	
Malignancy [†]	
Obesity	
Organ transplantation	
Peptic ulcer disease	
Smoking	

[†] Excluding non-melanoma skin cancer

2.3 STUDY ENDPOINTS

Acute myocardial infarction was defined by ICD-9 code 410 in the first or second position of the hospital discharge diagnosis. In recent studies, code 410 had a positive predictive value (PPV) between 89% and 97% in a variety of US and Canadian administrative claims databases.⁶⁰⁻⁶⁴ Of note, code 410 in the first or second position had a PPV of 94% in a recent study using a Medicare Part A data.⁶³ Out of hospital death occurring within one day of an emergency department visit for acute ischemic heart disease was also classified as a fatal AMI.⁶⁵ Stroke was identified by ICD-9 hospital discharge diagnosis codes

430, 431, 433.x1, 434.x1, and 436, located in the first position only. When listed as the first discharge diagnosis, these codes have a PPV of 92% - 100%.⁶⁶⁻⁶⁸ Heart failure was identified by ICD-9 hospital discharge diagnosis codes 402.x1, 404.x3, and 428 in the first position only. These codes have a PPV of 85% - 96%.⁶⁹⁻⁷¹ Death was ascertained by linkage to the Social Security Master Beneficiary Record database, which provides the date, but not cause, of death and captures over 95% of deaths in the US of persons age 65 years or older.⁷²

Table 4. Definitions of study endpoints.

Endpoint	ICD-9 codes (hospital discharge)
Acute myocardial infarction	410 (all) 1st or 2nd position
Stroke	
Acute ischemic	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01 434.11 434.91 436 (all) (1^o position)
Intracerebral hemorrhage	431 (1^o only)
Subarachnoid hemorrhage	430 (1^o only)
Heart failure	402.01 402.11 402.91 404.01 404.03 404.11 404.13 404.91 404.93 428 (all) (1^o position as endpoint; 1^o or 2^o position for past history)
AMI-related and stroke-related mortality	Hospital or ER death with discharge diagnosis of AMI or stroke; ER death with diagnosis of cardiac arrest (427.5) or sudden cardiac death (V12.53) will be classified as AMI-related; out-of-hospital deaths within the day following discharge from an ER with an ischemic heart disease diagnosis (ICD 410-414) will be classified as AMI-related
All-cause mortality	All deaths

Because cardiovascular disease accounts for nearly 70% of deaths in patients with diabetes,⁷³ all-cause mortality may be an indicator of cardiovascular mortality in this study. For this reason, besides evaluating time-to-event for the individual endpoints of AMI, stroke, HF, and death, we also evaluated time-to-event for the composite endpoints of AMI or death, AMI, stroke or death, and AMI, stroke, HF, or death.

2.4 FOLLOW-UP AND ANALYSIS

New users of rosiglitazone and pioglitazone were followed from t_0 until the earliest occurrence of a study endpoint, a gap in continuous TZD treatment exceeding seven days, a prescription fill for a different TZD, a non-endpoint hospitalization, or end of the study period (June 30, 2009). To guard against bias arising from informative censoring, most importantly by events leading to death, any endpoint events occurring within 14 days following a gap in continuous treatment or admission to hospital were counted in the analysis. This 14-day period of extended follow-up was not applied to TZD switching because it would not be possible to distinguish effects due to rosiglitazone from those due to pioglitazone, nor was it applied to censoring at the end of the study window because no data were collected after that date.

Baseline characteristics of the TZD cohorts were compared using standardized mean differences, calculated as the difference in means or proportions of a variable divided by a pooled estimate of the standard deviation of the variable.⁷⁴ This measure is not influenced by sample size and is useful for

comparing cohorts in large observational studies. A value of 0.1 standard deviations or less indicates a negligible difference in means between groups.⁷⁴ Kaplan-Meier cumulative incidence plots were generated showing time-to-event for all endpoints. Unadjusted incidence rates and rate differences (attributable risk) with 95% confidence intervals (CI) were calculated using cumulative cohort follow-up time. Hazard ratios with 95% CIs were calculated using Cox proportional hazards models, stratified by prior history of a cardiovascular endpoint and cancer, with adjustment for all remaining covariates (see lists from tables 1-3). The proportional hazards assumption was assessed using a test of weighted Schoenfeld residuals.⁷⁵ The number needed to harm (NNH) was estimated using the attributable risk, and the number of excess cardiovascular events in patients age 65 years or older occurring in the US between 1999 and 2009 was estimated using national drug usage data⁷⁶ and the NNH. Pre-planned sensitivity analyses included repetition of the main analysis with 0-days of follow-up after a gap in thiazolidinedione therapy or hospitalization to look for evidence of informative censoring, and repetition of the main analysis restricted to strata defined by baseline treatment with insulin, metformin, sulfonylureas, nitrates, or statins. Several unplanned, *post hoc* analyses were performed to evaluate the failure of some Cox proportional hazards models to meet the proportional hazards assumption. These included analyses restricted to patients who entered the study before or after publication of a widely publicized meta-analysis of rosiglitazone randomized trials on May 21, 2007,¹ and partitioning of follow-up time into intervals of 0-2 months, 2-4 months, and > 4 months.

This study was performed as part of the SafeRx Project, a joint initiative of the Centers for Medicare and Medicaid Services (CMS), the US Food and Drug Administration (FDA), and the Office of the Assistant Secretary for Planning and Evaluation (ASPE). It was approved by the Research in Human Subjects Committee of the FDA's Center for Drug Evaluation and Research. Analyses were performed using Stata v. 11 (College Station, TX).

3 RESULTS

3.1 BASELINE CHARACTERISTICS

Over the period of study, 227571 patients entered the study and contributed 101126 to 101323 person-years of TZD follow-up, depending on the endpoint being analyzed. The two TZD cohorts were similar with respect to a variety of background characteristics with the exception of a slightly increased proportion of rosiglitazone patients receiving a prescription co-pay subsidy (table 5). The mean age in both cohorts was 74.4 years and the mean number of medication classes prescribed over the six months prior to t_0 was 7.7. Mean follow-up was 162 days and median follow-up was 105 days (range 1-1093). The two cohorts were also similar with respect to the core and additional (general medical) variables for which data were collected prior to cohort entry (tables 6, 7).

For the majority of cohort members (75.1% rosiglitazone, 77.7% pioglitazone), TZD was added to other ongoing diabetes therapy. In the six months prior to t_0 , these patients used multiple other anti-diabetic medications (mean (SD) = 1.6 (0.6)), suggesting more advanced diabetes. In these patients, insulin was used by 18%, metformin by 67%, and sulfonylurea agents by 64%. For the remaining patients, TZD use appeared to be the initial, first-line pharmacologic treatment for their diabetes.

Table 5. Baseline characteristics of cohort members at initiation of thiazolidinedione therapy.

Characteristic, No. (%)	Rosiglitazone (67593)	Pioglitazone (159978)	Standardized mean difference
Female	41072 (60.8)	95125 (59.5)	0.03
Age			
65-69	19605 (29.0)	46359 (29.0)	0.00
70-74	18359 (27.2)	43871 (27.4)	0.01
75-79	14411 (21.3)	33600 (21.0)	0.01
80+	15218 (22.5)	36148 (22.6)	0.00
Race/ethnicity			
Asian	3813 (5.6)	7630 (4.8)	0.04
Black	7993 (11.8)	17267 (10.8)	0.03
Hispanic	4231 (6.3)	8603 (5.4)	0.04
White, non-			
Hispanic	49519 (73.3)	120749 (75.5)	0.05
Other	2037 (3.0)	5729 (3.5)	0.03
Low income subsidy	34776 (51.4)	73041 (45.7)	0.12
Extended care [†]	3134 (4.6)	6747 (4.2)	0.02
Charlson score			
0	50466 (74.7)	121067 (75.7)	0.02
1	5429 (8.0)	12316 (7.7)	0.01
2	4632 (6.9)	10551 (6.6)	0.01
3+	7066 (10.5)	16044 (10.0)	0.01
Medication classes			
1-6	28712 (42.5)	67549 (42.2)	0.01
7-9	19639 (29.1)	47555 (29.7)	0.02
10+	19242 (28.5)	44874 (28.1)	0.01

[†] Nursing home or skilled nursing facility residence during year before cohort entry

Table 6. Core cardiovascular medical conditions and medications used among cohort members during the 12-month (medical conditions) or 6-month (medications) period preceding initiation of thiazolidinedione therapy.

Condition, No. (%)	Rosiglitazone (67593)	Pioglitazone (159978)	Standardized mean difference
Cardiovascular disease			
Acute myocardial infarction [†]	743 (1.1)	1646 (1.0)	0.01
Coronary revascularization	5498 (8.1)	12760 (8.0)	0.01
Heart failure [†]	4690 (6.9)	9634 (6.0)	0.04
Other ischemic heart disease	14228 (21.0)	33235 (20.8)	0.01
Stroke [†]	895 (1.3)	1801 (1.1)	0.02
Diabetes-related disorders			
Microvascular disease	24660 (36.5)	59646 (37.3)	0.02
Peripheral vascular disease	3951 (5.8)	9024 (5.6)	0.01
Cardiovascular medications			
ACE inhibitors and ARBs	44838 (66.3)	107762 (67.4)	0.02
Antiarrhythmics	1270 (1.9)	2895 (1.8)	0.01
Anti-coagulants	5601 (8.3)	13693 (8.6)	0.01
Anti-platelets	9681 (14.3)	22804 (14.3)	0.00
Beta-blockers	28327 (41.9)	68752 (43.0)	0.02
Calcium channel blockers	21948 (32.5)	52696 (32.9)	0.01
Digoxin	4800 (7.1)	11012 (6.9)	0.01
Diuretics			
Loop	14671 (21.7)	34243 (21.4)	0.01
Potassium sparing	1953 (2.9)	4677 (2.9)	0.00
Thiazide	23847 (35.3)	57148 (35.7)	0.01
Nitrates	7516 (11.1)	16695 (10.4)	0.02
Diabetes-related medications			
Insulin	9281 (13.7)	21952 (13.7)	0.00
Oral			
Metformin	32989 (48.8)	83716 (52.3)	0.07
Sulfonylureas	32566 (48.2)	79696 (49.8)	0.03
Other	4107 (6.1)	13526 (8.5)	0.09
Lipid lowering			
Fibrates	5061 (7.5)	13146 (8.2)	0.03
Statins	38807 (57.4)	94759 (59.2)	0.04

[†]Hospitalized events only

Table 7. Additional medical conditions and medications used among cohort members during the 12-month (medical conditions) and 6-month (medications) period preceding initiation of thiazolidinedione therapy.

Characteristic, No. (%)	Rosiglitazone (67593)	Pioglitazone (159978)	Standardized mean difference
Medical conditions			
Alcohol abuse	658 (1.0)	1316 (0.8)	0.02
Chronic liver disease	827 (1.2)	2150 (1.3)	0.01
COPD	15158 (22.4)	34481 (21.6)	0.02
Dementia	2610 (3.9)	5636 (3.5)	0.02
Gout	3598 (5.3)	8593 (5.4)	0.00
Hypercholesterolemia	32671 (48.3)	78140 (48.8)	0.01
Hypertension	61042 (90.3)	144989 (90.6)	0.01
Hypertriglyceridemia	20300 (30.0)	51299 (32.1)	0.04
Hypothyroidism	14580 (21.6)	35062 (21.9)	0.01
Inflammatory arthritis	2794 (4.1)	6138 (3.8)	0.02
Kidney failure	6244 (9.2)	16850 (10.5)	0.04
Malignancy [†]	7387 (10.9)	18282 (11.4)	0.02
Obesity	5978 (8.8)	15069 (9.4)	0.02
Organ transplantation	275 (0.4)	715 (0.4)	0.01
Peptic ulcer disease	894 (1.3)	2024 (1.3)	0.01
Smoking	4700 (7.0)	11547 (7.2)	0.01
Medications			
Antidepressants	14686 (21.7)	34899 (21.8)	0.00
Biphosphonates	6798 (10.1)	15315 (9.6)	0.02
Estrogen replacement	1336 (2.0)	3097 (1.9)	0.00
H2-antagonists	4087 (6.0)	8844 (5.5)	0.02
NSAIDs	13005 (19.2)	28744 (18.0)	0.03
Proton pump inhibitors	16490 (24.4)	39687 (24.8)	0.01
Thyroid replacement	10259 (15.2)	26040 (16.3)	0.03

[†] Excluding non-melanoma skin cancer

3.2 EVENT RATES

During follow-up, there were 1746 AMIs (21.7% fatal), 1052 strokes (7.3% fatal), 3307 hospitalizations for HF (2.6% fatal), and 2562 deaths from all causes among cohort members (table 8). The incidence rates for all composite and individual endpoints were statistically significantly greater for rosiglitazone than pioglitazone except for AMI, where the confidence interval included zero. For the composite of AMI, stroke, HF, or death, the attributable risk was 1.68 excess events per 100 person-years of rosiglitazone treatment.

Table 8. Incidence and attributable risk (rate difference) of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in patients treated with rosiglitazone or pioglitazone.

Endpoint	Endpoints (No.)		Incidence rate [†]		Attributable risk [†] (95% CI)
	Rosiglitazone	Pioglitazone	Rosiglitazone	Pioglitazone	
Acute myocardial infarction	523	1223	1.83	1.68	0.15 (-0.03-0.33)
Stroke	363	689	1.27	0.95	0.32 (0.17-0.47)
Heart failure	1125	2182	3.94	3.00	0.94 (0.68-1.20)
All-cause mortality	814	1748	2.85	2.40	0.45 (0.22-0.67)
AMI or death	1222	2706	4.28	3.72	0.56 (0.28-0.83)
AMI, stroke, or death	1550	3325	5.43	4.57	0.85 (0.54-1.17)
AMI, stroke, heart failure, or death	2593	5386	9.10	7.42	1.68 (1.27-2.08)

[†] per 100 person-years

3.3 KAPLAN-MEIER PLOTS

All Kaplan-Meier cumulative incidence plots were truncated at 18 months of follow-up because of attrition of cohort size by that time. The cumulative incidence plots of rosiglitazone and pioglitazone were similar for AMI. For stroke and all-cause mortality, an increased risk with rosiglitazone was evident after less than two months of treatment, and for heart failure, an increase in rosiglitazone risk was seen by one month (figures 1-4). The cumulative incidence plots showed statistically significant increases in risk for all composite endpoints with rosiglitazone compared to pioglitazone (figures 5-7).

Figure 1. Kaplan-Meier cumulative incidence plot of time-to-event for acute myocardial infarction in elderly Medicare patients treated with rosiglitazone or pioglitazone.

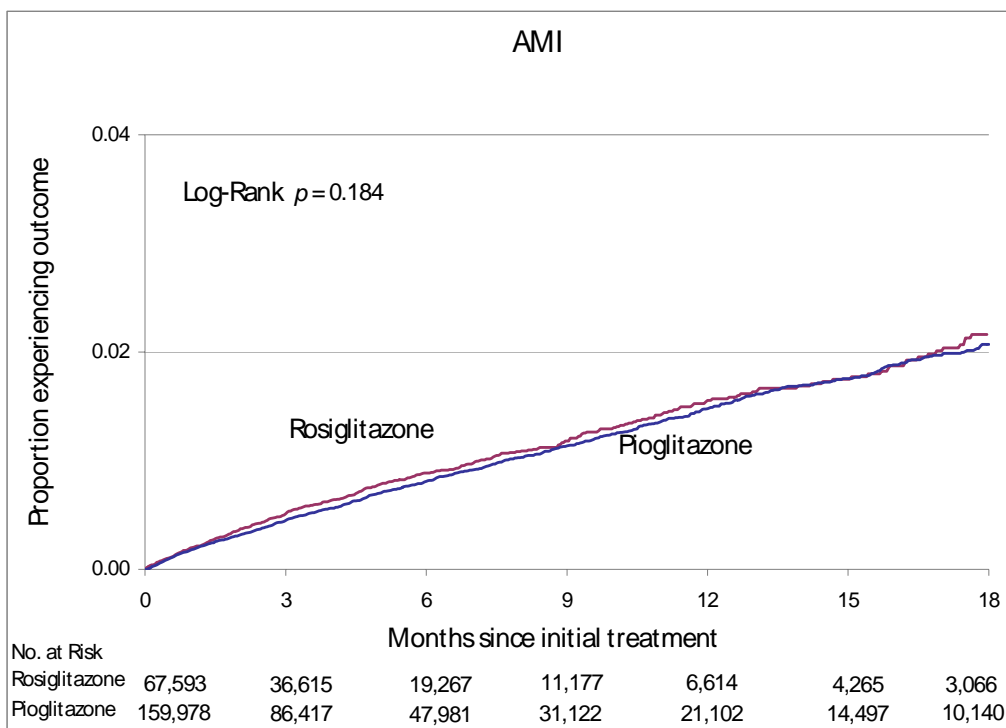


Figure 2. Kaplan-Meier cumulative incidence plot of time-to-event for stroke in elderly Medicare patients treated with rosiglitazone or pioglitazone.

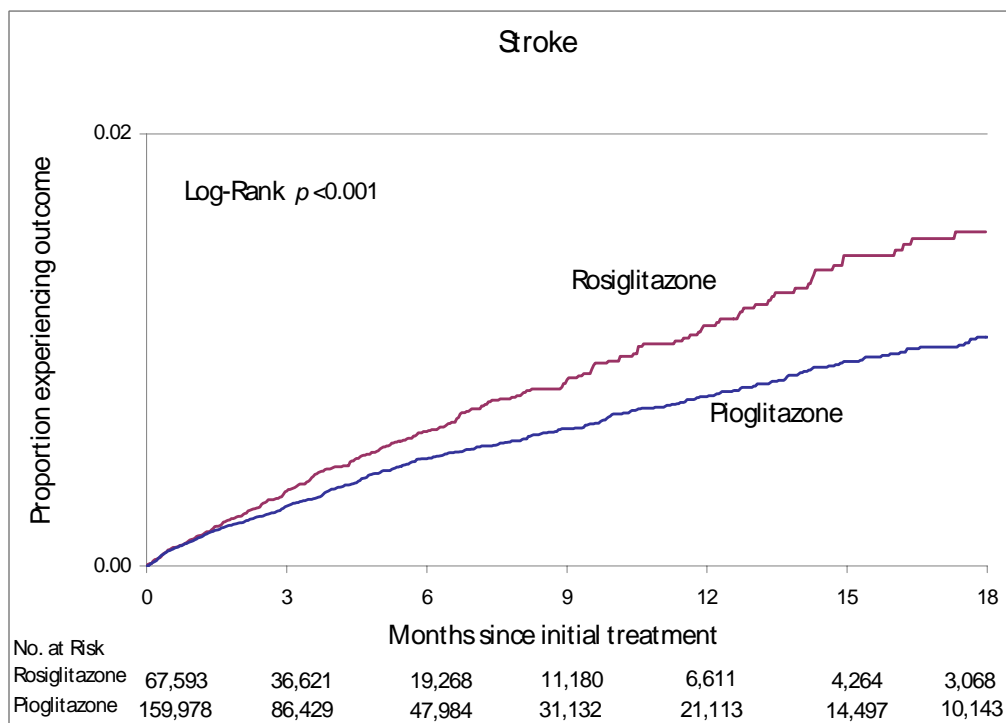


Figure 3. Kaplan-Meier cumulative incidence plot of time-to-event for heart failure in elderly Medicare patients treated with rosiglitazone or pioglitazone.

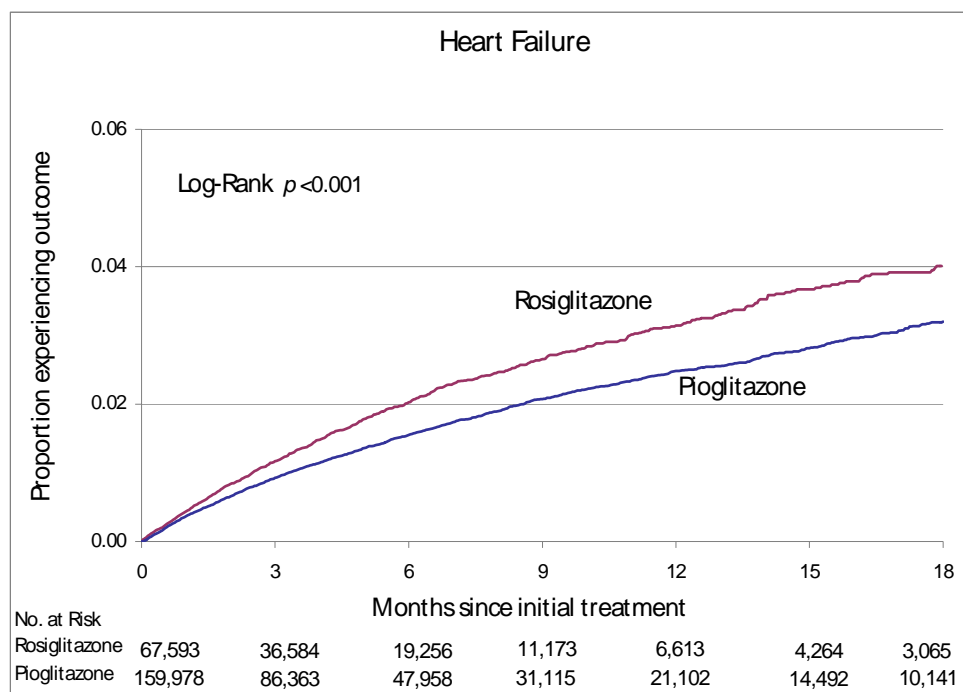


Figure 4. Kaplan-Meier cumulative incidence plot of time-to-event for all-cause mortality in elderly Medicare patients treated with rosiglitazone or pioglitazone.

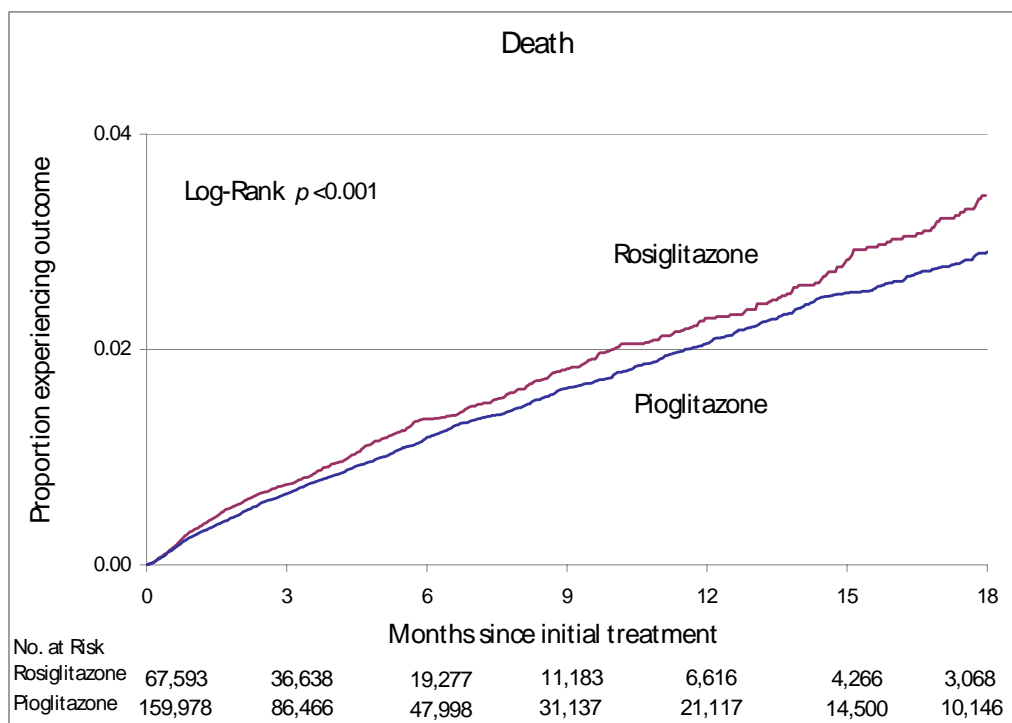


Figure 5. Kaplan-Meier cumulative incidence plot of time-to-event for the composite of AMI or all-cause mortality in elderly Medicare patients treated with rosiglitazone or pioglitazone.

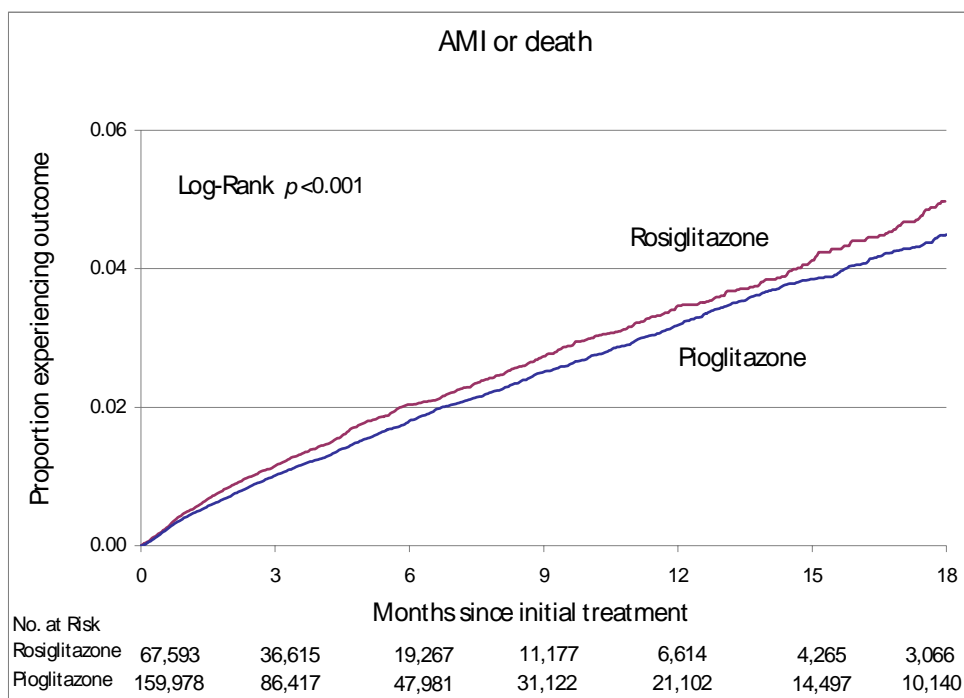


Figure 6. Kaplan-Meier cumulative incidence plot of time-to-event for the composite of AMI, stroke, or all-cause mortality in elderly Medicare patients treated with rosiglitazone or pioglitazone.

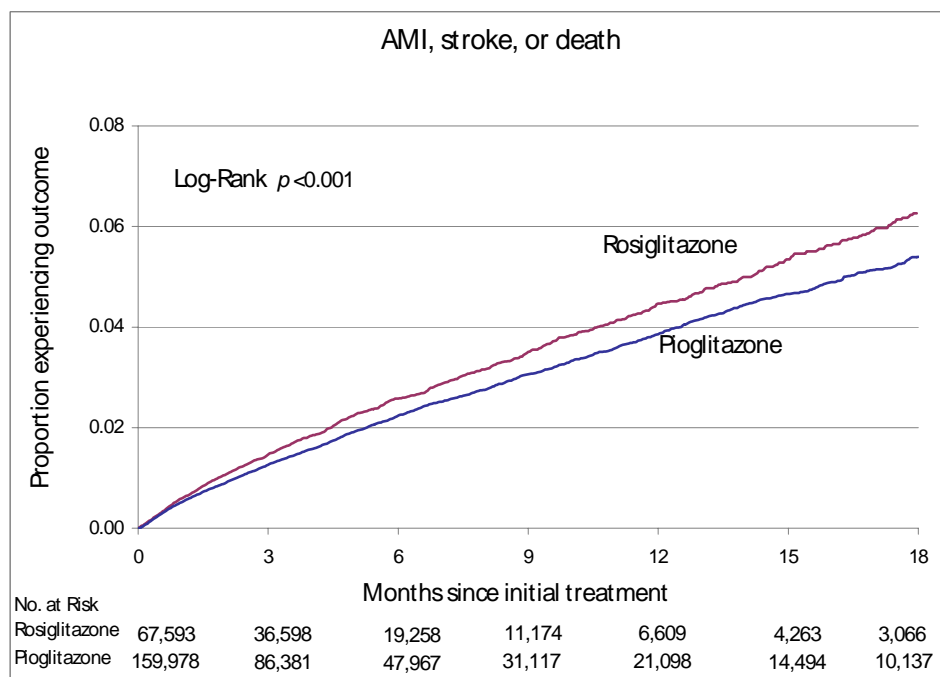
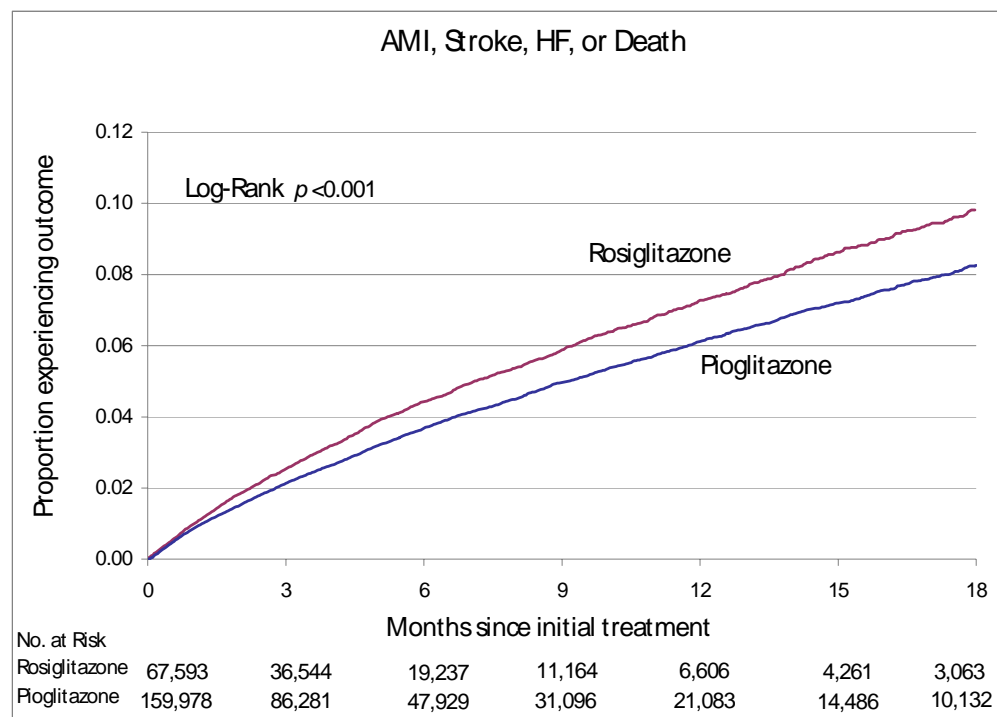


Figure 7. Kaplan-Meier cumulative incidence plot of time-to-event for the composite of AMI, stroke, heart failure, or all-cause mortality in elderly Medicare patients treated with rosiglitazone or pioglitazone.



3.4 HAZARD RATIOS

The unadjusted hazard ratios were increased for rosiglitazone compared with pioglitazone with all endpoints, statistically significantly so in all but AMI (table 9). After adjustment for all background, core cardiovascular, and additional medical variables, the hazard ratios associated with rosiglitazone use remained statistically significantly elevated compared with pioglitazone for all endpoints except AMI. Of note, rosiglitazone was associated with a hazard ratio of 1.27 (95% CI 1.12-1.45) for stroke, 1.25 (95% CI 1.16-1.34) for HF, 1.14 (95% CI 1.05-1.24) for death, and 1.18 (95% CI 1.12-1.23) for the composite of AMI, stroke, HF, or death, compared with pioglitazone. In the adjusted analysis, the proportional hazards assumption was met for AMI, stroke, and HF, but not for death or any of the composite endpoints that included death.

Table 9. Hazard ratios (95% CI) of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in patients treated with rosiglitazone or pioglitazone (n=227571).

Endpoint	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio [†] (95% CI)
Acute myocardial infarction	1.07 (0.97-1.19)	1.06 (0.96-1.18)
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)
All-cause mortality	1.17 (1.07-1.27)	1.14 (1.05-1.24) [‡]
AMI or death	1.13 (1.06-1.21)	1.11 (1.04-1.19) [‡]
AMI, stroke, or death	1.17 (1.10-1.24)	1.15 (1.08-1.22) [‡]
AMI, stroke, heart failure, or death	1.20 (1.14-1.26)	1.18 (1.12-1.23) [‡]

[†] Cox proportional hazards model stratified by prior endpoint and cancer and adjusted for variables in tables 1-3

[‡] Test of proportional hazards assumption not met

To explore this non-proportionality further, we performed a series of unplanned, *post hoc* analyses. We restricted our analysis to the 110950 patients who entered the study prior to the widely publicized publication of rosiglitazone meta-analysis by Nissen and Wolski on May 21, 2007.¹⁶ Nearly identical results were obtained (table 10) to those of the main pre-specified analysis and the proportional hazards assumption was now also met for death and AMI or death, suggesting that changes in physician prescribing behavior after May 2007 may have contributed to the non-proportionality of death-related hazard ratios seen with the entire study population.

Table 10. Hazard ratios (95% CI) of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in patients treated with rosiglitazone vs. pioglitazone, stratified by time of study entry pre- or post-May 21, 2007.

Endpoint	Pre-period (n=110950) Adjusted hazard ratio [†] (95% CI)	Post-period (n=116621) Adjusted hazard ratio [†] (95% CI)
Acute myocardial infarction	1.06 (0.93-1.20)	1.03 (0.82-1.28)
Stroke	1.20 (1.02-1.41)	1.26 (0.97-1.65)
Heart failure	1.18 (1.08-1.29)	1.35 (1.15-1.57)
All-cause mortality	1.17 (1.05-1.30)	1.10 (0.92-1.31) [‡]
AMI or death	1.14 (1.04-1.24)	1.06 (0.92-1.23) [‡]
AMI, stroke, or death	1.14 (1.06-1.23) [‡]	1.11 (0.98-1.27) [‡]
AMI, stroke, heart failure, or death	1.15 (1.08-1.22) [‡]	1.19 (1.08-1.32)

[†] Cox proportional hazards model stratified by prior endpoint and cancer and adjusted for variables in tables 1-3

[‡] Test of proportional hazards not met

A similar *post hoc* analysis restricted to patients who entered the study after the May 2007 publication date produced results similar to the pre-publication period (table 10) and the proportional hazards assumption was met for the composite of AMI, stroke, HF, or death. Of note, there were only 15009 rosiglitazone patients during this latter period who contributed 5400 person-years of exposed observation time, compared to 101612 pioglitazone patients followed for 40,100 person-years. Limited follow-up and relatively low event counts in the rosiglitazone group during the post-publication period accounted for the wide 95% confidence intervals we obtained (table 11).

Table 11. Event counts in rosiglitazone and pioglitazone cohorts during the post-May 21, 2007 time period.

	Rosiglitazone (n=15009)	Pioglitazone (n=101612)
Acute myocardial infarction	88	658
Stroke	63	373
Heart failure	187	1150
All-cause mortality	142	965
AMI or death	210	1490
AMI, stroke, or death	269	1818
AMI, stroke, heart failure, or death	444	2910

To examine further the contour of the hazard function for death, we partitioned follow-up time into three periods (0-2 months, 2-4 months, >4 months) and repeated the main analysis for death-related endpoints using the entire (pre- and post-publication) study population (table 12). The hazard ratios for all death-related endpoints were increased with rosiglitazone during the first interval though confidence intervals were wide for some endpoints due to limited numbers of events; were somewhat lower but still

increased during the second interval; and were increased to a greater degree in the third interval than during the first. This suggests that the hazard for death may vary during the first few months of rosiglitazone use before becoming constant. Importantly, the proportional hazard assumption was met during each follow-up interval for all death-related endpoints and all increases in the hazard ratio were statistically significant for the third and final interval (all-cause mortality: 1.21 (1.05-1.39); AMI or death: 1.13 (1.01-1.27); AMI, stroke, or death: 1.19 (1.08-1.32); AMI, stroke, HF, or death: 1.23 (1.14-1.34)).

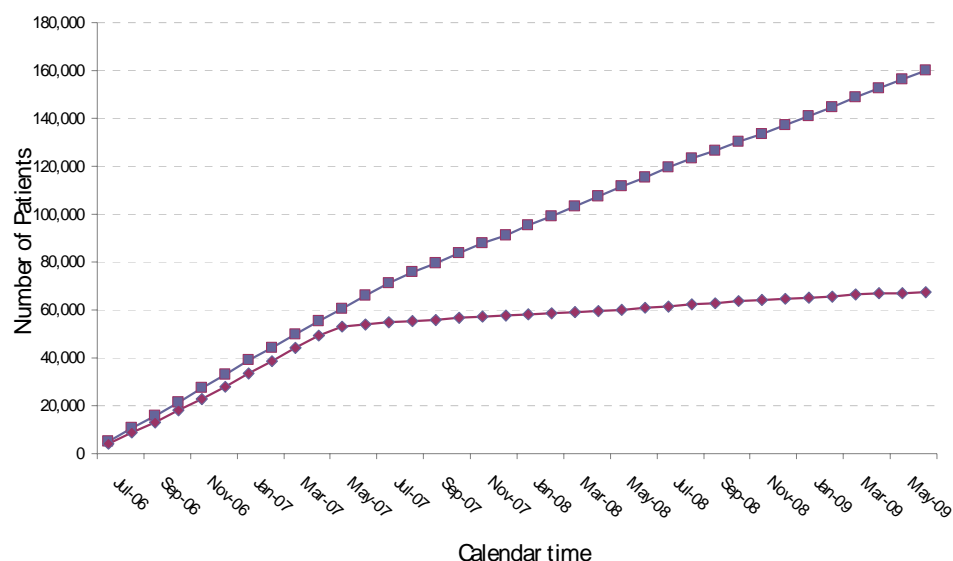
Table 12. Hazard ratios (95% CI) for death from all causes and for composite endpoints including death in patients treated with rosiglitazone vs. pioglitazone, by length of cohort follow-up.

	0-2 months	2-4 months	> 4 months
All-cause mortality	1.13 (1.00-1.28)	1.04 (0.85-1.27)	1.21 (1.05-1.39)
AMI or death	1.12 (1.02-1.24)	1.07 (0.91-1.25)	1.13 (1.01-1.27)
AMI, stroke, or death	1.12 (1.03-1.23)	1.13 (0.98-1.30)	1.19 (1.08-1.32)
AMI, stroke, heart failure, or death	1.14 (1.06-1.22)	1.19 (1.08-1.33)	1.23 (1.14-1.34)

3.5 EFFECT OF MAY 2007 PUBLICATION OF META-ANALYSIS

Prior to the May 2007 meta-analysis by Nissen and Wolski,¹⁶ entry into both TZD cohorts occurred at nearly identical rates. Following this date, entry into the rosiglitazone cohort decreased sharply, such that only 22.2% of cohort members commenced treatment during the remaining 25 months of the study, compared to 63.5% of the pioglitazone cohort. A number of unplanned post hoc analyses were performed to examine the potential effect of this publication on our study results.

Figure 8. Entry into rosiglitazone and pioglitazone cohorts by calendar time, July 2006-June 2009.



Analysis of baseline covariates suggested that patients entering either TZD cohort after this date were younger and healthier than those who entered prior to this date (tables 13 and 14).

Table 13. Selected baseline covariates of patients entering the rosiglitazone cohort before and after May 21, 2007. All values shown as %s.

	Rosiglitazone pre-May'07 (n=52584)	Rosiglitazone post-May'07 (n=15009)	Std mean diff
Age=65-69	28.3	31.3	0.07
Charlson score=0	73.9	81.4	0.18
Medication use			
ACE inhibitors/ARBs	66.9	64.5	0.05
β -blockers	42.7	39.2	0.07
Calcium channel blockers	33.0	30.6	0.05
Digoxin	7.4	6.0	0.06
Loop diuretics	22.4	19.1	0.08
Nitrates	11.8	8.7	0.10
Insulin	14.3	11.8	0.07
Statins	57.6	56.6	0.02
Medical conditions			
Acute myocardial infarction	1.2	0.8	0.03
Heart failure	7.4	5.3	0.09
Stroke	1.3	1.3	0.01

Table 14. Selected baseline covariates of patients entering the pioglitazone cohort before and after May 21, 2007. All values shown as %s.

	Pioglitazone pre-May'07 (n=58366)	Pioglitazone post-May'07 (n=101652)	Std mean diff
Age=65-69	27.9	29.6	0.04
Charlson score=0	74.3	81.5	0.18
Medication use			
ACE inhibitors/ARBs	66.9	67.6	0.01
β -blockers	42.6	43.2	0.01
Calcium channel blockers	32.8	33.0	0.01
Digoxin	7.8	6.3	0.06
Loop diuretics	23.6	20.1	0.09
Nitrates	11.7	9.7	0.06
Insulin	15.0	13.0	0.06
Statins	57.1	60.5	0.07
Medical conditions			
Acute myocardial infarction	1.2	0.9	0.03
Heart failure	7.2	5.3	0.08
Stroke	1.2	1.1	0.01

To evaluate the potential for confounding arising from this change in characteristics of patients entering the study, we analyzed the distribution of baseline covariates in patients entering the rosiglitazone and pioglitazone cohorts after the publication date and found the post-publication study cohorts to be nearly identical, as was the case for the pre-publication cohorts (tables 15, 16).

Table 15. Comparison of baseline characteristics of patients entering the rosiglitazone or pioglitazone cohorts prior to May 21, 2007. All values shown as %s.

	Rosiglitazone (n=52584)	Pioglitazone (n=58366)	Std mean diff
Background (%)			
Female	61.7	60.7	0.02
Age			
65-69	28.3	27.9	0.01
70-74	27.2	27.2	0.00
75-79	21.8	21.9	0.00
80+	22.7	23.0	0.01
Charlson score			
0	73.9	74.3	0.01
1	8.2	8.0	0.01
2	7.2	7.1	0.00
3+	10.7	10.6	0.00
Medications (%)			
<i>General Medical</i>			
Antidepressants	21.9	21.9	0.00
Estrogen	2.0	2.1	0.01
H2-antagonists	6.3	5.6	0.03
NSAIDs	18.9	17.3	0.04
Proton pump inhibitors	24.3	23.2	0.03
Thyroid replacement	15.3	16.6	0.03
<i>Cardiovascular</i>			
ACE Inhibitors and ARBs	66.9	66.9	0.00
Antiarrhythmics	2.0	1.9	0.00
Anti-coagulants	8.6	9.1	0.02
Anti-platelets	14.5	14.6	0.00
Beta-blockers	42.7	42.6	0.00
Calcium channel blockers	33.0	32.8	0.00
Digoxin	7.4	7.8	0.02
Diuretics			
Loop	22.4	23.6	0.03
Potassium sparing	3.0	3.1	0.01
Thiazide	35.4	35.5	0.00
Nitrates	11.8	11.7	0.00
<i>Diabetes-related</i>			
Insulin	14.3	15.0	0.02
Oral			
Metformin	48.1	47.1	0.02
Sulfonylureas	48.8	48.2	0.01
Other	5.2	5.7	0.02
<i>Lipid lowering</i>			
Fibrates	7.3	7.7	0.02
Statins	57.6	57.1	0.01

Table 16. Comparison of baseline characteristics of patients entering the rosiglitazone or pioglitazone cohorts after May 21, 2007. All values shown as %s.

	Rosiglitazone (n=19237)	Pioglitazone (n=47929)	Std mean diff
Background (%)			
Female	57.6	58.7	0.02
Age			
65-69	31.3	29.6	0.04
70-74	27.0	27.5	0.01
75-79	19.7	20.5	0.02
80+	22.0	22.4	0.01
Charlson score			
0	77.4	76.4	0.02
1	7.4	7.6	0.00
2	5.7	6.3	0.03
3+	9.5	9.7	0.01
Medications (%)			
<i>General Medical</i>			
Antidepressants	21.1	21.7	0.01
Estrogen	2.0	1.8	0.01
H2-antagonists	5.1	5.5	0.01
NSAIDs	20.3	18.4	0.05
Proton pump inhibitors	24.7	25.8	0.02
Thyroid replacement	14.9	16.1	0.03
<i>Cardiovascular</i>			
ACE Inhibitors and ARBs	64.5	67.6	0.07
Antiarrhythmics	1.5	1.7	0.02
Anti-coagulants	7.2	8.3	0.04
Anti-platelets	13.7	14.0	0.01
Beta-blockers	39.2	43.2	0.08
Calcium channel blockers	30.6	33.0	0.05
Digoxin	6.0	6.3	0.02
Diuretics			
Loop	19.1	20.1	0.02
Potassium sparing	2.7	2.8	0.01
Thiazide	34.9	35.8	0.02
Nitrates	8.7	9.7	0.03
<i>Diabetes-related</i>			
Insulin	11.8	13.0	0.03
Oral			
Metformin	51.3	55.3	0.08
Sulfonylureas	46.0	50.7	0.09
Other	9.2	10.0	0.03
<i>Lipid lowering</i>			
Fibrates	8.3	8.5	0.01
Statins	56.6	60.5	0.08

We also examined baseline characteristics of patients remaining in the study at 6, 12, 18, and 24 months of follow-up, to examine whether differential censoring might lead to cohorts that became imbalanced over time. At each time-point, the rosiglitazone and pioglitazone cohorts remained closely similar, with no meaningful differences emerging (Appendix, tables A1-A4).

In addition, we examined the effect of differential entry into the rosiglitazone and pioglitazone cohorts on incidence rates by recalculating them by stratifying on pre- vs. post-cohort entry and pooling the incidence rates using Mantel-Haenszel methods (table 17). There was relatively little change from the pre-specified analysis (table 8).

Table 17. Mantel-Haenszel rate differences (attributable risk) with 95% confidence intervals of study endpoints for rosiglitazone compared to pioglitazone.

	Mantel-Haenszel rate difference, per 100 person-years	95% confidence interval, per 100 person-years
Acute myocardial infarction	0.0966	(-0.082 - 0.275)
Stroke	0.2985	(0.148 - 0.449)
Heart failure	0.7962	(0.536 - 1.056)
All-cause mortality	0.4172	(0.191 - 0.644)
AMI or death	0.5020	(0.226 - 0.778)
AMI, stroke, or death	0.7691	(0.457 - 1.081)
AMI, stroke, heart failure, or death	1.4684	(1.067 - 1.869)

Finally, we also performed *post hoc* Cox regression stratified by pre- vs. post-publication time period (table 18). The results were very similar to those of the pre-specified analysis. Of note, allowing different baseline hazards in the pre- vs. post-publication period for the different endpoints did not resolve the issue of non-proportionality. Another observation to note is that Cox models that failed to pass the test for proportional hazards yielded identical results to other models where the proportional hazards assumption was met (see heart failure below).

Table 18. Hazard ratios (95% CI) of various study endpoints for the rosiglitazone cohort compared with the pioglitazone cohort. The Cox model was stratified by time of study entry (pre- vs. post May 21, 2007), with additional adjustment or stratification as indicated.

	Adjusted for core + additional variables	Also stratified by prior endpoint and cancer, + adjusted for all variables
Acute myocardial infarction	1.05 (0.94-1.18)	1.05 (0.94-1.17)
Stroke	1.22 (1.06-1.40)	1.22 (1.07-1.40)
Heart failure	1.22 (1.13-1.32) [†]	1.22 (1.13-1.32)
All-cause mortality	1.15 (1.05-1.25) [†]	1.14 (1.04-1.25) [†]
AMI or death	1.12 (1.04-1.20) [†]	1.11 (1.04-1.20) [†]
AMI, stroke, or death	1.14 (1.07-1.21) [†]	1.13 (1.06-1.21) [†]
AMI, stroke, heart failure, or death	1.16 (1.11-1.22) [†]	1.16 (1.10-1.22) [†]

[†] Test of proportional hazards assumption not met

3.6 SENSITIVITY ANALYSES

Several pre-specified sensitivity analyses were performed. We repeated the main analyses on the entire study population without allowing for the 14-day follow-up after admission to hospital or a break in TZD use. In this analysis, patients dying after hospital admission or experiencing any study endpoint shortly after stopping their TZD were not counted. The hazard ratio for stroke and HF with rosiglitazone compared to pioglitazone remained statistically significantly increased, as did the hazard ratios for the composite endpoints of AMI, stroke, or death, and AMI, stroke, HF, or death. The hazard ratio for all-

cause mortality was no longer increased (hazard ratio 1.06, 95% CI 0.94-1.21). This difference from the main analysis highlights the presence of informative censoring for death that occurred when follow-up did not continue for some period beyond hospital admission or interruption in drug therapy.

Table 19. Hazard ratios (95% CI) of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in patients treated with rosiglitazone compared with pioglitazone (n=227571), with 0-days of extended follow-up.

0-day extended follow-up	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio [†] (95% CI)
Acute myocardial infarction	1.03 (0.92-1.15)	1.02 (0.91-1.14)
Stroke	1.24 (1.08-1.42)	1.21 (1.05-1.39)
Heart failure	1.26 (1.17-1.37)	1.24 (1.15-1.35) [‡]
All-cause mortality	1.10 (0.97-1.25)	1.07 (0.95-1.22)
AMI/D	1.07 (0.98-1.17)	1.05 (0.97-1.15)
AMI/S/D	1.12 (1.04-1.20)	1.10 (1.02-1.18) [‡]
AMI/S/HF/D	1.18 (1.11-1.24)	1.16 (1.10-1.22) [‡]

[†] Cox proportional hazards model stratified by prior endpoint and cancer and adjusted for variables in tables 1-3

[‡] Test of proportional hazards assumption not met

We also examined the effect of rosiglitazone on risk of study endpoints, stratified separately by baseline use of insulin, metformin, sulfonylureas, nitrates, and statins. The hazard ratios for each endpoint were similar in those with and without baseline use of these agents (Appendix, tables A5-A11).

In an unplanned *post hoc* analysis, we restricted the cohorts to patients without prior history of AMI, stroke, or HF, or to patients without prior diagnosis of cancer, and obtained results consistent with the main analyses (table 20).

Table 20. Hazard ratios (95% CI) of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in patients treated with rosiglitazone compared with pioglitazone, restricted to the subgroups without history of cancer and without history of a previous endpoint event.

	No prior cancer (n=201902) Hazard ratio (95% CI) [†]	No prior study endpoint (n=209789) Hazard ratio (95% CI) [†]
Acute myocardial infarction	1.08 (0.96-1.20)	1.09 (0.97-1.22)
Stroke	1.27 (1.11-1.45)	1.34 (1.16-1.54)
Heart failure	1.27 (1.18-1.38) [‡]	1.33 (1.21-1.45)
All-cause mortality	1.15 (1.04-1.26) [‡]	1.12 (1.01-1.23) [‡]
AMI/D	1.12 (1.04-1.20) [‡]	1.10 (1.02-1.19) [‡]
AMI/S/D	1.15 (1.07-1.22) [‡]	1.15 (1.07-1.23) [‡]
AMI/S/HF/D	1.19 (1.13-1.25) [‡]	1.20 (1.13-1.26) [‡]

[†] Cox proportional hazards model for variables in tables 1-3

[‡] Test of proportional hazards assumption not met

Finally, we performed a *post hoc* life-table analysis of each endpoint to examine consistency of the hazard ratio over different periods of follow-up time. The results are shown in tables A12-A19 of the Appendix. The interval-specific hazard ratio for AMI with rosiglitazone compared to pioglitazone was increased and of borderline statistical significance during the 0-4 month interval (1.13 (95% CI 0.99-1.28)) and was close to the null value for the subsequent intervals (4-8 months, 8-12 months, and 12+ months). The hazard ratios for stroke and heart failure were consistently elevated across all intervals for rosiglitazone compared to pioglitazone. All-cause mortality was increased during the first year, with the suggestion of a possible further increase in rosiglitazone risk beyond 12 months of treatment.

3.7 POPULATION IMPACT

From the start of marketing in 1999 through 2009, an estimated 82.5 million prescriptions for rosiglitazone were filled in the US. Over the past eight years for which data were available, 38.4% of these prescriptions were for patients age 65 years or older.⁷⁶ The mean prescription length was 32.7 days, leading to a total exposure time of 2.84 million years in the elderly from the start of marketing through December 2009. Based on the observed rate differences (table 8), the NNH was calculated for each endpoint except AMI (table 21). We did not calculate NNH for AMI because the 95% CI for the rate difference (attributable risk) included the null value, 0. Using these estimates of NNH, we arrived at the estimates shown in table 21 of the number of excess events expected to have occurred in US elderly who used rosiglitazone instead of pioglitazone from 1999-2009. For the composite of AMI, stroke, HF, or death, the NNH was 60 treated for one year, yielding an estimated excess of 48000 events attributable to rosiglitazone from 1999 through 2009.

Table 21. Estimated number of excess cases of acute myocardial infarction, stroke, heart failure, all-cause mortality, and composite cardiovascular endpoints in US patients age 65 years and older who were treated with rosiglitazone instead of pioglitazone from 1999-2009.

Endpoint events	Number needed to harm [†] (95% CI)	Excess events (No.)
Acute myocardial infarction	---	---
Stroke	313 (213-588)	9250
Heart failure	106 (83-147)	26900
All-cause mortality	222 (147-455)	12800
AMI or death	179 (120-357)	15900
AMI, stroke, or death	118 (85-185)	24500
AMI, stroke, heart failure, or death	60 (48-79)	48000

[†] Number treated for one year to generate one excess event

4 DISCUSSION

4.1 SUMMARY OF RESULTS

Use of rosiglitazone was associated with an increased risk of stroke, HF, death, and the composite of AMI, stroke, HF, or death compared with pioglitazone among Medicare beneficiaries age 65 years or older. Both thiazolidinediones have been shown to increase the risk of heart failure compared with treatment with placebo or other antidiabetic medications.^{77,78} Our study found that rosiglitazone was associated with a 1.25-fold (95% CI 1.16-1.34) increase in heart failure risk compared with pioglitazone, similar to that reported in two other studies of the elderly.^{46,49} Of note, a differentially increased risk of heart failure with rosiglitazone was also suggested by a meta-analysis of randomized trials for both drugs.⁷⁹ Heart failure is associated with increased one-year and four-year mortality and this mortality effect is greater in patients with diabetes,⁸⁰ an effect that would not be captured by our study because of limited longer-term follow-up.

We were unable to determine whether one or both thiazolidinediones increase or decrease the absolute risk of any outcome because we did not have a reference group treated with non-thiazolidinedione medications only. However, these data suggest that rosiglitazone was associated with a 1.27-fold (95% CI 1.11-1.44) increased risk of stroke and a 1.14-fold (95% CI 1.05-1.24) increased risk of death compared with pioglitazone. Increased mortality in elderly patients treated with rosiglitazone compared with pioglitazone, of a magnitude similar to that described here, has also been reported in other studies.^{46,49}

The risk of AMI was not different between the two thiazolidinediones in this study of Medicare elderly, although the Kaplan-Meier plot was slightly elevated for rosiglitazone compared to pioglitazone and the point estimate for the hazard ratio was slightly increased as well. Two other studies conducted in the elderly, where the mean age was 72-76 years, also found no difference in AMI risk between the two thiazolidinediones.^{46,49} In contrast, most studies that have reported an increased risk of AMI with rosiglitazone were conducted in younger populations, with a mean age of 54-65 years and most required that patients survive to hospitalization to be counted.^{16,44,45,50,51} There may be no difference in AMI risk between the two drugs in the elderly. However, it is also possible that the pattern of cardiovascular outcomes for rosiglitazone compared with pioglitazone changes with advancing age. The incidence of sudden cardiac death increases nearly 6-fold between the sixth and eighth decades of life,⁸¹ perhaps contributing to a shift towards fatal AMI that does not reach hospital to be counted. In an older population of patients with diabetes, where nearly 70% of deaths have an underlying cardiovascular cause,⁷³ the effect of an increase in sudden cardiac death might be even greater. While the reason for the increased risk of death with rosiglitazone compared with pioglitazone seen in the elderly in our study and others is not known,^{46,49} it is plausibly due to an increase in a specific cause rather than to a diffuse increase in all causes of death. We believe that this specific cause is most likely cardiovascular.

The incidence rates of AMI, stroke, HF, and death observed for the pioglitazone cohort in our study were similar to those that can be calculated for the pioglitazone arm of the PROactive trial, a large cardiovascular endpoint trial that compared pioglitazone to other diabetes therapies (calculated incidence rates from PROactive per 100 person-years: AMI: 1.6; stroke: 1.2; HF: 2.8; death: 2.4).¹⁰ Although the mean age of patients in PROactive was younger than our cohort (61.1 years vs. 74.4 years), it was enriched in patients with established macrovascular disease, thereby making it more similar to an older population with longer-standing diabetes. This similarity in rates suggests that event capture in our study was relatively complete. The event rates in our study were also similar to those obtained by Juurlink et al. in a study of elderly patients with diabetes from Ontario, Canada.⁴⁹

Based on commercially available drug usage data purchased by the FDA, there were an estimated 2.84 million person-years of rosiglitazone used by patients age 65 years or older in the US from 1999-2009.⁷⁶ With a NNH of 60 treated for one year to produce one excess event of AMI, stroke, HF, or death attributable to use of rosiglitazone rather than pioglitazone, the negative population impact of rosiglitazone has probably been great. We have estimated 48000 excess events attributable to use of rosiglitazone instead of pioglitazone in US elderly from the start of marketing through the end of 2009. The national impact is probably much greater because our estimate does not account for rosiglitazone use among patients under the age of 65 years, where an estimated 61.6% of rosiglitazone use occurred through 2009,⁷⁶ nor does it account for delayed excess mortality and disability from stroke or HF.^{80,82}

There are a number of limitations to this study that should be mentioned. This was an observational study, not a randomized trial, and so could be subject to biases arising from confounding. To guard against this, we collected data on a wide array of variables known or suspected to be associated with the outcomes under study, as well as many variables related to general health. The two cohorts were virtually indistinguishable with respect to these numerous baseline characteristics. In this regard, other observational studies that directly compared rosiglitazone to pioglitazone also noted a marked similarity between drug groups with respect to baseline characteristics and risk factors,⁴⁴⁻⁵⁰ suggesting to us that the thiazolidinediones are probably prescribed to comparable types of patients. Misclassification of exposure or outcome is another potential limitation of observational studies, but usually acts to reduce the strength of associations. We did not independently validate the diagnosis of AMI, stroke, or HF. There is currently no mechanism in place under the SafeRx Project to obtain medical record data. However, the ICD-9 diagnosis coded case definitions that we adhered to in this study have been consistently well-validated in previous studies using the same or similar hospitalization claims data.⁶⁰⁻⁷¹ Finally, because prescription drug data from Medicare Part D have not been used extensively for purposes of comparative safety, issues related to data quality must be considered. The Medicare Part D data are collected and

processed by CMS in exactly the same manner as prescription data from Medicaid and a detailed study of Medicaid prescription data found it to be complete and of high quality.⁸³

In conclusion, in a population of more than 227000 elderly new users of a thiazolidinedione, we found that rosiglitazone was associated with an increased the risk of stroke, HF, death and the composites of AMI or death, AMI, stroke, or death, and AMI, stroke, HF, or death compared with pioglitazone.

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6 APPENDIX

Table A1. Baseline characteristics of patients remaining in the rosiglitazone and pioglitazone beyond 6-months of study follow-up.

6-months follow-up	Rosiglitazone (n=19237)	Pioglitazone (n=47929)	Std mean diff
Background (%)			
Female	11472 (59.6)	27950 (58.3)	0.03
Age			
65-69	5848 (30.4)	14312 (29.8)	0.01
70-74	5238 (27.2)	13013 (27.2)	0.00
75-79	4078 (21.2)	10063 (21.0)	0.00
80+	4073 (21.1)	10541 (22.0)	0.02
Charlson score			
0	15365 (79.9)	38502 (80.3)	0.01
1	1431 (7.4)	3399 (7.1)	0.01
2	1107 (5.8)	2724 (5.7)	0.00
3+	1334 (6.9)	3304 (6.9)	0.00
Medications (%)			
<i>General Medical</i>			
Antidepressants	4193 (21.8)	10364 (21.6)	0.00
Estrogen	439 (2.3)	977 (2.0)	0.02
H2-antagonists	1103 (5.7)	2680 (5.6)	0.01
NSAIDs	3657 (19.0)	8326 (17.4)	0.04
Proton pump inhibitors	4326 (22.5)	11460 (23.9)	0.03
Thyroid replacement	2935 (15.3)	7845 (16.4)	0.03
<i>Cardiovascular</i>			
ACE Inhibitors and ARBs	13088 (68.0)	33168 (69.2)	0.03
Antiarrhythmics	254 (1.3)	694 (1.4)	0.01
Anti-coagulants	1432 (7.4)	3749 (7.8)	0.01
Anti-platelets	2322 (12.1)	6036 (12.6)	0.02
Beta-blockers	7840 (40.8)	20369 (42.5)	0.04
Calcium channel blockers	6254 (32.5)	15743 (32.8)	0.01
Digoxin	1333 (6.9)	3185 (6.6)	0.01
Diuretics			
Loop	3701 (19.2)	9207 (19.2)	0.00
Potassium sparing	485 (2.5)	1176 (2.4)	0.00
Thiazide	7169 (37.3)	18254 (38.1)	0.02
Nitrates	1808 (9.4)	4365 (9.1)	0.01
<i>Diabetes-related</i>			
Insulin	2099 (10.9)	5415 (11.3)	0.01
Oral			
Metformin	9981 (51.9)	26344 (55.0)	0.06
Sulfonylureas	9560 (49.7)	24021 (50.1)	0.01
Other	1105 (5.7)	3667 (7.7)	0.07
<i>Lipid lowering</i>			
Fibrates	1508 (7.8)	4134 (8.6)	0.03
Statins	11636 (60.5)	30085 (62.8)	0.05

Table A2. Baseline characteristics of patients remaining in the rosiglitazone and pioglitazone beyond 12-months of study follow-up.

12-months follow-up	Rosiglitazone (n=6606)	Pioglitazone (n=21083)	Std mean diff
Background (%)			
Female	59.2	58.7	0.01
Age			
65-69	31.7	29.6	0.05
70-74	26.9	27.3	0.01
75-79	21.0	21.3	0.01
80+	20.3	21.8	0.04
Charlson score			
0	82.2	82.1	0.00
1	6.7	6.7	0.00
2	5.4	5.2	0.01
3+	5.7	5.9	0.01
Medications (%)			
<i>General Medical</i>			
Antidepressants	22.1	21.5	0.01
Estrogen	2.6	2.1	0.03
H2-antagonists	5.5	5.8	0.01
NSAIDs	18.7	17.2	0.04
Proton pump inhibitors	20.6	23.2	0.06
Thyroid replacement	14.5	16.1	0.04
<i>Cardiovascular</i>			
ACE Inhibitors and ARBs	68.2	69.3	0.02
Antiarrhythmics	1.2	1.4	0.02
Anti-coagulants	6.6	7.5	0.04
Anti-platelets	10.1	11.5	0.05
Beta-blockers	39.3	42.0	0.06
Calcium channel blockers	32.0	32.9	0.02
Digoxin	6.2	6.6	0.02
Diuretics			
Loop	17.6	18.1	0.01
Potassium sparing	2.1	2.2	0.01
Thiazide	38.2	39.0	0.02
Nitrates	7.7	8.7	0.04
<i>Diabetes-related</i>			
Insulin	9.3	10.1	0.03
Oral			
Metformin	51.9	54.9	0.06
Sulfonylureas	49.6	49.6	0.00
Other	5.0	6.7	0.07
<i>Lipid lowering</i>			
Fibrates	7.6	8.3	0.03
Statins	60.6	63.5	0.06

Table A3. Baseline characteristics of patients remaining in the rosiglitazone and pioglitazone beyond 18-months of study follow-up.

18-months follow-up	Rosiglitazone (n=3063)	Pioglitazone (n=10132)	Std mean diff
Background (%)			
Female	58.8	59.2	0.01
Age			
65-69	32.5	29.1	0.07
70-74	27.2	27.2	0.00
75-79	21.6	22.3	0.02
80+	18.8	21.4	0.06
Charlson score			
0	83.7	83.3	0.01
1	6.7	6.6	0.00
2	5.0	4.8	0.01
3+	4.7	5.3	0.03
Medications (%)			
<i>General Medical</i>			
Antidepressants	20.8	21.1	0.01
Estrogen	2.7	2.1	0.04
H2-antagonists	5.6	5.8	0.01
NSAIDs	18.4	17.3	0.03
Proton pump inhibitors	19.3	22.8	0.09
Thyroid replacement	14.7	15.9	0.03
<i>Cardiovascular</i>			
ACE Inhibitors and ARBs	67.7	69.3	0.03
Antiarrhythmics	0.9	1.5	0.04
Anti-coagulants	5.9	7.2	0.05
Anti-platelets	9.2	10.8	0.05
Beta-blockers	38.1	42.1	0.08
Calcium channel blockers	31.8	33.0	0.03
Digoxin	5.6	6.4	0.03
Diuretics			
Loop	16.7	16.7	0.00
Potassium sparing	1.8	2.0	0.01
Thiazide	38.2	40.5	0.05
Nitrates	7.1	8.3	0.04
<i>Diabetes-related</i>			
Insulin	8.3	9.4	0.04
Oral			
Metformin	51.4	54.1	0.05
Sulfonylureas	48.0	49.3	0.03
Other	4.6	5.6	0.04
<i>Lipid lowering</i>			
Fibrates	7.3	8.2	0.03
Statins	60.5	63.8	0.07

Table A4. Baseline characteristics of patients remaining in the rosiglitazone and pioglitazone beyond 24-months of study follow-up.

24-months follow-up	Rosiglitazone (n=1762)	Pioglitazone (n=5335)	Std mean diff
Background (%)			
Female	59.8	59.9	0.00
Age			
65-69	32.6	29.3	0.07
70-74	27.4	27.9	0.01
75-79	22.8	22.3	0.01
80+	17.2	20.5	0.08
Charlson score			
0	85.0	84.4	0.02
1	6.3	6.4	0.00
2	4.4	4.2	0.01
3+	4.3	5.0	0.03
Medications (%)			
<i>General Medical</i>			
Antidepressants	19.7	20.5	0.02
Estrogen	2.8	2.4	0.03
H2-antagonists	5.7	6.0	0.01
NSAIDs	19.4	17.5	0.05
Proton pump inhibitors	18.7	22.0	0.08
Thyroid replacement	14.6	16.1	0.04
<i>Cardiovascular</i>			
ACE Inhibitors and ARBs	67.3	68.6	0.03
Antiarrhythmics	0.9	1.2	0.04
Anti-coagulants	5.7	6.5	0.03
Anti-platelets	8.5	10.2	0.06
Beta-blockers	37.9	41.5	0.07
Calcium channel blockers	32.5	32.7	0.00
Digoxin	4.7	6.0	0.06
Diuretics			
Loop	15.9	15.9	0.00
Potassium sparing	1.7	1.9	0.01
Thiazide	39.2	41.7	0.05
Nitrates	6.7	7.5	0.03
<i>Diabetes-related</i>			
Insulin	7.5	9.0	0.05
Oral			
Metformin	51.1	52.8	0.04
Sulfonylureas	46.9	48.0	0.02
Other	4.4	4.4	0.00
<i>Lipid lowering</i>			
Fibrates	7.6	7.8	0.01
Statins	61.1	63.5	0.05

Tables A5-A11. Adjusted hazard ratios (95% CI) of AMI, stroke, heart failure, death, and composite cardiovascular endpoints in patients treated with rosiglitazone compared to pioglitazone, stratified by baseline use of selected medications. Hazard ratio (HR), lower 95% CI (LL), upper 95% CI (UL)

Table A5.

AMI		HR	LL	UL
Insulin	Yes	1.11	0.89	1.38
	No	1.05	0.93	1.18
Metformin	Yes	1.04	0.89	1.21
	No	1.08	0.94	1.24
Sulfonylurea	Yes	1.06	0.93	1.22
	No	1.05	0.91	1.23
Nitrates	Yes	1.08	0.88	1.33
	No	1.05	0.93	1.18
Statins	Yes	1.07	0.94	1.23
	No	1.03	0.89	1.21

Table A6.

Stroke (S)		HR	LL	UL
Insulin	Yes	1.18	0.87	1.60
	No	1.28	1.11	1.48
Metformin	Yes	1.31	1.10	1.57
	No	1.22	1.02	1.47
Sulfonylurea	Yes	1.36	1.14	1.62
	No	1.17	0.97	1.41
Nitrates	Yes	1.57	1.13	2.18
	No	1.22	1.06	1.40
Statins	Yes	1.25	1.04	1.49
	No	1.29	1.08	1.55

Table A7.

HF		HR	LL	UL
Insulin	Yes	1.19	1.03	1.37
	No	1.26	1.16	1.38
Metformin	Yes	1.27	1.14	1.42
	No	1.22	1.11	1.35
Sulfonylurea	Yes	1.30	1.18	1.43
	No	1.17	1.05	1.31
Nitrates	Yes	1.12	0.97	1.28
	No	1.30	1.20	1.42
Statins	Yes	1.29	1.17	1.41
	No	1.19	1.06	1.33

Table A8.

Death (D)		HR	LL	UL
Insulin	Yes	1.17	0.98	1.39
	No	1.12	1.01	1.23
Metformin	Yes	1.11	0.98	1.27
	No	1.14	1.02	1.26
Sulfonylurea	Yes	1.14	1.01	1.28
	No	1.12	0.99	1.26
Nitrates	Yes	1.14	0.93	1.40
	No	1.13	1.03	1.24
Statins	Yes	1.15	1.02	1.30
	No	1.11	0.98	1.24

Table A9.

AMI/D		HR	LL	UL
Insulin	Yes	1.15	1.00	1.33
	No	1.09	1.01	1.18
Metformin	Yes	1.08	0.97	1.20
	No	1.12	1.02	1.22
Sulfonylurea	Yes	1.10	1.00	1.21
	No	1.10	1.00	1.21
Nitrates	Yes	1.11	0.95	1.29
	No	1.11	1.02	1.19
Statins	Yes	1.13	1.03	1.24
	No	1.08	0.98	1.19

Table A10.

AMI/S/D		HR	LL	UL
Insulin	Yes	1.17	1.03	1.34
	No	1.13	1.05	1.21
Metformin	Yes	1.13	1.03	1.24
	No	1.14	1.05	1.24
Sulfonylurea	Yes	1.14	1.05	1.24
	No	1.13	1.03	1.23
Nitrates	Yes	1.17	1.01	1.34
	No	1.13	1.06	1.21
Statins	Yes	1.15	1.06	1.26
	No	1.11	1.02	1.22

Table A11.

AMI/S/HF/D		HR	LL	UL
Insulin	Yes	1.18	1.07	1.30
	No	1.17	1.11	1.23
Metformin	Yes	1.17	1.09	1.26
	No	1.17	1.10	1.24
Sulfonylurea	Yes	1.19	1.12	1.27
	No	1.14	1.06	1.22
Nitrates	Yes	1.11	1.10	1.23
	No	1.19	1.13	1.25
Statins	Yes	1.20	1.13	1.28
	No	1.13	1.06	1.21

Tables A12-A18. Life-table analysis showing number of endpoint events (AMI, stroke, heart failure, death, and composite cardiovascular endpoints) in patients treated with rosiglitazone compared to pioglitazone, along with interval-specific hazard ratios (95% CI).

Table A12. Acute myocardial infarction

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	329	692	1.13 (0.99-1.28)
4-8	93	235	0.98 (0.77-1.25)
8-12	44	126	0.98 (0.71-1.40)
>12	57	170	1.07 (0.79-1.44)

Table A13. Stroke

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	231	438	1.25 (1.07-1.47)
4-8	68	117	1.44 (1.07-1.94)
8-12	31	58	1.52 (0.98-2.35)
>12	33	76	1.38 (0.92-2.08)

Table A14. Heart failure

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	769	1424	1.28 (1.17-1.40)
4-8	205	382	1.33 (1.12-1.57)
8-12	70	170	1.17 (0.89-1.55)
>12	81	206	1.25 (0.97-1.62)

Table A15. All-cause mortality

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	501	1026	1.16 (1.04-1.29)
4-8	144	321	1.11 (0.91-1.35)
8-12	66	171	1.10 (0.83-1.46)
>12	103	230	1.42 (1.13-1.80)

Table A16. Composite of AMI or death

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	760	1557	1.16 (1.06-1.26)
4-8	216	509	1.05 (0.90-1.23)
8-12	99	270	1.04 (0.83-1.32)
>12	147	370	1.26 (1.04-1.53)

Table A17. Composite of AMI, stroke, or death

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	969	1955	1.17 (1.09-1.27)
4-8	277	611	1.12 (0.97-1.29)
8-12	130	320	1.16 (0.94-1.42)
>12	174	439	1.26 (1.06-1.50)

Table A18. Composite of AMI, stroke, HF, or death

Interval (months)	Rosiglitazone events	Pioglitazone events	Interval-specific hazard ratio (95% CI)
0-4	1684	3302	1.21 (1.14-1.28)
4-8	467	973	1.19 (1.06-1.33)
8-12	196	480	1.16 (0.98-1.37)
>12	246	631	1.24 (1.07-1.43)

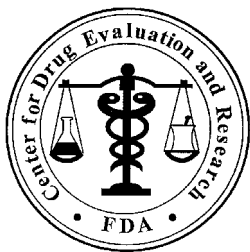
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21073	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	ACTOS (PIOGLITAZONE HCL)15/30/45MG TABS
NDA-21071	ORIG-1	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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/s/

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06/15/2010

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06/15/2010



**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: June 15, 2010

To: Mary Parks, MD, Director
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Subject: Comments on RECORD, TIDE, and the benefit-risk assessment of
rosiglitazone vs. pioglitazone

Drug Name(s): Rosiglitazone (AVANDIA[®], GlaxoSmithKline, IND 43,468, NDA
21-071)
Pioglitazone (ACTOS[®], Takeda, NDA 21-073)

Submission Number:

Application Type/Number:

Applicant/sponsor: GlaxoSmithKline (GSK)

OSE RCM #:

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**THIS REVIEW REPRESENTS THE VIEWS OF THE AUTHORS AND NOT
NECESSARILY THOSE OF THE OFFICE OF SURVEILLANCE AND
EPIDEMIOLOGY**

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1 BACKGROUND

1.1 INTRODUCTION

At the 2007 advisory committee on the subject of cardiovascular risk with rosiglitazone, the Office of Surveillance and Epidemiology (OSE) recommended that rosiglitazone be withdrawn from the market.¹ In documents prepared for that committee and in a presentation before the committee, a critique of the study named Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycemia in Diabetes (RECORD) was presented.

In October 2008, epidemiologists from the Office of Surveillance and Epidemiology (OSE) performed an in-depth benefit-risk assessment of rosiglitazone compared with pioglitazone.² This report found that there were no proven, unique, health benefits associated with rosiglitazone use that were not also present with pioglitazone. However, with respect to health harms, rosiglitazone was associated with an increased risk of acute myocardial infarction (AMI) and heart failure (HF) compared to pioglitazone. With OSE concurrence, the authors concluded that the risks of rosiglitazone use exceeded its health benefits and that rosiglitazone should be removed from the market.

This report also discussed the Thiazolidinedione Intervention with vitamin D Evaluation trial (TIDE), a cardiovascular outcomes trial which the Office of New Drugs was requiring the manufacturer of rosiglitazone to perform. We concluded that TIDE was a “bad deal” trial that offered no realistic health benefits at the substantial likelihood of increased harm. As such, it was “unethical and exploitative.” A separate review from OSE concluded that TIDE was unethical, but were that not an issue, the primary analysis should compare rosiglitazone to pioglitazone since that is the therapeutic choice faced by prescribers and patients once the decision to use a thiazolidinedione (TZD) has been made.³

The purpose of this document is to focus attention on what we believe are methodologic and/or ethical shortcomings of RECORD and TIDE, and to offer a recommendation regarding the future marketing of rosiglitazone.

2 RECORD

2.1 BRIEF DESCRIPTION OF RECORD

RECORD was a noninferiority design, open-label, parallel group clinical trial comparing patients who failed monotherapy with either metformin (Met) or sulfonylurea (SU) and were then randomized to add-on rosiglitazone or add-on Met or SU. Patients were followed for a mean of 5.5 years for occurrence of the primary cardiovascular outcome, defined as time to occurrence of cardiovascular death (CVD) and/or cardiovascular hospitalization (CVH). The primary objective of the study was to test the null hypothesis that RSG was not inferior to non-RSG (Met+SU) with respect to the combined outcome of CVD/CVH.^{4,5}

2.2 OPEN-LABEL DESIGN

Investigators and patients were not blinded to the therapy being used and this has potentially serious implications for the objectivity and validity of outcome ascertainment. Specifically, differential case ascertainment between treatment groups, even of a relatively small degree, would easily mask and dilute a 20% difference in outcomes, especially if one focused on the more relevant outcomes of AMI or AMI + sudden death, where event numbers are smaller. This is particularly worrisome because the

investigators were fully aware of the hypothesis under study and the origins of the European Union's concerns regarding RSG's cardiovascular safety.

There is an extensive literature that suggests the existence of substantial bias within industry-funded clinical trials. Several recent meta-analyses of this subject found that published studies with industry sponsorship were 4-5-times more likely to report a result favorable to the sponsoring company's interests than independently funded studies of the same topic.⁶⁻⁸ The study by Wang et al. is particularly relevant since it focused specifically on studies reporting about cardiovascular risks with rosiglitazone.⁶ These authors found that studies funded by the manufacturer of rosiglitazone were 4.3-fold (95% CI 2.6-7.0) more likely to present a favorable view of AMI risk with rosiglitazone than studies funded by independent sources.⁸ Company-funded publications were 6.5-fold (95% CI 2.6-16.5) more likely to present a favorable view of rosiglitazone's cardiovascular risks.⁸ Failure to implement double-blinding of treatment allocation is a well-recognized source of bias leading to results favorable to a company's interests.^{9,10} A recently published review of statin comparative trials examined the contribution of various factors to bias favoring the sponsoring pharmaceutical company.¹¹ Among 112 trials comparing one statin against another, inadequate blinding of subjects and investigators was associated with a 3.6 fold increased likelihood of results favorable to the sponsoring company (95% CI 1.4-9.0).¹¹

The failure to blind patients and investigators is especially dangerous to the validity of a noninferiority trial because bias, either intentional or unintentional, can easily be introduced.¹² Investigators may be more likely to "cointervene," that is, treat certain patients more aggressively or with additional medications for other conditions that influence the outcome being measured.¹² Investigators may also be more likely to classify or interpret observations of adverse events in a manner that favors the treatment they think is superior.¹² The end result is a marked increase in the likelihood that noninferiority will be concluded when clinically meaningful differences exist between treatments.¹³

The debate within FDA about RECORD has ignored the implications of this study's open-label design but it should not be. An observational study with a similarly serious design defect would be dismissed with almost no comment, and considered no further. But RECORD has been treated within FDA as if it provides accurate and trustworthy results. We believe that the data from RECORD are not accurate and should not be trusted. Every investigator knew what the study question was, why it was important to the manufacturer of rosiglitazone, who was paying for the study, who was remunerating them for every patient enrolled in the study, and what the desired result of the study was. Every investigator knew what drug their enrolled patients were randomized to. This set-up is an open invitation for bias to occur. For those who argue that an open-label study provides accurate and trustworthy results, free of bias, our question is, then why have double-blinding for any study? In a cursory review of major cardiovascular outcomes trials, we could find none that were open-label in design. The question arises whether FDA has two different standards for the trials it reviews: requiring randomized double-blind studies for most efficacy settings, but accepting open-label studies, with their vulnerability to bias, for safety studies. It should be noted that the bias most likely to result from an open-label safety study will produce a result that does not place patient well-being first.

2.3 NON-INFERIORITY DESIGN

While RECORD was designed as a non-inferiority trial, presumably because it was considered unethical to randomize patients to placebo or placebo add-on therapy, it is possible to conduct an ethically rigorous randomized, double-blind placebo (add-on) controlled trial in diabetes, as was done with pioglitazone in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial.¹⁴

There are a number of issues specific to the use of a non-inferiority design that should be considered. Of note, in a superiority trial, careful attention to detail and study execution is essential to minimize any factors that might blur the difference between a test treatment and its control, such as poor compliance, missing data or cross-overs.¹⁵ In a non-inferiority trial, these incentives don't exist because

the goal of the study is to show that there is “no difference” between treatments.¹⁵ In other words, a non-inferiority design “rewards” sloppy or poor study implementation because such performance creates more background “noise” that serves to mask or cover-up differences between drugs, increasing the likelihood that they will appear to be similar with respect to the outcome of interest.

Related to this concern, the protocol for RECORD specified that 370 investigators throughout Europe, New Zealand, and Australia would each enroll 5-20 patients. The protocol did not specify the qualifications, experience or expertise of those it had enlisted as investigators. If a sizable proportion of investigators are inexperienced, the probability that there was less than optimal study implementation will be high.

Another concern is that the non-inferiority design is usually used in the context of an efficacy trial (even in oncology, where reduction in death is the efficacy measure), not a trial the primary purpose of which is to address safety.^{16,17} That means there is very limited experience using this design for the specific purpose of establishing a safety claim. Indeed, a worrisome aspect of this design as employed for safety is that the null hypothesis is: rosiglitazone increases cardiovascular risk. Only by rejecting this null hypothesis can one conclude that rosiglitazone is non-inferior. But this poses a serious dilemma in our minds because we don’t see how it is possible to ethically enroll patients into a study, let alone conduct it, when the null hypothesis, representing the accepted state of nature, is that rosiglitazone increases cardiovascular risk.

Given the variety of difficulties documented with use of the non-inferiority design for efficacy studies, whereby non-inferiority is frequently falsely claimed,¹⁵⁻¹⁸ caution and close scrutiny of the application of this method to safety is necessary because the consequence of a false claim of non-inferiority is that a drug will be considered equally safe to other drugs when it is actually more dangerous.

A critical element for using the non-inferiority design is deciding upon the appropriate margin, or difference between the test treatment and the active control, that will be accepted as being compatible with non-inferiority. This margin must be smaller than or equal to the smallest value that would represent a *clinically important difference* (emphasis added) between treatments being tested.¹⁵⁻¹⁹ It is also important that a justification be given for selection of the noninferiority margin chosen.¹⁵⁻¹⁹ The protocol for RECORD stated that a 20% margin was chosen. No justification for selecting a 20% margin was given in the protocol. We would argue that a 20% margin is too large to be *clinically acceptable*. Cardiovascular disease accounts for nearly 70% of deaths in patients with diabetes.²⁰ The most important reasons for treating diabetes are to reduce the long-term complications of microvascular disease, and if possible, macrovascular disease.²¹⁻²⁵ In this context, it seems counter-intuitive why a 20% increase in cardiovascular events would be *clinically acceptable*.

For the more relevant and clinically important outcomes of AMI, or CVD+AMI, a 20% relative increase in risk in a population already at substantially increased baseline risk (diabetic patients) would not be considered acceptable unless there was some ancillary attribute of great clinical relevance to offset this potential increase in morbidity and mortality.^{15,16} Indeed, were a drug for the treatment of diabetes to be shown to reduce the risk of AMI or CVD+AMI by 20%, it would be viewed as a major advance (the reductions in AMI risk conferred by statin therapy or aspirin use are in the 20%-25% range and are viewed as clinically important). No ancillary attributes were cited by the sponsor to justify accepting a 20% increase in cardiovascular risk, nor have they been offered by the Office of New Drugs, nor identified by our Office. From a study design perspective, a major problem with setting a wide margin is that it makes it easier for a sponsor to claim non-inferiority compared to another treatment.^{16,19} From a public health and population perspective, the problem is that by setting a wide margin, the likelihood of allowing a harmful drug to masquerade as equivalent to safer drugs, is markedly increased.

2.4 OUTCOME DEFINITIONS

RECORD was designed to evaluate the composite outcome of cardiovascular hospitalization (CVH) and cardiovascular death (CVD). The components of this outcome include many events that are not pertinent to the issues raised by either the sponsor's or FDA's meta-analysis of the company's clinical trials program, and which are not customarily considered as endpoints in cardiovascular outcomes trials (table 1). The core definition for hospitalization events in most cardiovascular outcomes trials are usually restricted to AMI and stroke. Given the issue of HF with the TZDs, this also is reasonable to include in an outcome composite. However, the remaining event types, accounting for 64% of CVH events, are either unrelated or remotely related to the cardiovascular concerns that have attracted the most attention with rosiglitazone, and which most directly impact longevity. The category "other" accounts for 17% of events, yet it is not possible to assess their validity or relatedness to risk of hospitalization for AMI, stroke, or HF.

The category of CVD suffers from similar problems or remote or non-relatedness to the outcomes of most concern. The first four event types fall into the category of outcomes that are understandably directly relevant to the issue of rosiglitazone's safety. The categories of "other vascular events" and "other cardiovascular mortality" are vague and non-specific, and it's far from clear how these differ from deaths due the first four event types. Particularly worrisome from a methods perspective is that 47% of CVD events were due to "unknown cause." In our view, this is a serious warning sign of poor data quality because cause of death should be known, even if it's "sudden" or presumed to be "sudden." For example, in the Scandinavian Simvastatin Survival Study (4S), a large cardiovascular outcomes trial, there were no patients with unknown cause of death.²⁶ Similarly careful attention to outcome ascertainment was present for many other cardiovascular outcomes trials published over the past 16 years.²⁷⁻³⁵

Regarding outcome definitions, 58% of events contributing to CVD are remotely or non-related to the major safety concerns with rosiglitazone. The entire composite is driven by the category "unknown," which suggests poor and incomplete follow-up of identified deaths. The presence of 47% of deaths being due to "unknown" causes is a clear indication of poor study execution. Were the causes of these deaths "known," it is reasonable to believe that many, perhaps most, would no longer be classifiable as "CVD."

Table 1. List of events types contributing to composite endpoints in RECORD, with percentage of outcome events attributed to each event type.

Cardiovascular hospitalization	Cardiovascular death
Acute myocardial infarction (13%)	Sudden death (15%)
Stroke (12%)	Acute myocardial infarction (13%)
Heart failure (11%)	Stroke (5%)
Angina (6%)	Heart failure (9%)
Unstable angina (6%)	"Other acute vascular events" (5%)
Atrial fibrillation (9%)	"Other cardiovascular mortality" (8%)
Transient ischemic attack (2%)	Unknown cause (47%)
"Invasive" procedures (2%)	
Amputation (3%)	
"Other" (17%)	

Per protocol, deaths of unknown cause will be counted as cardiovascular deaths. If follow-up efforts were suboptimal, a large number of deaths would be labeled as “unknown” and thereby included in the CVD category, even though they are not due to cardiovascular causes. This will create non-differential misclassification of CVD deaths with the result being that any differences between RSG and non-RSG groups will be reduced and perhaps eliminated altogether (such misclassification creates a bias toward the null, or no-effect level).

The effect of using a broad and non-specific composite outcome (CVD+CVH) for RECORD is that it substantially increases the likelihood that a null result will be obtained, even if a true association exists between RSG use and ischemic cardiac disease (AMI, AMI + sudden cardiac death). The inclusion of these other events will mask the association of greatest concern, basically by increasing background “noise.” There is a real consequence to this. By inflating the count of outcome events in RECORD, the company has been able to achieve confidence intervals that enable it to claim it has met the 20% non-inferiority margin. However, the non-specific, weakly or unrelated events that contribute to the composite of CVH + CVD severely bias the point estimate around which the confidence interval is set towards the null value of 1.00. Were the analysis to be restricted to AMI, stroke, HF, or sudden death, the confidence intervals would likely be wide, extending beyond a hazard ratio of 1.20.

2.5 MULTICENTER-MULTI-COUNTRY

RECORD was conducted in 25 countries and 364 different centers. Problems related to heterogeneity of populations, variations in baseline risk of outcome events, and differences in standards of medical care and underlying health status introduce a potential bias toward the null by creating a high level of background noise in the study design. Additionally, it’s difficult to gauge the experience and qualifications of so many different investigators. This could contribute to issues of data quality.

2.6 LOWER THAN EXPECTED EVENT CAPTURE

RECORD was powered under the assumption of a 3% per year rate of CVD and an 8% per year rate of CVH, for a combined CVD+CVH rate of 11% per year. A review of recently published literature suggests that these assumptions greatly overestimated the actual expected rates (table 2).

Table 2. Cardiovascular event rates from various diabetes outcome studies.

Study	N	PYRs	AMI	Rates per 100 person-years			CVD+CVH
				CVD	AMI+CVD	APTC	
Pre-diabetes							
DREAM ³⁷	2634	7902	0.11	0.13	0.24	0.29	
Early diabetes							
ADOPT ³⁶	2895	10571	0.11		0.39	0.73	
Established diabetes							
ARIC ³⁸	1558	14019		0.96	1.23		
UKPDS ²¹	1138	11188	0.95	1.09	2.04	2.40	
Diabetes with documented vascular disease							
HOPE ³⁹	1769	7961	2.88	2.16		4.41	
PROactive ¹⁴	2633	7570		2.46	3.70	5.11	
RECORD^{4,5}							
Planned	1978	11868		3.0			11.0
Actual	2227	7969	0.39	0.28 (0.14) [†]	0.67 (0.53) [†]	0.98	2.56

[†] The rate shown without parentheses is based on the definition of CVD used by the RECORD investigators; the rate shown in parentheses is based on the definition of sudden death+fatal/nonfatal AMI or CVA.

In the DREAM trial, patients with impaired glucose tolerance were treated with ramipril and or rosiglitazone and followed for development of diabetes.³⁷ The placebo group in this randomized trial experienced rates per 100 person-years of AMI, CVD, AMI+CVD, and the Antiplatelet Trialists' Collaboration (APTC)²⁷ outcome (CVD+nonfatal AMI + nonfatal CVA) of 0.11, 0.13, 0.24 and 0.29 respectively.³⁷ In A Diabetes Outcome Progression Trial (ADOPT), patients newly diagnosed with diabetes were randomized to receive Met, SU or RSG.³⁶ The rates per 100 person-years of AMI, AMI+CVD, and APTC in the combined Met+SU groups from ADOPT were 0.11, 0.39 and 0.73, respectively.

Several longer-term studies were performed in patients with more established diabetes. From the Atherosclerosis Risk in the Community (ARIC) study,³⁸ a population-based, NIH-funded, observational cohort study (not a randomized clinical trial), diabetic patients with and without past history of AMI were included. In these diabetic patients, the rates per 100 person-years for CVD and AMI+CVD were 0.96 and 1.23, respectively. Among the subset of patients without documented cardiovascular diseases, the rates of CVD and AMI+CVD were 0.76 and 1.08, respectively.

The UK Prospective Diabetes Study (UKPDS) was a randomized clinical trial involving the long-term follow-up of 3867 patients with type 2 diabetes, of whom 1138 were randomized to "conventional" (non-intensive) blood glucose management.²¹ Over 10 years of follow-up, the rates per 100 person-years of AMI, AMI+CVD, and the APTC outcome were 0.95, 2.04, and 2.40, respectively.

The Heart Outcomes Prevention Evaluation (HOPE) was a clinical trial in patients with and without diabetes randomized to receive ramipril or placebo and followed for the development of AMI, CVA, or cardiovascular death.³⁹ Diabetic patients enrolled in this study had either experienced a previous cardiovascular event or had one or more cardiovascular risk factors in addition to diabetes. In this group of diabetic patients at risk for a cardiovascular outcome, the rate of fatal+nonfatal AMI was 2.88 per 100 person-years and the rate for the APTC outcome was 4.12 per 100 person-years. By way of comparison, from ARIC, in the group of diabetic patients at highest cardiovascular risk (those with a prior history of AMI), the rates of CVD and AMI+CVD were 2.4 and 3.2 per 100 person-years.³⁸

In the PROactive trial, diabetic patients with documented macrovascular disease (past AMI, CVA, coronary revascularization, acute coronary syndrome, or obstructive vascular disease of a lower extremity or coronary artery) were randomized to pioglitazone or placebo in addition to their standard diabetes therapy.¹⁴ The rates per 100 person-years for CVD, AMI+CVD, and the APTC outcome in this very high risk population were 2.46, 3.70, and 5.11, respectively.

These rates stand in stark contrast to the rates used by the sponsor to power RECORD, 3% per year for CVD and 11% per year for CVD+CVH.

Another way to look at event capture in RECORD^{4,5} is to compare it directly against DREAM,³⁷ ADOPT,³⁶ and PROactive.¹⁴ As shown in table 3, the control population studied in RECORD was much closer to that of PROactive in terms of duration of diabetes, and HbA1c than it was to the controls from the pre-diabetic population in DREAM or newly diagnosed diabetics in ADOPT. Of note, the incidence rate of AMI in RECORD controls was about one-quarter that of PROactive, and was very close to that of ADOPT. For HF, the disparity with PROactive was even greater (about one-tenth the rate), and again, was virtually identical to the HF rate from ADOPT (actually slightly lower).

Table 3. Comparison of **event rates per 100 person-years** in control-treated patients from randomized controlled trials of rosiglitazone and pioglitazone.

	DREAM ³⁷	Rosiglitazone ADOPT ³⁶	RECORD ^{4,5}	Pioglitazone PROactive ¹⁴
Person-years	8517	9123	12272	7570
Age yrs (mean)	54.8	57.2	58.5	61.6
Duration DM yrs (mean)	0		7.1	8.0
HgbA1c % (mean)	---	7.4	7.9	7.9
AMI	0.11	0.37	0.46	1.90
CV death	0.12	0.13	0.58	2.46*
AMI/CVA/CVD	0.27	0.72	1.34	4.73*
CHF	0.02	0.31	0.24	2.62

* All-cause mortality; not limited to CV mortality

A similar comparison of the TZD-exposed arms of these trials shows the same pattern (table 4). Despite the fact that RECORD identified an increased HF risk compared with combined metformin + sulfonylurea, the underlying control rates were far below what should have been found. This discrepancy strongly suggests that study results from RECORD are not credible, that event ascertainment was far from complete.

Table 4. Comparison of **event rates per 100 person-years** in patients treated with rosiglitazone or pioglitazone from randomized controlled trials.

	DREAM ³⁷	Rosiglitazone ADOPT ³⁶	RECORD ^{4,5}	Pioglitazone PROactive ¹⁴
Person-years	8492	4950	12338	7489
Age yrs (mean)	54.6	56.3	58.4	61.9
Duration DM yrs (mean)	0	1.1	7.0	8.0
HgbA1c % (mean)	---	7.4	7.9	7.8
AMI	0.19	0.48	0.52	1.59
CV death	0.14	0.10	0.49	2.36*
AMI/CVA/CVD	0.39	0.81	1.25	4.02*
CHF	0.16	0.44	0.49	3.75

* All-cause mortality; not limited to CV mortality

2.7 ITT ANALYSIS IS A BIASED APPROACH FOR SAFETY ENDPOINTS

The primary analysis for RECORD was intention-to-treat (ITT), which is generally accepted as the preferred analytic method for trials conducted to show efficacy. It is conservative in that poor study execution or inadequate follow-up will serve to make it more difficult to show a difference from the null. For purposes of safety, where a safety concern has been raised and is under evaluation, the ITT approach is protective of the drug at the potential expense of patient safety. Patients who drop out of a study and for whom outcomes might not be counted, and patients who stop the drug and hence are probably not at the same risk of a cardiovascular event off the drug as they were while on it, will bias the estimated event rates towards the null under an ITT approach. In studies for safety, the preferred analytic approach is on-treatment.

2.8 CONCLUSION REGARDING RECORD

From the perspective of postmarketing safety, nearly every feature of the design and analytic method of RECORD will operate in concert to underestimate, or more likely obscure, any true difference in cardiovascular risk between rosiglitazone and its comparator in this trial, metformin + sulfonylurea. The open-label design compromises any advantage that might have been conferred by randomization and makes it very easy for bias to affect every aspect of the study. In examining a long list of cardiovascular outcomes trials, double-blinding was the norm,²⁶⁻³⁵ and we believe, with good reason. The non-inferiority design, with a *clinically excessive* margin of 20% also contributes to masking rosiglitazone risk. The outcome definitions employed were overly broad, non-specific, and guaranteed to introduce a substantial degree of background noise, created by the contribution of outcome events for which there should be no difference between study treatments and mixing them with the minority of events where a difference is possible. The multi-country, multi-center design introduces many issues related to heterogeneity of patient populations, quality control, and investigator experience and expertise. As we have shown, RECORD did not identify anywhere near the number of events that should have been observed. This, by itself, renders RECORD unreliable and uninterpretable. Finally, an ITT analysis for a safety endpoint (measurement of harm) is biased in favor of protecting the drug at the expense of patient safety.

3 TIDE

3.1 BRIEF DESCRIPTION OF TIDE

In the wake of the July 2007 FDA advisory committee meeting on the cardiovascular risks of rosiglitazone, FDA required that the manufacturer conduct a cardiovascular outcomes trial of rosiglitazone.

3.2 OSE SCIENTIFIC CRITIQUE OF TIDE

The primary analysis for TIDE is rosiglitazone vs. Other non-TZD therapies. Reviewers from OSE had serious objections to TIDE based on ethical considerations (see next section) but advocated the position that were it somehow ethical to undertake, that the preferable primary comparison be rosiglitazone vs. pioglitazone since this was the therapeutic decision faced by prescribers and patients once the decision to use a TZD had been made. The protocol spends almost no time discussing this comparison, which is the most important one clinically.

Other criticisms to the scientific design of TIDE were that the protocol allowed the enrollment of patients for whom FDA labeling stated rosiglitazone should not be used, such as patients with known ischemic heart disease, patients who used or had used nitrates, and even patients with unstable angina.

The planned analyses will be conducted under a non-inferiority design. The null hypothesis in this study is that rosiglitazone increases cardiovascular risk under such a design, raising ethical concerns to these reviewers. The margin was set at 30%. If 20% was far too large an allowable margin for RECORD, why would 30% with TIDE be acceptable?

3.3 OSE ETHICAL CRITIQUE OF TIDE

In light of our systematic review of observational studies, our own study of rosiglitazone risk in Medicare elderly, and previous FDA reports, we have serious reservations regarding the FDA-sanctioned head-to-head cardiovascular outcomes trial of rosiglitazone vs. pioglitazone, originally announced in a FDA press release in November 2007.⁴⁰ First, equipoise does not exist. There are a number of different working definitions of “equipoise.” Freedman described equipoise as a condition reflected by “*equivalent evidence*” (emphasis added) for alternative hypotheses.⁴¹ That is, there must be equal evidence favoring both therapies. But that is not the case here because no one has argued that rosiglitazone is safer than or

preferable to pioglitazone. It is also difficult to argue that there is “imminent conflict in the clinical community over what treatment is preferred,”⁴¹ given that the ratio of pioglitazone to rosiglitazone use in the US stands at 3:1, suggesting a clear preference in favor of pioglitazone.

In another formulation, Djulbegovic described equipoise as a condition of “maximum uncertainty” regarding the choice of one therapy over another.⁴² He proposed that for equipoise to exist, there must be “equally distributed uncertainty” about the relative effects of competing therapies.⁴² With the TZDs, there appears to be no meaningful difference regarding glycemic control and the evidence for cardiovascular harm is decidedly one-sided, implicating rosiglitazone but not pioglitazone.

The Belmont Report concluded that for clinical research to be ethical, the risks to subjects must be outweighed by the sum of the anticipated benefits to the subject.⁴³ The proposed clinical trial of rosiglitazone vs. pioglitazone⁴⁰ fails this standard of “positive expected value” because the two drugs are equivalent with respect to glycemic control but are likely very different with respect to risks and harms.

The question reduces to whether it is ethical to conduct a clinical trial when there is no unique health benefit to be gained from trial participation, but there are substantial likely risks if subjects are treated with the drug associated with a greater risk of serious injury or harm (in this case, rosiglitazone). The ethical argument against such a study is increased when the true purpose of the study is to establish whether one drug is more harmful than another, rather than one drug being more beneficial or efficacious than another. No one would argue about the ethical permissibility of a trial that offered subjects a treatment that is better than any alternative they could receive outside the trial, or that if it didn’t offer such benefits, imposed insignificant or no risks of harm. However, when there is no prospect of a clinically meaningful added benefit, but one of the options offered poses a “non-negligible risk of significant harm,” you have what has been described as a “bad deal” trial.⁴⁴ Participation in such a trial is not in the best interests of at least some of the subjects who will be enrolled. The performance of such a trial ultimately relies on exploitation of study participants for its completion.⁴⁴ This exploitation is not mitigated by “informed consent” because the distribution of “benefits” arising from the study are too one-sided.⁴⁴ As noted by Nycum and Reid, most “bad deal” trials are likely to occur during Phase 1, where small numbers of usually healthy subjects are exposed to an experimental agent and where the “benefits,” if any, are minimal, while the potential for harm is relatively greater.⁴⁵ Applying their reasoning to the currently proposed head-to-head trial, there is at best only a remote to non-existent possibility that individual study participants randomized to rosiglitazone will experience a clinically meaningful health benefit above that of pioglitazone, while the *a priori* likelihood of clinically meaningful excess harm from rosiglitazone is much very high.⁴⁵

Two “tests” have been offered to help establish if exploitation is present within a “bad deal” trial. The first test requires that all participants be “completely altruistic” and that there be an important net societal benefit to knowing the results of such a trial.⁴⁴ It is virtually impossible to be certain that “complete altruism” is present in a given potential study subject, let alone the many thousands that would be needed for the proposed TZD trial. It also is difficult to argue that there is a substantial societal benefit to knowing with definitive certainty that rosiglitazone increases AMI or heart failure risk when the concern relates to safety and harms rather than efficacy and health benefits. The medical community and patients would be no worse off were rosiglitazone no longer marketed. The second “test” requires that we examine the distribution of benefits and costs (including harms) associated with the trial. If the benefits and harms are not equally distributed among study participants, the trial is exploitative.⁴⁴ In the TZD setting, none of the participants will derive any additional meaningful health benefit from rosiglitazone, but among the 50% of subjects who receive rosiglitazone, they will be subjected to a treatment that poses a “non-negligible risk of significant harm.” The requirement for balanced distribution of benefits and harms is especially important when dealing with a severe harm (e.g., AMI, heart failure), where the tolerance for an imbalance in risk between treatments must be very low.⁴⁴

The proposed head-to-head trial of rosiglitazone vs. pioglitazone is a “bad deal” trial, and by its nature, exploitative. While a utilitarian argument holds that the social value of certain research may be sufficient to override the welfare of individual study participants, investigators and regulators have a “duty of non-exploitation,” whereby utilitarian considerations are constrained and limited, and individual subjects are protected.⁴⁶ Of note, informed consent does not render an exploitative study non-exploitative because it does not alter the underlying dynamic whereby some study participants are placed at increased risk of severe harm without expectation of added or enhanced health benefits.⁴⁷

Djulgovic examined clinical trial participation and ethics from the perspective of game theory, where one seeks to optimize the Nash equilibrium, which he conceptualized as “the probability of random allocation at which both researcher and patient are most likely to achieve their strategic goals.”⁴⁸ Under this analysis, randomization is only rational if the distribution of success with one of the therapies is about equal to that of the comparator.⁴⁸ Deviation from the optimal solution of Nash equilibrium suggests that a trial is unethical.⁴⁸ On the basis of rationality, patients would be expected to select the therapeutic “option with the highest expected utility,”⁴⁸ which based on the available evidence, would be pioglitazone.

As discussed, the patients participating in a head-to-head trial of rosiglitazone vs. pioglitazone would not benefit from the trial, but the organization sponsoring the trial (e.g., the drug manufacturer) could very well benefit. This is an exploitative distribution of trial benefits because study participants do not benefit from participation, but the company potentially does.^{42,44,45,48} The ethics literature states that risks within a trial that are not offset by benefits to individuals could still be ethical if they are sufficiently offset by gains in knowledge that the research is designed to generate. In a “bad deal” trial, there is only a remote possibility of individual benefit and relatively low possibility of social benefit.⁴⁵

Emmanuel et al. have explored why informed consent, by itself, does not make clinical research ethical.⁴⁷ To be ethical, clinical research must improve patient health or develop knowledge that improves patient health. In the latter context, the potential for exploitation exists because the risk of harm would be experienced by study participants while the benefit, if any, would accrue to others not in the study.⁴⁷ The proposed TZD study fails to meet this first requirement because the two drugs in question are comparable with respect to glycemic control and any other putative health benefit, but differ with respect to risk of serious harms. As a result, this research will not improve the health of participants. Since there is no expectation that rosiglitazone provides better treatment of type 2 diabetes or is meaningfully safer than pioglitazone, it’s also difficult to maintain that this trial would improve the health of other patients.

The methodology employed in the study must be rigorous and valid. Unsound research is unethical.⁴⁷ If the proposed study asks the wrong question, or is underpowered, or can’t enroll sufficient numbers of subjects, it would be unethical. In this regard, what level of excess cardiovascular risk with rosiglitazone can be justified, given that it confers no additional or unique health benefits compared to pioglitazone? Even a 5% increase in AMI or heart failure risk with rosiglitazone would translate into hundreds of excess cases per year in exchange for no material benefit.

To be ethical, a study must also adhere to “fair subject selection.”⁴⁷ There are two components to this requirement. Those who bear the risks and burdens of the research should be in a position to enjoy its benefits.⁴³ This presumes that the study under consideration is focused on establishing superior benefits. However, the proposed TZD study is about harms. There are no “net benefits” to be shared or enjoyed by the study participants. This asymmetry of benefits (none) and harms (potentially severe and relatively frequent) violate the principle of fair subject selection.⁴⁷ The second component of this requirement is that eligible patients at substantially higher risk of experiencing harm should be excluded from the study.⁴⁷ The proposed TZD study may also violate this component because the harms under study (AMI, heart failure) are known to be increased in patients with T2DM, and diabetic patients with underlying macrovascular disease would be expected to be at even greater risk.

A fourth requirement of an ethical study is that there is a favorable benefit-risk balance within the study.⁴⁷ For this to be so, potential risks to subjects must be minimized, potential benefits to individual subjects must be maximized, and the potential benefits to individuals and society must be proportionate to or outweigh the risks.⁴⁷ The proposed TZD study appears to fail this requirement. Risks can not be minimized because the risks in question are intrinsic properties of one of the study drugs. There are no health benefits to be maximized because both rosiglitazone and pioglitazone are comparable with respect to glycemic control. Finally, given there is no unique and substantial health benefit associated with rosiglitazone compared to pioglitazone, there are no net benefits for study subjects or society that will exceed the risks experienced by subjects randomized to rosiglitazone.

A fifth requirement for an ethical study is that there be independent review.⁴⁷ This poses a problem because most of those involved in the design or review of a proposed TZD study will have received compensation from the sponsoring company. More importantly, it is well-established that industry funded studies are much more likely to obtain results favorable to the sponsoring company's drug than similar studies funded by public entities.⁴⁹⁻⁵⁵

An ethical study also requires informed consent.^{43,47} What would informed consent for a proposed TZD study look like? Would patients be told that there are no unique health advantages for rosiglitazone over pioglitazone and that there is nothing beneficial to be gained by participating in the study? Would patients be told that there is no net societal benefit to this study because pioglitazone treats T2DM just as well as rosiglitazone, but rosiglitazone probably increases the risk of AMI and heart failure? The Agency's standard of "definitive proof" (generally defined as a p-value < 0.05 for some effect) may be appropriate for the evaluation of drug efficacy, but it is not an appropriate standard of evidence for harm, especially when the harm is serious and there is no unique and off-setting health benefit for the drug in question. Nonetheless, that is the standard that has been applied to the present time. Finally, would patients be fully informed about what is known about the comparative risks of rosiglitazone and pioglitazone? Even if all these concerns were fully addressed, there would still remain the problem that informed consent can not render a "bad deal" trial ethical.^{44,45}

The final requirement of an ethical study is that there be respect for study subjects.⁴⁴ The proposed TZD study may not be able to meet this requirement because it probably would be exploitative, a direct violation of respect for subjects.⁴²⁻⁴⁵ In addition, it is difficult to convincingly claim that the welfare of study subjects (a component of "respect") is a primary value of investigators who are conducting a study, the purpose of which is to establish if one of the study drugs (rosiglitazone) is more harmful than an equally effective alternative (pioglitazone).

3.4 DISCUSSION OF THE INFORMED CONSENT FORM FOR TIDE

In this section, we would like to review elements of the informed consent form for TIDE, submitted to FDA by the manufacturer.

3.4.1 Study title

The title of this study is Thiazolidinedione Intervention with vitamin-D Evaluation (TIDE). Its sole purpose is to evaluate whether rosiglitazone increases the risk of cardiovascular harm compared to use of non-TZD therapies and compared to pioglitazone. In this regard, it is impossible to discern from the title that this is a cardiovascular outcomes trial. This is in contrast to many published cardiovascular outcomes trials, where the title or a word or phrase derived from the title indicate that the study is about cardiovascular disease risk.²⁶⁻³⁵ The title is more misleading because of the reference to vitamin-D, which has no scientific basis for being included in this trial, and which serves only to distract attention from the true purpose of the study, and its "bad deal" format.

3.4.2 Purpose section

CONSENT FORM: TIDE TRIAL
Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE)
Sponsor: GlaxoSmithKline Inc

Study Title

Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE). A Multicenter Randomized Double-Blind Placebo-Controlled Trial of a Thiazolidinedione (TZD) or Placebo and of Vitamin D or Placebo In People With Type 2 Diabetes at Risk For Cardiovascular Disease (AVD 111960)

Purpose
People with type 2 diabetes are at risk of having a heart attack, stroke and even death. They are also at risk for broken bones and some cancers. Some studies suggest that a class of diabetes drugs called thiazolidinediones (TZDs) and/or vitamin D may lower the chance of some or all of these diseases occurring. Other studies have suggested that the TZDs rosiglitazone or pioglitazone may increase the risk of some or all of these outcomes. This study will compare adding a TZD (either rosiglitazone or pioglitazone) to adding a placebo (a pill with no active ingredients). The effects of these study drugs, both good and bad, on the chance of heart attacks, stroke and death will be studied. It will also compare adding vitamin D to adding a vitamin D placebo to see if vitamin D can reduce the number of deaths or cancers requiring hospitalization, chemotherapy or surgery.

Side Effects Reported with Thiazolidinediones (Rosiglitazone and/or Pioglitazone)
Rosiglitazone is the active ingredient in Avandia and pioglitazone is the active ingredient of Actos. Some people who have taken rosiglitazone or pioglitazone had the following side effects: GlaxoSmithKline (GSK) has analyzed heart safety data from their studies previously conducted in patients with diabetes. The results suggested that rosiglitazone might increase the chance of a heart attack especially in the presence of insulin or nitrate medication. However, other studies have not confirmed this observation.

Released by Senator Grassley, February 18, 2010

The purpose blends effects attributable to both TZDs with effects that are of concern for only rosiglitazone. For example, bone fractures, cancer, and AMI risks are grouped together, and the informed consent implies that the evidence of cardiovascular risk with rosiglitazone is comparable to that of pioglitazone. This is false. As evident from other reports submitted for evaluation by the advisory committee, the evidence for cardiovascular risk from rosiglitazone compared with pioglitazone is very asymmetric, suggesting risk with rosiglitazone and less risk or a protective effect with pioglitazone.

The addition of vitamin-D to this study is also problematic. FDA asked for a cardiovascular outcomes study, not a chemo-prevention study.

Most importantly, the “Purpose” avoids any mention of the actual reasons why this study is being conducted. 1) FDA required that this study be done because of concerns that rosiglitazone increases cardiovascular risk. FDA had no comparable concerns regarding pioglitazone. 2) An FDA advisory committee voted 20-3 that rosiglitazone increases cardiovascular risk. Why is this fact not mentioned anywhere in the informed consent? 3) The labeling for Avandia (rosiglitazone) has a boxed warning for cardiovascular disease; the labeling for pioglitazone has no such boxed warning. Why is this fact not highlighted in the informed consent? 4) The American Diabetes Association and its European counterpart have explicitly recommended that rosiglitazone not be used to treat diabetes.⁵⁶ Why is this fact not described in the informed consent?

3.5 OTHER SECTIONS

As we read through the informed consent, we were struck by how misleading it was. For example, AMI was mentioned 5-times, cancer 4-times, and vitamin-D 18-times. The argument and rationale for including vitamin-D in a cardiovascular outcomes trial was weak, and poorly documented. We believe that the primary reason for inclusion of the vitamin-D arm in this trial is to distract patient and physician

attention from the “bad deal” nature of this trial, and to lull patients into believing that they might derive a health benefit from participation in the trial.

3.6 CONCLUSIONS REGARDING TIDE

Given the weight of evidence regarding cardiovascular risks with rosiglitazone, we believe that TIDE is an unethical study and that it was unethical before it was started. It is difficult to argue that equipoise exists when so many studies have observed an increase in risk with rosiglitazone and a decrease or non-risk with pioglitazone, and when every observational study that has tested rosiglitazone and pioglitazone head-to-head has favored pioglitazone. It is further difficult to argue that equipoise exists when the leading diabetes professional association recommends that rosiglitazone not be used and when an FDA advisory committee has voted that rosiglitazone increases cardiovascular risk, reflected in differential labeling for rosiglitazone.

4 BENEFITS AND RISKS OF THIAZOLIDINEDIONES

This section summarizes the literature pertaining to potential health benefits and non-cardiovascular harms with the TZDs.

4.1 GLYCEMIC CONTROL

Thiazolidinediones bind to the nuclear transcription factor peroxisome-proliferator-activated-receptor γ (PPAR γ), which regulates the transcription of a variety of different genes.⁵⁷ The TZDs increase insulin sensitivity of adipose and muscle tissue and inhibit gluconeogenesis, and reduce fasting and postprandial blood glucose levels.⁵⁷ The two marketed TZDs are comparable in the degree of glycemic control achieved, generally amounting to a reduction of HbA1c ranging from 0.5% to 1.5% depending on dose,⁵⁷⁻⁶² a somewhat lower effect than seen with recommended doses of sulfonylureas or metformin.^{57,61} There is no evidence to suggest a difference in degree of glycemic control with either rosiglitazone or pioglitazone,⁶⁰ and in one randomized trial comparing the two drugs, the level of glycemic control was identical.⁶² There are no data to suggest that either rosiglitazone or pioglitazone would achieve glycemic control in the setting where control had not been achieved with use of the other TZD.⁵⁹⁻⁶¹

4.2 LIPID EFFECTS

One head-to-head randomized trial has been performed comparing lipid effect in patients treated with rosiglitazone vs. pioglitazone.⁶³ Rosiglitazone increased triglyceride levels and resulted in greater increases in LDL cholesterol and smaller increases in HDL cholesterol than pioglitazone. LDL particle concentration and LDL particle size also changed more favorably with pioglitazone than rosiglitazone.^{63,64} Overall, compared to rosiglitazone, pioglitazone was associated with significantly greater improvement in a variety of lipid indices. These differences in lipid effects may relate to differential agonist effects of the two TZDs, with pioglitazone being a partial PPAR α agonist in addition to being a PPAR γ agonist while rosiglitazone is a pure PPAR γ agonist.⁵⁷ A meta-analysis of 23 TZD clinical trials also concluded that pioglitazone produced a more favorable lipid profile than rosiglitazone, from a cardiovascular perspective.⁶⁵

4.3 BODY COMPOSITION AND BLOOD PRESSURE EFFECTS

Both rosiglitazone and pioglitazone cause similar increases in body weight (primarily fluid retention and subcutaneous fat) for comparable levels of HbA1c reduction (2-3 kg increase per 1% reduction in HbA1c).⁵⁷ Fluid retention and edema also are associated with both TZDs.^{57,59-61} A systematic review of the literature from 2004 concluded that neither TZD exerted an effect on blood pressure,⁶⁴ although since then, several large trials have reported modest reductions in blood pressure with both TZDs.^{14,37,67,68}

4.4 KIDNEY EFFECTS

The first study suggesting a renoprotective effect of TZD was published nearly 15 years ago, when troglitazone was shown to reduce urine protein excretion and blood pressure in obese Zucker rats.^{69,70} Since then, other animal studies of TZDs have shown anti-inflammatory, anti-proliferative, and anti-fibrotic effects in glomeruli and proximal tubule cells, as well as prevention of proteinuria or delay in progression to nephropathy.⁷¹⁻⁷⁴ Rosiglitazone prevented glomerular injury in diabetic rats by reducing reactive oxygen species (a mediator of vascular complications in diabetes) and by reducing activation of nuclear factor- κ B and the expression of MCP-1, both involved in the pathogenesis of diabetic nephropathy.⁷³ Pioglitazone was shown to limit cyclosporine nephrotoxicity in adult male Wistar rats through down regulation of pro-fibrotic cytokine PAI-1 and overexpression of an intermediate protein that modulates the transcription of specific genes involved in cyclosporine nephrotoxicity.⁷⁴ Pioglitazone also reduced renovascular injury in obese Zucker rats with nephropathy, presumably by reducing oxidative stress.⁷⁵

Several studies in humans have shown significant reductions in urine albumin-to-creatinine ratio (ACR), considered to be an intermediate marker of diabetic nephropathy. Of note, decreases in ACR were independent of glycemic control in these studies, but were confounded by blood pressure reductions.⁶⁸ Human studies reporting decreased urine albumin excretion have been published for troglitazone, pioglitazone, and rosiglitazone.⁷⁰

The DREAM trial assessed pre-specified renal composite and individual component outcomes in 5269 people with impaired glucose tolerance and/or impaired fasting glucose during a 3-year observation period. Patients were randomized to ramipril vs. placebo and rosiglitazone vs. placebo according to a 2 x 2 factorial design.⁷²

The pre-specified composite cardiorenal outcome in DREAM included either: 1) a composite cardiovascular outcome defined as the first occurrence of any cardiovascular death, successful cardiac resuscitation, nonfatal MI, stroke, revascularization, new stable or unstable angina with documented ischemia, or heart failure; or 2) a composite renal outcome defined as any of the following: progression from normoalbuminuria to either microalbuminuria or proteinuria; progression from microalbuminuria to proteinuria; a decrease in estimated glomerular filtration rate (eGFR) of $\geq 30\%$; or renal insufficiency requiring dialysis or transplantation.⁷⁶

Compared to placebo, neither ramipril nor rosiglitazone reduced the risk of the cardiorenal composite outcome. However, rosiglitazone reduced the risk of the renal component (HR 0.80, 95% CI 0.68 – 0.93, $p=0.005$). This was due to a reduction in progression of albuminuria (HR 0.82, 95% CI 0.69 – 0.98, $p=0.031$). Although reduction of cardiovascular outcomes and progression of albuminuria in patients at high risk of cardiovascular disease was shown for ramipril in the HOPE study,³⁹ no such benefit was seen for ramipril in DREAM, possibly due to low activation of the renin-angiotensin system in the lower risk DREAM participants. A potential limitation of DREAM was that renal outcomes were only available for 78% of participants at study end.⁷⁶

In an open-label randomized cross-over study of 40 adults with chronic non-diabetic kidney disease, rosiglitazone reduced proteinuria. This finding was confounded by an associated 7.8 mmHg (95% CI 2.6 – 13.1, $p=0.006$) reduction in systolic blood pressure in the rosiglitazone group.⁷⁷ In a *post hoc* analysis of the PROactive trial, the relationship between chronic kidney disease (CKD) and incident cardiovascular disease was evaluated.⁷⁵ Patients with baseline CKD (defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m²) who were treated with pioglitazone had a greater decline in eGFR than those treated with placebo (between-group difference 0.8 ml/min per 1.73 m²/yr). Results of urinary albumin measurements were not reported.⁷⁸

4.5 BONE FRACTURES

An increased risk of fractures was observed with rosiglitazone in ADOPT.³⁶ The increased fracture risk was observed in women only (RR=2.17, 95% CI 1.52-3.13, $p<0.001$) and primarily involved the upper and lower limbs. No specific risk factors were identified. Increased risk of fractures was also seen with pioglitazone. Takeda conducted an analysis of clinical trials with pioglitazone and found more reports of fractures in women taking pioglitazone than those taking a comparator drug.⁷⁹ The majority of fractures were in the distal upper forearm or distal lower limb. The fracture incidence calculated was 1.9 fractures per 100 patient-years in the pioglitazone group and 1.1 fractures per 100 patient-years in the comparator group, yielding a point estimate for the relative risk of 1.7 (estimated 95% CI 1.2-2.5).⁷⁹ An observational study using the UK General Practice Research Database showed an association between longer-term (12 to 18 months) therapy and bone fractures with both rosiglitazone and pioglitazone.⁸⁰ This effect was independent of patient age and gender and tended to increase with dose. Fractures were primarily localized to the hip or wrist.

Preclinical data provide insight into TZD effects on bone. Rosiglitazone was found to counteract osteoblastogenesis and induce a preferential differentiation into adipocytes in human mesenchymal stem cells.⁸¹ In a mouse model, Wan et al. showed that PPAR- γ and its ligands have a previously unrecognized role in promoting osteoclast differentiation and bone resorption.⁸² The likely mechanism of TZD-induced skeletal fragility is inhibition of bone formation by PPAR- γ mediated diversion of mesenchymal progenitor cells into the adipocyte lineage at the expense of osteoblastogenesis.^{83,84}

Potential mechanisms underlying this risk were studied in 50 postmenopausal women randomized to rosiglitazone or placebo for 14 weeks.⁸⁵ The primary endpoint was biochemical markers of bone formation. Secondary outcomes were biochemical markers of bone resorption and bone mineral density measured at the spine and hip. In patients randomized to rosiglitazone, two specific markers of bone formation declined by 10%-12% compared with placebo. There was no change in a biochemical marker of bone resorption. Changes in bone turnover were accompanied by a significant 2% decline in total hip bone mineral density in the rosiglitazone group, even within the short time frame of the study. In another study of rosiglitazone using a retrospective case-control design, increased bone loss at total hip and femoral neck areas in diabetic men was observed.⁸⁶

4.6 MALIGNANCY RISK

In pre-approval animal studies, pioglitazone was found to increase the occurrence of urinary bladder cancer in male rats.⁵⁸ The formation of urinary calculi was raised as a potential explanation for the findings in male rats.⁵⁸ No tumors were noted in similar studies performed in mice.⁵⁸ In over 1800 patients from clinical trials treated with pioglitazone for up to one year, no new bladder tumors were noted.⁵⁸ Abnormal cytology results were noted in 0.72% of pioglitazone-treated patients and in 0.88% of placebo-treated patients.⁸⁷ In the PROactive study, a marginally significant increase in bladder cancer and a statistically significant decrease in breast cancer were observed in pioglitazone-treated patients.¹⁴ Cancer incidence with antidiabetic drugs including TZDs has been evaluated using observational study designs in US population-based databases. Results were inconsistent, and in some studies, suggested a protective effect.⁸⁸⁻⁹⁰ No published literature was identified that provides a meaningful basis for differentiation of cancer risk with rosiglitazone or pioglitazone.

4.7 SURROGATE MEASURES OF CARDIOVASCULAR RISK OR DISEASE

Several studies have been performed to assess the effect of TZDs on potential cardiovascular risk factors related to inflammation. Both rosiglitazone⁹¹ and pioglitazone⁹² reduce blood levels of C-reactive protein, a non-specific marker of inflammation that may important to cardiovascular risk.^{93,94} Both TZDs

also reduce circulating levels of adipocytokines, also theorized by some to be a cardiovascular risk factor.⁹⁵

Several studies have also been performed to examine the effect of TZD use on progression of documented vascular disease. In a 72-week randomized controlled trial of pioglitazone vs. glimepiride, pioglitazone was shown to statistically significantly reduce progression of carotid artery intima-media thickness (atherosclerotic plaque), a marker of coronary atherosclerosis.⁹⁶ In an 18-month randomized controlled trial of pioglitazone vs. glimepiride, pioglitazone was found to statistically significantly reduce progression of coronary atherosclerosis, using coronary intravascular ultrasonography.⁹⁷ Similar studies with rosiglitazone have not been published.

A meta-analysis of published randomized trials concluded that both rosiglitazone and pioglitazone reduced the rate of in-stent restenosis and the need for target-vessel revascularization among patients who had undergone percutaneous coronary intervention.⁹⁸

4.8 HEART FAILURE

While both TZDs have been reported to cause heart failure, and product labeling for both includes a boxed warning for heart failure,^{58,62} our review of the literature, including 4 published meta-analyses,⁹⁹⁻¹⁰² suggests that there is a medically important and statistically significant difference in heart failure risk between rosiglitazone and pioglitazone. Although pioglitazone does increase heart failure risk (RR=1.4), the risk with rosiglitazone (RR=2.1) is about 50% greater than the risk conferred by pioglitazone. The meta-analysis by Lago et al.¹⁰¹ suggested that this increase in heart failure risk is not associated with an increase in mortality. Two recent observational studies reported an increased risk of heart failure in elderly patients treated with rosiglitazone compared to pioglitazone.^{103,104}

4.9 MICROVASCULAR DISEASE PREVENTION

Through 2007, there were no published randomized controlled trials showing a protective effect of either TZD against microvascular complications of T2DM such as retinopathy, peripheral neuropathy, or nephropathy.⁵⁹⁻⁶¹

In June 2008, a small observational study was published that reported a borderline statistically significant reduction in progression from severe non-proliferative to proliferative diabetic retinopathy in a subset of 7 patients treated with rosiglitazone vs. 12 patients treated with other therapies (including diet).¹⁰⁵ This study was poorly described and designed, was not embedded within a definable base population, involved multiple subgroup analyses, and did not adjust for the effect of lower HbA1c in the rosiglitazone group or for duration of treatment with rosiglitazone, so that it was not possible to distinguish an effect due to rosiglitazone from an effect due to improved glycemic control. Also, at baseline, patients in the control group were 2.8-times (95% CI 1.3-6.0) more likely to have established proliferative diabetic retinopathy than patients in the rosiglitazone group (p=0.008) and were 1.6-times (95% CI 1.1-2.2) more likely to have moderate-to-severe non-proliferative diabetic retinopathy (p=0.006). These differences cast doubt on the study findings.

Also in 2008, additional analyses from the DREAM trial reported that rosiglitazone reduced the occurrence of the renal component of a composite cardiorenal outcome (HR=0.80, 95% CI 0.68-0.93).⁷⁶ A small (n=60) randomized clinical trial in diabetic patients with stage 3 or 4 chronic kidney disease reported that pioglitazone added to losartan significantly slowed the progression of proteinuria and decline in glomerular filtration rate compared to treatment with losartan alone.¹⁰⁶

4.10 MACROVASCULAR DISEASE PREVENTION

Rosiglitazone. There are no published randomized controlled trials that demonstrate a reduction in cardiovascular death, AMI, stroke, or peripheral vascular disease risk with rosiglitazone. As described above, the risk of AMI in patients with impaired fasting glucose treated with rosiglitazone was greater than that of patients treated with placebo in the DREAM trial (RR=1.66, 95% CI 0.73-3.80), and so was the risk of the composite outcome of cardiovascular death, AMI, or stroke (RR=1.39, 95% CI 0.81-2.37), although neither reached statistical significance.¹⁴ In the ADOPT trial of patients recently diagnosed with T2DM, the risk of AMI was higher in patients treated with rosiglitazone than in patients treated with either metformin or glyburide.³⁶ Pooling both comparator groups from this trial, the risk of AMI was greater in patients treated with rosiglitazone (RR=1.4; 95% CI 1.1-1.9).⁹⁷ In a third large, longer-term, open-label trial (RECORD), interim results showed an increased risk of AMI (RR=1.16, 95% CI 0.75-1.81)⁴ and the final analysis reported a hazard ratio for AMI of 1.14 (0.80-1.63).⁵ A meta-analysis of published and unpublished randomized controlled trials involving rosiglitazone found an increased risk of AMI (RR=1.43, 95% CI 1.03-1.98) and cardiovascular death (RR=1.64, 95% CI 0.98-2.74).¹⁰⁷ Most of the studies included in this meta-analysis were of short duration (24-26 weeks). A patient-level meta-analysis of short-term trials involving rosiglitazone by FDA found an increased risk of cardiac ischemic events (RR=1.4, 95% CI 1.1-1.8).¹⁰⁸ A meta-analysis of longer-term trials (≥ 12 months duration) involving rosiglitazone found an increased risk of AMI (RR=1.42, 95% CI 1.06-1.91).⁹⁹ This analysis included findings from DREAM,³⁷ ADOPT,³⁶ and RECORD.^{4,5}

Pioglitazone. One large randomized controlled trial in patients with established macrovascular disease (PROactive) found a non-statistically significant decrease in risk for the composite outcome of all-cause mortality, nonfatal AMI, nonfatal stroke, ACS, revascularization of coronary or leg arteries, or amputation of the lower extremity (RR=0.90; 95% CI 0.80-1.02).¹⁴ A secondary analysis for the outcome of all-cause mortality, nonfatal AMI, or nonfatal stroke found a statistically significant reduction in risk with pioglitazone (RR=0.84, 95% CI 0.72-0.98). A meta-analysis of 19 clinical trials with pioglitazone reported a borderline statistically significant reduction in AMI (RR= 0.81, 95% CI 0.64-1.02, p=0.08) and a statistically significant reduction in the composite outcome of all-cause mortality, nonfatal AMI, and nonfatal stroke (RR=0.82, 95% CI 0.72-0.94, p=0.005).³⁵

Rosiglitazone vs. pioglitazone. A comparison of rosiglitazone vs. pioglitazone, based on available meta-analyses^{99,100,107} suggests that the risk of AMI is increased with rosiglitazone compared with pioglitazone. Review of published observational studies comparing rosiglitazone with pioglitazone suggest that rosiglitazone increases the risk of AMI, in non-elderly patients¹⁰⁹⁻¹¹⁵ and heart failure and all-cause mortality in the elderly.¹¹⁶⁻¹¹⁸

5 DISCUSSION

5.1 MAIN FINDINGS

Our review of RECORD leads us to conclude that its design and execution were biased in a manner that consistently favored not finding a cardiovascular effect if it was present. In our view, it provides no credible evidence of rosiglitazone's cardiovascular safety. In our view, the TIDE trial is unethical because it subjects human beings to unnecessary risks without any possibility of a meaningful, unique health benefit from rosiglitazone. Patients bear the full burden of risk of AMI, heart failure, and death, for the purpose of establishing with definitive certainty that rosiglitazone increases cardiovascular risk (the null hypothesis for the non-inferiority components of this trial), with no likely expectation of unique benefit. This reality makes TIDE a "bad deal" trial.

The evidence suggesting differential cardiovascular risk between rosiglitazone and pioglitazone is compelling in our view. Data from both randomized trials and observational studies point to the same

conclusion, namely, rosiglitazone increases cardiovascular risk compared to pioglitazone. This difference in risk between rosiglitazone and pioglitazone was evident to OSE when it presented before the July 2007 advisory committee convened to consider this issue.¹ What has been disconcerting to us is that even though the 2007 advisory committee voted 20-3 that rosiglitazone increases cardiovascular risk, it voted 22-1 that rosiglitazone's benefits exceeded its risks.¹ It did this without enunciating what these benefits were or on what basis, these benefits exceed the cardiovascular risks it had just agreed were real.

In the three years since that advisory committee meeting, the Office of New Drugs has not answered the question of what are the unique health benefits of rosiglitazone that have justified its continued marketing. Instead, we have been told that "definitive proof" of harm is needed before taking action to remove rosiglitazone from the market. In our opinion, this approach is inconsistent with public health policy that places patient safety first. In our view, it amounts to an asymmetric handling of harms and benefits. The underlying presumption has been that rosiglitazone is safe and remains so until "definitive proof" forces reconsideration. At the same time, rosiglitazone's benefits exceed all harms, and no evidence is required to justify its continued marketing. Our review of the literature finds no evidence of a unique or meaningful health benefit from rosiglitazone that is not also provided by pioglitazone (table 5) and there is substantial evidence that rosiglitazone increases cardiovascular risk compared with pioglitazone.

Table 5. Comparison of rosiglitazone and pioglitazone for benefits and risks

	Rosiglitazone (RSG)	Pioglitazone (PIO)
Glycemic control	Lowers HbA1c	Lowers HbA1c
Lipid effects	Unfavorable vs. PIO	Favorable vs. RSG
Body mass	Increases weight and body fat	Increases weight and body fat
Blood pressure	Small reduction	Small reduction
Kidney effects	Possible reduction in proteinuria	Possible reduction in proteinuria
Bone Fractures	Increases risk ~2-fold in women	Increases risk ~2-fold in women
Malignancy risk	No convincing evidence	No convincing evidence
Cardiovascular surrogates	Reduces inflammatory markers Reduces in-stent restenosis	Reduces inflammatory markers Reduces in-stent restenosis Reduces progression of coronary atherosclerosis
Heart failure	Increases risk 2.1-fold vs. other (50% higher risk vs. PIO)	Increases risk 1.4-fold vs. other
Microvascular disease	Minimal evidence for prevention	Minimal evidence for prevention
Cardiovascular disease	Increased risk vs. PIO	Reduced risk vs. RSG
Mortality	Neutral	Neutral

6 CONCLUSIONS

Rosiglitazone and pioglitazone have comparable efficacy with respect to glycemic control in patients with T2DM. Rosiglitazone confers no known unique health benefits beyond those conferred by pioglitazone. While both rosiglitazone and pioglitazone increase the risk of heart failure, the increase caused by rosiglitazone is substantially greater than that caused by pioglitazone. Rosiglitazone increases AMI risk compared to pioglitazone in the non-elderly and increases all-cause mortality in the elderly. Based on these findings, any proposed head-to-head trial of rosiglitazone vs. pioglitazone is unethical and exploitative.

7 RECOMMENDATIONS

The risks of rosiglitazone use are serious and exceed those for pioglitazone. Rosiglitazone confers no unique and medically important benefit that distinguishes it from pioglitazone. The risks of rosiglitazone use exceed its benefits compared to pioglitazone. Rosiglitazone should be removed from the market.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21073	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	ACTOS (PIOGLITAZONE HCL)15/30/45MG TABS
NDA-21071	ORIG-1	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

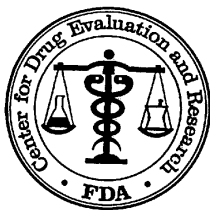
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/s/

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The opinions expressed in this review are those of Dr. Graham and Dr. Gelperin. The Office of Surveillance and Epidemiology will issue its final opinion and recommendation once we have read the reviews for all disciplines and have heard all the various opinions.



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FDA Rosiglitazone and Pioglitazone Meta-Analyses

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1 EXECUTIVE SUMMARY

1.1 Conclusion

Differences in trial characteristics and patient populations between two FDA meta-analyses that separately investigated the association of cardiovascular risk with Avandia (rosiglitazone) and Actos (pioglitazone) limit the ability to make direct comparisons of risks between the two drugs. Overall, across all trials for rosiglitazone, the estimated risk of MACE (major adverse cardiovascular event, defined as cardiovascular death, stroke, or myocardial infarction) was higher for rosiglitazone compared to control and nearly statistically significant (OR=1.44; 95% CI=[0.95, 2.20]). Overall, across all trials for pioglitazone, the estimated MACE risk was lower for pioglitazone compared to control (OR=0.83; 95% CI=[0.56, 1.21]). Overall, for congestive heart failure, the estimated risk was higher compared to control and statistically significant for both drugs.

To improve the comparability of the two meta-analyses, the two drugs were compared within trial-level groups based on randomized comparator and other trial-level characteristics. Within these trial-level groups, there were still important differences in trial and patient characteristics.

For placebo controlled trials, in the rosiglitazone meta-analysis, the odds ratio estimates were greater than one for all safety outcomes considered (MACE, cardiovascular death, myocardial infarction, total myocardial ischemia, serious myocardial ischemia, and congestive heart failure) except stroke and statistically significant for myocardial infarction, serious myocardial ischemia, total myocardial ischemia, and congestive heart failure. For placebo controlled trials, in the pioglitazone meta-analysis, there was not an obvious pattern in the safety outcome. For active controlled trials, neither drug generally showed negative effects on the safety outcomes.

For insulin add-on trials (trials in which all patients were on insulin), for rosiglitazone, the odds ratio estimates were greater than one for all safety outcomes other than stroke and were statistically significant for serious myocardial ischemia and total myocardial ischemia. For these trials, in the pioglitazone meta-analysis, there was not an obvious trend in the odds ratio estimates; although the odds ratio estimate for congestive heart failure was greater than one and statistically significant. For sulfonylurea controlled trials, for pioglitazone, the odds ratio estimates were greater than one for all safety outcomes other than total myocardial ischemia but were statistically significant only for congestive heart failure.

Overall and across a range of trial groups, both drugs showed negative effects on congestive heart failure.

1.2 Background

Cardiovascular safety concerns have been raised for the U.S. FDA approved thiazolidinedione (TZD) class of antidiabetic drugs, which include pioglitazone and rosiglitazone. In June 2010 FDA completed two meta-analyses that evaluated the association of cardiovascular safety outcomes separately for pioglitazone and rosiglitazone. The meta-analyses used patient-level data from clinical trials available to GlaxoSmithKline for rosiglitazone and Takeda for pioglitazone. The meta-analyses had two goals: (1) to update the 2007 FDA meta-analysis of rosiglitazone of 42 trials with 10 newly available trials and (2) to conduct a pioglitazone meta-analysis in order to compare indirectly the cardiovascular profile of the two drugs.

Trials were included into the meta-analysis if they were randomized, double-blind trials between 2 months and 2 years in duration completed by December 2009 with targeted total daily dose for pioglitazone of 30 or 45 mg, and 4 or 8 mg for rosiglitazone with available patient-level data.

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, all-cause death, serious myocardial ischemia, total myocardial ischemia, and congestive heart failure. The primary analysis method was the exact method for an odds ratio and associated 95% confidence interval, stratified by trial. The analysis was conducted on several subgroups of trials based on randomized comparator and baseline drug in add-on trials.

1.3 Findings

Overall, the findings of the 2007 FDA meta-analysis of rosiglitazone were generally supported or strengthened. In the 2010 meta-analysis of the 52 trials, rosiglitazone had a statistically significant greater risk than comparator for myocardial infarction (OR=1.80; 95% CI=[1.03, 3.25]) and a nearly statistically significant greater risk than comparator for MACE (OR=1.44; 95% CI=[0.95, 2.20]). In the 2007 FDA meta-analysis, myocardial infarction was nearly statistically significant (OR=1.5; 95% CI=[0.9, 2.7]) and the odds ratio for MACE was 1.2 (95% CI=[0.8, 1.8]). In both 2007 and 2010 meta-analyses, total myocardial ischemia was statistically significant: in 2007, OR=1.4 (95% CI=[1.1, 1.8]); in 2010, OR=1.34 (95% CI=[1.07, 1.70]). The odds ratio estimates for cardiovascular deaths was slightly lower in the 2010 meta-analysis (OR=1.46; 95% CI=[0.60, 3.77]) than in the 2007 meta-analysis (OR=1.7; 95% CI=[0.7, 5]).

The rosiglitazone meta-analysis consisted of more trials and patients than the pioglitazone meta-analysis. The rosiglitazone meta-analysis had 52 trials with 16995 patients, 10039 (59%) randomized to rosiglitazone and 6956 (41%) to the comparator. The pioglitazone meta-analysis had 29 trials with 11774 patients, 6132 (52%) randomized to pioglitazone and 5642 (48%) to the comparator. There were differences in trial characteristics across meta-analyses based on grouping of trials. The pioglitazone meta-analysis had proportionately more patients in the monotherapy trial group (49% compared to 32%) and less in the placebo controlled trial group (39% compared to 81% compared). The distribution of patients by nominal trial duration differed by meta-analysis. More rosiglitazone patients were 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%), while the distribution of pioglitazone patients was more uniform across the different trial duration categories; 47% in trials between 2 and 6 months, 30% in trials 6 months to 1 year, and 24% in trials between 1 and 2 years. Patients in the pioglitazone meta-analysis had treatment for 77 days on average longer.

Differences were observed in patient characteristics between meta-analyses. The patients in both meta-analyses had similar average age (57 for pioglitazone and 58 for rosiglitazone) and BMI (31 for pioglitazone and 30 for rosiglitazone). The rosiglitazone meta-analysis had slightly more males (59% compared to 55%) and more US patients (44% compared to 30%, 13% of patients in the pioglitazone meta-analysis had region missing and there was no missing in the rosiglitazone meta-analysis). Patients in the pioglitazone meta-analysis had diabetes for an average of 6 years and 59% received prior treatment; in the rosiglitazone meta-analysis average diabetes duration was 7 years and 78% received previous treatment.

Overall, in the rosiglitazone meta-analysis the odds ratio estimate for MACE was greater than one and nearly statistically significant (OR=1.44; 95% CI=[0.95, 2.20]). Whereas, in the pioglitazone meta-analysis, the odds ratio estimate for MACE was less than one and not statistically significant (OR=0.83; 95% CI=[0.56, 1.21]). In the rosiglitazone meta-analysis, the odds ratio estimates were greater than one for all safety outcomes other than stroke and were statistically significant for myocardial infarction, serious myocardial ischemia, total myocardial ischemia, and congestive heart failure. In the pioglitazone meta-analysis, there was not an obvious trend in the odds ratio estimates; although the odds ratio estimate for congestive heart failure was greater than one and statistically significant.

For 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]). For active controlled trials, rosiglitazone and pioglitazone had similar estimated odds ratios for MACE (OR=1.05; 95% CI=[0.48, 2.34]) and (OR=0.88; 95% CI=[0.58, 1.34]), respectively.

For insulin add-on trials (trials in which all patients were on insulin), for rosiglitazone, the odds ratio estimates were greater than one for all safety outcomes other than stroke and were statistically significant for serious myocardial ischemia and total myocardial ischemia. For these trials, in the pioglitazone meta-analysis, there was not an obvious trend in the odds ratio estimates; although the odds ratio estimate for congestive heart failure was greater than one and statistically significant. For sulfonylurea controlled trials, for pioglitazone, the odds ratio estimates were greater than one for all safety outcomes other than total myocardial ischemia but were statistically significant only for congestive heart failure.

Overall and across a range of trial groups, both drugs showed negative effects on congestive heart failure. The overall odds ratios were OR=1.93 (95% CI= [1.30, 2.93]) and OR=1.47 (95% CI= [1.01, 2.16]) for rosiglitazone and pioglitazone, respectively.

2 BACKGROUND

Cardiovascular safety concerns have been raised for the thiazolidinedione (TZD) class of antidiabetic drugs. The U.S. FDA approved TZD class includes Actos (pioglitazone, marketed by Takeda) and Avandia (rosiglitazone, marketed by GlaxoSmithKline). Both drugs were FDA approved in 1999 for glycemic control in patients with type-2 diabetes. In July 2007, the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met to discuss the cardiovascular risks of the TZDs, with focus on rosiglitazone. In August 2007 both drugs received a boxed warning on the risk of congestive heart failure. In November 2007 rosiglitazone received an additional boxed warning for a potential increased risk of myocardial ischemia.

GlaxoSmithKline (GSK) has performed two meta-analyses of rosiglitazone, one on 42 trials (submitted to FDA August 4, 2006) and an updated meta-analysis on 52 trials (submitted to the FDA April 9, 2009). Lincoff¹ et al in 2007 reported on a meta-analysis of pioglitazone of 19 randomized trials. The same pioglitazone trials and similar statistical methodology were used in a Takeda meta-analysis (submitted to FDA on October 10, 2006). An amended report (submitted to FDA on August 26, 2008) included four additional trials.

In June 2010 FDA completed two meta-analyses that evaluated the association of cardiovascular safety outcomes separately for pioglitazone and rosiglitazone. The meta-analyses used patient-level data from clinical trials available to GlaxoSmithKline for rosiglitazone and Takeda for pioglitazone. FDA provided instructions to both companies on the inclusion criteria for trials, the definition cardiovascular outcomes and baseline risk factors, and the format of the data.

One of the goals of the 2010 FDA rosiglitazone meta-analysis was to update the previous FDA meta-analysis of rosiglitazone (completed June 4, 2007, addendum added July 3, 2007) with 10 newly available trials. The 10 new trials provide independent information to assess the consistency of the findings of the original FDA meta-analysis of 42 trials.

The second goal of the two FDA meta-analyses was to enable qualitative comparisons of safety profiles between pioglitazone and rosiglitazone. Direct overall comparisons of the meta-analyses are limited because of systematic differences in the trial designs, trial populations and data collection of the two drugs. To improve the comparability of the two meta-analyses, both meta-analyses utilized the same statistical analysis plan, including common trial inclusion criteria, endpoint definition, trial-level and patient-level subgroups, and statistical methods. Safety profiles of the two drugs were compared within trial-level groups to allow for a more direct comparison of the drugs. However, systematic differences between trials in the comparisons still existed, both on the trial and patient-level, limiting the ability to make comparisons between the two drugs. This limitation is further discussed in the Methods section.

This document summarizes (1) the update of the FDA meta-analysis of rosiglitazone and (2) the comparison between the FDA rosiglitazone and pioglitazone meta-analyses.

3 METHODS

This section summarizes the design and statistical methodology used in the FDA two meta-analyses. Additionally, it briefly describes differences in the methodology between the 2010 FDA meta-analyses and the 2007 FDA rosiglitazone meta-analysis, the GSK meta-analysis, and the Takeda meta-analysis.

Trials 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 for pioglitazone of 30 or 45 mg, and 4

¹Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. JAMA; 298:1180-8.

or 8 mg for rosiglitazone with available patient-level data. Non-randomized or open-label trial extension phases were excluded.

Safety endpoints were identified by GSK and Takeda using a FDA specified list of preferred terms (PT) from the Medical Dictionary for Regulatory Activity (MedDRA) coding system (see appendix 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 (CV) 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.

The primary analysis method was the exact method for a stratified odds ratio and associated 95% confidence interval². Statistical significance refers to the 95% confidence interval (CI) not containing the null value of no difference between pioglitazone or rosiglitazone and the comparator. The stratification factor was the trial. The term relative risk is used to describe the odds ratios and is expressed as rosiglitazone or pioglitazone versus control.

The analyses considered several subgroups of trials (trial-level groups). The first set of trial-level groups was based on randomized comparator and consisted of the following: (1) placebo controlled, (2) active controlled, (3) sulfonylurea controlled, and (4) metformin control. Active controlled was a group that included both sulfonylurea controlled, metformin controlled, and other non-placebo comparators.

The second set of trial-level groups was based on the baseline drug in add-on trials. For example, a trial that compared rosiglitazone + metformin to placebo + metformin was considered a placebo controlled trials and a metformin add-on trial. Table 1 lists the 6 treatment add-on trial-level groups considered. Note that multi-arm trials (≥ 3) may contribute to more than one trial-level group.

Other trial-level groupings investigated but not presented in this document were based on treatment dose and duration.

Table 1. Classification add-on trial groups.

	Label for trial types	TZD Group	Control
1	Monotherapy	Monotherapy TZD	PLA, MET, SU, OTZD
2	Background add-on	TZD +Background	PLA+Background, SU+Background, or MET+Background
3	Sulfonylurea add-on	TZD +Sulfonylurea	PLA+SU or MET+SU
4	Metformin add-on	TZD +Metformin	PLA+MET, SU+MET
5 ¹	Insulin add-on	TZD +Insulin	PLA+INS, MET+INS, SU+INS
6	MET and SU add-on	TZD +Metformin+Sulfonylurea	PLA+MET+SU

MET-Metformin; SU-Sulfonylurea; INS-Insulin; TZD: Rosiglitazone for rosiglitazone analysis and pioglitazone for pioglitazone analysis; OTZD: Other TZD, pioglitazone for rosiglitazone analysis, and rosiglitazone for pioglitazone analysis.

¹Treatment arms may include background medications.

The use of trial-level groups was designed to allow for better comparison between the two drugs. However, trials within a trial-level group may differ in other trial-level or patient-level characteristics. For example, metformin add-on trials for the two drugs may differ in the randomized comparator (eg, placebo controlled versus active controlled). In the results for trial-level groups, summary of other trial-level factors are provided to assist in the assessment of the comparability between the two drugs.

² Agresti A. Categorical Data Analysis. John Wiley & Sons. 1990.

In addition to the primary analysis methods, FDA employed several sensitivity analyses including examining random effect models, proportional hazard models, the effect of trials without events, and the effect of long-duration trials.

3.1 Other Meta-Analyses Methods

The previous FDA meta-analysis of rosiglitazone employed similar methodology to the present FDA meta-analysis. Important difference in the previous meta-analysis included (1) outcome definitions, (2) stratification factor, and (3) metformin add-on group definition. The previous outcome definitions were based on GlaxoSmithKline lists of MedDRA lower-level terms. The previous stratification factor in the estimation of the odds ratio was based on add-on group. The previous metformin add-on group consisted of only placebo controlled trials, as opposed to all metformin add-on trials.

The GSK meta-analysis was based on the outcome definitions of GlaxoSmithKline lists of MedDRA lower-level terms. The GSK meta-analysis pooled all data and did not stratify on trial or any other factor. The GSK meta-analysis used a Cox proportional hazard model as the primary analysis.

The Takeda meta-analysis was based on other MedDRA preferred terms and outcome definitions. In particular, the MACE outcome used all-cause death as opposed to cardiovascular death. The Takeda meta-analysis stratified on categories of trial duration. The Takeda meta-analysis used a Cox proportional hazard model as the primary analysis.

4 RESULTS: Update to FDA Meta-Analysis of Rosiglitazone

The section summarizes the update of the primary findings of the FDA 2010 rosiglitazone meta-analysis from the FDA 2007 meta-analysis. Refer to the Methods section for differences in methodology between the two meta-analyses.

Tables 2 through 4 give the results for the original 42 trials, the 10 new trials, and the entire set of 52 trials for the primary analysis based on the methodology used for the 2010 FDA meta-analysis. Of the 52 trials, 16 had no primary outcome events (i.e. MACE), and of the 10 new trials, 5 had no MACE events. The 10 new trials contributed 21 MACE events (13 RSG, 8 Control)³, which made for a total of 109 events (70 RSG, 39 Control) in the 52 trials. The 10 new trials contributed 4 CV death events (1 RSG, 3 Control), which made for a total of 26 events (17 RSG, 9 Control) in the 52 trials. Based on the 10 trials alone, the event counts were too small to support any pattern, (many outcomes had wide confidence intervals).

Using the 2010 methodology, the results for the 42 and the 52 studies were consistent. For the 52 studies, MACE was nearly statistically significant (OR=1.44; 95% CI=[0.95, 2.20]). For the 42 studies, the point estimate for MACE was similar to that of the 52 studies but the confidence interval was wider (OR 1.40; 95% CI=[0.88, 2.27]). For the 42 studies, serious ischemia, total ischemia and CHF were statistically significant and myocardial infarction was nearly statistically significant. For the 52 studies, myocardial infarction, serious myocardial ischemia, total myocardial ischemia and CHF were all significant. Comparing the 2007 analysis of the 42 studies to the 2010 analysis of the 52 studies, a notable change was that myocardial infarction went from borderline significant in the 2007 analysis (OR=1.5; 95% CI=[0.9, 2.7])⁴ to significant in the 2010 analysis of the 52 trials (OR=1.80; 95% CI=[1.03, 3.25]). When the 42 studies were analyzed using the 2010 methodology, myocardial infarction was even closer to statistical significance (OR=1.84; 95% CI=[0.99, 3.57]). In both 2007 and 2010 meta-analyses, total myocardial ischemia was statistically significant: in 2007, OR=1.4 (95% CI=[1.1, 1.8]); in 2010, OR=1.34 (95% CI = [1.07, 1.70]). The odds ratio estimates for CV deaths was slightly lower in the 2010 meta-analysis (OR=1.46; 95% CI=[0.60, 3.77]) than in the 2007 meta-analysis (OR=1.7; 95% CI=[0.7, 5]).

³ Note that the total numbers of patients differ between the rosiglitazone and control groups, particularly for the 52 trials.

⁴ Note that results taken from other documents are quoted to the same degree of precision that is present in the original document, in this case 1 decimal place.

Several sensitivity analyses agreed with the findings for MACE for 52 studies. The risk difference estimate for the 52 studies was 23 events per 10,000 patients (95% CI=[-2.5, 49]). The risk difference estimates makes use of all 52 trials including those with no events. A random effect model gave an odds ratio estimate of 1.40 (95% CI=[0.93, 2.11]) and proportional hazard model gave a hazard ratio estimate of 1.42 (95% CI=[0.95, 2.11]).

Table 2: Rosiglitazone, primary and secondary endpoints, stratified by trial, 42 trials

Endpoint	Comparator N=5633 n (%)	Rosiglitazone N=8604 n (%)	Total N=14237 n (%)	Crude ¹ OR (95% CI)	Stratified OR (95% CI)
MACE	31 (0.55)	57 (0.66)	88 (0.62)	1.21 (0.76,1.93)	1.40 (0.88,2.27)
CV Death	6 (0.11)	16 (0.19)	22 (0.15)	1.75 (0.65,5.45)	1.97 (0.72,6.26)
MIF	16 (0.28)	38 (0.44)	54 (0.38)	1.56 (0.85,2.99)	1.84 (0.99,3.57)
Stroke	14 (0.25)	13 (0.15)	27 (0.19)	0.61 (0.26,1.39)	0.64 (0.27,1.52)
All-cause Death	9 (0.16)	23 (0.27)	32 (0.22)	1.67 (0.75,4.12)	1.89 (0.83,4.71)
Serious M. Isch.	40 (0.71)	95 (1.1)	135 (0.95)	1.56 (1.07,2.32)	1.80 (1.22,2.70)
Total M. Isch.	82 (1.46)	180 (2.09)	262 (1.84)	1.45 (1.11,1.91)	1.63 (1.24,2.17)
CHF	34 (0.6)	80 (0.93)	114 (0.8)	1.55 (1.02,2.39)	2.03 (1.32,3.19)

¹Crude OR CI based on exact method.**Table 3: Rosiglitazone, primary and secondary outcomes, stratified by trial, 10 trials**

Endpoint	Comparator N=1323 n (%)	Rosiglitazone N=1435 n (%)	Total N=2758 n (%)	Crude ¹ OR (95% CI)	Stratified OR (95% CI)
MACE	8 (0.6)	13 (0.91)	21 (0.76)	1.50 (0.58,4.20)	1.59 (0.60,4.48)
CV Death	3 (0.23)	1 (0.07)	4 (0.15)	0.31 (0.01,3.83)	0.34 (0.01,4.24)
MIF	4 (0.3)	7 (0.49)	11 (0.4)	1.62 (0.41,7.55)	1.64 (0.41,7.76)
Stroke	2 (0.15)	5 (0.35)	7 (0.25)	2.31 (0.38,24.28)	2.56 (0.42,26.92)
All-cause Death	8 (0.6)	6 (0.42)	14 (0.51)	0.69 (0.20,2.28)	0.76 (0.22,2.52)
Serious M. Isch.	26 (1.97)	23 (1.6)	49 (1.78)	0.81 (0.44,1.49)	0.87 (0.47,1.63)
Total M. Isch.	50 (3.78)	41 (2.86)	91 (3.3)	0.75 (0.48,1.16)	0.79 (0.50,1.26)
CHF	6 (0.45)	8 (0.56)	14 (0.51)	1.23 (0.37,4.31)	1.37 (0.41,4.81)

¹Crude OR CI based on exact method.**Table 4: Rosiglitazone, primary and secondary endpoints stratified by trial, 52 trials**

Endpoint	Comparator N=6956 n (%)	Rosiglitazone N=10039 n (%)	Total N=16995 n (%)	Crude ¹ OR (95% CI)	Stratified OR (95% CI)
MACE	39 (0.56)	70 (0.7)	109 (0.64)	1.25 (0.83,1.90)	1.44 (0.95,2.20)
CV Death	9 (0.13)	17 (0.17)	26 (0.15)	1.31 (0.55,3.34)	1.46 (0.60,3.77)
MIF	20 (0.29)	45 (0.45)	65 (0.38)	1.56 (0.90,2.79)	1.80 (1.03,3.25)
Stroke	16 (0.23)	18 (0.18)	34 (0.2)	0.78 (0.37,1.63)	0.86 (0.40,1.83)
All-cause Death	17 (0.24)	29 (0.29)	46 (0.27)	1.18 (0.63,2.30)	1.38 (0.72,2.72)
Serious M. Isch.	66 (0.95)	118 (1.18)	184 (1.08)	1.24 (0.91,1.71)	1.46 (1.06,2.03)
Total M. Isch.	132 (1.9)	221 (2.2)	353 (2.08)	1.16 (0.93,1.46)	1.34 (1.07,1.70)
CHF	40 (0.58)	88 (0.88)	128 (0.75)	1.53 (1.04,2.28)	1.93 (1.30,2.93)

¹Crude OR CI based on exact method.

5 RESULTS: Comparison of FDA Meta-Analyses of Rosiglitazone and Pioglitazone

This section compares the results from the FDA meta-analyses of rosiglitazone and pioglitazone. As noted in the methods section, the FDA rosiglitazone and pioglitazone meta-analyses consisted of trials of different designs and patient populations. These differences limit the ability to make direct comparisons between the two meta-analyses. The use of a common analysis plan and trial-level groups was intended to address these limitations. However, it is important to note that systematic differences between the two meta-analyses still exist. In particular, the trial-level groups account for only one factor at a time. For example, the placebo controlled trials for the two meta-analyses do not have identical distributions of the base drug in add-on trials or trial durations. For each trial-level group, the characteristics of the trials from the two meta-analyses are summarized before the risk estimates are presented.

5.1 *Primary analysis set*

5.1.1 Comparison of primary analysis trials and patient populations

Table 5 summarizes trial characteristics by meta-analysis. The rosiglitazone meta-analysis had more trials and patients than the pioglitazone meta-analysis. The pioglitazone meta-analysis consisted of 29 trials with 11774 patients, 6132 (52%) randomized to pioglitazone and 5642 (48%) to the comparator. The rosiglitazone meta-analysis had 52 trials with 16995 patients, 10039 (59%) randomized to rosiglitazone and 6956 (41%) to the comparator.

Between meta-analyses there were differences in trial characteristics. Note that some trial groupings were not exclusive since treatment arms in multi-armed trials (≥ 3) may have been used in more than one group. The distribution of type of comparator groups differed between meta-analyses. The rosiglitazone meta-analysis had 81% of patients enrolled in the placebo controlled trial-group compared to 39% in the pioglitazone meta-analysis. The pioglitazone meta-analysis had proportionately more patients in the monotherapy trial-level group (49% compared to 32%) and fewer in the sulfonylurea add-on trial-level group (10% compared to 26%).

The distribution of patients by nominal trial duration differed by meta-analysis. There were more rosiglitazone patients 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%). For the pioglitazone meta-analysis the distribution of patients was more uniform across the different trial duration categories; 47% in trials between 2 and 6 months, 30% in trials 6 months to 1 year, and 24% in trials between 1 and 2 years.

Table 5. Summary of trials by meta-analysis

Meta-analysis	Trial Groups	Trials	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)
Pioglitazone	Primary Analysis set (N=)	29	5642	6132	11774
	Placebo controlled	18	2097 (37)	2477 (40)	4574 (39)
	Active controlled	12	3682 (65)	3668 (60)	7350 (62)
	Sulfonylurea controlled	8	2189 (39)	2194 (36)	4383 (37)
	Metformin controlled	3	1127 (20)	1105 (18)	2232 (19)
	Monotherapy	13	2814 (50)	2972 (48)	5786 (49)
	Background add-on	3	650 (12)	651 (11)	1301 (11)
	Sulfonylurea add-on	3	580 (10)	584 (10)	1164 (10)
	Metformin add-on	6	1059 (19)	1185 (19)	2244 (19)
	Insulin add-on	5	595 (11)	595 (10)	1190 (10)
	Sulfonylurea and Metformin add-on	1	154 (3)	145 (2)	299 (3)
	Add-on or background therapy	18	3038 (54)	3160 (52)	6198 (53)
	Trial duration: > 2 mos to ≤ 6 mos	18	2495 (44)	3002 (49)	5497 (47)
	Trial duration: > 6 mos to ≤ 1 year	6	1762 (31)	1743 (28)	3505 (30)
	Trial duration: > 1 yr to ≤ 2 yrs	5	1385 (25)	1387 (23)	2772 (24)
Rosiglitazone	Primary Analysis set (N=)	52	6956	10039	16995
	Placebo controlled	46	5636 (81)	8124 (81)	13760 (81)
	Active controlled	13	1918 (28)	2119 (21)	4037 (24)
	Sulfonylurea controlled	8	1457 (21)	1649 (16)	3106 (18)
	Metformin controlled	4	302 (4)	311 (3)	613 (4)
	Background add-on	5	361 (5)	543 (5)	904 (5)
	Monotherapy	18	2223 (32)	3261 (32)	5484 (32)
	Sulfonylurea add-on	16	1945 (28)	2526 (25)	4471 (26)
	Metformin add-on	11	1934 (28)	2130 (21)	4064 (24)
	Insulin add-on	7	815 (12)	1018 (10)	1833 (11)
	Sulfonylurea and Metformin add-on	1	276 (4)	561 (6)	837 (5)
	Add-on or background therapy	39	5331 (77)	6778 (68)	12109 (71)
	Trial duration: > 2 mos to ≤ 6 mos	40	4716 (68)	7068 (70)	11784 (69)
	Trial duration: > 6 mos to ≤ 1 year	10	1792 (26)	2524 (25)	4316 (25)
	Trial duration: > 1 yr to ≤ 2 yrs	2	448 (6)	447 (4)	895 (5)

Table 6 and Table 7 summarize patient characteristics and cardiovascular risk conditions, respectively, for each meta-analysis. The patients in both meta-analyses had similar average age (57 in the pioglitazone meta-analysis and 58 in the rosiglitazone meta-analysis) and BMI (31 in the pioglitazone meta-analysis and 30 in the rosiglitazone meta-analysis). In the rosiglitazone meta-analysis there were slightly more males (59% compared to 55%). Forty-four percent (44%) of patients in the rosiglitazone meta-analysis were in the US compared to 30% in the pioglitazone meta-analysis (13% had region missing). Patients in the pioglitazone meta-analysis had treatment for 77 days on average longer (265 days compared to 188).

Patients in both meta-analyses had on average diabetes for a similar period of time, while patients in the pioglitazone meta-analysis were less likely to have received previous treatment (59% compared to 78%). There were slightly fewer patients in the pioglitazone meta-analysis with a history of coronary heart disease (15% compared to 17%) but slightly more with a history of congestive heart failure (6% versus 3%, 2% of patients in the pioglitazone meta-analysis did not have cardiovascular history reported). There were slightly more patients in the pioglitazone meta-analysis with baseline nitrate use (8% compared to 5%) and slightly less patients with baseline ACE inhibitors use (31% compared to 35%).

Table 6. Patient characteristics by meta-analysis

Characteristic		Pioglitazone N=11774 n (%)	Rosiglitazone N=16995 n (%)
Age	< 65	8886 (75)	12069 (71)
	≥ 65	2888 (25)	4926 (29)
	Mean (Std.)	57 (10)	58 (10)
	Range (min-max)	(18-91)	(26-88)
Body mass index	< 30	5641 (48)	8822 (52)
	≥ 30	6119 (52)	8173 (48)
	Missing	14 (0)	11 (0)
	Mean (Std.)	31 (5)	30 (6)
	Range (min-max)	(14-84)	(16-75)
Gender	Male	6496 (55)	10059 (59)
	Female	5278 (45)	6936 (41)
Location	United States	3532 (30)	7450 (44)
	Other	6675 (57)	9545 (56)
	Missing	1567 (13)	0 (0)
Treatment duration (days)	Mean (Std.)	265 (194)	188 (116)
	Range (min-max)	(1- 758)	(1-758)

Table 7. Patient cardiovascular risk by meta-analysis

Characteristic		Pioglitazone N=11774 n (%)	Rosiglitazone N=16995 n (%)
Duration diabetes (yrs)	≥ 10 yrs	2651 (23)	4241 (25)
	< 10 yrs	9088 (77)	12754 (75)
	Missing	35 (0)	4 (0)
	Mean (Std.)	6 (7)	7 (6)
	Range (min-max)	(0-70)	(0-45)
Previously treated for diabetes	Yes	6935 (59)	13248 (78)
	No	4065 (35)	3737 (22)
	Missing	774 (7)	10 (0)
History of coronary heart disease	Yes	1749 (15)	2806 (17)
	No	9736 (83)	14189 (83)
	Missing	289 (2)	0 (0)
History of coronary heart disease & baseline nitrate use	Yes	639 (5)	824 (5)
	No	10846 (92)	16171 (95)
	Missing	289 (2)	0 (0)
History of CHF	Yes	662 (6)	523 (3)
	No	10823 (92)	16472 (97)
	Missing	289 (2)	0 (0)
Nitrate	Yes	958 (8)	901 (5)
	No	10816 (92)	16094 (95)
ACE inhibitors	Yes	3636 (31)	5912 (35)
	No	8138 (69)	11083 (65)
Loop diuretic	Yes	802 (7)	831 (5)
	No	10972 (93)	16164 (95)
Beta-blockers	Yes	2114 (18)	2692 (16)
	No	9660 (82)	14303 (84)

5.1.2 Comparison of results from the primary analysis set

Table 8 displays counts and estimates of odds ratios for the safety endpoints for the two meta-analyses. It is important to note, as previously stated, there were differences in the trial designs and trial populations between the two drugs that confounded the direct comparison between the meta-analyses, particularly for the overall analysis set. To exemplify this point, there were proportionately more events occurring in the pioglitazone meta-analysis than in the rosiglitazone meta-analysis. One possible explanation for this was the larger average treatment duration for pioglitazone compared to rosiglitazone.

In the rosiglitazone meta-analysis, the relative risk estimates were greater than one across the safety endpoints except for stroke; there was not an obvious trend in the pioglitazone meta-analysis.

For the primary endpoint MACE, in the rosiglitazone meta-analysis, the relative risk estimate was greater than one (OR=1.44; 95% CI=[0.95, 2.20]) and was nearly statistically significant. For the primary endpoint MACE, the relative risk estimate in the pioglitazone meta-analysis was less than one (OR=0.83; 95% CI=[0.56, 1.21]) and not statistically significant.

Among the individual MACE components, the relative risk estimate for myocardial infarction for rosiglitazone was greater than one and statistically significant (OR=1.80; 95% CI=[1.03, 3.25]); the relative risk estimate for myocardial infarction for pioglitazone was less than one for myocardial infarction and not statistically significant (OR=0.91; 95% CI=[0.53, 1.53]).

For serious myocardial ischemia, the relative risk estimate for rosiglitazone was greater than one and statistically significant (OR=1.46; 95% CI=[1.06, 2.03]); the relative risk estimate for pioglitazone was near 1 (OR=1.05; 95% CI=[0.76, 1.47]). For congestive heart failure both pioglitazone and rosiglitazone had relative risk estimates greater than one and statistically significant.

Table 8. Analysis of safety endpoints by meta-analysis

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		5642	6132	11774	
	MACE	63 (1.1)	54 (0.9)	117 (1.0)	0.83 (0.56, 1.21)
	CV death	18 (0.3)	22 (0.4)	40 (0.3)	1.18 (0.60, 2.34)
	MIF	33 (0.6)	31 (0.5)	64 (0.5)	0.91 (0.53, 1.53)
	Stroke	16 (0.3)	10 (0.2)	26 (0.2)	0.61 (0.24, 1.43)
	All-cause death	28 (0.5)	31 (0.5)	59 (0.5)	1.06 (0.61, 1.85)
	Serious MIS	76 (1.3)	81 (1.3)	157 (1.3)	1.05 (0.76, 1.47)
	Total MIS	162 (2.9)	143 (2.3)	305 (2.6)	0.86 (0.68, 1.09)
	CHF	50 (0.9)	75 (1.2)	125 (1.1)	1.47 (1.01, 2.16)
Rosiglitazone (N=)		6956	10039	16995	
	MACE	39 (0.6)	70 (0.7)	109 (0.6)	1.44 (0.95, 2.20)
	CV death	9 (0.1)	17 (0.2)	26 (0.2)	1.46 (0.60, 3.77)
	MIF	20 (0.3)	45 (0.4)	65 (0.4)	1.80 (1.03, 3.25)
	Stroke	16 (0.2)	18 (0.2)	34 (0.2)	0.86 (0.40, 1.83)
	All-cause death	17 (0.2)	29 (0.3)	46 (0.3)	1.38 (0.72, 2.72)
	Serious MIS	66 (0.9)	118 (1.2)	184 (1.1)	1.46 (1.06, 2.03)
	Total MIS	132 (1.9)	221 (2.2)	353 (2.1)	1.34 (1.07, 1.70)
	CHF	40 (0.6)	88 (0.9)	128 (0.8)	1.93 (1.30, 2.93)

5.2 Placebo controlled trial group

Table 19 and Table 20 in Appendix 7.1 describe trial characteristics for the pioglitazone and rosiglitazone meta-analysis, respectively, for the placebo controlled trial group. The rosiglitazone meta-analysis had considerably more trials and patients in this trial group. In the rosiglitazone meta-analysis this trial group consisted of 46 trials with 13760 patients, 8124 randomized to rosiglitazone and 5636 to placebo. In the pioglitazone meta-analysis this trial group consisted of 18 trials with 4574 patients, 2477 randomized to pioglitazone and 2097 to placebo.

There were differences in trial duration between meta-analyses. Trials in the pioglitazone meta-analysis ranged in duration from 12 to 52 weeks while the rosiglitazone meta-analysis trials were between 8 and 104 weeks. There were notable differences in the treatment add-on groups between the meta-analyses. The rosiglitazone meta-analysis had more patients in the sulfonylurea add-on group (33% to 12%) but fewer in both the metformin add-on group (21% to 35%) and insulin add-on group (13% to 22%). There were no background add-on trials in the pioglitazone meta-analysis but there were 5 trials in the rosiglitazone meta-analysis consisting of 904 patients.

Table 9 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the placebo controlled trial group. In the rosiglitazone meta-analysis, the relative risk estimates were greater than one across the safety endpoints except for stroke; there was not an obvious trend in the pioglitazone meta-analysis. For MACE, rosiglitazone had a relative risk estimate greater than one and approaching statistical significance (OR=1.53; 95% CI=[0.94, 2.54]). For MACE, pioglitazone had a relative risk estimate less than one that was not statistically significant (OR=0.56; 95% CI=[0.18, 1.67]).

For rosiglitazone, among the individual MACE components, the relative risk estimates for myocardial infarction was greater than one and statistically significant (OR=2.23; 95% CI=[1.14, 4.64]); the relative risk estimate for stroke was less than one and not statistically significant; and the relative risk estimates for CV death was greater than one and not statistically significant. For pioglitazone among the individual MACE components, the relative risk estimates for myocardial infarction was less than one and not statistically significant; the relative risk estimate for stroke was greater than one and not statistically significant; and the relative risk estimates for CV death was less than one and not statistically significant. For congestive heart failure both the pioglitazone and rosiglitazone had relative risk estimates greater than one; the relative risk estimate for rosiglitazone was statistically significant.

Table 9. Analysis of safety endpoints by meta-analysis for placebo controlled trial

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		2097	2477	4574	
	MACE	10 (0.5)	7 (0.3)	17 (0.4)	0.56 (0.18, 1.67)
	CV death	3 (0.1)	3 (0.1)	6 (0.1)	0.80 (0.10, 6.14)
	MIF	8 (0.4)	4 (0.2)	12 (0.3)	0.41 (0.09, 1.56)
	Stroke	1 (0.0)	2 (0.1)	3 (0.1)	1.64 (0.08, 99.71)
	All-cause death	5 (0.2)	4 (0.2)	9 (0.2)	0.63 (0.12, 3.01)
	Serious MIS	10 (0.5)	14 (0.6)	24 (0.5)	1.27 (0.52, 3.22)
	Total MIS	18 (0.9)	21 (0.8)	39 (0.9)	1.02 (0.51, 2.06)
	CHF	6 (0.3)	13 (0.5)	19 (0.4)	1.77 (0.62, 5.75)
Rosiglitazone (N=)		5636	8124	13760	
	MACE	28 (0.5)	54 (0.66)	82 (0.6)	1.53 (0.94, 2.54)
	CV death	5 (0.09)	15 (0.18)	20 (0.15)	2.32 (0.78, 8.32)
	MIF	13 (0.23)	35 (0.43)	48 (0.35)	2.23 (1.14, 4.64)
	Stroke	14 (0.25)	13 (0.16)	27 (0.2)	0.65 (0.27, 1.52)
	All-cause death	9 (0.16)	22 (0.27)	31 (0.23)	1.89 (0.82, 4.73)
	Serious MIS	32 (0.57)	82 (1.01)	114 (0.83)	2.05 (1.33, 3.22)
	Total MIS	70 (1.24)	154 (1.9)	224 (1.63)	1.73 (1.28, 2.35)
	CHF	31 (0.55)	76 (0.94)	107 (0.78)	2.20 (1.40, 3.52)

5.3 Active controlled trial group

Table 21 in Appendix 7.2 describes trial characteristics by meta-analysis for the active controlled trial group. In the pioglitazone meta-analysis this trial group consisted of 12 trials with 7350 patients, 3668 randomized to pioglitazone and 3682 to control. In the rosiglitazone meta-analysis this trial group consisted of 13 trials with 4037 patients, 2119 randomized to rosiglitazone and 1918 to an active control.

There were differences in trial characteristics between the two meta-analyses. Trials in the pioglitazone meta-analysis ranged in duration from 24 to 104 weeks while the rosiglitazone meta-analysis trials were between 12 and 77 weeks. Both meta-analyses had 8 sulfonylurea controlled trials and had similar number of metformin controlled trials. The pioglitazone meta-analysis had proportionately less patients in sulfonylurea controlled trials (60% compared to 77%) but more in trials that were metformin controlled (30% compared to 15%). There were also differences in the treatment add-on group between the meta-analyses. The rosiglitazone meta-analysis had proportionately more patients in the metformin add-on group (28% compared to 9%) and no patients in the background add-on group (0% compared to 18%) and sulfonylurea add-on group (0% compared to 9%). The percentages of patients and number of trials in the monotherapy add-on group were not too different between the meta-analyses.

Table 10 displays events counts and estimates of odds ratios by meta-analysis for the active controlled trial group. For MACE, the relative risk estimate for rosiglitazone was fairly close to 1 and not statistically significant (OR=1.05; 95% CI=[0.48, 2.34]). For MACE the relative risk estimate for pioglitazone was less the one and not statistically significant 0.88 (95% CI=[0.58, 1.34]). For congestive heart failure both the pioglitazone and rosiglitazone had relative risk estimates greater than one and not statistically significant.

Table 10. Analysis of safety endpoints by meta-analysis for active controlled trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		3682	3668	7350	
	MACE	53 (1.4)	47 (1.3)	100 (1.4)	0.88 (0.58, 1.34)
	CV death	15 (0.4)	19 (0.5)	34 (0.5)	1.26 (0.60, 2.67)
	MIF	25 (0.7)	27 (0.7)	52 (0.7)	1.08 (0.60, 1.94)
	Stroke	15 (0.4)	8 (0.2)	23 (0.3)	0.53 (0.19, 1.34)
	All-cause death	23 (0.6)	27 (0.7)	50 (0.7)	1.17 (0.64, 2.14)
	Serious MIS	66 (1.8)	68 (1.9)	134 (1.8)	1.03 (0.72, 1.47)
	Total MIS	145 (3.9)	124 (3.4)	269 (3.7)	0.84 (0.65, 1.09)
	CHF	44 (1.2)	63 (1.7)	107 (1.5)	1.44 (0.96, 2.19)
Rosiglitazone (N=)		1918	2119	4037	
	MACE	14 (0.73)	16 (0.76)	30 (0.74)	1.05 (0.48,2.34)
	CV death	5 (0.26)	2 (0.09)	7 (0.17)	0.40 (0.04,2.45)
	MIF	9 (0.47)	10 (0.47)	19 (0.47)	1.00 (0.36,2.82)
	Stroke	3 (0.16)	5 (0.24)	8 (0.2)	1.54 (0.29,10.02)
	All-cause death	9 (0.47)	7 (0.33)	16 (0.4)	0.79 (0.25,2.38)
	Serious MIS	37 (1.93)	36 (1.7)	73 (1.81)	0.90 (0.54,1.48)
	Total MIS	68 (3.55)	67 (3.16)	135 (3.34)	0.88 (0.61,1.28)
	CHF	9 (0.47)	12 (0.57)	21 (0.52)	1.23 (0.47,3.32)

5.4 Sulfonylurea controlled trial group

Table 22 in Appendix 7.3 describes each trial in the sulfonylurea controlled trial group by meta-analysis. Both meta-analyses had 8 trials in this group but the pioglitazone meta-analysis had more patients. The pioglitazone meta-analysis 4383 patients, 2194 randomized to pioglitazone and 2189 to sulfonylurea. The rosiglitazone meta-analysis had 3106 patients, 1649 randomized to rosiglitazone and 1457 to sulfonylurea.

The rosiglitazone trials ranged in duration from 24 to 77 weeks, while the pioglitazone trials had treatment duration between 24 and 104 weeks. Three of the pioglitazone trials were in the background add-on group compared to zero in the rosiglitazone meta-analysis. The pioglitazone meta-analysis had proportionately fewer patients in both the monotherapy trial-level group (52% compared to 64%) and the metformin add-on group (14% to 36%).

Table 11 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for sulfonylurea controlled trial groups. Pioglitazone consistently had relative risk estimates greater than one across the safety endpoints except for total myocardial ischemia. For MACE the relative risk estimates were greater than one for both pioglitazone and rosiglitazone; neither relative risk estimate was statistically significant. For congestive heart failure both pioglitazone and rosiglitazone had relative risk estimates greater than one; the relative risk estimate for pioglitazone was statistically significant.

Table 11. Analysis of safety endpoints by meta-analysis for sulfonylurea controlled trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		2189	2194	4383	
	MACE	30 (1.4)	35 (1.6)	65 (1.5)	1.16 (0.69, 1.97)
	CV death	12 (0.5)	16 (0.7)	28 (0.6)	1.32 (0.58, 3.09)
	MIF	14 (0.6)	18 (0.8)	32 (0.7)	1.28 (0.60, 2.79)
	Stroke	5 (0.2)	6 (0.3)	11 (0.3)	1.19 (0.30, 4.96)
	All-cause death	18 (0.8)	20 (0.9)	38 (0.9)	1.10 (0.55, 2.22)
	Serious MIS	46 (2.1)	57 (2.6)	103 (2.3)	1.24 (0.82, 1.89)
	Total MIS	111 (5.1)	101 (4.6)	212 (4.8)	0.90 (0.67, 1.20)
	CHF	35 (1.6)	56 (2.6)	91 (2.1)	1.62 (1.03, 2.57)
Rosiglitazone (N=)		1457	1649	3106	
	MACE	12 (0.82)	15 (0.91)	27 (0.87)	1.17 (0.51, 2.77)
	CV death	5 (0.34)	2 (0.12)	7 (0.23)	0.40 (0.04, 2.45)
	MIF	8 (0.55)	9 (0.55)	17 (0.55)	1.00 (0.34, 3.02)
	Stroke	2 (0.14)	5 (0.3)	7 (0.23)	2.52 (0.41, 26.51)
	All-cause death	9 (0.62)	7 (0.42)	16 (0.52)	0.79 (0.25, 2.38)
	Serious MIS	35 (2.4)	34 (2.06)	69 (2.22)	0.89 (0.53, 1.49)
	Total MIS	64 (4.39)	63 (3.82)	127 (4.09)	0.88 (0.60, 1.29)
	CHF	9 (0.62)	12 (0.73)	21 (0.68)	1.23 (0.47, 3.32)

5.5 Metformin controlled trial group

Table 23 in Appendix 7.4 describes each trial in the metformin controlled trial group by meta-analysis. In this group the pioglitazone meta-analysis consisted of 3 trials with 2232 patients, 1105 randomized to pioglitazone and 1127 to metformin. In the rosiglitazone meta-analysis this group consisted of 4 trials with 613 patients, 311 randomized to rosiglitazone and 302 to metformin. The rosiglitazone trials ranged between 16 and 32 weeks in duration and all were in the monotherapy add-on group. For pioglitazone, one trial was in the sulfonylurea add-on trial group and had a treatment duration of 104 weeks. The remaining 2 pioglitazone trials were in the monotherapy trial group and had treatment durations of 24 and 52 weeks.

Table 12 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the metformin controlled trial group. Summary of safety endpoints is primarily limited to the pioglitazone meta-analysis since the rosiglitazone meta-analysis did not have a substantial number of patients and events. For MACE, the relative risk estimate for pioglitazone was less than one and not statistically significant (OR=0.58; 95% CI=[0.25, 1.28]). For congestive heart failure, pioglitazone had a relative risk estimate less than one and not statistically significant.

Table 12. Analysis of safety endpoints by meta-analysis for metformin controlled trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		1127	1105	2232	
	MACE	19 (1.7)	11 (1.0)	30 (1.3)	0.58 (0.25, 1.28)
	CV death	2 (0.2)	3 (0.3)	5 (0.2)	1.50 (0.17, 18.02)
	MIF	9 (0.8)	8 (0.7)	17 (0.8)	0.90 (0.30, 2.63)
	Stroke	9 (0.8)	2 (0.2)	11 (0.5)	0.22 (0.02, 1.07)
	All-cause death	3 (0.3)	6 (0.5)	9 (0.4)	2.01 (0.43, 12.44)
	Serious MIS	15 (1.3)	10 (0.9)	25 (1.1)	0.67 (0.27, 1.60)
	Total MIS	26 (2.3)	20 (1.8)	46 (2.1)	0.77 (0.40, 1.44)
	CHF	7 (0.6)	6 (0.5)	13 (0.6)	0.86 (0.24, 2.99)
Rosiglitazone (N=)		302	311	613	
	MACE	2 (0.66)	1 (0.32)	3 (0.49)	0.38 (0.01, 7.63)
	CV death	0 (0)	0 (0)	0 (0)	-
	MIF	1 (0.33)	1 (0.32)	2 (0.33)	0.99 (0.01, 78.00)
	Stroke	1 (0.33)	0 (0)	1 (0.16)	0.00 (0.00, 18.20)
	All-cause death	0 (0)	0 (0)	0 (0)	-
	Serious MIS	2 (0.66)	2 (0.64)	4 (0.65)	0.99 (0.07, 13.77)
	Total MIS	4 (1.32)	4 (1.29)	8 (1.31)	1.00 (0.18, 5.40)
	CHF	0 (0)	0 (0)	0 (0)	-

5.6 Monotherapy trial group

Table 24 in Appendix 7.5 describes trial characteristics for the pioglitazone and rosiglitazone monotherapy trial-level groups. The pioglitazone meta-analysis consisted of fewer trials but had a similar number of patients. The pioglitazone meta-analysis monotherapy trial-level group consisted of 13 trials with 5786 patients, 2814 patients randomized to the comparator and 2972 to pioglitazone. Treatment duration for these trials ranged between 12 and 56 weeks. The rosiglitazone meta-analysis had 18 trials with 5484 patients, 2223 randomized to the comparator and 3261 to rosiglitazone. The rosiglitazone trials had treatment durations between 8 and 77 weeks.

For this trial-level group there were multiple comparator treatments. For the pioglitazone meta-analysis this group consisted of 8 placebo controlled trials, 2 metformin controlled, 3 sulfonylurea controlled, and one rosiglitazone controlled. The rosiglitazone meta-analysis consisted of 11 placebo controlled trials, 4 metformin controlled, 5 sulfonylurea controlled and one pioglitazone controlled.

Table 13 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the monotherapy trial group. For MACE, the relative risk estimate for rosiglitazone was greater than one and not statistically significant (OR=1.21; 95% CI=[0.57, 2.67]). For MACE, the relative risk estimate for pioglitazone was near 1 and not statistically significant (OR=0.99; 95% CI=[0.54, 1.80]). For congestive heart failure both the pioglitazone and rosiglitazone had relative risk estimates greater than one and not statistically significant.

Table 13. Analysis of safety endpoints by meta-analysis for monotherapy trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		2814	2972	5786	
	MACE	25 (0.9)	25 (0.8)	50 (0.9)	0.99 (0.54, 1.80)
	CV death	8 (0.3)	11 (0.4)	19 (0.3)	1.33 (0.48, 3.86)
	MIF	15 (0.5)	11 (0.4)	26 (0.4)	0.71 (0.29, 1.67)
	Stroke	4 (0.1)	6 (0.2)	10 (0.2)	1.50 (0.35, 7.22)
	All-cause death	16 (0.6)	14 (0.5)	30 (0.5)	0.83 (0.37, 1.83)
	Serious MIS	32 (1.1)	25 (0.8)	57 (1.0)	0.78 (0.44, 1.36)
	Total MIS	54 (1.9)	46 (1.5)	100 (1.7)	0.86 (0.56, 1.31)
	CHF	22 (0.8)	27 (0.9)	49 (0.8)	1.20 (0.65, 2.24)
Rosiglitazone (N=)		2223	3261	5484	
	MACE	13 (0.58)	22 (0.67)	35 (0.64)	1.21 (0.57, 2.67)
	CV death	4 (0.18)	3 (0.09)	7 (0.13)	0.55 (0.08, 3.44)
	MIF	8 (0.36)	15 (0.46)	23 (0.42)	1.36 (0.53, 3.80)
	Stroke	4 (0.18)	7 (0.21)	11 (0.2)	1.17 (0.28, 5.69)
	All-cause death	7 (0.31)	9 (0.28)	16 (0.29)	1.02 (0.33, 3.33)
	Serious MIS	32 (1.44)	50 (1.53)	82 (1.5)	1.22 (0.75, 2.01)
	Total MIS	69 (3.1)	92 (2.82)	161 (2.94)	1.02 (0.72, 1.45)
	CHF	7 (0.31)	11 (0.34)	18 (0.33)	1.25 (0.43, 3.89)

5.7 Background add-on trial group

Table 25 in Appendix 7.6 describes trials characteristics of the pioglitazone and rosiglitazone background add-on trial groups. In the pioglitazone meta-analysis the background add-on trial-level group consisted of fewer trials (3 compared to 5) but had more patients (1301 compared to 904). The pioglitazone meta-analysis had similar number of patients in both treatment arms (651 randomized to pioglitazone and 650 to the comparator), while trials in the rosiglitazone meta-analysis had more patients that received rosiglitazone (543 compared to 361).

Between meta-analyses trials differed in treatment duration and randomized comparators. Trials in the pioglitazone meta-analysis had treatment duration between 52 and 72 weeks, while the rosiglitazone trials treatment duration ranged from 16 to 52 weeks. There was no common comparator treatment group between meta-analyses. All pioglitazone trials were sulfonylurea controlled, while the rosiglitazone trials were placebo controlled (trial AVS101946 was a statin controlled trial).

Table 14 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the background add-on trial group. For MACE, the relative risk estimate for pioglitazone was less one (OR=0.63; 95% CI=[0.21, 1.80]), while the relative risk estimate for rosiglitazone was greater than one (OR=1.78; 95% CI=[0.52, 7.01]); neither estimate was statistically significant. For congestive heart failure both pioglitazone and rosiglitazone had relative risk estimates greater than one and not statistically significant.

Table 14. Analysis of safety endpoints by meta-analysis for background add-on trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		650	651	1301	
	MACE	11 (1.7)	7 (1.1)	18 (1.4)	0.63 (0.21, 1.80)
	CV death	2 (0.3)	3 (0.5)	5 (0.4)	1.51 (0.17, 18.18)
	MIF	7 (1.1)	4 (0.6)	11 (0.8)	0.57 (0.12, 2.25)
	Stroke	2 (0.3)	0 (0.0)	0 (0.0)	0.41 (. , 5.33)
	All-cause death	3 (0.5)	4 (0.6)	7 (0.5)	1.34 (0.23, 9.21)
	Serious MIS	22 (3.4)	23 (3.5)	45 (3.5)	1.05 (0.55, 2.01)
	Total MIS	67 (10.3)	46 (7.1)	113 (8.7)	0.66 (0.43, 0.99)
	CHF	13 (2.0)	18 (2.8)	31 (2.4)	1.40 (0.64, 3.15)
Rosiglitazone (N=)		361	543	904	
	MACE	5 (1.39)	9 (1.66)	14 (1.55)	1.78 (0.52,7.01)
	CV death	1 (0.28)	2 (0.37)	3 (0.33)	2.09 (0.11,124.53)
	MIF	2 (0.55)	6 (1.1)	8 (0.88)	2.82 (0.49,29.32)
	Stroke	3 (0.83)	1 (0.18)	4 (0.44)	0.34 (0.01,4.32)
	All-cause death	2 (0.55)	3 (0.55)	5 (0.55)	1.57 (0.18,19.10)
	Serious MIS	5 (1.39)	13 (2.39)	18 (1.99)	2.63 (0.85,9.65)
	Total MIS	12 (3.32)	22 (4.05)	34 (3.76)	1.84 (0.84,4.24)
	CHF	13 (3.6)	22 (4.05)	35 (3.87)	1.92 (0.87,4.39)

5.8 Sulfonylurea add-on trial group

Table 26 in Appendix 7.7 describes trial characteristics for the sulfonylurea add-on trial-level group by meta-analysis. The rosiglitazone meta-analysis had more trials and patients for this trial-level group than the pioglitazone meta-analysis. This group in the rosiglitazone meta-analysis consisted of 16 trials with 4471 patients, 2526 randomized to rosiglitazone and 1945 to control. The pioglitazone meta-analysis had 3 trials with 1164 patients, 584 randomized to pioglitazone and 580 to the comparator.

All rosiglitazone trials were placebo controlled and, except for trial 135, had treatment duration between 16 and 28 weeks (trial 135 had a treatment duration of 104 weeks). One trial in the pioglitazone meta-analysis was metformin controlled with treatment duration 104 weeks; the other two trials were placebo controlled with treatment durations of 12 and 16 weeks.

Table 15 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the sulfonylurea add-on trial group. For MACE, the relative risk estimate for pioglitazone was less than one (OR=0.49; 95% CI=[0.17, 1.32]), while the relative risk estimate for rosiglitazone was greater than one (OR=1.43; 95% CI=[0.59, 3.59]); neither relative risk estimate was statistically significant. For congestive heart failure, the relative risk estimate for rosiglitazone was greater than one and statistically significant (OR=2.77; 95% CI=[1.03, 8.63]), while the relative risk estimate for pioglitazone was less than one and not statistically significant.

Table 15. Analysis of safety endpoints by meta-analysis for sulfonylurea add-on trials

Table 15: Analysis of Safety Endpoints by Meta-analysis for Saturated and on trials					
Meta-analysis	Endpoint	Comparator	Pioglitazone/ Rosiglitazone	Total	Stratified OR (95% CI)
		n (%)	n (%)	n (%)	
Pioglitazone (N=)		580	584	1164	
	MACE	14 (2.4)	7 (1.2)	21 (1.8)	0.49 (0.17, 1.32)
	CV death	2 (0.3)	2 (0.3)	4 (0.3)	1.00 (0.07, 13.78)
	MIF	7 (1.2)	6 (1.0)	13 (1.1)	0.85 (0.24, 2.99)
	Stroke	7 (1.2)	1 (0.2)	8 (0.7)	0.14 (0.00, 1.11)
	All-cause death	3 (0.5)	4 (0.7)	7 (0.6)	1.33 (0.22, 9.13)
	Serious MIS	7 (1.2)	9 (1.5)	16 (1.4)	1.29 (0.42, 4.10)
	Total MIS	14 (2.4)	15 (2.6)	29 (2.5)	1.07 (0.48, 2.43)
	CHF	7 (1.2)	2 (0.3)	9 (0.8)	0.28 (0.03, 1.49)
Rosiglitazone (N=)		1945	2526	4471	
	MACE	10 (0.51)	15 (0.59)	25 (0.56)	1.43 (0.59,3.59)
	CV death	3 (0.15)	5 (0.2)	8 (0.18)	1.46 (0.27,9.61)
	MIF	5 (0.26)	11 (0.44)	16 (0.36)	2.07 (0.65,7.67)
	Stroke	4 (0.21)	3 (0.12)	7 (0.16)	0.73 (0.11,4.34)
	All-cause death	4 (0.21)	5 (0.2)	9 (0.2)	1.10 (0.23,5.70)
	Serious MIS	14 (0.72)	23 (0.91)	37 (0.83)	1.60 (0.78,3.40)
	Total MIS	28 (1.44)	46 (1.82)	74 (1.66)	1.53 (0.92,2.58)
	CHF	6 (0.31)	17 (0.67)	23 (0.51)	2.77 (1.03,8.63)

5.9 Metformin add-on trial group

Table 27 in Appendix 7.8 describes trial characteristics from the pioglitazone and rosiglitazone meta-analysis for the metformin add-on group. For this group the rosiglitazone meta-analysis consisted of more patients and trials. In total, the rosiglitazone meta-analysis consisted of 11 trials with 4064 patients, 2130 randomized to rosiglitazone and 1934 randomized to the comparator. The pioglitazone meta-analysis had 6 trials with 2244 patients, 1085 randomized to pioglitazone and 1059 randomized to the comparator.

The 11 rosiglitazone trials had treatment durations ranging between 12 and 52 weeks. Three (3) rosiglitazone trials were sulfonylurea controlled and 8 were placebo controlled. For the pioglitazone meta-analysis, one trial was sulfonylurea controlled with a treatment duration of 104 weeks. The remaining 5 pioglitazone trials were placebo controlled with treatment durations ranging between 16 and 28 weeks.

Table 16 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the metformin add-on trial group. For MACE, the relative risk estimates for both pioglitazone and rosiglitazone were greater than one and not statistically significant. For congestive heart failure both the pioglitazone and rosiglitazone had relative risk estimates greater than one and not statistically significant.

Table 16. Analysis of safety endpoints by meta-analysis for metformin add-on trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		1059	1085	2244	
	MACE	6 (0.6)	10 (0.8)	16 (0.7)	1.48 (0.48, 5.03)
	CV death	2 (0.2)	2 (0.2)	4 (0.2)	0.83 (0.06, 11.83)
	MIF	1 (0.1)	7 (0.6)	8 (0.4)	6.58 (0.83, 298.84)
	Stroke	3 (0.3)	2 (0.2)	5 (0.2)	0.57 (0.05, 5.10)
	All-cause death	2 (0.2)	2 (0.2)	4 (0.2)	0.83 (0.06, 11.83)
	Serious MIS	4 (0.4)	13 (1.1)	17 (0.8)	3.07 (0.93, 13.08)
	Total MIS	7 (0.7)	20 (1.7)	27 (1.2)	2.54 (1.01, 7.21)
	CHF	3 (0.3)	9 (0.8)	12 (0.5)	2.57 (0.63, 14.93)
Rosiglitazone (N=)		1934	2130	4064	
	MACE	7 (0.36)	10 (0.47)	17 (0.42)	1.21 (0.40, 3.81)
	CV death	2 (0.1)	2 (0.09)	4 (0.1)	0.83 (0.06, 11.77)
	MIF	4 (0.21)	7 (0.33)	11 (0.27)	1.63 (0.41, 7.64)
	Stroke	2 (0.1)	2 (0.09)	4 (0.1)	0.54 (0.03, 8.43)
	All-cause death	3 (0.16)	5 (0.23)	8 (0.2)	1.55 (0.30, 10.05)
	Serious MIS	12 (0.62)	13 (0.61)	25 (0.62)	0.97 (0.40, 2.35)
	Total MIS	15 (0.78)	24 (1.13)	39 (0.96)	1.48 (0.74, 3.06)
	CHF	6 (0.31)	8 (0.38)	14 (0.34)	1.14 (0.34, 4.08)

5.10 Insulin add-on trial group

Table 28 in Appendix 7.9 describes trial characteristics for the pioglitazone and rosiglitazone insulin add-on trial-level groups. This trial-level group for the pioglitazone meta-analysis had 5 trials with 1190 patients, 595 patients were in each treatment group. The rosiglitazone meta-analysis consisted of 7 trials with 1833 patients, 1018 that received rosiglitazone and 815 the comparator. All trials in the rosiglitazone meta-analysis were placebo controlled with treatment durations between 16 and 26 weeks. For the pioglitazone meta-analysis trials ranged in duration between 16 and 52 weeks. One pioglitazone trial was sulfonylurea controlled⁵, the rest were placebo controlled.

Table 17 displays events counts and estimates of odds ratios for the safety endpoints by meta-analysis for the insulin add-on trial group. In the rosiglitazone meta-analysis, the relative risk estimates were greater than one across the safety endpoints except for stroke; there was not an obvious trend in the pioglitazone meta-analysis. For MACE, the relative risk estimate for pioglitazone was less than one and not statistically significant (OR=0.54; 95% CI=[0.11, 2.16]). For MACE, the relative risk estimate for rosiglitazone was greater than one and not statistically significant (OR=2.14; 95% CI=[0.70, 7.83]). For congestive heart failure both pioglitazone and rosiglitazone had relative risk estimates greater than one; the relative risk estimate for rosiglitazone was statistically significant.

Table 17. Analysis of safety endpoints by meta-analysis for insulin add-on trials

Meta-analysis	Endpoint	Comparator n (%)	Pioglitazone/ Rosiglitazone n (%)	Total n (%)	Stratified OR (95% CI)
Pioglitazone (N=)		595	595	1190	
	MACE	7 (1.2)	4 (0.7)	11 (0.9)	0.54 (0.11, 2.16)
	CV death	4 (0.7)	3 (0.5)	7 (0.6)	0.70 (0.10, 4.26)
	MIF	3 (0.5)	3 (0.5)	6 (0.5)	0.96 (0.13, 7.27)
	Stroke	0 (0.0)	0 (0.0)	0 (0.0)	-
	All-cause death	4 (0.7)	6 (1.0)	10 (0.8)	1.45 (0.33, 7.13)
	Serious MIS	11 (1.8)	10 (1.7)	21 (1.8)	0.88 (0.33, 2.33)
	Total MIS	21 (3.5)	15 (2.5)	36 (3.0)	0.67 (0.31, 1.41)
	CHF	5 (0.8)	19 (3.2)	24 (2.0)	3.97 (1.38, 13.99)
Rosiglitazone (N=)		815	1018	1833	
	MACE	5 (0.61)	13 (1.28)	18 (0.98)	2.14 (0.70,7.83)
	CV death	0 (0)	4 (0.39)	4 (0.22)	Inf (0.47,Inf)
	MIF				5.64
		1 (0.12)	6 (0.59)	7 (0.38)	(0.67,262.72)
	Stroke	4 (0.49)	5 (0.49)	9 (0.49)	0.92 (0.19,4.78)
	All-cause death	2 (0.25)	6 (0.59)	8 (0.44)	2.19 (0.38,22.61)
	Serious MIS	3 (0.37)	15 (1.47)	18 (0.98)	4.16 (1.15,22.67)
	Total MIS	10 (1.23)	28 (2.75)	38 (2.07)	2.18 (1.01,5.10)
	CHF	8 (0.98)	23 (2.26)	31 (1.69)	2.19 (0.92,5.77)

⁵ The sulfonylurea controlled trial had a stratified design based on baseline insulin use. The insulin strata was included in the insulin add-on group.

5.11 Sulfonylurea and metformin add-on trial group

This trial-level group is excluded from this review since each meta-analysis had one trial that qualified as sulfonylurea and metformin trial-level group. Both trials were placebo controlled. The pioglitazone trial was 28 weeks and had 299 patients, 154 randomized to the comparator and 145 to pioglitazone. The rosiglitazone trial was 26 weeks and had 837 patients, 561 randomize to rosiglitazone and 276 to the comparator.

In summary, in the pioglitazone trial there was one MACE event that occurred in the pioglitazone group. In the rosiglitazone meta-analysis trial there was a total of three MACE events, 1 in the rosiglitazone group and 2 in the comparator.

6 SUMMARY

In June 2010 FDA completed two meta-analyses that evaluated the association of cardiovascular safety outcomes separately for pioglitazone and rosiglitazone. The meta-analyses used patient-level data from clinical trials available to GlaxoSmithKline for rosiglitazone and Takeda for pioglitazone. The meta-analyses had two goals: (1) to update the 2007 FDA meta-analysis of rosiglitazone of 42 trials with 10 newly available trials and (2) to conduct a pioglitazone meta-analysis in order to compare indirectly the cardiovascular profile of the two drugs.

Direct overall comparisons of the meta-analyses are limited because of systematic differences in the trial designs, trial populations and data collection of the two drugs. To improve the comparability of the two meta-analyses, both meta-analyses utilized the same statistical analysis plan, including common trial inclusion criteria, endpoint definition, trial-level and patient-level subgroups, and statistical methods. Safety profiles of the two drugs were compared within trial-level groups to allow for a more direct comparison of the drugs. However, systematic differences between trials in the comparisons still existed, both on the trial and patient-level, limiting the ability to make comparisons between the two drugs.

Trials were included into the meta-analysis if they were randomized, double-blind trials between 2 months and 2 years in duration completed by December 2009 with targeted total daily dose for pioglitazone of 30 or 45 mg, and 4 or 8 mg for rosiglitazone with available patient-level data.

Overall for the primary analysis, the findings of the 2007 FDA meta-analysis of rosiglitazone were generally supported or strengthened. In the 2010 meta-analysis of the 52 trials, rosiglitazone had a statistically significant greater risk than comparator for myocardial infarction (OR=1.80; 95% CI=[1.03, 3.25]) and a nearly statistically significant greater risk than comparator for MACE (OR=1.44; 95% CI=[0.95, 2.20]). In the 2007 FDA meta-analysis, myocardial infarction was nearly statistically significant (OR=1.5; 95% CI=[0.9, 2.7]) and the odds ratio for MACE was 1.2 (95% CI=[0.8, 1.8]). In both 2007 and 2010 meta-analyses, total myocardial ischemia was statistically significant: in 2007, OR=1.4 (95% CI=[1.1, 1.8]); in 2010, OR=1.34 (95% CI = [1.07, 1.70]). The odds ratio estimates for CV deaths was slightly lower in the 2010 meta-analysis (OR=1.46; 95% CI=[0.60, 3.77]) than in the 2007 meta-analysis (OR=1.7; 95% CI=[0.7, 5]).

The rosiglitazone meta-analysis consisted of more trials and patients than the pioglitazone meta-analysis. The rosiglitazone meta-analysis had 52 trials with 16995 patients, 10039 (59%) randomized to rosiglitazone and 6956 (41%) to the comparator. The pioglitazone meta-analysis had 29 trials with 11774 patients, 6132 (52%) randomized to pioglitazone and 5642 (48%) to the comparator. There were differences in trial characteristics across meta-analyses based on grouping of trials. The pioglitazone meta-analysis had proportionately more patients in monotherapy trial group (49% compared to 32%) and less in the placebo controlled trial group (39% compared to 81% compared). The distribution of patients by nominal trial duration differed by meta-analysis. More rosiglitazone patients were 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%), while the distribution of pioglitazone patients was more uniform across the different trial duration categories; 47% in trials between 2 and 6 months, 30% in trials 6 months to 1 year, and 24% in trials between 1 and 2 years. Patients in the pioglitazone meta-analysis had treatment for 77 days on average longer.

Differences were observed in patient characteristics between meta-analyses. Patients had a similar average age and BMI. The rosiglitazone meta-analysis had slightly more males (59% compared to 55%) and more US patients (44% compared to 30%, 13% of patients in the pioglitazone meta-analysis had region missing and there was no missing in the rosiglitazone meta-analysis). Patients in the pioglitazone meta-analysis had diabetes for an average of 6 years and 59% received prior treatment; in the rosiglitazone meta-analysis average diabetes duration was 7 years and 78% received previous treatment.

Overall, in the rosiglitazone meta-analysis the odds ratio estimate for MACE was greater than one and nearly statistically significant (OR=1.44; 95% CI=[0.95, 2.20]). Whereas, in the pioglitazone meta-analysis, the odds ratio estimate for MACE was less than one and not statistically significant (OR=0.83; 95% CI=[0.56, 1.21]). In the rosiglitazone meta-analysis, the odds ratio estimates were greater than one for all safety outcomes other than stroke and were statistically significant for myocardial infarction, serious myocardial ischemia, total myocardial ischemia, and congestive heart failure. In the pioglitazone meta-analysis, there was not an obvious trend in the odds ratio estimates; although the odds ratio estimate for congestive heart failure was greater than one and statistically significant.

Table 18 displays odds ratio estimates for MACE and congestive heart failure outcomes from the two meta-analyses across different randomized-treatment trial-level groups. A placebo controlled trial was one in which rosiglitazone or pioglitazone was compared to placebo. An active controlled trial was one in which rosiglitazone or pioglitazone was compared to either metformin, sulfonylurea, or any active drug. Within these trial-level groups, there were still important differences in trial and patient characteristics. The table also gives the breakdown by add-on drug trial groups. For example, metformin add-on trials were trials in which all patients received metformin in addition to the randomized drug.

For placebo controlled trials, rosiglitazone had a higher estimated odds ratio for MACE (OR=1.5; 95% CI=[0.9, 2.5]) than pioglitazone (OR=0.6, 95% CI=[0.2, 1.7]). For active controlled trials, rosiglitazone and pioglitazone had similar estimated odds ratios for MACE (OR=1.1; 95% CI=[0.5, 2.3]) and (OR=0.9; 95% CI=[0.6, 1.3]), respectively. Within the active controlled trials, the two drugs had similar odds ratios estimates to each other for MACE for both sulfonylurea and metformin controlled trials. For congestive heart failure, for both placebo controlled and active controlled trials, the two drugs had similar odds ratios to each other.

Table 18. Odds ratio estimates for MACE across different trial groups by meta-analysis

Randomized Comparator	Meta-analysis	Trials (Patients)	Trt Dur (range)	Treatment add-on group number of trials [†] (% of patients [‡])						Stratified OR (95% CI)	
				MONO	BACK	SU	MET	INS	MET + SU	MACE	CHF
Primary	PIO	29 (11774)	12-104	13 (49)	3 (11)	3 (10)	6 (19)	5 (10)	1 (3)	0.8 (0.6, 1.2)	1.5 (1.0, 2.2)
	ROSI	52 (16995)	8-104	18 (32)	5 (5)	16 (26)	11 (24)	7 (11)	1 (5)	1.4 (0.95, 2.2)	1.9 (1.3, 2.9)
Placebo	PIO	18 (4574)	12-52	6 (24)	-	2 (12)	5 (35)	4 (22)	1 (7)	0.6 (0.2, 1.7)	1.8 (0.6, 5.8)
	ROSI	46 (13760)	8-104	11 (20)	5 (7)	16 (33)	8(21)	7(13)	1 (6)	1.5 (0.9,2.5)	1.7 (1.3, 2.4)
Active	PIO	12 (7350)	24-104	7 (63)	3 (18)	1 (9)	1 (9)	1(2)	-	0.9 (0.6, 1.3)	1.4 (1.0, 2.2)
	ROSI	13 (4037)	12-77	10 (72)	-	-	3 (28)	-	-	1.1 (0.5, 2.3)	1.2 (0.5, 3.3)
Sulfonylurea	PIO	8 (4383)	24-104	4 (52)	3 (30)	-	1 (14)	1 (4)	-	1.2 (0.7, 2.0)	1.6 (1.0, 2.6)
	ROSI	8 (3106)	24-77	5 (64)	-	-	3 (36)	-	-	1.2 (0.5, 2.8)	1.2 (0.5, 3.3)
Metformin	PIO	3 (2232)	24-104	2 (71)	-	1 (29)	-	-	-	0.6 (0.3, 1.3)	0.9 (0.2, 3.0)
	ROSI	4 (613)	16-32	4 (100)	-	-	-	-	-	0.4 (0.0, 7.6)	-

Abbreviations: PIO-Pioglitazone; ROSI-Rosiglitazone; MONO-Monotherapy; BACK-Background; SU-Sulfonylurea; MET-Metformin.

[†] Number of trials may not sum to the total number of trials because multi-armed trials may have been used in more than one group.

[‡] Percentage of patients may not sum to 100 because multi-armed trials may have been used in more than one group

For insulin add-on trials (trials in which all patients were on insulin), for rosiglitazone, the odds ratio estimates were greater than one for all safety outcomes other than stroke and were statistically significant for serious myocardial ischemia and total myocardial ischemia. For these trials, in the pioglitazone meta-analysis, there was not an obvious trend in the odds ratio estimates; although the odds ratio estimate for congestive heart failure was greater than one and statistically significant. For sulfonylurea controlled trials, for pioglitazone, the odds ratio estimates were greater than one for all safety outcomes other than total myocardial ischemia but were statistically significant only for congestive heart failure.

In conclusion, there were differences in trial and patient characteristics between the pioglitazone and rosiglitazone meta-analyses. These differences limit the comparability of the safety profile of the two drugs. Overall, the meta-analyses for both rosiglitazone and pioglitazone did not show a statistically significant increased risk of major adverse cardiovascular events (MACE), defined as cardiovascular death, stroke, or myocardial infarction. However, in the rosiglitazone meta-analyses, the estimated risk for MACE of rosiglitazone was greater relative to comparator and was nearly statistically significant.

For placebo controlled trials, in the rosiglitazone meta-analysis, the odds ratio estimates were greater than one for all safety outcomes considered (MACE, cardiovascular death, myocardial infarction, total myocardial ischemia, serious myocardial ischemia, and congestive heart failure) except stroke and statistically significant for myocardial infarction, serious myocardial ischemia, total myocardial ischemia, and congestive heart failure. For placebo controlled trials, in the pioglitazone meta-analysis, there were no obvious patterns in the safety outcome. For active controlled trials, neither drug generally showed negative effects on the safety outcomes.

Overall and across a range of trial groups, both drugs showed negative effects on congestive heart failure.

7 APPENDIX

7.1 *Placebo controlled trial group*

Table 19. Summary of trials in the placebo controlled trial group for the pioglitazone meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Treatment add-on group	Comparator	Trial size	
					Pioglitazone/ Rosiglitazone	Total
Pioglitazone	CPH-030A	12	Monotherapy	10	23	33
	CCT-011	12	Sulfonylurea	75	77	152
	CCT-001	12	Monotherapy	66	136	202
	PNFP-014	16	Insulin	187	188	375
	PNFP-027	16	Metformin	160	168	328
	PNFP-010	16	Sulfonylurea	187	189	376
	PNFP-026	16	Monotherapy	96	101	197
	CCT-101	16	Insulin	66	66	132
	OPIXT-010	16	Metformin	158	157	315
	OPI-502	20	Insulin	112	110	222
	PNFP-012	24	Monotherapy	84	176	260
	OPIMET-008	24	Metformin	210	201	411
	PNFP-001	26	Monotherapy	79	167	246
	EC204	26	Monotherapy	88	89	177
	322OPI-001	26	Metformin	129	258	387
	F-PIO-100	28	MET+SU	154	145	299
	CCT-100	28	Metformin	89	84	173
	GLAT	52	Insulin	147	142	289
				2097	2477	4574

Table 20. Summary of trials in the placebo controlled trial group for the rosiglitazone meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Treatment add-on group	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Rosiglitazone	6	12	Monotherapy	69	74	143
	11	26	Monotherapy	176	357	533
	15	26	Sulfonylurea	198	190	388
	24	26	Monotherapy	185	774	959
	25	16	Monotherapy	31	30	61
	44	26	Metformin	51	101	152
	79	26	Sulfonylurea	106	99	215
	82	26	Insulin	107	212	319
	83	16	Monotherapy	17	16	33
	85	26	Insulin	139	138	277
	90	8	Monotherapy	75	149	224
	93	26	Metformin	109	106	205
	94	26	Metformin	116	232	348
	95	26	Insulin	96	196	292
	96	26	Sulfonylurea	115	116	231
	98	8	Monotherapy	96	191	287
	127	26	Sulfonylurea	58	56	114
	128	24	Sulfonylurea	38	39	77
	132	24	Sulfonylurea	110	437	547
	134	26	MET+SU	276	561	837
	135	104	Sulfonylurea	111	116	227
	136	26	Insulin, Sulfonylurea	142	148	290
	140	12	Monotherapy	71	65	136
	143	24	Sulfonylurea	124	121	245
	145	26	Sulfonylurea	242	231	473
	147	26	Sulfonylurea	88	89	177
	162	26	Sulfonylurea	172	168	340
	209	24	Insulin	131	132	263
	211	52	Background	114	110	224
	234	26	Sulfonylurea	58	116	174
	284	24	Metformin	384	382	766
	311	12	Metformin, Monotherapy	14	58	72
	325	24	Sulfonylurea	195	196	391
	334	52	Background	95	99	194
	347	24	Insulin	212	209	421
	351	52	Background	29	27	56
	352	16	Background	30	31	61
	374	16	Monotherapy	85	84	169
	49653/376	16	Insulin	21	19	40
	712753/002	24	Metformin	280	289	569
	712753/003	32	Metformin	272	254	526
	712753/007	32	Metformin	154	155	309
	797620/004	28	Sulfonylurea	222	442	664
	AVD104742	28	Monotherapy	54	159	213
	AVD105248	16	Sulfonylurea	75	74	149
	AVS101946	16	Background	93	276	369
				5636	8124	13760

7.2 Active controlled trial group

Table 21. Summary of trials in the active controlled trial group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Randomized Comparator	Treatment add-on group	Trial size		
					Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	OPI-504	24	Sulfonylurea	Monotherapy, Insulin	256	262	518
	GLAI	24	Rosiglitazone	Monotherapy	366	369	735
	OPIMET-008	24	Metformin	Monotherapy	210	189	399
	EC204	26	Sulfonylurea	Monotherapy	93	89	182
	EC405	52	Sulfonylurea	Monotherapy	626	624	1250
	OPI-520	52	Sulfonylurea	Background	149	151	300
	EC404	52	Metformin	Monotherapy	597	597	1194
	OPI-501	56	Sulfonylurea	Monotherapy	251	251	502
	OPI-516	72	Sulfonylurea	Background	273	270	543
	OPI-518	72	Sulfonylurea	Background	228	230	458
	EC409	104	Metformin	Sulfonylurea	320	319	639
	EC410	104	Sulfonylurea	Metformin	313	317	630
					3682	3668	7350
Rosiglitazone	20	52	Sulfonylurea	Monotherapy	207	391	598
	25	16	Metformin	Monotherapy	32	30	62
	79	26	Sulfonylurea	Monotherapy	106	104	210
	93	26	Metformin	Monotherapy	109	107	216
	137	32	Sulfonylurea	Metformin	185	204	389
	282	24	Sulfonylurea	Metformin	75	70	145
	311	12	Metformin	Monotherapy	7	15	22
	369	26	Sulfonylurea	Monotherapy	24	25	49
	712753/007	32	Metformin	Monotherapy	154	159	313
	797620/004	28	Sulfonylurea	Monotherapy	222	230	452
	AVD100521	77	Sulfonylurea	Monotherapy	337	331	668
	AVD104742	28	Pioglitazone	Monotherapy	159	159	318
	AVM100264	52	Sulfonylurea	Metformin	301	294	595
					1918	2119	4037

7.3 Sulfonylurea controlled trial group

Table 22. Summary of trials in the sulfonylurea controlled trial group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Treatment add-on group	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	OPI-504	24	Insulin, Monotherapy	256	262	518
	EC204	26	Monotherapy	93	89	182
	EC405	52	Monotherapy	626	624	1250
	OPI-520	52	Background	149	151	300
	OPI-501	56	Monotherapy	251	251	502
	OPI-516	72	Background	273	270	543
	OPI-518	72	Background	228	230	458
	EC410	104	Metformin	313	317	630
				2189	2194	4383
Rosiglitazone	20	52	Monotherapy	207	391	598
	79	26	Monotherapy	106	104	210
	137	32	Metformin	185	204	389
	282	24	Metformin	75	70	145
	369	26	Monotherapy	24	25	49
	797620/004	28	Monotherapy	222	230	452
	AVD100521	77	Monotherapy	337	331	668
	AVM100264	52	Metformin	301	294	595
				1457	1649	3106

7.4 Metformin controlled trial group

Table 23. Summary of trials in the metformin controlled trial group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Treatment add-on group	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	OPIMET-008	24	Monotherapy	210	189	399
	EC404	52	Monotherapy	597	597	1194
	EC409	104	Sulfonylurea	320	319	639
				1127	1105	2232
Rosiglitazone	25	16	Monotherapy	32	30	62
	93	26	Monotherapy	109	107	216
	311	12	Monotherapy	7	15	22
	712753/007	32	Monotherapy	154	159	313
				302	311	613

7.5 Monotherapy add-on group

Table 24. Summary of trials in the monotherapy trial group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Randomized comparator	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	CPH-030A	12	Placebo	10	23	33
	CCT-011	12	Placebo	75	77	152
	CCT-001	12	Placebo	66	136	202
	PNFP-026	16	Placebo	96	101	197
	PNFP-012	24	Placebo	84	176	260
	OPI-504	24	Sulfonylurea	173	173	346
	GLAI	24	Rosiglitazone	366	369	735
	OPIMET-008	24	Metformin	210	189	399
	PNFP-001	26	Placebo	79	167	246
	EC204	26	Placebo, Sulfonylurea	181	89	270
	EC405	52	Placebo	626	624	1250
	EC404	52	Metformin	597	597	1194
	OPI-501	56	Sulfonylurea	251	251	502
				2814	2972	5786
Rosiglitazone	6	12	Placebo	69	74	143
	11	26	Placebo	176	357	533
	20	52	Sulfonylurea	207	391	598
	24	26	Placebo	185	774	959
	25	16	Placebo, Metformin	63	30	93
	79	26	Sulfonylurea	106	104	210
	83	16	Placebo	17	16	33
	90	8	Placebo	75	149	224
	93	26	Metformin	109	107	216
	98	8	Placebo	96	191	287
	140	12	Placebo	71	65	136
	311	12	Placebo, Metformin	14	15	29
	369	26	Sulfonylurea	24	25	49
	374	16	Placebo	85	84	169
	712753/007	32	Metformin	154	159	313
	797620/004	28	Sulfonylurea	222	230	452
	AVD100521	77	Sulfonylurea	337	331	668
	AVD104742	28	Placebo, Pioglitazone	213	159	372
				2223	3261	5484

7.6 Background add-on group

Table 25. Summary of trials in the background add-on group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Randomized comparator	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	OPI-520	52	Sulfonylurea	149	151	300
	OPI-516	72	Sulfonylurea	273	270	543
	OPI-518	72	Sulfonylurea	228	230	458
				650	651	1301
Rosiglitazone	211	52	Placebo	114	110	224
	334	52	Placebo	95	99	194
	351	52	Placebo	29	27	56
	352	16	Placebo	30	31	61
	AVS101946	16	Statin	93	276	369
				361	543	904

7.7 Sulfonylurea add-on group

Table 26. Summary of trials in the sulfonylurea add-on group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Randomized comparator	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	CCT-012	12	Placebo	73	76	149
	PNFP-010	16	Placebo	187	189	376
	EC409	104	Metformin	320	319	639
				580	584	1164
Rosiglitazone	15	26	Placebo	198	190	388
	79	26	Placebo	106	99	205
	96	26	Placebo	115	116	231
	127	26	Placebo	58	56	114
	128	24	Placebo	38	39	77
	132	24	Placebo	110	437	547
	135	104	Placebo	111	116	227
	136	26	Placebo	33	36	69
	143	24	Placebo	124	121	245
	145	26	Placebo	242	231	473
	147	26	Placebo	88	89	177
	162	26	Placebo	172	168	340
	234	26	Placebo	58	116	174
	325	24	Placebo	195	196	391
	797620/004	28	Placebo	222	442	664
	AVD105248	16	Placebo	75	74	149
				1945	2526	4471

7.8 Metformin add-on trial group

Table 27. Summary of trials in the metformin add-on group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Randomized comparator	Trial size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	PNFP-027	16	Placebo	160	168	328
	OPIXT-010	16	Placebo	158	157	315
	OPIMET-008	24	Placebo	210	201	411
	322OPI-001	26	Placebo	129	258	387
	CCT-100	28	Placebo	89	84	173
	EC410	104	Sulfonylurea	313	317	630
				1059	1185	2244
Rosiglitazone	44	26	Placebo	51	101	152
	93	26	Placebo	109	106	215
	94	26	Placebo	116	232	348
	137	32	Sulfonylurea	185	204	389
	282	24	Sulfonylurea	75	70	145
	284	24	Placebo	384	382	766
	311	12	Placebo	7	43	50
	712753/002	24	Placebo	280	289	569
	712753/003	32	Placebo	272	254	526
	712753/007	32	Placebo	154	155	309
	AVM100264	52	Sulfonylurea	301	294	595
				1934	2130	4064

7.9 Insulin add-on trial group

Table 28. Summary of trials in the insulin add-on group by meta-analysis

Meta-analysis	Trial	Treatment Duration (wks)	Randomized comparator	Sample size		
				Comparator	Pioglitazone/ Rosiglitazone	Total
Pioglitazone	PNFP-014	16	Placebo	187	188	375
	CCT-101	16	Placebo	66	66	132
	OPI-502	20	Placebo	112	110	222
	OPI-504	24	Sulfonylurea	83	89	172
	GLAT	52	Placebo	147	142	289
				595	595	1190
Rosiglitazone	82	26	Placebo	107	212	319
	85	26	Placebo	139	138	277
	95	26	Placebo	96	196	292
	136	26	Placebo	109	112	221
	209	26	Placebo	131	132	263
	347	24	Placebo	212	209	421
	49653/376	16	Placebo	21	19	40
				815	1018	1833

7.10 Sulfonylurea and Metformin add-on group

Trial-level information not provided for this treatment add-on group. Refer to the individual meta-analyses for information in each meta-analysis.

7.11 MedDRA Preferred Terms Defining Endpoints

Myocardial ischemia terms:

Acute coronary syndrome
Acute myocardial infarction
Angina pectoris
Angina unstable
Arteriospasm coronary
Cardiac arrest
Cardiac death
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery thrombosis
Coronary bypass thrombosis
Electrocardiogram ST segment elevation
Electrocardiogram ST-T segment elevation
Myocardial infarction
Myocardial ischemia
Papillary muscle infarction
Postinfarction angina
Prinzmetal angina
Silent myocardial infarction
Subendocardial ischemia
Sudden cardiac death
Sudden death
Ventricular asystole
Ventricular fibrillation
Ventricular tachycardia

Heart failure terms:

Acute pulmonary edema
Cardiac failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure not otherwise specified (NOS)
Cardiogenic shock
Congestive cardiac failure
Cor pulmonale acute
Cor pulmonale chronic
Cor pulmonale NOS
Left ventricular failure
Pulmonary congestion
Pulmonary edema
Pulmonary edema NOS
Right ventricular failure
Ventricular failure NOS

Stroke terms:

Basilar artery thrombosis
Brain stem infarction
Brain stem stroke
Brain stem thrombosis
Carotid arterial embolus
Carotid artery thrombosis
Cerebellar infarction
Cerebral artery embolism
Cerebral artery thrombosis
Cerebral infarction
Cerebral thrombosis
Cerebrovascular accident
Embolic cerebral infarction
Embolic stroke
Hemorrhagic cerebral infarction
Hemorrhagic stroke
Hemorrhagic transformation stroke
Ischemic cerebral infarction
Ischemic stroke
Lacunar infarction
Lateral medullary syndrome
Moyamoya disease
Postprocedural stroke
Stroke in evolution
Thalamic infarction
Thrombotic cerebral infarction
Thrombotic stroke
Wallenberg syndrome

Myocardial infarction terms:

Acute myocardial infarction
Coronary artery thrombosis
Myocardial infarction
Papillary muscle infarction
Postprocedural myocardial infarction
Silent myocardial infarction

Cardiovascular death terms:

Cardiovascular death is based on all MedDRA preferred terms in the cardiac disorders and vascular disorder system organ classes when event information is available or the blinded review of the cause of the death when event information is not available.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21073	ORIG-1	TAKEDA PHARMACEUTICA LS NORTH AMERICA INC	ACTOS (PIOGLITAZONE HCL)15/30/45MG TABS
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

ADDENDUM TO REVIEW COMPLETED 6/4/07

NDA/Serial Number: NDA 21-071/S-022 and S-026

Drug Name: Avandia (rosiglitazone)

Indication(s): Treatment of Type 2 diabetes

Applicant: GSK

Date(s): S-022 Submitted 8/4/06
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Completion date for this review 7/3/07

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

Rosiglitazone, a thiazolidinedione (TZD), was approved in 1999 for the treatment of Type 2 diabetes. To determine if fluid retention leads to more serious conditions, GlaxoSmithKline (GSK) has performed an analysis of clinical trial data which examines the association between the use of rosiglitazone and the incidence of congestive heart failure (CHF) and myocardial ischemia (IHD). The clinical trial data consists of 42 short-term studies of rosiglitazone as monotherapy and in combination with a sulfonylurea, metformin and insulin and 3 long-term studies; ADOPT, DREAM and RECORD.

This FDA statistician has written two reviews to examine the risk of myocardial ischemia due to rosiglitazone. The first review focused on NDA submission 022 which included the database of 42 short-term rosiglitazone studies. This second review includes further analyses of the 42 studies, a review of ADOPT and a summary of the results of the 42 studies with the results of ADOPT, DREAM and RECORD based on information available in submission 026 and in a submission dated May 31, 2007, as well as published results for the long-term studies. The results of both reviews are summarized in this section.

The results for non-serious plus serious myocardial ischemic events in the overall database of 42 studies showed an overall risk for rosiglitazone compared to control (OR of 1.4 with 95% CI of 1.1 to 1.8, $p=0.02$). The risks were seen to be strongest for the combination of rosiglitazone plus metformin compared to placebo plus metformin and for rosiglitazone plus insulin compared to placebo plus insulin (odds ratios generally greater than 2). The results for the combination with insulin are particularly concerning since these results were seen to be consistent across the five studies provided and were consistent considering both total ischemic events and more serious ischemic events including cardiovascular (CV) death. In the group of studies of rosiglitazone plus metformin, there was heterogeneity in the designs (e.g. active and placebo-controlled) and in the results (OR over 1 compared to placebo and under 1 when compared to sulfonylurea). Studies where rosiglitazone plus metformin is compared to placebo plus metformin showed a higher risk due to rosiglitazone across all three measures of ischemia (see Table 3.1.3). Also overall comparisons of rosiglitazone to placebo showed increased risk (OR>1.5) while comparisons head-to-head against metformin or sulfonylurea did not demonstrate an increased risk, although the active-controlled data is limited to only 9 trials in the database of 42 trials.

To examine the risk of ischemia in the population of patients not taking insulin (37 trials and ~13,000 patients), this reviewer analyzed subgroups and also looked at the results of the short-term studies in the context of the three long-term studies.

Tests for interaction for various subgroups with treatment revealed a higher OR for rosiglitazone for patients using nitrates at baseline based both on analyses performed by this reviewer (with and without the 5 insulin trials) and by the applicant. This interaction was only statistically significant for the endpoint of total myocardial ischemic events ($p=0.03$) though higher ORs were seen for other endpoints as well (see Table 3.3.1). Exclusion of a small number of patients taking nitrates (~500 patients) yielded non-significant results for total IHD (OR 1.15, 95% CI 0.8, 1.6, $p=0.4$), for serious IHD (OR 1.3, 95% CI 0.8, 2.0, $p=0.3$) and for the composite of CV death, MI or stroke (OR 1.0, 95% CI 0.6, 1.7, $p>0.9$) for the 37 non-insulin studies. The impact of nitrate use in combination with rosiglitazone could not be assessed in ADOPT and DREAM because few patients were taking nitrates in these studies (~3% in ADOPT and <1% in DREAM) nor for RECORD because data were not available to FDA for this ongoing trial. Considering the magnitude of the interaction and how early events are seen in patients on nitrates taking rosiglitazone, consideration should be given to warning patients presently on rosiglitazone of the potential interaction with nitrates. Also a test for this interaction should be considered using the RECORD data to determine whether the interaction of rosiglitazone and nitrates is present in head-to-head comparisons

against metformin and sulfonylurea since the majority of the trials in the RSG short-term database are placebo-controlled.

Patients presenting with baseline use of an ACE inhibitor in the 42 short-term trials were seen to have a higher risk of an ischemic event (OR 1.8, 95% CI of 1.1 to 2.8) than those not on ACE inhibitors (OR 1.2, CI of 0.8 to 1.8) although the interaction was not statistically significant. However, the results from DREAM appear to support this finding with significant interactions for the combination of rosiglitazone and ramipril on two cardiovascular endpoints; MI ($p=0.09$) and any cardiovascular event (MI, stroke, cardiovascular death, CHF, new angina and revascularization) ($p=0.07$) meeting an alpha level below 0.1 for this underpowered test. The similarity of the results from DREAM and from the short-term studies for a common endpoint of CV death, MI or stroke is illustrated in Figure 4.2.3 on page 30 of this review.

For the short-term studies, a difference in the results for the placebo-controlled 6-month trials (OR ~1.6) and the active-controlled 6-month trials (OR ~0.8) was observed; however the active control data were very limited and so the estimate was accompanied by a wide-confidence interval and uncertainty as to the true effect. Both ADOPT and RECORD are active-controlled trials with more than 4,000 patients in each study and exposure to drug of 4 years or more; ADOPT is a completed study while RECORD is an ongoing study with interim results. The results for these large studies, displayed with the active-controlled results of the short-term studies in Figure 4.2.4 on page 31 of this review, show no statistically significant difference between RSG and metformin or sulfonylurea based on the composite endpoint of CV death, MI or stroke. The confidence intervals for pairwise comparisons in the long-term trials rule out a doubling of risk and suggest that the hazard ratios could range from a low of 0.7 up to 1.9 (see Table 4.1.6 for ADOPT results). The lack of a significant difference between rosiglitazone and metformin or sulfonylurea is an important finding since metformin or sulfonylurea are medications (along with pioglitazone) that may be considered as alternatives to rosiglitazone treatment. It appears that neither of these drugs offer a clear advantage over rosiglitazone.

Overall this reviewer observed the following:

- Statistically significant risk for rosiglitazone over comparators was only seen for the endpoint of total myocardial ischemic events which included both non-serious and serious events. The results for serious myocardial events were borderline significant ($p=0.06$) when considering all 42 short-term trials but not significant when excluding the 5 insulin trials ($p=0.15$).
- Nitrate users constitute a high-risk population in general but also show increased risk of an ischemic event when rosiglitazone is added to nitrates based on both the results of the short-term studies and the results of DREAM. These results are based primarily on placebo comparisons and not supported by the limited active-controlled data from ADOPT. Subgroup analyses of the RECORD data are needed to establish if rosiglitazone poses a problem to nitrate users that differs from metformin or sulfonylurea.
- The results for the insulin trials consistently suggest increased risk of serious ischemic events due to rosiglitazone compared to placebo.
- Exclusion of nitrate users and the insulin trials renders the results for all ischemia endpoints non-significant ($p>0.3$) but the confidence intervals do not rule out odds ratios of about 1.8.
- Event rates for a composite endpoint of CV death, MI or stroke were low in the 42 short-term studies (<1%) as well as in the long-term studies (maximum of about 4% in RECORD) so comparisons based on this endpoint yielded confidence intervals that were wide and therefore the data did not convincingly rule out the a myocardial ischemic risk due to rosiglitazone. However, comparisons against metformin or sulfonylurea generally yielded risk ratios close to 1.

2 Introduction

2.1 Overview

Rosiglitazone (RSG), a thiazolidinedione (TZD), was approved in 1999 for the treatment of Type 2 diabetes. Two safety issues noted at the time of approval were dose-related increases in lipids and decreases in hematocrit and hemoglobin. The latter is related to fluid retention seen with TZDs. To determine if this fluid retention leads to more serious conditions, GlaxoSmithKline (GSK) has performed an analysis of clinical trial data which examines the association between the use of RSG and the incidence of congestive heart failure (CHF) and myocardial ischemia (IHD). The results of GSK's analysis of a pooled clinical trial database and an FDA meta-analysis performed by this reviewer were reported in a statistical review dated June 4, 2007. At the time of completion of the review, there were several issues that had not been fully addressed regarding risk of myocardial ischemia due to RSG (note that this review does not address risks of congestive heart failure). In addition, the results of three large long-term studies (ADOPT, DREAM and RECORD) became available for review. The goal of this review is to further examine the issues that arose in the first review and to show the results of the meta-analysis in the context of the long-term studies. For the latter, results for a composite endpoint of cardiovascular (CV) death, myocardial infarction (MI) and stroke, an endpoint common to the long-term studies and now available for the short-term studies, will be presented.

The FDA meta-analysis results presented in the previous review showed the following:

- Greater risk due to RSG for previously treated patients than naïve patients
- Significant estimates of risk for comparisons against placebo but not against active-controls
- Notably increased risk for patients treated with rosiglitazone (RSG) plus metformin (MET) and for patients treated with rosiglitazone (RSG) plus insulin (INS) versus other treatment paradigms
- Differential treatment effects across several subgroups

The first two issues are best addressed with the results of DREAM (a placebo-controlled trial in naïve patients), ADOPT (an active-controlled trial in naïve patients) and RECORD (an active-controlled trial in previously treated patients). The third bulleted issue will be further examined with analyses of the composite endpoint of CV death, MI and stroke. Lastly subgroups presented in the original submission will be examined with an emphasis on nitrate use.

While completing an FDA meta-analysis on GSK's pooled database of 42 short-term studies, a meta-analysis of RSG trials was published by Nissen and Wolski in the NEJM 2007:356. There was a great deal of interest in the NEJM publication both in the press and in the US Congress. In this document, this reviewer will compare the FDA meta-analysis methods to those of Nissen-Wolski.

To address the issues mentioned, this review is divided into three main parts:

- In Section 3, the composite endpoint of CV death, MI and stroke is analyzed using the RSG database of 42 studies followed by a section summarizing the results in the RSG+insulin studies. Lastly in this section, the subgroup results shown in the original review are further examined.
- In Section 4, the ADOPT study is reviewed. Also the results of the meta-analyses are examined in the context of the three large, long-term studies (ADOPT, DREAM and RECORD).
- In Section 5, a comparison of the FDA meta-analysis to the meta-analysis published by Nissen and Wolski (NEJM 2007:356) is presented.

2.2 Data Sources

This review focuses on the database of 42 short-term studies and on the three long-term studies of ADOPT, DREAM and RECORD (Table 2.2.1). At the time of this review, an NDA report and datasets were available for both the 42 short-term studies and for the ADOPT study. Therefore more detail is provided here for these studies than for DREAM and RECORD. For DREAM, a dataset was provided by GSK and analyzed by FDA statistical reviewer John Lawrence; results shown here are based on his analyses. RECORD was ongoing at the time of this review and only interim analyses were available; no data for RECORD was available to FDA so only the published interim results are presented here.

Table 2.2.1 Rosiglitazone Clinical trials

	TRT ARMS (Sample size)	Duration	Population	Primary outcome
rosiglitazone database of 42 studies	RSG as monotherapy and combination therapy (8604) Placebo and active controls (5633)	3 months to 2 years	T2DM Variable entry criteria	Myocardial ischemia defined post-hoc was a primary endpoint for the meta-analysis. Most studies were efficacy studies with HbA1c as a primary endpoint.
DREAM	Placebo (1321) Ramipril (1313) Rosiglitazone (1325) RAM+RSG (1310)	Completed Median 3 years	Impaired FPG or impaired glucose tolerance No pts with hx of T2DM, or CV disease	Time to incident diabetes or death
ADOPT	Rosiglitazone (1456) Metformin (1454) Sulfonylurea (1441)	Completed Median 4 years	T2DM diagnosed w/i last 3 years No NYHA CHF Class 3&4 nor CHF requiring meds	Time to monotherapy failure
RECORD (OL due to added insulin therapy)	MET+RSG (1117) MET+SU (1105) SU+RSG (1103) SU+MET (1122)	On-going Minimum 5 years Median 6 years	T2DM No Hospitalization for CV event in last 3 mos No CHF requiring meds	Time to CV death or CV hospitalization

On May 25, 2007, FDA (DMEP) requested datasets for the long-term studies of ADOPT and DREAM that included data for a composite endpoint of stroke, myocardial infarction (MI) and cardiovascular (CV) death, as well as for each of the components.

On May 31, 2007, data for the composite endpoint for the 42 short-term studies, ADOPT and DREAM was submitted to FDA. The paragraph below (from page 27 in the study report submitted May 31, 2007) describes how the cases for the composite endpoint were identified for the 42 short-term studies.

Since the outcomes of cardiovascular mortality, myocardial infarction and stroke were not defined for the CV modeling project, these outcomes for all subjects (i.e., both those from the 42 study ICT and ADOPT) will be defined based on a pre-defined set of lower level terms (LLTs) within the MedDRA coding dictionary (section 12, Appendix 3). These event definitions were those that were pre-defined for ADOPT. Note that the earlier studies within the CV Modeling ICT database were originally coded using the WHO dictionary. These studies were subsequently recoded to MedDRA retrospectively, thus allowing definitions based on the MedDRA dictionary to be uniformly applied to all studies.

Note that the serious ischemic events in the original database of the 42 short-term studies were identified by retrospective blinded adjudication while the components of the composite endpoint were identified as described above. Due to the limited time between the May 31st submission and the required completion of reviews for the advisory committee FDA briefing packet by July 9th, a thorough review of the composite endpoints for the 42 short-term studies by FDA clinicians was not possible. Dr. Karen Mahoney did perform a thorough review of this endpoint for ADOPT. Results for this endpoint for the 42 short-term studies should be considered as preliminary.

In addition, the results for DREAM and RECORD presented here should also be considered preliminary since no full FDA review of these studies is possible at this time due to limited information. Study reports and complete data were not available for these studies.

Results for both serious ischemic events and the composite endpoint of MI, CV death and stroke are summarized to compare the results for the short-term studies to the results of the long-term studies. It is important to understand the similarities and differences between these outcomes as defined for the database of 42 trials (for a description of how endpoints were defined in the long-term studies, see the FDA clinical review of Dr. Mahoney). Both of these outcomes are composite endpoints of first events. As already mentioned, serious ischemic events were identified by a blinded retrospective review (more details are available in the clinical reviews of Drs. Gelperin and Mahoney) while MIs, CV deaths and strokes for the newly defined composite were identified as described above. Though both composite endpoints include MIs and CHD deaths (the new composite also includes CHF deaths), there are differences in the numbers of these events since the process of identification differed. To determine whether these differences impact the results, clinical review of the endpoints is necessary. From a statistical perspective, unless the numbers change largely in one treatment group and not the other, it is unlikely that the overall results will change appreciably.

3 Additional meta-analyses of 42 short-term studies

3.1 Analysis of composite endpoint of CV mortality, MI or stroke

For the primary analysis of the 42 short-term RSG studies, the focus was on total myocardial ischemic events (IHD) which included both serious and non-serious events. An analysis of only serious myocardial ischemic events provided similar results (see pages 26 to 28 of the original review). A third endpoint of clinical importance and of interest to DMEP clinicians is a composite endpoint of cardiovascular (CV) mortality, myocardial infarction (MI) and stroke¹. The composite endpoint was not prospectively defined as an endpoint for the meta-analysis and the data for this endpoint became available after completion of the original FDA meta-analysis.

The disadvantage to this endpoint, from a statistical perspective, compared to total ischemic events is that the event rate is low for both the composite and its individual components and therefore, many studies have either no events in one arm or no events in both arms. Rare events present analytical problems when stratifying on individual studies since trials with no events must be either dropped or a continuity correction used in order to compute an odds ratio using frequentist methods. This reviewer has approached this problem by presenting the results of several approaches which will be defined with the results. The applicant has analyzed the data by pooling the studies. Some authors have suggested that pooling may be an acceptable approach for those cases where events are very rare but have also warned that if the sample sizes are uneven across groups within trials that pooling may produce results contrary to the results of the individual studies (see Appendix 6 for a reference regarding Simpson's paradox). The latter may be an issue with this database since doses of rosiglitazone were pooled and so about ¼ of the trials do not have a 1:1 ratio of rosiglitazone to control (see Appendix 1).

The applicant performed a proportional hazards analysis using a model including a covariate for baseline risk and a term for treatment. The results for the composite (p=0.5) and for CV mortality (p=0.2) and MI (p=0.09) were not statistically significant but trended against RSG (Table 3.1.1). The results for stroke favor RSG with a borderline p-value of 0.04.

Table 3.1.1 Applicant's results for composite of CV mortality, MI or stroke and reviewer's results for serious and all myocardial ischemic (IHD) events

	Hazard Ratio (95% CI)	RSG n (%) (N=8604)	Control n (%) (N=5633)
Composite	1.16 (0.8, 1.7)	63 (0.7%)	38 (0.7%)
CV mortality	1.9 (0.8, 4.6)	18 (0.2%)	7 (0.1%)
MI	1.6 (0.9, 2.7)	45 (0.5%)	20 (0.4%)
Stroke	0.5 (0.2, 0.98)	13 (0.15%)	18 (0.3%)
All IHD events	1.4 (1.1, 1.8)**	171 (2%)	85 (1.5%)
Serious IHD events	1.4 (1, 2.1)*	86 (1%)	44 (0.8%)

**p=0.02 *p=0.06

1 This composite endpoint is referred to in the applicant's study report as MACE. MACE is an acronym for major adverse cardiac events. A cursory search by this reviewer showed that MACE is a general term and that several definitions are used in the literature including: death, MI or revascularization; death, MI, revascularization or stroke; death, MI, revascularization or angina; cardiac death, MI or repeat target vessel revascularization – to name a few. Because there appears to be no consistent definition, this reviewer has avoided using the term MACE.

Since the applicant's analysis of the composite endpoint did not account for study, this reviewer did additional analyses of the composite endpoint stratifying on either meta-group or on study. Also additional analyses were performed to determine if the results are sensitive to the meta-analytic method used. There were 12 studies with zero events in both treatment arms so in addition to performing analyses that drop those studies (exact test and stratified proportional hazards), analyses stratifying on meta-group (studies within meta-groups pooled), overall pooled analyses and analyses including a continuity correction (addition of 0.5 to each cell in studies with zero events in either one arm or both arms) were conducted by this reviewer. Based on these analyses, an estimate of 1.2 seems reasonable (Table 3.1.2). The comparison of RSG to control is not statistically significant and so these results do not demonstrate increased risk due to RSG based on the composite endpoint of CV mortality, MI or stroke. The confidence intervals, however, suggest that an OR as high as 1.8 is consistent with the observed data and so the data does not definitively show that there is no potential risk associated with RSG compared to control.

Table 3.1.2 Reviewer's results for composite of CV mortality, MI or stroke

Stratification	OR (95%CI) (exact test)	HR (95% CI) (proportional hazards)	OR (95% CI) (M-H fixed effects)
None	1.09 (0.7, 1.6) (Fisher's exact)	1.07 (0.7, 1.6)	NA
Meta-group	1.20 (0.8, 1.8) ¹ (all data included)	1.18 (0.8, 1.8)	1.20 (0.8, 1.8) ¹ (no continuity correction needed)
Study	1.24 (0.8, 1.9) ² (12 studies with 0 events in both arms excluded)	1.18 (0.8, 1.8)	1.15 (0.8, 1.6) ³ (with continuity correction)

¹ Test of homogeneity p=0.08 ² Test of homogeneity p=0.17 ³ Test of homogeneity p>0.9

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The results for tests of homogeneity of the composite endpoint suggest there is heterogeneity across the meta-groups defined in the original meta-analysis (test for homogeneity across meta-groups, $p=0.08$). As shown in Table 3.1.3, the pattern seen across the meta-groups for the composite endpoint was also seen for total and serious myocardial ischemic events with higher risk seen for the add-on trials for insulin and metformin (MET). Only the results for all myocardial ischemic events for RSG+MET vs MET and for the overall comparison of RSG vs. comparator are statistically significant at $p<0.05$; borderline significant results are seen for the insulin group and for the overall results of serious IHD.

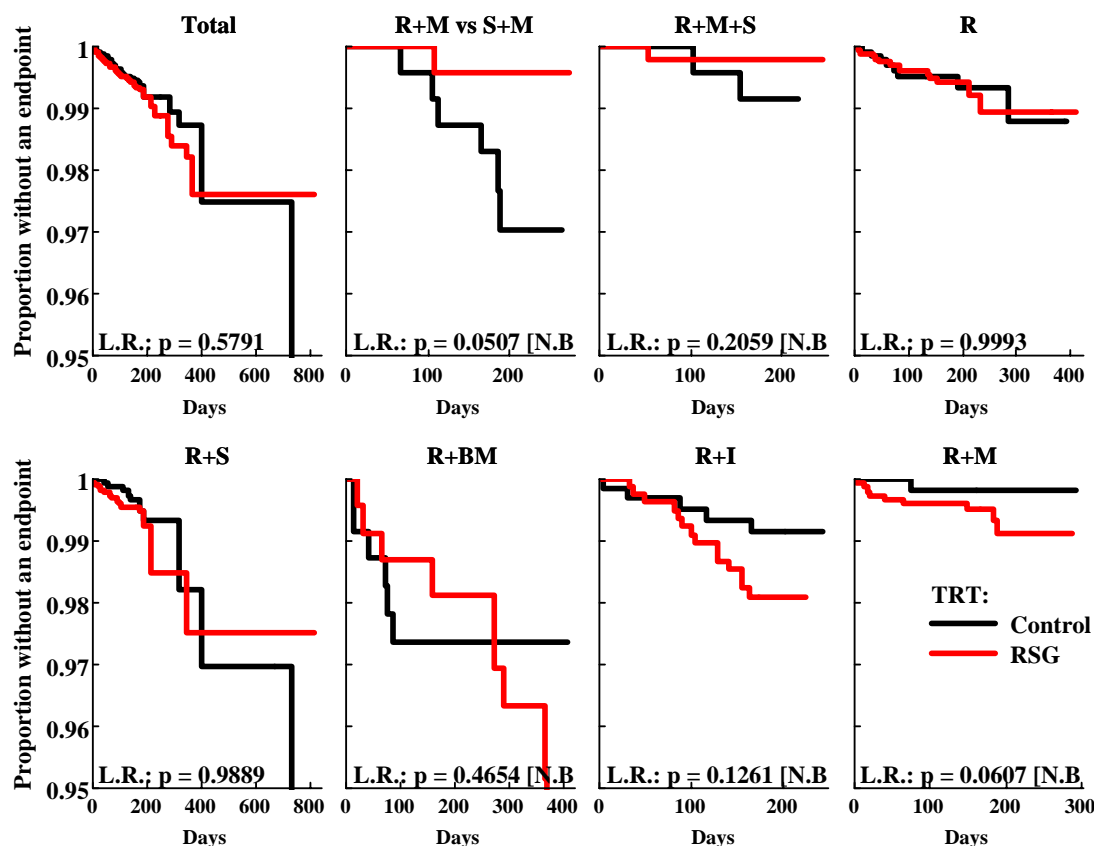
Table 3.1.3 Odds ratios (95% CI) by meta-group for all myocardial ischemic events, serious myocardial ischemic events and composite of CV death, MI or stroke. The results in the first 3 columns are from an exact test with conditional maximum likelihood estimates where studies with zeros in both arms are excluded; the results in the last column are from a Mantel-Haenszel fixed effects model with continuity correction where no trials are excluded. See Appendix 2 for forest plots of the by-study results for each meta-group.

Meta-group	All myocardial ischemic events	Serious myocardial ischemic events	CV death, MI or stroke (exact)	CV death, MI or stroke (MH)
R+M vs. S+M	0.5 (0.1, 2) [$p=0.4$]	0.4 (0.1, 2) [$p=0.3$]	0.1 (<0.01, 1.2) [$p=0.06$]	0.2 (<0.1, 1.3) [$p>0.1$]
R+M+S vs. P+M+S	1.1 (0.3, 5) [$p>0.9$]	0.8 (0.2, 5) [$p>0.9$]	0.2 (<0.1, 5) [$p=0.3$]	0.2 (<0.1, 3) [$p>0.5$]
R+S vs. P+S	1.4 (0.8, 2) [$p=0.24$]	1.4 (0.8, 3) [$p=0.3$]	1.3 (0.5, 3.2) [$p>0.5$]	1.1 (0.5, 2.2) [$p>0.5$]
R vs. P or M or S	1.3 (0.7, 2) [$p=0.3$]	1.5 (0.7, 4) [$p=0.4$]	0.9 (0.3, 2.5) [$p=0.8$]	0.9 (0.4, 1.8) [$p>0.5$]
R+BM vs. P+BM	1.4 (0.6, 4) [$p=0.4$]	1.5 (0.8, 3) [$p=0.2$]	1.6 (0.5, 6) [$p>0.4$]	1.6 (0.5, 5) [$p>0.4$]
R+I vs. P+I	2.1 (0.91, 5) [$p=0.07$]	2.6 (0.8, 11) [$p=0.1$]	2.3 (0.7, 8) [$p=0.16$]	1.9 (0.8, 5) [$p=0.12$]
R+M vs. P+M	3.2 (1.2, 10) [$p=0.01$]	2.9 (0.7, 17) [$p=0.1$]	3.7 (0.7, 36) [$p=0.12$]	1.6 (0.6, 4) [$p=0.07$]
Overall Stratified by Meta-groups	1.4 (1.1, 1.8) [$p=0.02$]	1.4 (1.0, 2.1) [$p=0.06$]	1.2 (0.8, 1.8) [$p=0.4$]	1.15 (0.8, 1.6) [$p>0.3$]

R=rosiglitazone M=metformin S=sulfonylurea P=placebo BM=Background diabetes medication

Kaplan-Meier curves for the composite endpoint illustrate the timing of events with events occurring after 3 months in the RSG plus insulin group and earlier in the RSG plus metformin group (this pattern is seen when considering all ischemic events as well).

Figure 3.1.1 Kaplan-Meier curves for time to first event of CV death, MI or stroke by meta-group



As with the composite, this reviewer performed several analyses of the components of the composite endpoint to check the robustness of the results given the low event rates and zero cells for several trials. An analysis of all deaths is also included here. For MI, both analyses shown in Table 3.1.2 yield an odds ratio of 1.5 while an Mantel-Haenszel estimate of the OR stratifying on study and using a continuity correction of 0.5 in studies with zero cells yielded an OR of 1.25 with a CI of 0.8 to 1.9 (13 studies had no MIs in both arms).

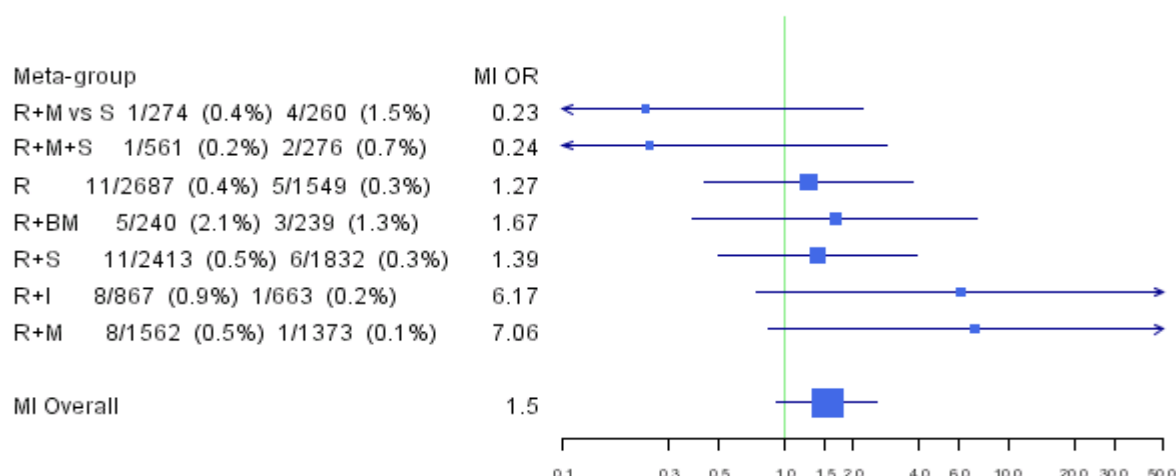
Table 3.1.2 Results for components of MI, stroke and CV death

	MI	Stroke	CV death	All deaths
Fisher's exact test of pooled data	1.5 (0.9, 2.5) $p=0.16$	0.5 (0.2, 0.96) $p=0.04$	1.7 (0.7, 4) $p=0.3$	1.7 (0.8, 4) $p=0.2$
Exact test stratified on meta-group	1.5 (0.9, 2.7) $p=0.11^*$	0.6 (0.2, 1.2) $p=0.10$	1.7 (0.7, 5) $p=0.2$	1.7 (0.8, 4) $p=0.16$
Risk difference stratified on study MH fixed effects model	+0.2% (-0.1%, +0.5%) $p=0.12$	-0.2% (-0.4%, 0.1%) $p=0.2$	+0.1% (-0.1%, 0.4%) $p=0.4$	+0.1% (-0.1%, 0.4%) $p=0.3$

*Test for homogeneity $p < 0.1$

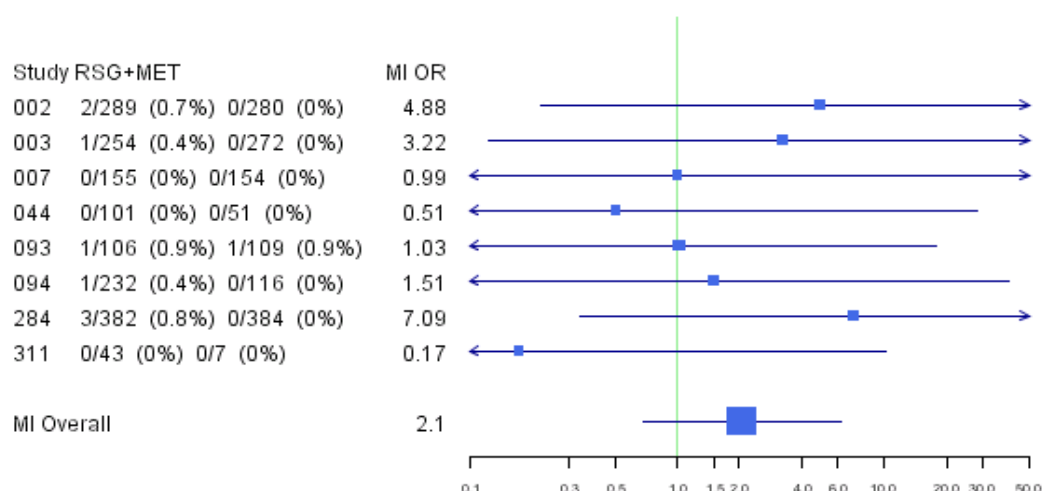
The heterogeneity across meta-groups for MI is illustrated by the forest plot below.

Figure 3.1.2 Forest plot by meta-groups for MI



The results for MI are borderline significant for two of the meta-groups; rosiglitazone plus insulin versus placebo plus insulin and rosiglitazone plus metformin versus placebo plus metformin. The insulin group will be discussed further in the next section of this review. The results by study (Figure 3.1.3) show some heterogeneity within the RSG+MET group though a test for homogeneity is not significant (use of a continuity correction reduces the power of this test). The estimate based on stratifying on study with continuity correction for zeros is 2.1 (NS) as shown below while the estimate in the plot above based on the studies pooled is 7.06, more than three times greater. This difference suggests the weighting by meta-group for this rare event should be more carefully explored.

Figure 3.1.3 Forest plot of the studies comparing RSG+MET to PLA+MET



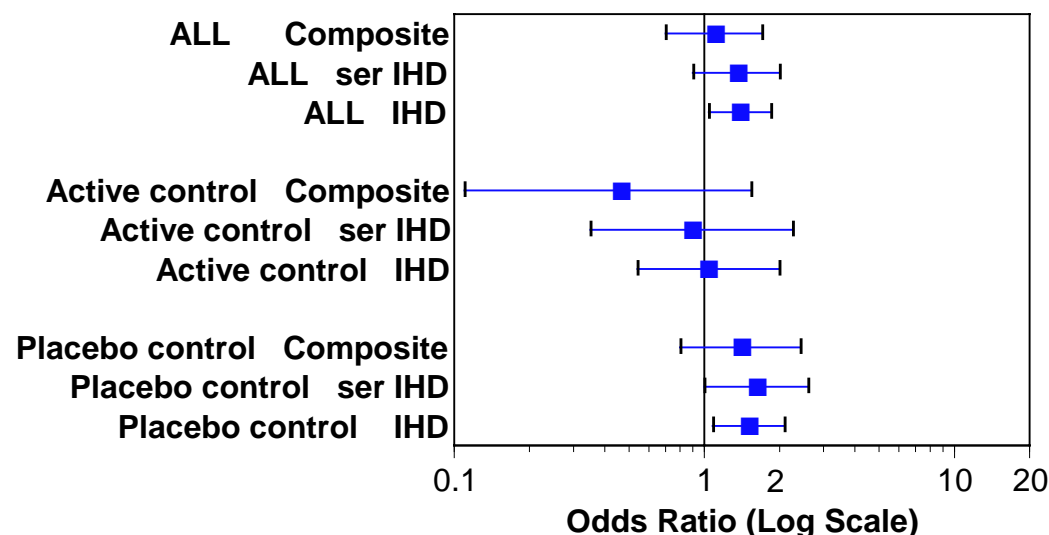
The rare events for the components of the composite present some analytical problems and no approach appears to be satisfactory for the case where there are numerous studies with no events in either one arm or in both arms. Use of a continuity correction appears to move estimates of risk towards one while

pooling across studies may give spurious results due to combining trials that are imbalanced regarding treatment allocation.

In spite of these analytical problems, it is clear that the results for the composite endpoint and the components of MI and CV death do not provide definitive evidence of increased myocardial ischemic risk overall but do suggest that the risk cannot be ruled out and should be further examined.

The results for the composite endpoint, for serious IHD and for all IHD are summarized in Figure 3.1.4. As was shown in the previous review of the 42 trial database for the endpoint of total IHD, the results for the composite endpoint and for the serious IHD show results are unfavorable to RSG in the placebo-controlled trials (even with the insulin trials excluded) and essentially neutral results for the active controlled trials; though for both comparisons the risks are not statistically significant. The overall results are clearly not significant for the composite endpoint but are significant for all IHD which includes both serious and non-serious myocardial ischemic events.

Figure 3.1.4 Results for short-term studies (~13,000 pts, insulin trials excluded)



The results for the composite endpoint and for serious ischemic events will be discussed further in the context of the long-term studies in Section 4.2 of this review. In the following section, the results for the insulin studies are shown. Because the long-term studies do not contain rosiglitazone plus insulin treatment, the insulin trials are excluded for the comparisons to the long-term studies.

3.2 Summary of results in rosiglitazone plus insulin trials

In the original review, this reviewer suggested that the indication for the combination of insulin and rosiglitazone should be reconsidered in light of the meta-analysis results as well as prior regulatory concerns with this combination. Additional data on the composite endpoint appears to further support this position.

A total of 5 studies (1,530 patients, 11% of the whole database) in the pooled database of short-term studies were designed to study the effects of add-on rosiglitazone to insulin. These trials were all 6-month studies with a run-in period on insulin alone and with similar patient populations. The results across several measures of ischemia consistently showed a doubling of risk or more with the exception of stroke (Table 3.2.1) and the results are homogeneous across trials with no trials showing favorable results for rosiglitazone. Although none of the results are statistically significant at the 0.05 level, all the results should be considered borderline significant, given that the trials are all about 6 months in duration, the sample size is small and the results highly consistent across studies.

Note that the exact test, used to compute a p-value based on 2X2 tables, excludes one study with zero events in both arms for analysis of the composite endpoint and its components; the risk difference is a weighted Mantel-Haenszel common estimate of the difference using all trials (fixed effects model).

Table 3.2.1 Overall results for five trials of RSG plus insulin compared to insulin

	RSG+INS (n=867)	INS (n=663)	Common RD (95% CI) Weighted by study	Common OR (95% CI) Weighted by study
All IHD	24 (2.8%)	9 (1.4%)	+1.4% (-0.05%, +2.9%)**	2.1 (0.9, 5.1)**
Serious IHD	12 (1.4%)	4 (0.6%)	+0.9% (-0.2%, +2%)**	2.6 (0.8, 11)*
CV death, MI or stroke	14 (1.6%)	5 (0.8%)	+0.9% (-0.3%, +2.1%)*	2.3 (0.7, 8)*
Stroke	5 (0.6%)	4 (0.6%)	-0.005% (-0.9%, +0.9%)	0.9 (0.2, 5)
MI	8 (0.9%)	1 (0.2%)	+0.8% (-0.08%, +1.7%)**	6.7 (1, 152)**
CV death	4 (0.5%)	0 (0%)	+0.5% (-0.3%, +1.2%)*	undefined*
All deaths	6 (0.7%)	1 (0.2%)	+0.5% (-0.3%, +1.3%)*	4.2 (0.5, 198)*

**P<0.10 *0.11<P<0.24

For forest plots showing individual study results, see page 24 of the original statistical review for results for all myocardial ischemic events and see Appendix 2 of this review for results for the composite endpoint. Except for stroke events in one trial, there were no trials where there were more events in the placebo arm than in the RSG arm. This is unlike any of the other meta-groups where estimates for individual studies were above and below an OR of one.

3.3 Subgroup Analyses

Subgroup analyses of the 42 short-term studies performed by this reviewer and by the applicant suggested that a small subgroup of CHD patients using nitrates were at particularly high risk of an ischemic event due to RSG. Results for other subgroups as well suggested that some patients may be at higher risk of an ischemic event than others (see Appendix 3).

Tests for interaction using a proportional hazards model stratified on study yielded significant results for nitrates ($p=0.03$), for history of CHD plus nitrates ($p=0.03$) and for history of CHF ($p=0.06$); the interaction for history of CHD was not significant ($p>0.7$). When nitrate users are removed from the analysis, the interaction goes away for the CHF group ($p=0.4$). The estimates in the table below illustrate the large impact of nitrate use on the results with an overall estimate of 1.3 with nitrates users included and an overall estimate of 1.1 without nitrate users, in analyses excluding the insulin trials. The interaction with nitrates is not significant when analyzing serious myocardial ischemic events or the composite endpoint of CV death, MI or stroke. So the removal of non-serious events results in removal of a statistically significant interaction; though the reason for a lack of a statistically significant interaction could be due to the small event rates not due to the lack of interaction for serious events. The majority of the non-serious events were cases of angina pectoris and about half of the serious events are recorded as angina pectoris.

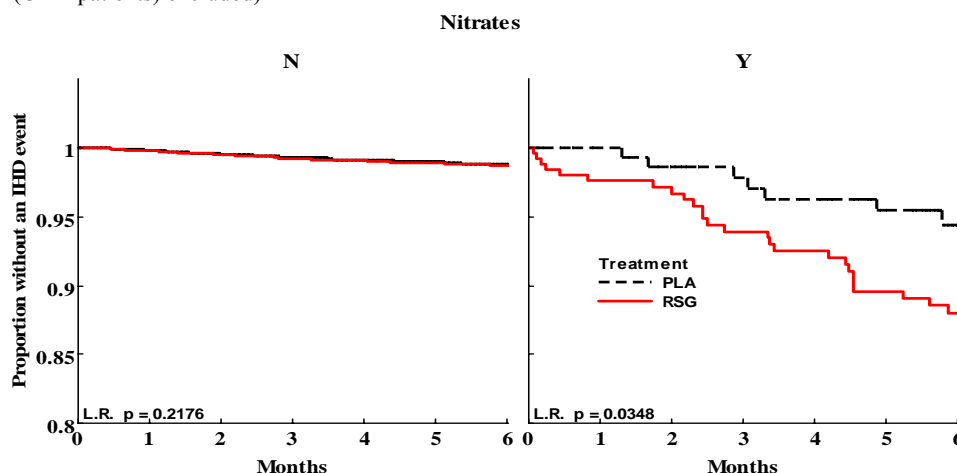
Table 3.3.1 OR (95% CI) using exact test stratifying on meta-group excluding the insulin studies

W/o insulin studies	Total IHD	Serious IHD	CV death, MI or stroke
All patients (N=13,266)	1.3 (1.0, 1.7) ($p=0.06$)	1.35 (0.9, 2.0) ($p=0.15$)	1.1 (0.7, 1.7) ($p>0.8$)
Nitrate Users only (N=523)	2.3 (1.2, 4.8) ($p=0.01$)	1.9 (0.7, 5.5) ($p=0.2$)	1.4 (0.5, 4.5) ($p=0.6$)
All patients Excluding nitrate users (N=12,743)	1.15 (0.8, 1.6) ($p=0.4$)	1.3 (0.8, 2.0) ($p=0.3$)	1.0 (0.6, 1.7) ($p>0.9$)

Note that the model that produced the results for this table is different from the one used to create the subgroup results shown in Appendix 3 and so the results differ though the interpretation is the same. Due to concerns regarding zero events for the sparse data for serious IHD and for the composite endpoint, this reviewer stratified on meta-group instead of study.

Kaplan-Meier curves of time-to any ischemic event illustrate the significant effects for nitrates in the 6-month studies (including the insulin trials) is seen early and that the effect is present even when excluding the high risk patients in Studies 211 and 352. The results for nitrates are similar when excluding insulin trials with log rank test results of $p=0.51$ for no nitrates and $p=0.03$ for nitrate users.

Figure 3.3.1 Kaplan-Meier curves of time to any ischemic event for 6 month studies (Studies 211 (CHF patients) and 352 (CHD patients) excluded)



The impact of nitrate use in combination with rosiglitazone could not be assessed in ADOPT and DREAM because few patients were taking nitrates in these studies (~3% in ADOPT and <1% in DREAM). Data for RECORD was not available to FDA since the trial was ongoing. A summary of the

subgroup results by nitrate use for ADOPT is shown on page 25 of this review.

4 Long-term studies of rosiglitazone

4.1 ADOPT (September, 2000 to August, 2006)

ADOPT was approximately a 4-6-year, randomized, parallel-group, blinded (double dummy), multi-national study of patients recently diagnosed with Type 2 diabetes comparing monotherapies of rosiglitazone (RSG), sulfonylurea (SU; US generic glyburide and EU generic glibenclamide) and metformin (MET).

Entry criteria included the following:

- Diagnosed with Type 2 diabetes within 3 years of screening
- $126 \leq \text{FPG} \leq 180$ after a placebo run-in including diet and exercise
- No NYHA class 3 or 4 angina nor angina requiring continual nitrate treatment
- No NYHA class congestive heart failure

Following a 6-week placebo single-blind run-in on diet and exercise, patients were randomized stratified by gender to RSG, SU or MET. Visits were scheduled at every 2 months the first year of treatment and every 3 months for the remaining 4 years of treatment.

The primary endpoint was time to monotherapy failure where monotherapy failure was defined as follows:

- $\text{FPG} > 180 \text{ mg/dL}$ on consecutive occasions after at least 6 weeks of therapy at the maximum tolerated dose
- OR
- Judged to have failed monotherapy therapy based by an independent adjudication committee

Time was measured from randomization to the first $\text{FPG} > 180$ for the first criterion and from randomization to the last on-therapy FPG for the second criterion. The primary outcome is not the focus of this review and therefore the results will only be briefly summarized.

The primary purpose of this review of ADOPT is to test some of the hypotheses generated by the meta-analysis. The meta-analysis results particularly pertinent to ADOPT are the following:

- An OR for myocardial ischemic events (IHD) of 1 for all naïve patients
- An OR for IHD of 0.8 (CI of 0.3 to 1.9) for head-to-head studies of rosiglitazone to SU or MET in 6-month studies

These estimates of 1 or less were accompanied by wide confidence intervals and uncertainty about the estimates. Results from ADOPT could confirm or refute these estimates.

ADOPT also may provide adequate patients to examine subgroups analyzed with the pooled database although the ADOPT population is generally a lower risk population (compare Table 4.1.4 to table in Appendix 4) then the population of the pooled database.

Serious adverse event data which suggested congestive heart failure (CHF) were reviewed by two independent cardiologists blinded to treatment. Time to event data was computed and analyzed for all cardiovascular adverse events.

Patients who withdrew due to monotherapy failure were given the option of continuing into an observational period where limited data was collected for 48 to 72 months from their randomization date.

According to the original protocol, a total of 3600 patients (1200 per group) were required for a power of 90% to show a 30% risk reduction for monotherapy failure in favor of RSG over SU or MET assuming an alpha of 0.05 and an annual incidence in each control of about 7.2%. Study enrollment was increased to 4182 (1394 per group, Amendment 10, March 2002) to account for the large early dropout rate. Also based on blinded power calculations, the treatment period was extended from 4 to 6 years (Amendment 12, February 2004) due to a lower than anticipated overall monotherapy failure rate (3.5% annual failure rate). Patients were given the option of dropping out at Month 48.

Four analysis populations were named: 1) all randomized patients=all randomized patients receiving at least one dose of randomized treatment; 2) intent-to-treat patients= all randomized patients receiving at least one dose of randomized treatment and having at least efficacy measure; 3) 48-month completers=randomized patients who completed 48 months on treatment and 4) completers=randomized patients who remained on study until at least March 15, 2006. For safety analyses in this review, the analysis population is the all randomized population.

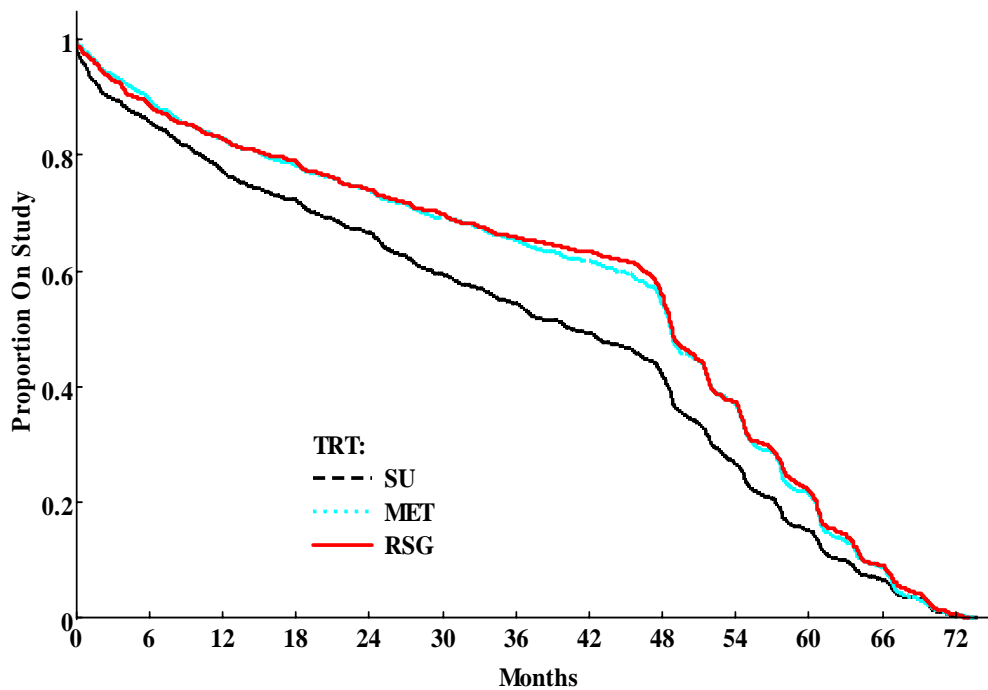
Of 6385 patients who were enrolled in the run-in period, 4351 (68%) were randomized. The disposition of patients by analysis populations show higher numbers for the RSG group than the comparators, particularly SU, though clearly completion rates are low in all groups with less than 60% of the patients completing 4 years on study.

Table 4.1.1 Patient disposition by analysis population and treatment (from Table 12 of ADOPT study report)

	RSG	SU	MET
Randomized	1456	1441	1454
ITT	1393 (96%)	1337 (93%)	1397 (96%)
48-month Completers	858 (59%)	639 (44%)	832 (57%)
Completers	692 (48%)	459 (32%)	645 (44%)

The significant difference in exposure between SU and both MET and RSG (Figure 4.1.1) needs to be considered when assessing event rates since the differences in exposure may bias the adverse event rates in favor of SU and against both MET and RSG.

Figure 4.1.1 Proportion of patients on study by treatment group



Patients drop out of ADOPT either due to monotherapy failure or for other reasons generally seen in clinical trials (e.g. adverse events, lost-to-follow-up, etc.) or because they have completed 48 months and chosen to discontinue (the latter reason explains the bumps in the curves shown in Figure 4.1.1). The next two tables show, respectively, the percentage of patients on study and dropping out by year and the number of patients dropping out by reason.

Looking at the monotherapy failures shows that the failures on RSG are consistently lower than those on either SU or MET for each year of the trial. The by-year data also illustrate the large number of discontinuations for various reasons other than monotherapy failure occurring during the first year in all the groups (16-21%).

Table 4.1.2 Percent of patients on study by end of each year and number of monotherapy failures and discontinuations for other reasons by year

End of Year	RSG N=1456			SU N=1441			MET N=1454		
	On-study	Failures	Dropouts	On-study	Failures	Dropouts	On-study	Failures	Dropouts
1	1203 (83%)	14	239	1109 (77%)	26	306	1202 (83%)	16	236
2	1076 (74%)	19	108	952 (66%)	58	99	1068 (73%)	29	105
3	954 (66%)	27	95	773 (54%)	63	116	942 (65%)	38	88
4	742 (51%)	19	193	644 (39%)	53	163	724 (50%)	26	192
5	261 (18%)	17	464	184 (13%)	35	338	252 (17%)	26	446

These numbers were computed by the reviewer using variables EXPOSE and MONOFDT.

Table 4.1.3 Reasons for dropout by treatment including the primary endpoint of monotherapy failure (numbers extracted from Table 8 of the applicant's study report, exposure computed by reviewer)

	RSG (n=1456)	SU (n=1441)	MET (n=1454)
Adverse event	169 (12%)	215 (15%)	178 (12%)
Lack of efficacy	36 (2%)	64 (4%)	53 (4%)
Protocol deviation	64 (4%)	61 (4%)	51 (4%)
Lost-to-follow-up	73 (5%)	79 (6%)	82 (6%)
Withdrew consent	111 (8%)	110 (8%)	107 (7%)
Withdrawn prior to 3/15/06	105 (7%)	68 (5%)	68 (5%)
Other	63 (4%)	74 (5%)	63 (4%)
Total Dropouts	621 (43%)	671 (47%)	602 (41%)
Monotherapy Failures	143 (10%)	311 (22%)	207 (14%)
Exposure Time (yrs)			
Mean (SD)	3.4 (1.8)	2.9 (1.8)	3.4 (1.8)
Median	4	3.3	4

The numbers of dropouts by reason are similar for RSG and MET. A time to event analysis by the applicant showed a statistically significant difference between RSG and SU for adverse events leading to therapy discontinuation with a hazard ratio (HR) of 0.8 favoring RSG and a difference in incidences of about 3%. A cumulative incidence graph of AE discontinuations (Figure 4 in the study report) suggests that a significant difference between MET and SU exists as well.

Of all the patients discontinuing treatment for any reason, about 45% continued into the optional observation period and about half of those patients completed the observation period; so only about one-fourth of the dropouts continued to be followed to study end.

Overall the exposure data shows that exposure to SU is significantly lower than exposure to either of the other two drugs, RSG and MET, with the differences occurring as early as the first year. Exposure must be considered in the assessment of ischemia.

The treatment groups were well-balanced at baseline; 58% were males, 89% Caucasian, 24% 65 years or older. About 18% presented with a history of cardiovascular disease and about ¼ were using baseline CV medications including ACE inhibitors. The patients in ADOPT have similar characteristics to the naïve patients and to the overall monotherapy group in the GSK pooled database of 42 studies.

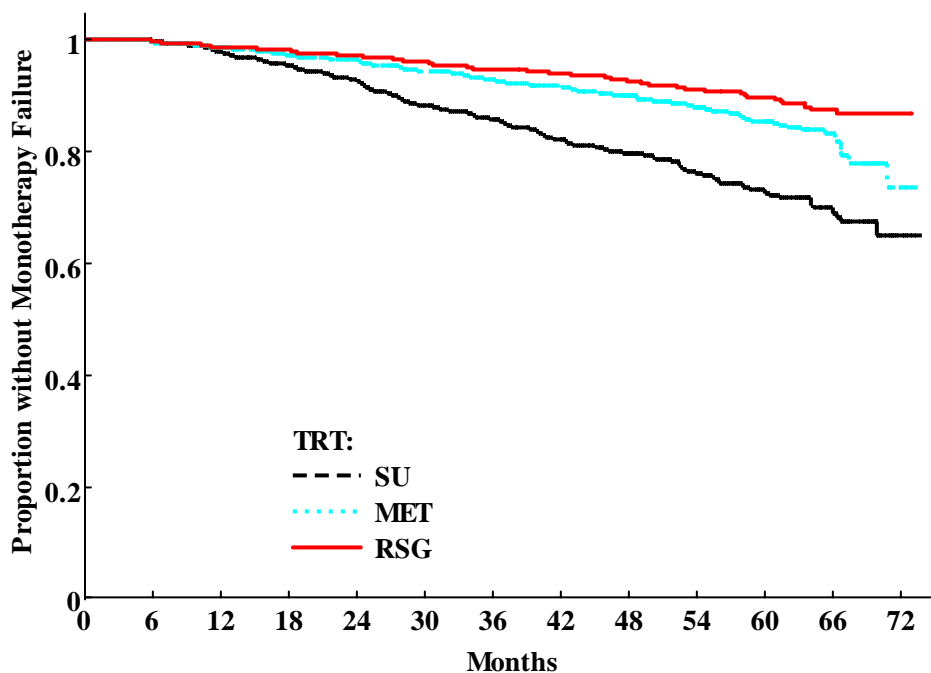
Table 4.1.4 ADOPT patient characteristics

	RSG (n=1456)	SU (n=1441)	MET (n=1454)
<u>Age</u>			
Mean (SD)	56 (10)	56 (10)	57 (10)
Range	30-76	26-75	29-76
%>65	23%	24%	25%
<u>Gender</u>			
% males	56%	58%	59%
<u>% Smokers</u>	16%	13%	15%
<u>BMI</u>			
Mean (SD)	32 (7)	32 (6)	32 (6)
Median	31	31	31
<u>Dur Diab</u>			
<2 years	79%	78%	78%
2 years or more	11%	12%	12%
Hx CV	16%	17%	19%
Hx hypertension	51%	52%	51%
<u>Baseline meds</u>			
Nitrates	2%	3%	3%
Statin	23%	22%	23%
Loop diuretic	6%	6%	6%
Alpha blocker	5%	4%	3%
Beta blocker	20%	20%	20%
CCB	13%	14%	12%
ACE inhibitor	24%	24%	24%
HbA1c Mean (SD)	7.4 (0.9)	7.4 (0.9)	7.4 (0.9)
HDL Mean (SD)	48 (12)	48 (12)	48 (12)
LDL Mean (SD)	122 (34)	122 (35)	121 (34)
DBP Mean (SD)	79 (9)	79 (9)	80 (9)

NA=not available

The results for the primary endpoint (Figure 4.1.2) showed statistically significant differences between RSG and each of the comparator arms of SU (HR 0.4, 95% CI of 0.3 to 0.5) and MET (HR 0.7, 95% CI of 0.6 to 0.9), $p \leq 0.0005$ based on the applicant's analysis.

Figure 4.1.2 Time to monotherapy failure



To assess safety in ADOPT, this reviewer looked at the following endpoints:

- Serious myocardial ischemia (serious IHD)
- Non-serious plus serious myocardial ischemia (IHD)
- Composite endpoint of CV death, MI or stroke
- Each component of the composite
- Total mortality

The first two endpoints are defined as in the database of the 42 short-term studies (see the FDA clinical review by Dr. Karen Mahoney for more details regarding the definitions of the endpoints).

The longer exposure time for the RSG group compared to SU could result in higher event rates for RSG compared to SU due an increased opportunity for having an event and not necessarily due to a treatment effect. Comparable event rates might be expected for MET and RSG due to comparable exposure times, if no treatment difference exists.

With the exception of mortality, the SU group had the fewest events over the full duration of the trial and generally the RSG and MET groups had comparable numbers of events (Table 4.1.5). It is clear that duration of drug exposure needs to be considered when comparing the groups in order to adjust for the differential exposure.

Table 4.1.5 Incidence of ischemic events by treatment group

	RSG (n=1456)	SU (n=1441)	MET (n=1454)
All IHD	7.3% (106)	5.7% (82)	7.6% (111)
Serious IHD	3.8% (55)	3.0% (43)	4.1% (60)
CV death, MI or stroke	2.8% (40)	2.0% (29)	2.5% (37)
CV death	0.3% (5)	0.6% (8)	0.3% (4)
All cause mortality	0.8% (12)	1.5% (21)	1.0% (15)
MI (SAE)	1.7% (24)	1.0% (14)	1.4% (20)
Stroke	0.9% (13)	0.8% (12)	1.2% (17)

Under the ADOPT protocol, time to adverse events was to be analyzed using a proportional hazards model with terms for treatment and number of major CV risk factors. This reviewer included gender as a stratifier since the randomization was stratified on gender. For a time-to-event analysis, patients who discontinue for any reason are censored and dropped from the group at risk at that point in time so the probability of not having an event at any given time is computed based on the number of patients in the risk group at that time. This adjustment to the number at risk as patients drop out allows one to obtain an overall risk accounting for changes in the risk set which is particularly important for this trial with differential dropout rates.

Table 4.1.6 Proportional Hazards Model results for ischemic events HR (95% CI)

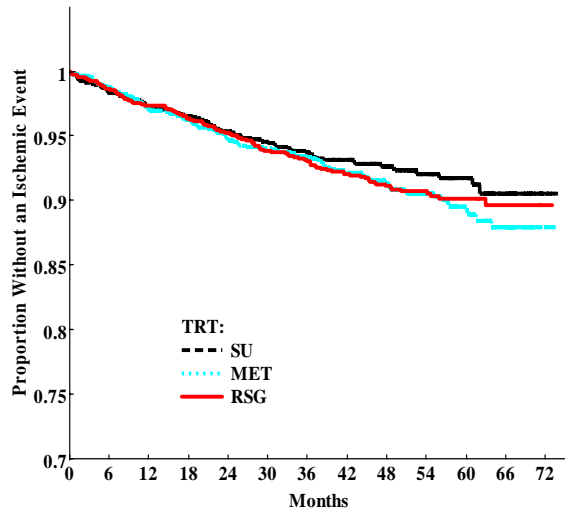
	RSG vs SU	RSG vs MET	MET vs SU ¹
All IHD	1.2 (0.9, 1.6) p=0.2	1.0 (0.8, 1.3) p=0.9	Not computed
Serious IHD	1.2 (0.8, 1.8) p=0.3	1.0 (0.7, 1.4) p>0.9	1.2 (0.8, 1.8) p=0.3
CV death, MI or stroke	1.2 (0.7, 1.9) p=0.3	1.1 (0.7, 1.8) p=0.6	1.1 (0.7, 1.7) p=0.8
CV death	0.6 (0.2, 1.9) p=0.4	1.3 (0.4, 5) p=0.7	0.4 (0.1, 1.5) p=0.2
All cause mortality	0.5 (0.3, 1.1) p=0.08	0.8 (0.4, 1.8) p=0.7	Not computed
MI	1.6 (0.8, 3.1) p=0.17	1.3 (0.7, 2.3) p=0.4	1.2 (0.6, 2.5) p=0.5
Stroke	0.9 (0.4, 2.1) p=0.9	0.8 (0.4, 1.6) p=0.5	1.2 (0.6, 2.6) p=0.6

1-Applicant's results, OR greater than 1 indicates higher risk on MET compared to SU

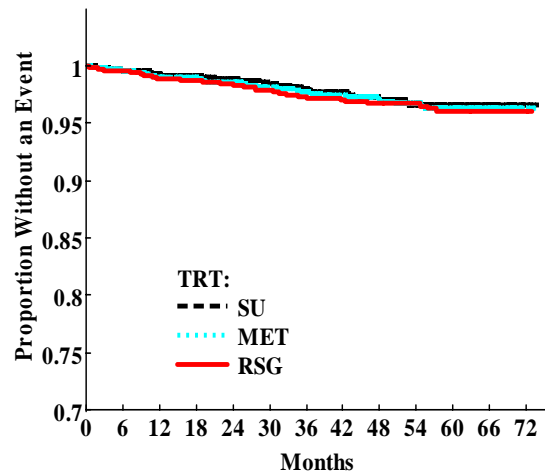
No statistically significant treatment differences were seen for any pairwise comparison for any endpoint Table 4.1.6). There were no pre-defined margins for establishing non-inferiority for safety in this study and the study was not powered for these comparisons. The generally wide confidence intervals may be due to the small event rates for most of the endpoints. For all IHD with event rates of about 7% for RSG and MET, the comparison of RSG and MET rules out an HR greater than 1.3 which may be adequate for establishing non-inferiority. In general though the results do not definitively establish a lack of risk for RSG over SU or MET.

The Kaplan-Meier curves (Figure 4.1.3) illustrate the lack of a difference among the treatment groups for the two outcome variables of total IHD and the composite of MI, CV death or stroke. A separation of the curves for total IHD is seen late in the trial when the risk set is notably smaller with about 60% of the patients on study during Year 4.

Figure 4.1.3 ADOPT Kaplan-Meier Curves
Time to Myocardial Ischemic Event

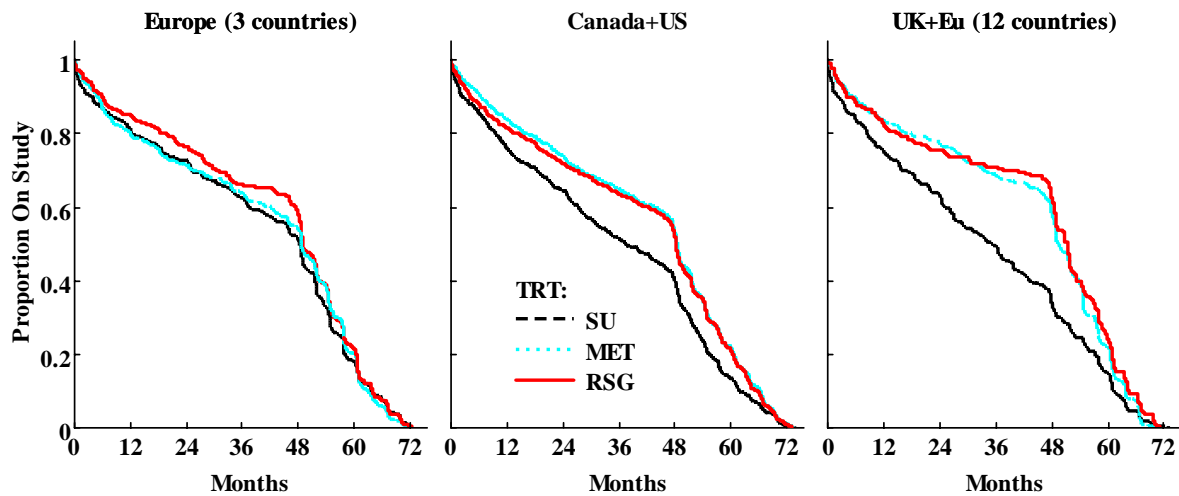


Time to MI, CV death or Stroke



Patients were enrolled in 17 different countries with the United States enrolling 38% of the patients. The results for three groups of countries show a difference in patterns of discontinuation (Figure 4.1.4) but this difference does not result in hazard ratios (Table 4.1.7) notably different from the overall results.

Figure 4.1.4 Patients on study by treatment group and region



	Europe			Canada+US			UK+EU		
Countries (N)	France (390), Germany (471), Spain (400)			Canada (618), United States (1656)			UK (320), Austria (42), Belgium (94), Czech Republic (29), Denmark (20), Finland (39), Hungary (6), Ireland (44), Italy (87), Netherlands (74), Norway (36), Sweden (25)		
	RSG (n=422)	SU (n=413)	MET (n=426)	RSG (n=758)	SU (n=758)	MET (n=758)	RSG (n=276)	SU (n=270)	MET (n=270)
Dropouts	39%	39%	42%	46%	50%	43%	39%	48%	35%
ADE	12%	13%	14%	11%	14%	12%	14%	21%	12%
Therapy Failures	10%	19%	12%	9%	21%	15%	10%	29%	16%

Table 4.1.7 Proportional Hazards Model results for ischemic events HR (95% CI) by Region

	Europe		Canada+US		UK+EU	
	RSG vs SU	RSG vs MET	RSG vs SU	RSG vs MET	RSG vs SU	RSG vs MET
All IHD	1.1 (0.6, 2)	1.0 (0.5, 1.7)	1.4 (1, 2)	1.1 (0.8, 1.5)	0.8 (0.4, 1.6)	1.0 (0.5, 1.8)
Serious IHD	1.4 (0.6, 3)	1.0 (0.5, 1.9)	1.4 (0.8, 2.5)	1.0 (0.6, 1.6)	0.7 (0.3, 1.7)	1.2 (0.5, 3.1)

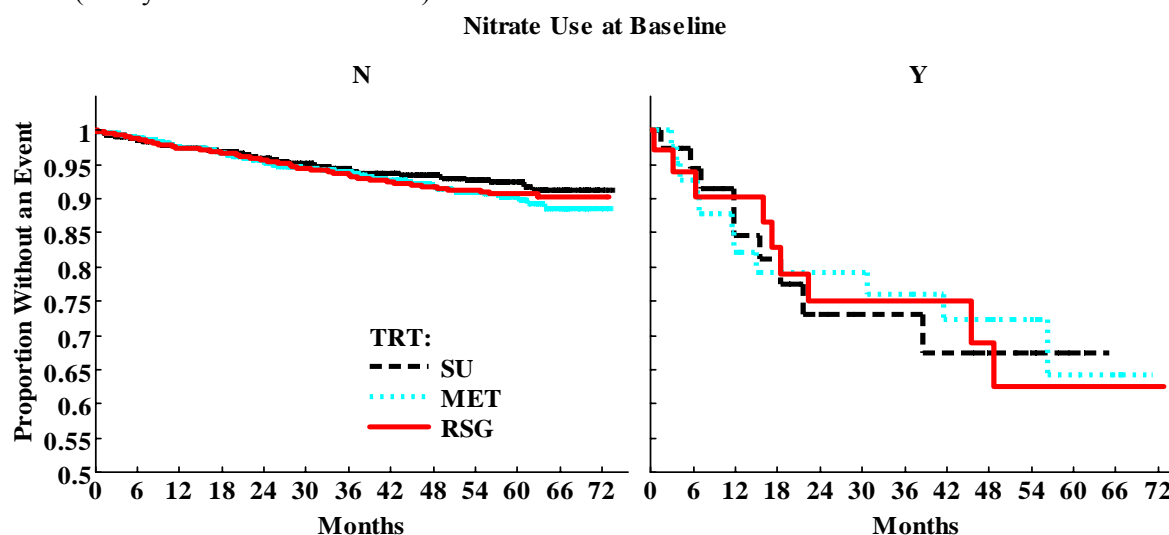
This reviewer performed analyses by subgroups identified in the analysis of the 42 short-term studies and found no higher risk in the RSG group over either comparator.

Nitrate use was shown to be a risk factor with rosiglitazone for myocardial ischemia (predominantly angina) based on subgroup analyses of the 42 short-term studies. The results for ACE inhibitors are also shown here since an interaction for RSG with ACE inhibitors was seen for some cardiovascular endpoints in DREAM. For ADOPT, the results for subgroups defined by baseline use do not show significant treatment differences or differential treatment effects in these subgroups (Table 4.18 and Figure 4.1.5). The number of patients on nitrates at baseline is too small to draw any conclusions regarding a nitrate interaction. The Kaplan-Meier curves illustrate that events occur early as was seen in the pooled database.

Table 4.1.8 Incidence of myocardial ischemic events by treatment group and by baseline nitrate & ACE inhibitor use

	RSG	SU	MET
All IHD	7.3% (106/1456)	5.7% (82/1441)	7.6% (111/1454)
Baseline nitrate use	26% (9/35)	21% (9/42)	25% (11/44)
No nitrate use at baseline	7% (97/1421)	5% (73/1399)	7% (100/1410)
Baseline ACE inhibitor use	8% (39/479)	6% (27/477)	9% (44/486)
No ACE inhibitor use at baseline	7% (67/977)	6% (55/964)	7% (67/968)

Figure 4.1.5 Kaplan-Meier curves for time to first myocardial ischemic event by nitrate use at baseline (note y-axis scale starts at 0.5)



4.2 Results of the meta-analysis with the results of ADOPT, DREAM and RECORD

In this section, the results from the 37 short-term studies (the 42 studies minus the 5 insulin studies) and the three long-term studies are presented together in an effort to understand similarities and differences among the results. Full databases and study reports were submitted for the short-term studies and for the ADOPT study. A limited dataset was submitted for DREAM and no data was available for RECORD, an ongoing study. Results were available from publications of DREAM and RECORD (see references for Dream investigators and for Home et al in Appendix 6). For more details regarding the designs and results of the long-term studies, see the FDA clinical review of Dr. Karen Mahoney.

Table 4.2.1 briefly summarizes the characteristics of the three large long-term trials. All the trials were randomized, multi-center, parallel controlled studies. DREAM and ADOPT were double-blind studies while RECORD is an open-label study. A factorial design was utilized by DREAM and patients were randomized to monotherapy of placebo, ramipril or rosiglitazone or to combination therapy of ramipril plus rosiglitazone. Both ADOPT and RECORD had active controls of metformin and sulfonylurea; ADOPT was a monotherapy trial while RECORD was an add-on trial where patients inadequately treated with MET or SU were randomized to RSG or either MET or SU. The patients in DREAM (pre-diabetic) and ADOPT (newly diagnosed with diabetes) were all naïve to diabetic treatment while all the patients in RECORD had been previously treated and had a mean history of diabetes of 7 years (similar to the patients in the short-term studies). The average age of patients in these three studies ranged from 55 years in DREAM to 58 years in RECORD. DREAM was about 60% women while the other studies had slightly more men. About 80% of the patients in DREAM had a history of hypertension while about half did in the other studies. The median BMI was 31 kg/m² in all the studies.

Table 4.2.1 Designs of three large long-term studies of rosiglitazone

	TRT ARMS (Sample size)	Duration	Population	Primary outcome
DREAM	Placebo (1321) Ramipril (1313) Rosiglitazone (1325) RAM+RSG (1310)	Completed Median 3 years	Impaired FPG or impaired glucose tolerance No pts with hx of T2DM, or CV disease	Time to incident diabetes or death
ADOPT	Rosiglitazone (1456) Metformin (1454) Sulfonylurea (1441)	Completed Median 4 years	T2DM diagnosed w/i last 3 years No NYHA CHF Class 3&4 nor CHF requiring meds	Time to monotherapy failure
RECORD (OL due to added insulin therapy)	MET+RSG (1117) MET+SU (1105) SU+RSG (1103) SU+MET (1122)	On-going Minimum 5 years Median 6 years	T2DM No Hospitalization for CV event in last 3 mos No CHF requiring meds	Time to CV death or CV hospitalization

On the following page, four tables display the incidence of the composite endpoint and the components by treatment group for the 37 short-term studies (excluding the 5 insulin studies) and the three long-term studies.

The event rates for the composite and for serious IHD in the short-term studies was less than 1%; the event rates in these short-term studies is most comparable to the rate of about 4% seen in the RECORD study with about 4 years of exposure which has a patient population most similar to the population in the short-term database. Lower rates are seen for the pre-diabetics and newly diagnosed diabetics studied in DREAM (~1%) and ADOPT (~2%), respectively.

Table 4.2.1 Cumulative incidence of events for first event of CV death, MI or stroke and for each component¹

37 short-term studies (insulin studies excluded); median exposure 6 months

	RSG (n=7737)	Control (n=4970)
CV death, MI or stroke	49 (0.63%)	33 (0.66%)
Stroke	8 (0.10%)	14 (0.28%)
MI	37 (0.48%)	19 (0.38%)
CV deaths	14 (0.18%)	7 (0.14%)
Total deaths	17 (0.22%)	8 (0.16%)
Serious IHD	74 (0.96%)	36 (0.72%)

DREAM; median exposure approximately 3 years

	RSG+RAM (n=1310)	RAM (n=1313)	RSG (n=1325)	PLA (n=1321)	Interaction
CV death, MI or stroke	18 (1.4%)	9 (0.7%)	15 (1.1%)	14 (1.1%)	0.25
Stroke	2 (0.2%)	2 (0.2%)	5 (0.4%)	3 (0.2%)	0.69
MI	11 (0.8%)	5 (0.2%)	5 (0.4%)	6 (0.5%)	0.09
CV deaths	7 (0.5%)	5 (0.2%)	5 (0.4%)	5 (0.4%)	0.69
Total deaths	15 (1.1%)	16 (1.2%)	15 (1.1%)	17 (1.3%)	0.88

ADOPT; median exposure approximately 4 years

	RSG (n=1456)	SU (n=1441)	MET (n=1454)
CV death, MI or stroke	40 (2.8%)	29 (2.0%)	37 (2.5%)
Stroke	13 (0.9%)	12 (0.8%)	17 (1.2%)
MI	24 (1.7%)	14 (1.0%)	20 (1.4%)
CV deaths	5 (0.3%)	8 (0.6%)	4 (0.3%)
Total deaths	12 (0.8%)	21 (1.5%)	15 (1.0%)

RECORD (interim analyses May 2007; adjudicated results) median exposure approximately 4 years

	<i>MET</i> +RSG (n=1117)	<i>MET</i> +SU (n=1105)	<i>SU</i> +RSG (n=1103)	<i>SU</i> +MET (n=1122)
CV death, MI or stroke	46 (4.1%)	47 (4.3%)	47 (4.3%)	49 (4.4%)
Stroke	11 (1.0%)	19 (1.7%)	18 (1.6%)	19 (1.7%)
MI	23 (2.1%)	16 (1.4%)	20 (1.8%)	21 (1.9%)
CV deaths	15 (1.3%)	17 (1.5%)	14 (1.3%)	18 (1.6%)
Total deaths	36 (3.2%)	36 (3.3%)	38 (3.4%)	44 (3.9%)

Italicized indicates the background medication

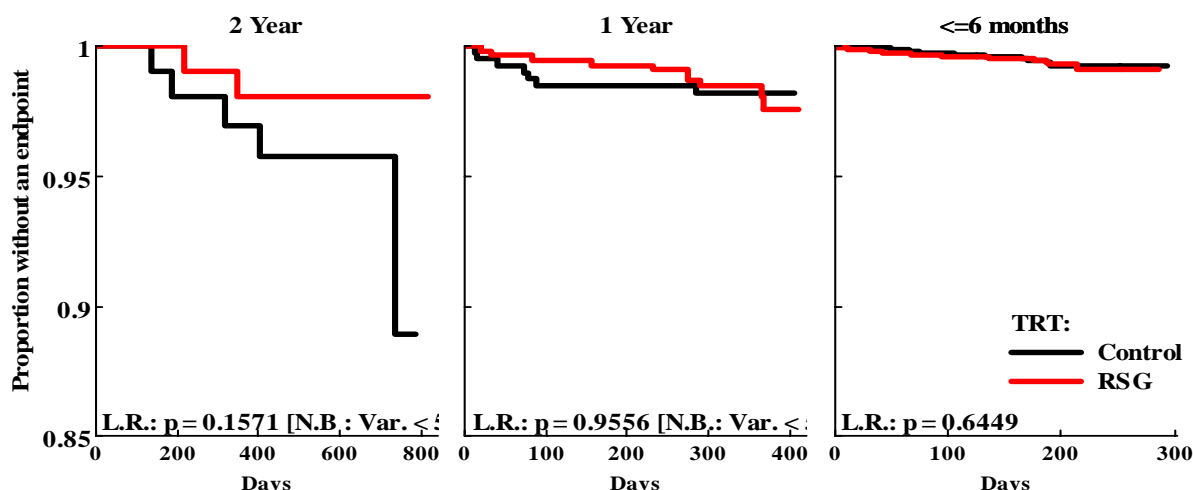
There is no endpoint where the incidence of events is consistently higher (or lower) for rosiglitazone compared to control across the pooled studies and the long-term studies.

1 For comparative statistics for the composite endpoint, see Table 3.3.1 for the results of the 37 short-term studies, Table 4.1.5 for the results of ADOPT and Appendix 5 for the results of DREAM.

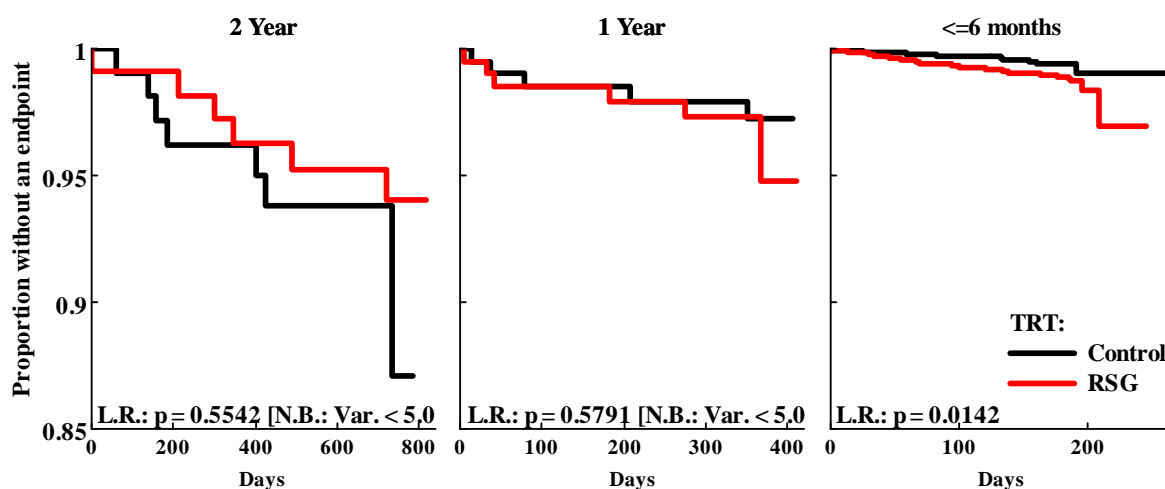
Figure 4.2.1 Kaplan-Meier curves for time to first event of the composite endpoint of CV death, MI or stroke and for serious ischemic events for the short term studies by length of study. One study (*Study 135; RSG+SU vs PLA+SU*, 227 pts over 60 years old) was 2 years in length, 3 studies (*Studies 211: RSG vs PLA*, 224 CHF pts on background medications; *334: RSG vs PLA*, 194 pts on background medications; and *020: RSG vs SU*, 598 pts) were 1 year and the rest (~11,500 patients on RSG, RSG+MET, RSG+SU or control) were about 6 months in length. The insulin studies are excluded.

Short-term studies by length of study

Composite endpoint of CV death, MI or stroke



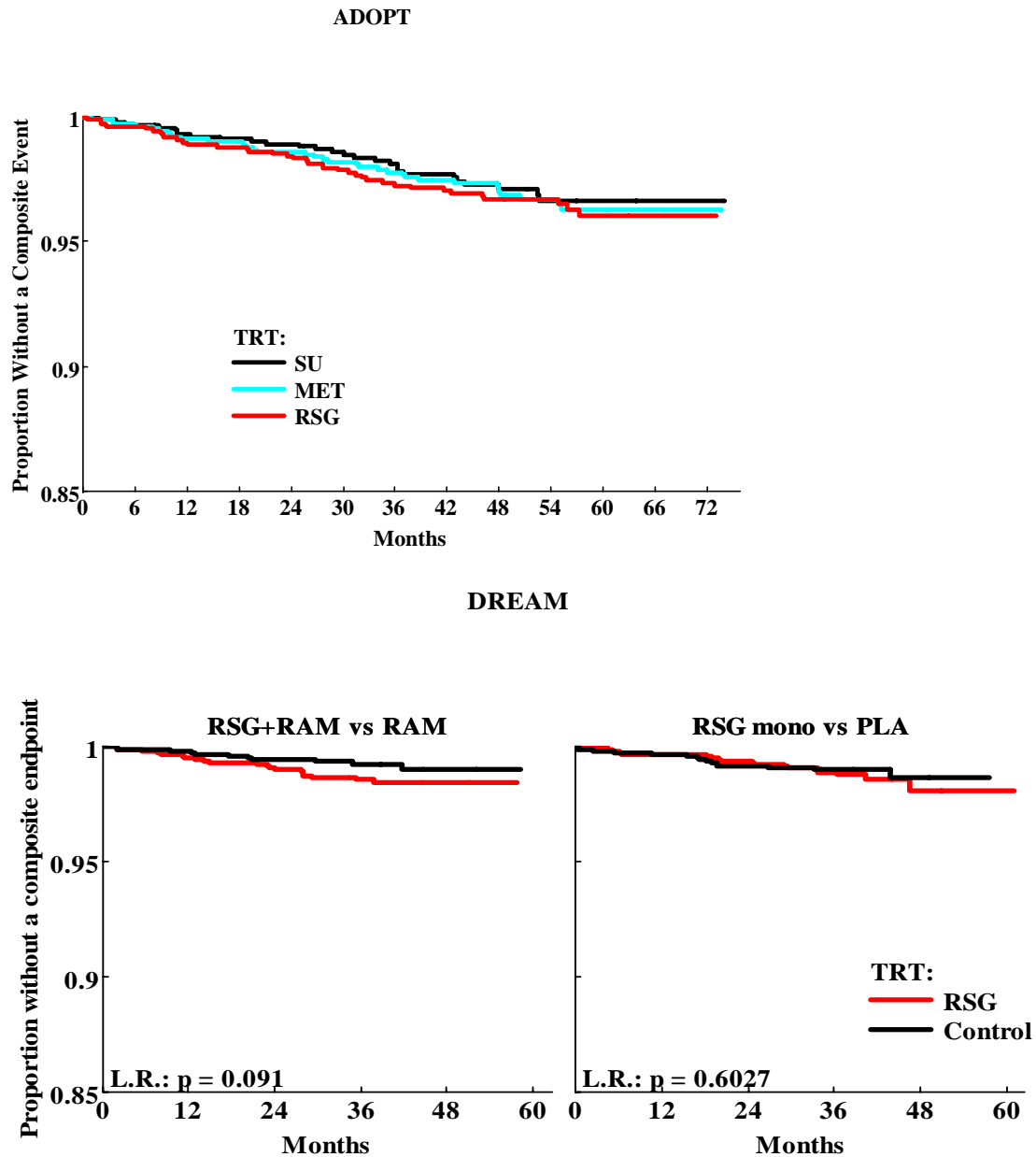
Serious Myocardial Ischemic events



The Kaplan-Meier curves for time to CV death, MI or stroke (top graphs) and for time to a serious myocardial ischemic event suggest no difference in risk in the 5 studies of 1 year or 2 year duration; studies with higher event rates than the 6 month studies. For the 6 month studies, a separation of the curves is seen as early as about 3 months for serious ischemic events while no separation is seen for the composite endpoint. When the results for all these trials are combined, a non-significant maximum likelihood estimate of the OR of 1.35 (CI of 0.9 to 2, $p=0.15$) for serious IHD was obtained with an exact

test stratifying on meta-group.

Figure 4.2.2 Kaplan-Meier curves for time to first event of the composite endpoint of CV death, MI or stroke for ADOPT and DREAM.



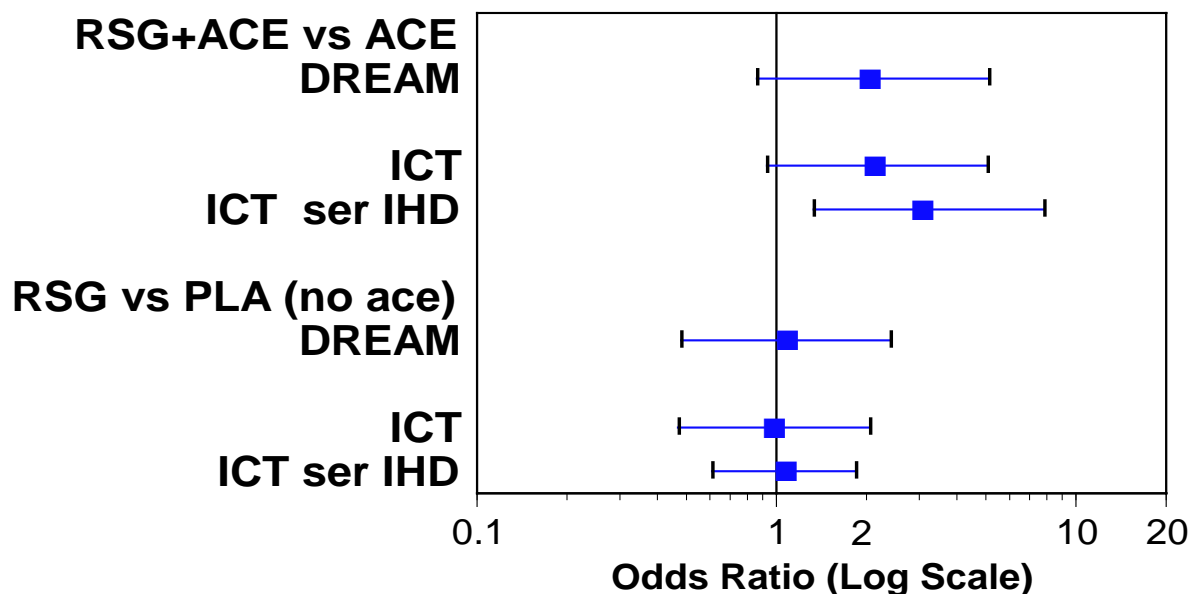
The Kaplan-Meier curves above illustrate the lack of a difference among the three treatment groups in ADOPT and, for DREAM, the difference in treatment effects between monotherapy versus placebo and combination therapy versus ramipril.

The graphs below are of odds ratios for the 37 short-term studies and DREAM and hazard ratios for ADOPT and RECORD. With small event rates, an estimate of the odds rate will be close to an estimate of the hazard ratio particularly if the hazard rate is assumed to be constant (for an example of the similarities between these measures, see Table 3.1.2).

To determine if the effects seen with short-term use of RSG are consistent with effects seen with long-term use, the results are summarized in the following to graphs making similar comparisons. For DREAM, a significant interaction for the combination of RSG+ramipril was seen for MI ($p=0.09$) and for any cardiovascular event ($p=0.07$), so it seems reasonable to look at the combination of RSG with an ACE inhibitor in both the short-term studies and DREAM. Since the DREAM comparisons are all against placebo, only the placebo-controlled short-term trials are included in Figure 4.2.3 (about 40% of the patients in the placebo-controlled trials were taking ACE inhibitors at baseline).

Though the interaction for ACE inhibitor use and treatment in the short-term placebo-controlled studies was not statistically significant; it is clear that the results for the short term studies are quite consistent with the results for DREAM (Figure 4.2.3).

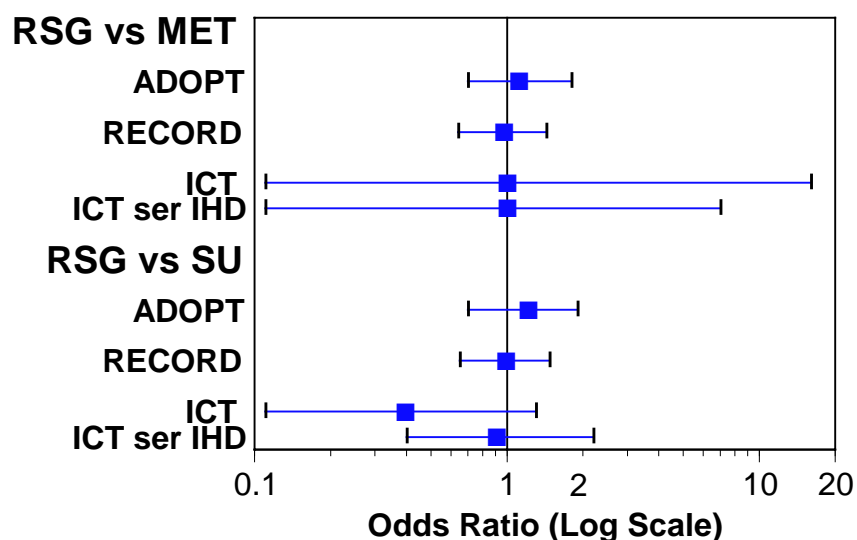
Figure 4.2.3 Plot of odds ratios for the combination of RSG with an ACE inhibitor in DREAM and in the database of short-term studies for the composite endpoint of CV death, MI or stroke and for serious ischemic (IHD) events



Results for the active-controlled short-term studies showed no difference in treatment effects in subgroups defined by ACE inhibitor use; also comparisons of RSG to MET or SU in ADOPT (Table 4.1.8) showed no interaction for this subgroup.

The comparisons in ADOPT and RECORD are of RSG to MET or to SU. The head-to-head active-controlled data in the short-term database was limited which is reflected in the very wide confidence intervals depicted in Figure 4.2.4. The estimates for ADOPT and RECORD are clearly quite similar with upper bounds for the 95% CI below 2. Note that RECORD was powered to rule-out an HR of 1.2 for the primary endpoint based on combining the groups; combining the groups, the overall interim adjudicated results for RECORD for the composite of CV death, MI or stroke was an HR of 0.97 with a 95% CI of 0.73 to 1.29 while for the primary endpoint the results were an HR of 1.08 with a 95% CI of 0.89 to 1.31.

Figure 4.2.4 Plot of odds/hazard ratios for the comparisons of RSG to MET or SU in ADOPT, RECORD and in the short-term studies (ICT) for the composite endpoint of CV death, MI or stroke and for serious IHD in the short-term studies.



5 Comparison of FDA meta-analysis to NEJM meta-analysis

While completing an FDA meta-analysis on GSK's pooled database of 42 short-term studies, a meta-analysis of RSG trials was published by Nissen and Wolski (henceforth referred to as N&W) in the NEJM 2007:356. There was a great deal of interest in the NEJM publication both in the press and in the US Congress. In this section, this reviewer will first briefly compare the GSK database of 42 studies to the database of N&W and secondly explain the reason for the difference between the cardiovascular death results reported by N&W for their 40 small studies (OR=2.4, p=0.02) and this reviewer's results for the 42 studies in the GSK database (OR=1.6, p=0.4).

5.1 Choice of studies

Though there are a total of 42 studies included in both the GSK pooled database used for the FDA meta-analysis and in the NEJM publication, the databases differed on 14 studies. N&W included ADOPT and DREAM in their analysis adding a total of about 9,600 patients. These two studies are long-term studies (median of 4 to 5 years) in patients newly diagnosed with diabetes (within 3 years for ADOPT) or in patients who are pre-diabetic (DREAM); all patients had not been previously treated with antidiabetic medications. These two trials are uniquely different from the trials in the GSK pooled database in size and duration and this reviewer thinks these trials are not suitable for combining with the short-term, small trials. Also due to the differing results for the treatment arms in DREAM and ADOPT, this reviewer thinks that combining the arms in the large studies as was done by N&W was inappropriate.

A total of 116 studies were screened by N&W and 48 were selected based on the following criteria:

- Randomized comparator group
- Similar duration of treatment in all groups
- More than 24 weeks of drug exposure

Six of the 48 studies were excluded because the trials "did not report any myocardial infarctions or deaths from cardiovascular causes and therefore were not included in the analysis because the effect measure could not be calculated." It is not clear whether zero events were reported for these studies or whether data was not available on the endpoints of interest. The wording seems to imply the former reason, however, the table of studies shown in the publication lists two studies with zero events for both MIs and deaths so perhaps the six studies were excluded for the latter reason. Looking at the outcome data when choosing studies to include in a meta-analysis would not generally be acceptable.

Three criteria used by GSK in the selection of studies and not used by N&W were the following:

- Double-blind
- Diabetic population
- Trials completed by 2005
- RSG doses of 4 and 8 mg daily (approved doses for diabetes)

Also since time-to-event data (patient-level data) were analyzed by GSK (and by FDA), non-IND studies without an available database were not included. The table on the next page (Table 5.1.1) shows the trials included in the N&W database and not in the GSK database; none of these trials met the criteria set by GSK.

Most of the trials in N&W's database are placebo-controlled trials (excluding ADOPT which is active-controlled) as are the studies in the GSK database. The trials where RSG is given in combination with another active diabetic drug were add-on trials where patients are treated with the active drug (MET, SU

or INS) during a run-in period and then randomized to either placebo or RSG add-on. So the comparison is rosiglitazone against placebo on a background of either MET, SU or INS. Table 5 of N&W's publication does not appear to reflect the design of the studies. For example, the entry for insulin seems to imply risk for rosiglitazone head-to-head with insulin when there were no trials of rosiglitazone head-to-head against insulin. Looking at the CV death results for metformin and sulfonylurea in Table 4 and then comparing those to the results for ADOPT, it is clear that the results for add-on trials were combined with head-to-head trials. The results in Table 4 may be misleading to some readers due to a poor description of the study data being used to create the estimates.

Table 5.1.1 Twelve studies included by N&W but not in the GSK database

Study #	Rosiglitazone Group Sample Size				Control Sample Size	Reason for exclusion	CV Deaths RSG/CTL
	RSG	RSG +MET	RSG+ SU	RSG +INS			
712753/008 48 wks		284			PLA+MET 135	Open Label	0/0
712753/009 24 wks				+MET 162	PLA+INS 160	Inadequate control	0/0
BRL049653 /080 148 wks	104				SU 99	Open label	0/0
BRL049653 /097 148 wks	122				SU 120	Open label	0/0
BRL049653 /125 26 wks			175		PLA+SU 173	Open Label	0/0
BRL049653 /128 24 wks			39		PLA+SU 38	Taiwan no database	0/0
BRL049653 /330 52 wks	2+mg 1181				PLA 382	Non-diabetics	1/0
BRL049653 /331 52 wks	2+mg 706				PLA 325	Non-diabetics	1/0
BRL049653 /185 32 wks	405	78			MET 158 PLA 64	Canada no database	0/0
454 (100684) 52 wks			43		PLA+SU 47	Korea no database Single blind	0/0
AVA100193 24 wks	2+mg 394				PLA 124	Alzheimer patients	1/0
AVM100264 52 wks		294			SU+MET 302	Did not meet cut-off date	2/1

5.2 Results

Since the databases for the FDA analysis and for the N&W analysis differ, a difference in results might be expected as well even if one only considers the results for the short-term, small studies. The myocardial infarction results reported for the small trials in Table 4 of the publication (OR of 1.45, $p=0.15$) are consistent with the results reported by the applicant (HR of 1.6) and by this reviewer (OR of 1.5, $p=0.11$ accompanied by a lack of homogeneity across the meta-groups). However, the CV death results reported for the small trials in Table 4 of the publication (OR of 2.4, CI of 1.17 to 4.91, $p=0.02$) show statistically significant results while the results produced by this reviewer (OR of 1.7, CI of 0.8 to 4, $p=0.2$) were not statistically significant.

N&W used the Peto method to compute odds ratios and confidence intervals. Trials with zeros in both arms are excluded from the analysis when using this approach as well as other approaches, such as the exact test used by this reviewer. In cases where only a few studies are excluded (as for MI where 4 studies were excluded), the impact is minimal but when about half the trials are excluded (as is the case for the CV mortality endpoint in both N&W's database and in the GSK database) there may be a greater impact on the results.

The latter point is illustrated with the database provided by GSK. This reviewer performed several analyses of the mortality data (both CV and all-cause; overall event rates less than 0.3%) and the results clearly show that the analytical approach can change non-significant results when including all the data ($p>0.3$) to borderline significant results when just considering those studies with at least one death (second row of table). The results for analyses using a continuity correction of 0.5 in each cell of those trials with zeros in either one arm or both arms are particularly striking with odds ratios close to one.

Table 3.1.2 Results for deaths – full GSK database

	CV death	All deaths
N&J results for their 40 small trials	2.4 (1.17, 4.91) $p=0.02$	not available
Fisher's exact test of pooled data	1.62 (0.7, 3.7) $p=0.3$	1.65 (0.8, 3.5) $p=0.2$
Exact test stratified on study Trials with zeros in both arms dropped	1.84 (0.7, 5) $p=0.16$ (20 studies)	1.80 (0.8, 4.3) $p=0.15$ (22 studies)
Mantel-Haenszel with continuity correction	1.04 (0.7, 1.7) $p>0.3$	1.1 (0.7, 1.7) $p>0.3$
Risk difference stratified on study MH fixed effects model	+0.1% (-0.1%, 0.4%) $p=0.4$	+0.1% (-0.1%, 0.4%) $p=0.3$

This reviewer thinks that these results demonstrate the problems with any meta-analytic technique when data is extremely sparse and suggest that performing additional analyses may be warranted under these circumstances.

Appendix 1 Trials Included in Analyses

Treatment groups were defined by the applicant based on randomized treatment and concomitant medication use; this table shows the treatment assignments used by the applicant; data for these individual studies is available in Appendix 4 of the FDA statistical review dated 6/4/07.

Trial	Treatment Group Sample Sizes										Total
	I+R	INS	M+R	MET	PLA	RSG	S+M+R	S+R	SU	S+M	
006	0	0	0	0	69	74	0	0	0	0	143
011	0	0	0	0	176	357	0	0	0	0	533
015	0	0	0	0	0	0	0	190	198	0	388
020	0	0	0	0	0	391	0	0	207	0	598
024	0	0	0	0	185	774	0	0	0	0	959
025	0	0	0	32	31	30	0	0	0	0	93
044	0	0	101	51	0	0	0	0	0	0	152
079	0	0	0	0	0	104	0	99	106	0	309
082	212	107	0	0	0	0	0	0	0	0	319
083	0	0	0	0	17	16	0	0	0	0	33
085	138	139	0	0	0	0	0	0	0	0	277
090	0	0	0	0	75	149	0	0	0	0	224
093	0	0	106	109	0	107	0	0	0	0	322
094	0	0	232	116	0	0	0	0	0	0	348
095	196	96	0	0	0	0	0	0	0	0	292
096	0	0	0	0	0	0	0	116	115	0	231
098	0	0	0	0	96	191	0	0	0	0	287
127	0	0	0	0	0	0	0	56	58	0	114
132	0	0	0	0	0	0	0	437	110	0	547
134	0	0	0	0	0	0	561	0	0	276	837
135	0	0	0	0	0	0	0	116	111	0	227
136	112	109	0	0	0	0	0	36	33	0	290
137	0	0	204	0	0	0	0	0	0	185	389
140	0	0	0	0	71	65	0	0	0	0	136
143	0	0	0	0	0	0	0	121	124	0	245
145	0	0	0	0	0	0	0	231	242	0	473
147	0	0	0	0	0	0	0	89	88	0	177
162	0	0	0	0	0	0	0	168	172	0	340

Appendix 1 Trials Included in Analyses

Treatment groups were defined by the applicant based on randomized treatment and concomitant medication use; this table shows the treatment assignments used by the applicant; data for these individual studies is available in Appendix 4 of the FDA statistical review dated 6/4/07.

Trial	Treatment Group Sample Sizes										Total
	I+R	INS	M+R	MET	PLA	RSG	S+M+R	S+R	SU	S+M	
211	0	0	4	12	19	17	22	67	59	24	224
234	0	0	0	0	0	0	0	116	58	0	174
282	0	0	70	0	0	0	0	0	0	75	145
284	0	0	382	384	0	0	0	0	0	0	766
311	0	0	43	7	7	15	0	0	0	0	72
325	0	0	0	0	0	0	0	196	195	0	391
334	0	0	35	27	38	45	0	19	30	0	194
347	209	212	0	0	0	0	0	0	0	0	421
352	0	0	7	7	8	4	14	6	5	10	61
369	0	0	0	0	0	25	0	0	24	0	49
712753/002	0	0	289	280	0	0	0	0	0	0	569
712753/003	0	0	254	272	0	0	0	0	0	0	526
712753/007	0	0	155	154	0	159	0	0	0	0	468
797620/004	0	0	0	0	0	230	0	442	222	0	894
Total	867	663	1882	1451	792	2753	597	2505	2157	570	14237

I+R=Insulin+Rosiglitazone

INS=Insulin

M+R=Metformin+Rosiglitazone

MET=Metformin

PLA=Placebo

RSG=Rosiglitazone

S+M+R= Sulfonylurea+Metformin+Rosiglitazone

S+R= Sulfonylurea+ Rosiglitazone

Su= Sulfonylurea

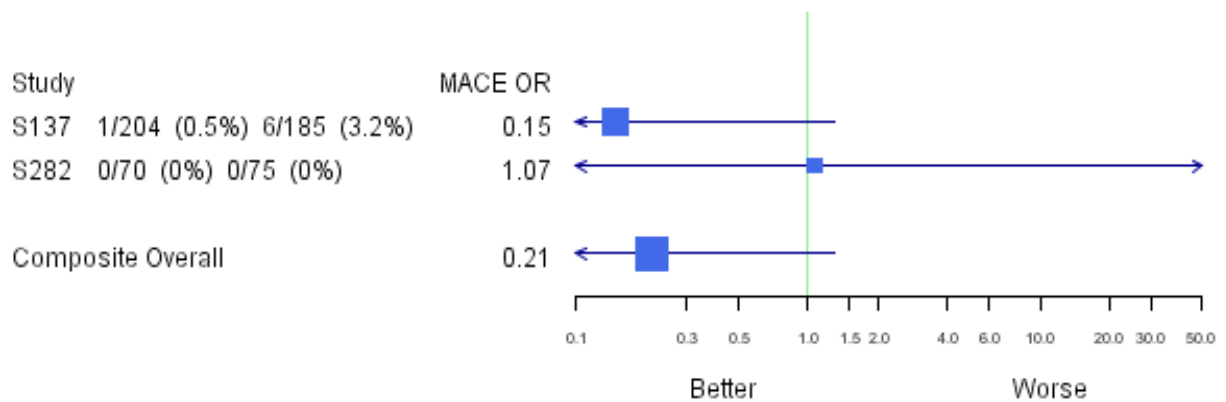
S+M= Sulfonylurea+Metformin

Studies 334, 712753/002, 712753/003, 712753/007 and 797620/004 were the 5 studies added to the original dataset to comprise the updated dataset.

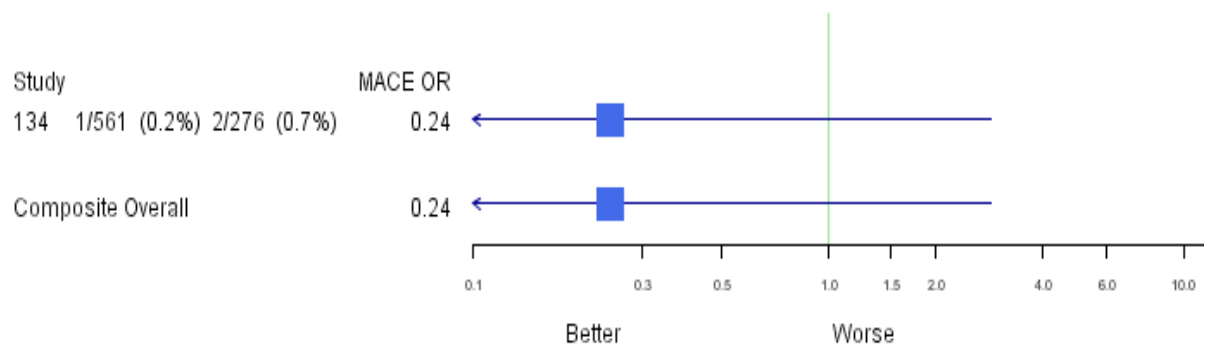
Appendix 2 Forest plots of composite endpoint by meta-groups

The ORs shown on the graphs are computed using a continuity correction (+0.5) for trials with zero events in either arm or both arms.

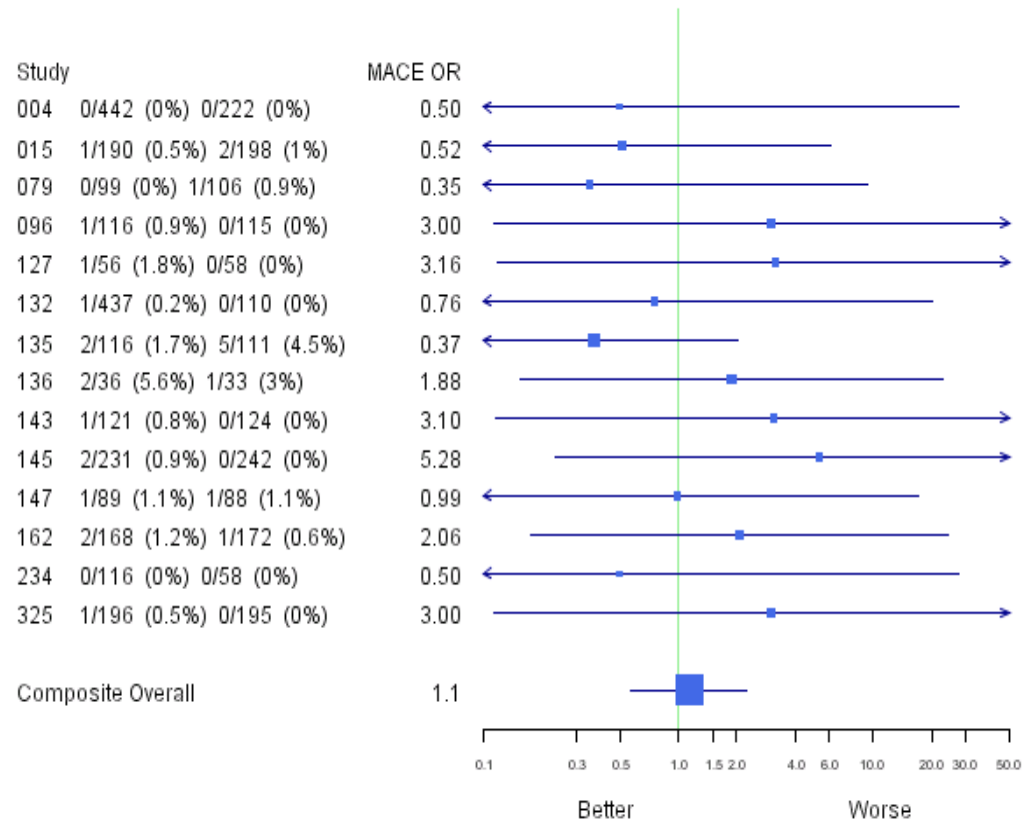
RSG+MET vs SU+MET



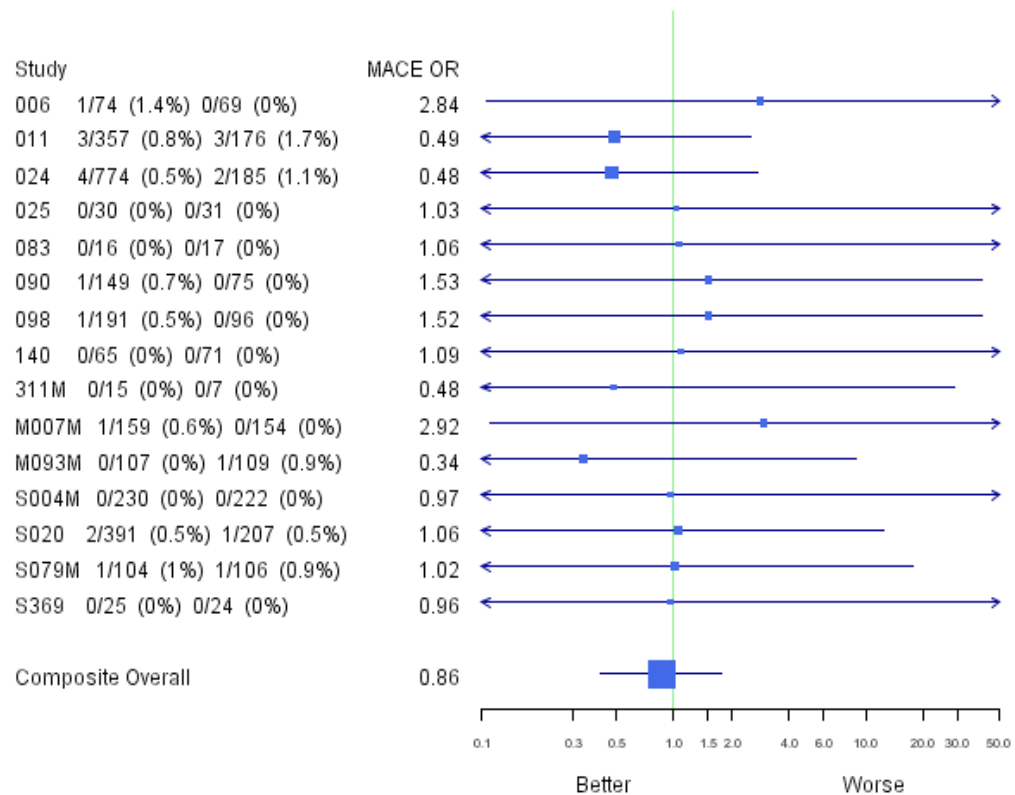
Triple therapy (RSG+MET+SU vs MET+SU) (axis upper limit reduced to 10)



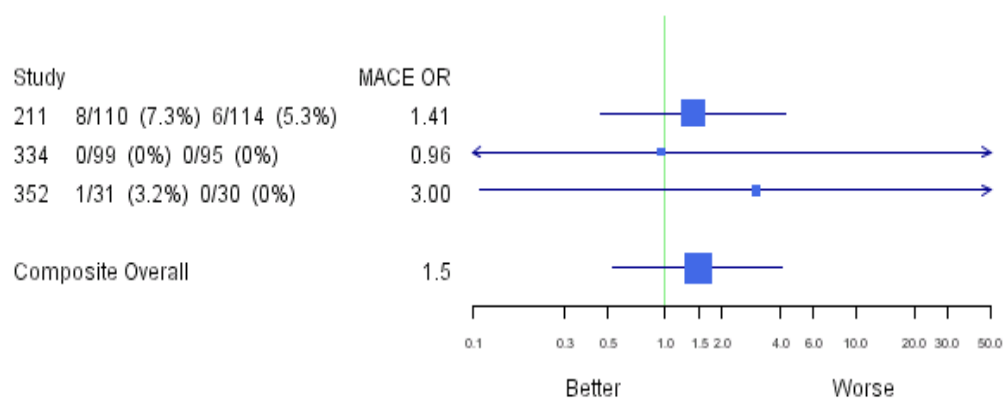
RSG+SU vs PLA+SU



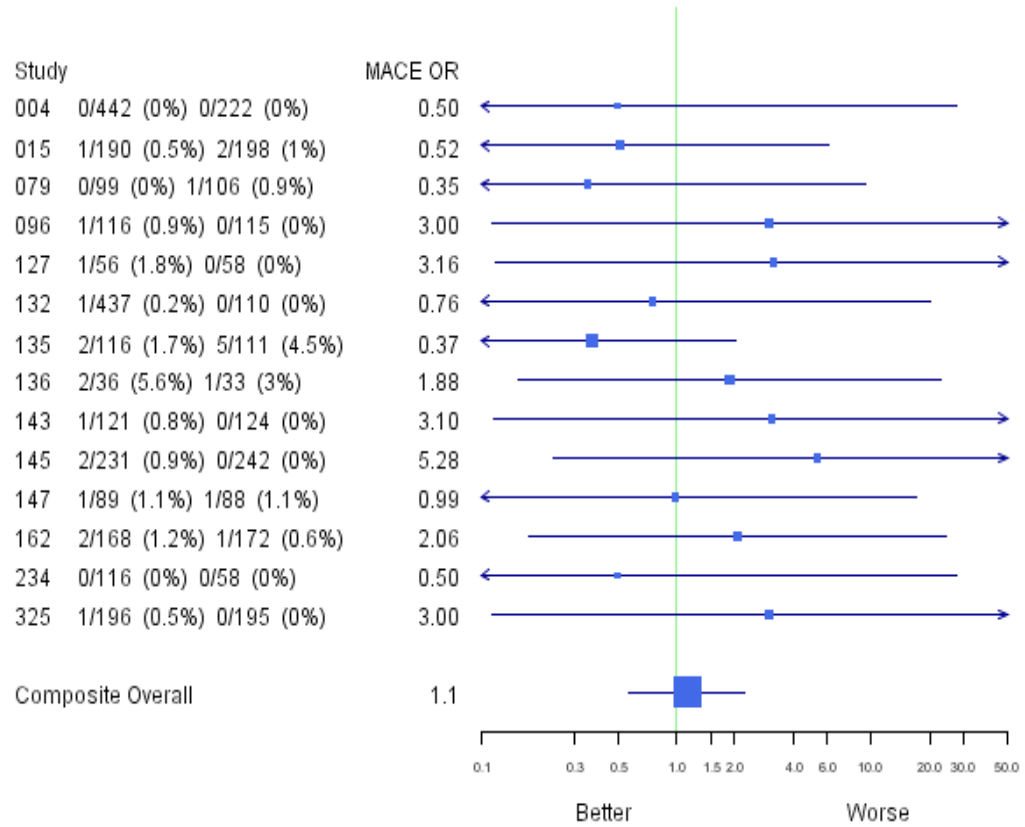
RSG Monotherapy vs placebo or MET (M) or SU (S)



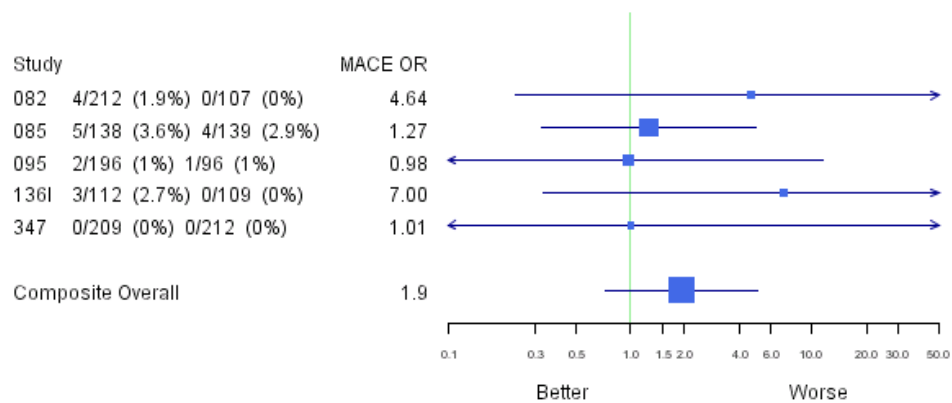
RSG+Background Medication vs PLA+ Background Medication (211-CHF pts & 352-CHD pts)



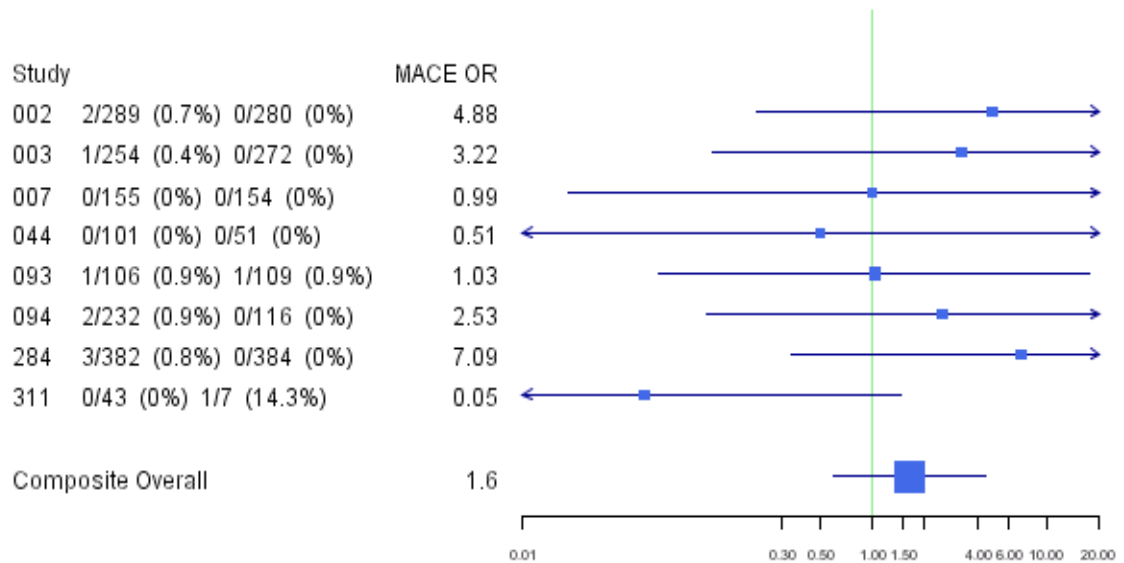
RSG+SU vs PLA+SU



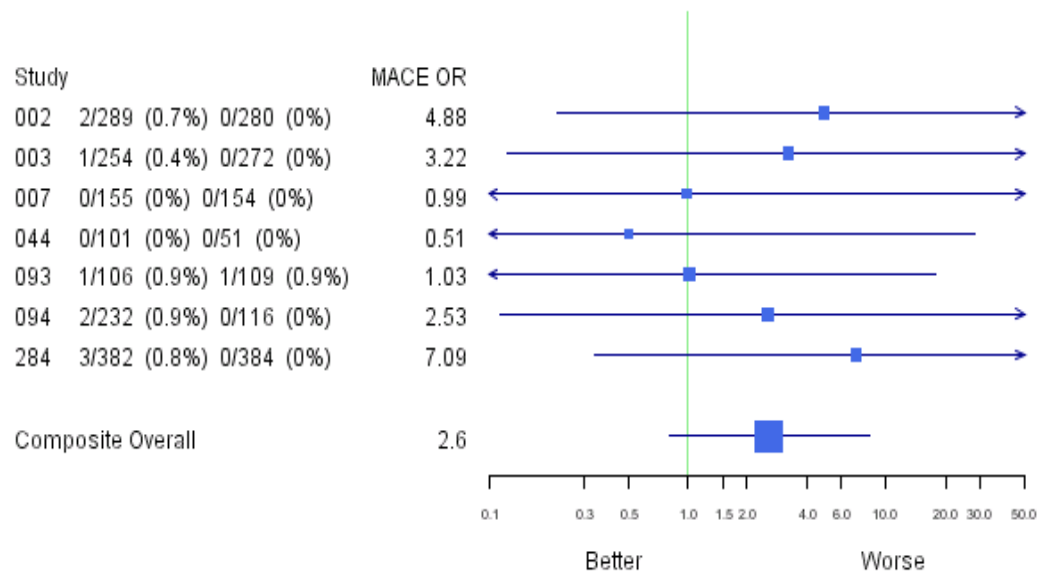
RSG+INS vs PLA+INS



RSG+MET vs PLA+MET



Given the size and duration of Study 311, this reviewer thinks the weight given to that study in the above analysis is too large with respect to the other larger and longer studies. Dropping Study 311 increases the OR estimate to 2.6 as shown below.



Appendix 3 Subgroup results for the 42 short-term studies

Table 3.3.12 extracted from statistical review dated 6/4/07.

All IHD events by subgroups for all trials and excluding the insulin trials

Baseline Characteristic	All Trials			Without Insulin Trials		
	N	OR (95% CI) weighted by study	exact p-value	N	OR (95% CI) weighted by study	exact p-value
Age						
<65	10,537	1.2 (0.9, 1.7)	0.25	9,458	1.2 (0.8, 1.7)	0.4
≥ 65	4,259	2.0 (1.3, 3.2)	0.002	3,808	1.9 (1.1, 3.1)	0.009
Males	8,787	1.4 (1, 2)	0.02	7,981	1.4 (1, 2)	0.04
Females	6,009	1.5 (0.9, 2.7)	0.09	5,285	1.3 (0.8, 2.4)	0.4
BMI						
≤30	7,378	1.2 (0.8, 1.8)	0.4	6,747	1.1 (0.8, 1.7)	0.6
>30	7,418	1.8 (1.2, 2.6)	0.003	6,519	1.8 (1.1, 2.7)	0.008
ACE I						
Y	5,126	1.8 (1.1, 2.8)	0.009	4,401	1.6 (1, 2.6)	0.04
N	9,670	1.3 (0.9, 1.8)	0.18	8,865	1.2 (0.8, 1.8)	0.3
Loop Diuretic						
Y	770	3.7 (1.5, 11)	0.003	599	2.8 (0.99, 9.5)	0.04
N	14,026	1.3 (0.98, 1.7)	0.06	12,667	1.3 (0.97, 1.8)	0.08
Nitrates						
Y	617	2.9 (1.4, 5.9)	0.002	523	3.1 (1.5, 6.8)	0.001
N	14,179	1.3 (0.9, 1.7)	0.14	12,743	1.2 (0.8, 1.6)	0.3
Hx of CHD						
Y	2,118	1.5 (1.0, 2.2)	0.03	1,834	1.5 (1, 2.3)	0.03
N	12,678	1.5 (0.98, 2.3)	0.06	11,432	1.3 (0.9, 2.1)	0.18
CHD+Nitrates						
Y	557	3.0 (1.5, 6.2)	0.001	474	3.3 (1.6, 7.3)	0.0006
N	14,239	1.3 (0.9, 1.7)	0.14	12,792	1.2 (0.8, 1.6)	0.3
Hx of CHF						
Y	450	3.2 (1.1, 10)	0.02	401	2.8 (0.98, 9.2)	0.04
N	14,346	1.3 (1, 1.8)	0.05	12,865	1.3 (0.9, 1.7)	0.12
Prev. Treated	11,448	1.6 (1.2, 2.1)	0.002	9,918	1.5 (1.1, 2.1)	0.01
Naive	3,348	0.97 (0.5, 1.9)	p>0.9	3,348	0.97 (0.5, 1.9)	p>0.9
# CV Meds						
≤ 2	11,109	1.3 (0.9, 1.8)	0.2	10,090	1.2 (0.8, 1.8)	0.3
> 2	3,687	1.7 (1.1, 2.7)	0.007	3,176	1.6 (1, 2.5)	0.03
Major CV risk Condition						
0	11,702	1.5 (0.98, 2.4)	0.06	10,603	1.4 (0.9, 2.2)	0.2
1	2,319	1.4 (0.9, 2.1)	0.15	2,020	1.4 (0.9, 2.3)	0.15
≥ 2	775	1.7 (0.9, 3.4)	0.09	643	1.7 (0.8, 3.5)	0.2

Appendix 4 Patient characteristics by meta-group

	RSG monotherapy (n=4236)	RSG+BM			RSG+SU		RSG+MET (n=3469)	RSG+INS (n=1530)	TRIPLE (n=837)
		211 (n=224)	334 (n=194)	352 (n=61)	All w/o 135 (n=4018)	135 (n=227)			
<u>Age</u>									
Mean (SD)	58 (10)	64 (9)	67 (7)	64 (7)	58 (10)	68 (6)	57 (10)	58 (9)	56 (9)
Range	33-78	42-78	35-78	48-77	33-78	59-78	33-78	33-78	33-78
<u>Gender</u>									
% males	63%	81%	56%	74%	57%	73%	57%	53%	60%
<u>BMI</u>									
Mean (SD)	30 (5)	29 (4)	29 (5)	30 (4)	30 (5)	31 (5)	32 (6)	32 (5)	33 (6)
%>30	48%	34%	40%	49%	41%	48%	58%	59%	63%
%>40	3%	0%	4%	2%	5%	4%	10%	9%	13%
<u>Dur Diab (yrs)</u>									
Mean (SD)	5 (6)	6 (6)	4 (4)	8 (7)	7 (6)	7 (6)	6 (5)	13 (8)	8 (6)
<u>Trt Exp (mos)</u>									
Mean (SD)	5.4 (3)	10.3 (4)	10.7 (4)	3.6 (1)	5.4 (2)	20.1 (7)	5.7 (2)	5.3 (2)	5.6 (1)
<u>CV Meds</u>									
0	42%	0%	25%	2%	42%	22%	33%	26%	28%
1	24%	0.5%	28%	15%	22%	21%	23%	21%	24%
2	16%	4%	18%	16%	16%	19%	18%	20%	20%
>2	18%	95.5%	29%	67%	20%	38%	26%	33%	28%
<u>CV Major Risk Cond</u>									
0	83%	0%	75%	0%	82%	60%	83%	72%	79%
1	14%	31%	24%	95%	15%	29%	13%	20%	15%
≥2	3%	69%	1%	5%	3%	11%	4%	9%	6%
Hx CHF	1%	100%	2%	0%	1%	5%	2%	3%	1%
Hx CHD	11%	67%	15%	100%	13%	29%	11%	19%	16%
Prev trt diab	60%	83%	53%	80%	98%	100%	78%	100%	100%
<u>Baseline meds</u>									
Nitrates	3%	30%	6%	48%	4%	10%	2%	6%	3%
Statin	13%	43%	32%	48%	15%	31%	25%	26%	28%
Loop diuretic	3%	60%	8%	5%	3%	7%	3%	11%	6%
Alpha blocker	3%	2%	2%	3%	4%	5%	4%	5%	3%
Beta blocker	12%	70%	28%	59%	13%	20%	15%	12%	13%
CCB	14%	10%	14%	23%	15%	22%	15%	19%	14%
ACE inhibitor	25%	98%	30%	52%	28%	41%	43%	47%	41%
<u>HbA1c</u>									
Mean (SD)	8.5 (1)	8 (1)	7 (1)	7 (1)	9 (1)	8 (1)	8 (1)	9 (1)	9 (1)
<u>HDL</u>									
Mean (SD)	45 (11)	42 (11)	47 (12)	43(11)	46 (12)	44(11)	47 (12)	48 (13)	50 (13)
<u>LDL</u>									
Mean (SD)	131 (36)	113 (32)	120 (32)	97 (25)	125 (34)	113 (30)	117 (33)	122 (34)	112 (33)
<u>HCT</u>									
Mean (SD)	44 (4)	43 (4)	41 (3)	42 (3)	43 (4)	43 (4)	42 (4)	42 (4)	42 (6)
<u>DBP</u>									
Mean (SD)	81 (9)	78 (8)	82 (8)	85 (8)	81 (9)	78 (9)	80 (8)	79 (9)	80 (8)

Appendix 5 DREAM results

This table was created by John Lawrence, PhD, a statistical reviewer in the CDER Division of Biometrics 1.

Event	Placebo N=1321 Rate ¹	RSG N=1325 Rate	OR ² 95% CI p-value	RAM N=1313 Rate	RSG+RAM N=1310 Rate	OR ³ 95% CI p-value	OR ⁴ 95% CI p-value
Any CV Event	33 (2.5%) 0.78	33 (2.5%) 0.77	1.00 (0.59, 1.68) 1	24 (1.8%) 0.56	45 (3.4%) 1.07	1.91 (1.13, 3.30) 0.01	1.38 (0.96, 1.98) 0.08
MACE	14 (1.1%) 0.33	15 (1.1%) 0.35	1.07 (0.48, 2.40) 1	9 (0.7%) 0.21	18 (1.4%) 0.43	2.02 (0.86, 5.12) 0.09	1.44 (0.82, 2.58) 0.23
CV Death	5 (0.4%) 0.12	5 (0.4%) 0.12	1.00 (0.23, 4.34) 1	5 (0.4%) 0.12	7 (0.5%) 0.17	1.41 (0.38, 5.63) 0.58	1.20 (0.47, 3.11) 0.83
MI	6 (0.5%) 0.14	5 (0.4%) 0.12	0.83 (0.20, 3.27) 0.77	3 (0.2%) 0.07	11 (0.8%) 0.26	3.70 (0.97, 20.7) 0.03	1.78 (0.74, 4.58) 0.23
Stroke	3 (0.2%) 0.07	5 (0.4%) 0.12	1.66 (0.32, 10.7) 0.73	2 (0.2%) 0.05	2 (0.2%) 0.05	1.00 (0.07, 13.8) 1	1.40 (0.38, 5.60) 0.77
CHF	1 (0.1%) 0.02	3 (0.2%) 0.07	2.99 (0.24, 157) 0.6247	1 (0.1%) 0.02	11 (0.8%) 0.26	11.1 (1.61, 477) 0.003	7.03 (1.61, 64) 0.004

¹ number of events per 100 patient years

² Conditional MLE of odds ratio, Fisher exact test p-value for RSG vs. Placebo

³ Comparison of RSG+RAM vs. RAM

⁴ Comparison of {RSG plus RSG+RAM} vs. {Placebo plus RAM}

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7/3/2007 02:13:43 PM
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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

CLINICAL STUDIES

NDA/Serial Number: NDA 21-071/S-022

Drug Name: Avandia (rosiglitazone)

Indication(s): Treatment of Type 2 diabetes

Applicant: GSK

Date(s): Submitted 8/4/2006; UFGD 6/4/2007

Review Priority: Standard

Biometrics Division: Division of Biometrics 2 (HFD-715)

Statistical Reviewer: Joy Mele, M.S.

Concurring Reviewers: Todd Sahlroot, Ph.D.
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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

Rosiglitazone, a thiazolidinedione (TZD), was approved in 1999 for the treatment of Type 2 diabetes. To determine if fluid retention leads to more serious conditions, GlaxoSmithKline (GSK) has performed an analysis of clinical trial data which examines the association between the use of rosiglitazone and the incidence of congestive heart failure (CHF) and myocardial ischemia (IHD). The clinical trial pooled data consists of 42 studies of rosiglitazone administered as monotherapy and in combination with sulfonylureas, metformin and insulin.

The applicant retrospectively identified adverse events that were defined as congestive heart failure events or as myocardial ischemic events. All events were defined through a blinded review of trial documentation, including narratives, by a panel of physicians. This approach to identifying events allowed for some consistency across studies not possible in meta-analyses where data is extracted from published reports.

This review presents both the applicant's results and this reviewer's meta-analyses. Both the applicant and this reviewer defined groups of patients or studies to analyze in order to try to assess risk in somewhat homogeneous groups. The applicant's methods are described in Section 3.2. For this reviewer's analysis, study was considered as a unit so analyses were performed stratifying on study within groups of studies of similar design; these groups were called meta-groups. This reviewer's approach allows one to recognize the heterogeneity amongst the studies and the contribution of the individual studies and of the meta-groups to the overall estimates.

Both this reviewer's and the applicant's analyses produced statistically significant overall estimates of risk of about 1.3 to 1.4 for both total (non-serious plus serious) myocardial ischemic events and serious myocardial ischemic events.

Given the heterogeneity of the study designs and populations, an overall estimate may not be sufficient for describing the risk of myocardial ischemia. The following inconsistencies in the risk of ischemia due to rosiglitazone were seen:

- The results for the placebo-controlled studies in the metformin plus rosiglitazone meta-group yielded an OR of 3.2 (95% CI of 1.2 to 10). Interpretation of this group is complicated by the fact that the designs varied including both combination trials of Avandamet and add-on trials. Patient characteristics also varied across the trials. The Avandamet studies showed the highest risk of ischemia due to rosiglitazone with a statistically significant OR of about 5, the highest seen from any of this reviewer's analysis. The results of RECORD (see Appendix 5 for a description of the long-term rosiglitazone trials not reviewed here) will directly address concerns related to the combination of metformin plus rosiglitazone.
- A doubling of risk due to rosiglitazone added to insulin was seen consistently across all endpoints, in a relatively small insulin population (about 11% of the database) of short-term studies. Given the history of combination use of rosiglitazone plus insulin (original FDA submission not approved and originally contraindicated in Europe) and the fact that this combination use is not addressed in the three long-term studies of rosiglitazone (DREAM, ADOPT and RECORD), the indication for use with insulin should be carefully re-assessed. Exclusion of the insulin trials (11% of the database) results in an overall estimate of 1.3 ($p=0.06$).
- Head-to-head comparisons of rosiglitazone to metformin or sulfonylurea were limited in the

pooled database; there were no head-to-head comparisons to insulin. Most of the trials were placebo-controlled trials of either rosiglitazone monotherapy against placebo or rosiglitazone add-on to run-in metformin, sulfonylurea or insulin against run-in therapy plus placebo. This reviewer's analyses of placebo-controlled trials and active-controlled trials yielded odds ratios of 1.6 ($p=0.02$) and 0.8 ($p=0.8$), respectively. The estimate of 1.6 is primarily driven by the rosiglitazone plus metformin trials; the monotherapy placebo-controlled studies yielded a non-significant OR of 1.2 (CI of 0.6 to 2.8). The estimate for the active-controlled comparisons is not precise and suggests that further data is needed to ascertain whether rosiglitazone head-to-head against metformin or sulfonylurea shows comparable results. Long-term studies, ADOPT and RECORD are both active-controlled and may provide sufficient data to determine if rosiglitazone is comparable to available alternative diabetes treatments.

- The results for naïve patients (3,687 patients, see Tables 3.3.1 and 3.3.12) suggest no increased risk with rosiglitazone (OR of about 1), but the confidence intervals are wide indicating a great deal of uncertainty with the estimates. The ADOPT and DREAM results may be helpful in establishing the risk in naïve, low-risk patients.
- Inconsistencies were seen across subgroups (see Table 3.3.12). The results from the long-term studies may be useful for establishing the risk in these subgroups; however, the data from ADOPT and DREAM may be of limited use since the patients may be predominantly low risk patients. This reviewer is concerned that patients like those shown to be particularly at high risk may be in the RECORD study. The addition of CV medications to rosiglitazone may put patients at high risk of an ischemic event. Consideration should be given to looking at the already collected data to see if the increased risk is seen in RECORD in the subgroups defined as high-risk. (Note that the applicant has also identified nitrate users and patients with a history of CHD as high risk populations.)

Additional areas to be covered in an addendum to this review include:

- Analysis of ischemic events in ADOPT, DREAM and RECORD as data is available
 - Analyses of subgroups identified in the analyses of the pooled database
- Examination of early ischemic events in the short-term and long-term studies
- Relationship of weight gain to cardiovascular outcomes
- Critique of the meta-analysis by Nissen and Wolski presented in the NEJM 2007:356
 - Comparison of methods and studies used
 - Risk difference analysis of CV deaths

Introduction

2.1 Overview

Rosiglitazone (RSG), a thiazolidinedione (TZD), was approved in 1999 for the treatment of Type 2 diabetes. Two safety issues noted at the time of approval were dose-related increases in lipids and decreases in hematocrit and hemoglobin. The latter is related to fluid retention seen with TZDs. To determine if this fluid retention leads to more serious conditions, GlaxoSmithKline (GSK) has performed an analysis of clinical trial data which examines the association between the use of rosiglitazone and the incidence of congestive heart failure (CHF) and myocardial ischemia (IHD) and proposed some labeling changes based on their conclusion that the incidence of CHF and IHD were low.

2.2 Data Sources

The database submitted by the applicant was composed of double-blind controlled (placebo or active controls) clinical trials using daily doses of 4 mg or 8 mg of rosiglitazone to treat patients with Type 2 diabetes. Most of the trials have been previously individually reviewed by FDA. Data from open-label extension studies were not included in the database. Initially the applicant performed analyses of a database composed of all trials completed prior to 9/30/2004 (37 trials with 11,586 patients); the results of these analyses were presented to FDA in March of 2006 and the database was requested from the applicant. The database was then updated to include all trials completed prior to 8/2005 and previously included in an FDA submission; this updated database includes 2,651 additional patients in 5 studies (a total of 14,237 patients in 42 studies). Studies without control data were not included in the database. This review focuses only on the updated database. See Appendix 1 for a listing of the trials; the treatment groups are listed as used in the applicant's analysis.

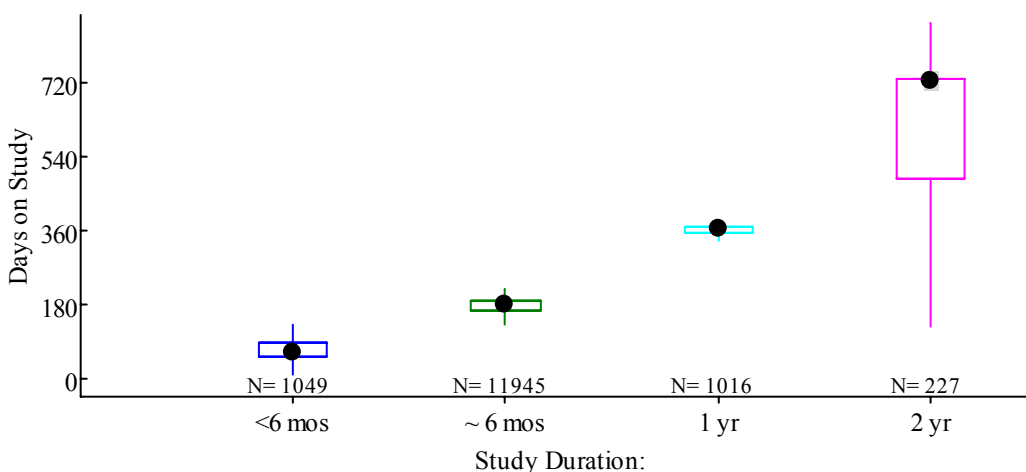
In the 42 studies included in the applicant's database, rosiglitazone was administered as monotherapy, combination therapy or as add-on therapy at the approved doses of 4 mg and 8 mg daily (either once a day or in divided doses, Table 2.2.1). For the add-on trials, patients were treated with metformin, sulfonylurea or insulin during a run-in period of usually 4 or 8 weeks and then randomized to rosiglitazone or placebo. For the combination trials, patients were randomized to a fixed dose combination (Avandamet or Avandaryl).

Table 2.2.1 Overview of Types of Trials in Rosiglitazone database.

	Study Numbers		
	Rosi 4 mg	Rosi 8 mg	Rosi 4 and 8 mg
Monotherapy Trials			
Rosi	6	25, 83 and 140	11, 20, 24, 90, 98, 311
Add-on/Combination Trials			
Rosi+Met		93	44, 94, 134
Rosi+SU	15, 79, 96, 325	127, 132, 143, 145, 147, 162	234
Rosi+Ins	347		82, 95
Rosi+Met+SU			134
Titration Trials			
Monotherapy	NA	NA	369, 211, 334, 352
Rosi+SU	NA	NA	797620/004, 135
Rosi+Met	NA	NA	712753/002, 003 and 007, 137, 282, 284
Rosi+Ins	NA	NA	85, 136

A total of 30 studies were 6 months in duration, 8 studies (7 monotherapy) were less than 6 months and 4 studies (studies 135, 20, 211 and 334) were a year or more. With the exception of the 2-year study (Study 135), dropouts were not a major issue in these studies with the majority of the patients completing the study. Figure 2.2.1 shows boxplots for duration of time on study by type of study and Appendix 2 shows boxplots for duration of exposure by each study.

Figure 2.2.1 Boxplots of time on study by duration of study



The types of adverse events included in the database were myocardial ischemic events (serious + non-serious IHD and serious only IHD) and congestive heart failure events (serious + non-serious CHF and serious only CHF). The applicant retrospectively identified adverse events that were defined through a blinded review of trial documentation, including narratives, by a panel of physicians. This approach to identifying events allowed for consistency across studies not possible in meta-analyses where data is extracted from published reports. Only one type of event was recorded for each patient so, for example, patients experiencing more than one serious myocardial ischemic event would only have the data for the first event recorded in the database. The FDA medical reviewers did not see this as a major issue (see the reviews of the FDA clinical reviewers for more detail regarding the process for defining events). Since most of the trials were of 6 months duration, it was decided that an analysis of first events would be adequate to ascertain risk. However, one potential problem with this approach is that it may be more difficult to examine associations based on time between outcomes such as edema or weight gain and the risk of an event.

2.3 Review Method

The applicant has presented the results from an analysis that could be interpreted as a pooled analysis since both the assignment of patients to a comparison group and the applicant's analysis model do not consider study as a unit. Patients are assigned to a comparison group based on treatment exposure (both randomized and background) not on study, though in some cases (e.g. insulin studies) there is no distinction between the two. (See page 8 for a listing of the applicant's seven comparisons.) The applicant's results have been reviewed by two FDA medical reviewers, Kate Gelperin, M.D. in the Division of Drug Risk Evaluation and Karen Mahoney, M.D. in the Division of Metabolic and Endocrine Products and so this reviewer will briefly summarize the applicant's methods and results.

The primary goal of this review, then, is not to perform a detailed critique of the applicant's methods but rather to present the results of alternative meta-analyses based on principles generally applied to these types of analyses. In this reviewer's approach, studies were combined based on similarity of design. In contrast to the applicant's analysis, this reviewer's approach utilizes the study as the unit of assessment by selecting two treatment arms within each study thereby preserving the randomization.

The FDA review team primarily focuses on the myocardial ischemic events because congestive heart failure is a known risk for the class of TZDs. This reviewer, likewise, focuses on myocardial ischemia (referred to as IHD in the review) and will only briefly summarize the applicant's results for congestive heart failure (referred to as CHF in the review). Because events were retrospectively defined and there was a potential for misclassification of events, this reviewer defined a new outcome variable as IHD/CHF where a patient with either a CHF event or IHD event would be counted as having an event.

More details regarding the applicant's methods and this reviewer's methods are provided in Sections 3.2 and 3.3, respectively.

3. Statistical Evaluation

3.1 Patient characteristics of the overall updated database

Patient baseline characteristics are summarized here across the database and by study and groups of studies. Characteristics by study are mentioned for those studies where the population is unique from the overall population. The groups of studies are those defined by the analysis unit (or meta-group) used in this reviewer's meta-analyses; the baseline characteristics for those groups are shown in a table in Appendix 3.

Characteristics summarized in Appendix 3 were chosen for presentation either because they help to define the different meta-groups (i.e. reflect the design of the studies within the meta-group) or they were found to be prognostic variables or related to prognostic variables identified through analyses by this reviewer or by the applicant.

Most patients in the database were between the ages of 50 and 66; about 29% were 65 years or older. Four studies had an average age of about 65 years; Study 135 (a 2-year study with an entry criterion of 60 or older, Study 211 (a study of patients with an history of CHF), Study 352 (a study of patients with an history of CHD) and Study 334. With the exception of Studies 135, 211 and 352 where more men than women were enrolled, the database was well-balanced for gender. The races were not sufficiently represented in the database to assess effects within racial groups; the majority of patients were Caucasian.

The median BMI for the database was about 30 kg/cm²; the highest proportion of overweight patients was seen in the studies of rosiglitazone plus metformin, rosiglitazone plus insulin and rosiglitazone plus metformin and sulfonylurea (See Appendix 3).

Median time since diagnosis of diabetes ranged from 5-7 years in most trials, with the exception being the insulin trials where the median was about 12-13 years. Median screening HbA1c varied considerably from study to study from a low of about 6.5 (Study 311) to about 10 (Study 44).

Baseline major cardiovascular risk was measured on a scale of 0 to 4 based on whether the patient had one or more of the following major risk factors: heart disease (CHD), cerebrovascular disease (CVD),

peripheral vascular disease (PVD) and congestive heart failure (CHF). A second variable (not presented in the table in Appendix 3) measured risk on a scale of 0 to 5 based on whether the patient had one or more of the following “minor” risk factors: dyslipidemia, hypertension, left ventricular hypertrophy, microvascular conditions and other conditions such as valve disorders, etc. Note that smoking and edema were not included as risk factors. Baseline medication use was also considered as a risk factor. The majority of patients in these studies presented with no major CV risk factors (about 70-80% in most of the studies); the exceptions are studies 211 (with 69% of patients having 2 or more major risk factors) and 352 (with 95% of patients having 1 major risk factor and 5% having 2 or more). The applicant counted the number of CV medications patients were taking at screening. Again Studies 211 and 352 are unique in this database with the majority of the patients taking 2 or more CV medications at baseline. A breakdown by specific baseline medications (Appendix 3) again shows the greatest use in Studies 211 and 352 as would be expected. Nitrate use (a risk factor identified by the applicant) was associated with multiple drug use with 87% of the nitrate users taking 3 or more CV medications at baseline. Patients treated with sulfonylureas are generally a lower CV risk population due to the restricted use of sulfonylureas according to prescription guidelines. There is a clear relationship between the use of statins and baseline LDL levels, with mean levels elevated where statin use was low.

3.2 Applicant’s methods and results

Applicant’s Methods:

Comparisons performed by the applicant were not based on combining studies but instead individual patients were assigned to an analysis group based on either their randomized treatment or their randomized treatment plus their background treatment at any time on-therapy¹ and based on the comparators in their source study (Appendix 1). For example, patients who were randomized to rosiglitazone monotherapy in the sulfonylurea-controlled Study 20, are only included in Comparison 2 below.

The following 7 comparisons were performed:

1. RSG monotherapy (n=1737) vs. Placebo (PLA) (n=792)
2. RSG monotherapy (n=1127) vs. sulfonylurea (SU) monotherapy / Metformin (MET) monotherapy (n=1001)
3. SU+RSG (n=2505) vs. SU monotherapy (n=1926)
4. MET+RSG (n=1608) vs. MET monotherapy (n=1419)
5. MET+RSG (n=285) vs. MET+SU (294)
6. SU+ MET+RSG (n=597) vs. SU+MET (n=310)
7. Insulin (INS) (n=867) +RSG vs. INS monotherapy (n=663)

Six studies provided patients for more than 1 of the comparisons above; patients from Study 211 (a study of CHF NYHA Class I and II patients designed to examine changes in ejection fraction) and Study 352 (a study in subjects with stable CHD) were included in all comparisons except number 7. So the applicant’s analysis groups were not based on a pooling of studies though for some groups, such as Group 7, the difference was negligible.

In addition to studies being represented in more than one comparison, about 10% of the patients were counted in more than one comparison. Therefore an analysis combining the comparison groups would not

1 Patients in Studies 211, 334 and 352 were randomized to placebo or rosiglitazone add-on therapy; their previous therapy was continued (i.e. there was no washout period). For the applicant’s analysis patients from these studies were assigned to treatment groups based on their background therapy as well as their randomized therapy (see Appendix 2 for the treatment groups used by the applicant).

be appropriate.

Outcome measures included serious ischemic events, serious congestive heart failure events, all ischemic events and all congestive heart failure events; for a description of how events were identified, see the clinical reviews. The analysis of serious events was considered the primary analysis by the applicant because more complete information was available for these events

Analyses of each comparison were repeated under the following conditions:

- By dose and with doses combined
- Using a full logistic regression and an exact logistic regression
- Excluding the data from Studies 211 and 352
- Testing the interaction of treatment with major baseline risk factors

The exact logistic regression model included a term for duration of treatment and also a covariate for number of major CV risk factors. The applicant decided not to include a factor for study in the analysis model for two reasons: 1) simulations showed that inclusion of study as a random effect did not “improve the performance of the model” (Section 3.6.4 of the study report) and 2) due to the large number of studies and small number of events, the applicant thought it was not feasible to include study as a fixed effect.

The applicant planned several exploratory analyses including a recursive partitioning analysis which is a stepwise procedure to identify groups of patients at risk for a myocardial ischemic AE and a proportional hazards stepwise regression with time-dependent covariates to assess the relationship between changing hematocrit, weight, edema or blood pressure and the risk of an ischemic event. The latter model was only performed for the original dataset so the results are not presented here.

Estimates of odds ratios (OR) and confidence intervals (CI) were provided in the study report. This reviewer agrees with the applicant that given the small number of cases there is little difference between a relative risk and an odds ratio.

Some analyses were only conducted on the original dataset and not repeated on the updated dataset. The applicant stated that only “key” analyses were repeated on the updated dataset. This reviewer presents only the results based on the updated database.

Applicant’s Results:

Due to the small number of events, only the results of the exact logistic regression analyses are presented. Since two medical officers have reviewed this application and will be including results of the applicant’s analyses in their reviews, this statistical reviewer is presenting a brief summary of the applicant’s results of CHF and IHD events.

In Section 4.1.1.1 of the study report, the applicant provided tables of baseline demographic data for their 7 comparison groups. Generally the treatment groups within the comparison groups looked well-balanced; the only exception was for major baseline risk factors. There were 3 comparison groups where the control group had notably more patients with 2 or more risk factors than in the rosiglitazone group; RSG versus SU/MET, RSG+MET versus MET+SU and triple therapy versus SU+MET. These imbalances are of particular interest given that the analysis groups are not created from randomized groups; inclusion of a factor for number of baseline major risks in the model attempts to address this issue.

The applicant’s results, using exact logistic regression analysis with time as an offset variable and major

baseline risk factors as a covariate, for all four outcome variables (Table 3.2.1) show statistically significant treatment effects for the comparison of metformin plus rosiglitazone versus metformin plus placebo for all ischemic events with an odds ratio of 2.7. Borderline significant results are seen for the triple therapy comparison group for CHF only. The results of all other comparisons suggest no statistically significant increased risk due to rosiglitazone though all estimates of the odds ratios for ischemic events were 1 or greater. The upper bounds for the confidence intervals range from 1.5 to 150 so the data does not show that the risk of rosiglitazone is comparable to control (either placebo, sulfonylurea or metformin controls); instead the individual comparisons fail to provide definitive results.

Table 3.2.1 Applicant's results: Odds ratios (CI) from exact logistic regression analysis on the updated dataset

RSG group	Control group	ALL CHF	Serious CHF	ALL IHD	Serious IHD
RSG	PLA	0.5 (0.03, 6.4)	0.3 (0.01, 4.8)	1.2 (0.6, 2.5)	2.0 (0.7, 8.2)
RSG	MET or SU	0.4 (0.1, 1.5)	0.2 (0.01, 2.1)	1.1 (0.6, 2.1)	1.2 (0.5, 3.2)
MET+RSG	MET+PLA	0.7 (0.1, 4.1)	0.95 (0.01, 75)	2.7 (1.2, 7)	3.3 (0.9, 19)
MET+RSG	MET+SU	0.95 (0.1, 7.0)	0.6 (0, 8.3)	1.3 (0.3, 4.5)	1.0 (0.2, 4.5)
SU+RSG	SU+PLA	1.5 (0.8, 3.1)	1.0 (0.4, 2.9)	1.1 (0.7, 1.7)	1.1 (0.6, 2.1)
SU+MET+RSG	SU+MET	4.4 (0.98, 40)	3.2 (0.4, 150)	1.8 (0.6, 7.6)	1.3 (0.3, 7.6)
INS+RSG	INS+PLA	2.3 (0.9, 6..3)	1.6 (0.5, 6.0)	2.1 (0.9, 5.1)	2.3 (0.7, 9.8)

The applicant's recursive partitioning analysis showed that pre-existing CHD was a strong predictor of myocardial ischemia (regardless of treatment) and that patients with pre-existing CHD and taking nitrates at baseline were at highest risk of myocardial ischemia. These results are consistent with what is seen in the database when examining the results by study. Studies 352, 211 and 135 had the highest proportion of patients with pre-existing CHD; 100% of Study 352, 67% of Study 211 and 29% of Study 135 and the highest proportion of patients taking nitrates (see Appendix 3). These 3 studies also had the highest incidence rates of ischemic events; a 6-month incidence of about 15% in Study 352, 6% 1-year incidence in Study 211 and a 9% 2-year cumulative incidence in Study 135; the odds ratios for all IHD for these studies were 1.25, 1.9 and 1.2, respectively, based on the reviewer's analyses (more details on these results are provided in Section 3.3 of this review).

The recursive partitioning analysis does not consider treatment group as part of the analysis; it was merely intended to identify risk factors for myocardial ischemia (serious+non-serious). This analysis then does not examine the relationship between treatment and risk factors but instead factors which are generally prognostic. To compare treatments, the applicant identified three subgroups; no pre-existing CHD (total of 12,183 patients), pre-existing CHD without nitrates (1,508 patients) and pre-existing CHD with nitrates (546 patients). The hazard ratios for those groups, based on a Cox proportional hazards model (a time-to-event analysis unlike the analyses for the 7 comparisons listed above in Table 3.2.1), were 1.4 (CI 0.96, 2.1), 1.1 (CI 0.7, 1.7) and 2.1 (CI 1.2, 3.8), respectively; so only patients with an history of CHD and taking nitrates at screening were shown to have a statistically significant increase in risk of myocardial ischemia due to rosiglitazone treatment according to this analysis performed by the applicant.

In the same table with the subgroup results just described (Table 59 of the applicant's study report), the applicant reported an overall estimate of 1.31 with a 95% confidence interval of 1.01 to 1.70 with event rates of 1.99% (171/8604) for RSG and 1.5% (85/5633) for comparators. This estimate is reported in the applicant's proposed labeling and has been presented at a meeting with FDA as the overall estimate of risk for the pooled database. There is no discussion of the estimate in the study report and no information regarding the model that produced the estimate is provided. A query to the applicant revealed that a

proportional hazards model (a time to event model) of the pooled data with only treatment in the model was used. So although prognostic variables were identified in the recursive partitioning analysis, these variables were not included in the model of the overall data.

This reviewer checked the sponsor's overall estimate for serious+non-serious IHD and then ran additional models including nitrates or CHD as covariates, as well as the exact logistic regression model used by the applicant for the seven comparisons. Also this reviewer ran a model of serious ischemic events. The estimate computed by the applicant is smaller than any estimates produced by the models run by this reviewer but not notably different with estimates ranging from 1.32 to 1.41 (Table 3.2.2).

Table 3.2.2 Analyses of total ischemic events for the pooled database

Model	Covariates	HR (95% CI)	p-value
Proportional hazards (applicant's model)	None	1.31 (1.01, 1.70)	0.04
Exact logistic regression (applicant's model)	# of major risk factors time as offset variable	1.4 (1.1, 1.8)	0.01
Fisher's exact test		1.32 (1.02, 1.72)	0.04
CMH stratified on CHD		1.38 (1.1, 1.8)	0.02
Proportional hazards	nitrates	1.37 (1.1, 1.8)	0.02
Proportional hazards	nitrates, CHD hx	1.41 (1.1, 1.8)	0.01
Proportional hazards	ace inhibitor	1.32 (1.0, 1.7)	0.04
Proportional hazards on serious IHD		1.4 (0.96, 2.0)	0.08

The main problem with the above models is that the data is pooled and therefore the comparison is no longer of randomized groups.

The applicant examined the relationship of three on-study outcomes (hematocrit, weight and blood pressure) to ischemic events and depicted the data graphically in the study report by plotting means over time separately for patients with and without events. The applicant concluded that these outcomes were not "robust enough to guide changes in the clinical management of individual subjects" (page 127 of the study report) but that "slightly greater weight gain may have occurred within the first 3 months of initiating RSG in subjects with subsequent ischemic events" (page 141 of the study report). This reviewer did not find the graphs to be helpful in understanding the relationship between the three outcomes and ischemia. The graphs themselves are difficult to interpret for several reasons. For example, the data is plotted out to 110 weeks while most patients had exposure of only 26 weeks so the sample sizes change drastically over time. Also, means computed based on subsetting on an outcome variable often produce spurious results since the randomization is ignored. Some concern regarding the weight gain has been expressed by FDA medical reviewers so this reviewer will revisit this issue in an addendum to this review.

Overall the applicant concluded that the incidence of CHF and IHD was low and that the findings regarding increased risk of ischemic events in patients with CHD history and nitrate use should be assessed in an independent database. The applicant recommended labeling that is addressed in detail in both of the clinical reviews.

3.3 Reviewer's Methods and Results

Reviewer's Methods

As already mentioned, one problem with the applicant's overall approach was the pooling across studies of differing designs/patient populations and not treating study as a unit. The contribution of individual studies to the applicant's results could not be discerned so one of the goals in this reviewer's analysis is to show the contribution of individual trials to the overall results; this is relevant to understanding how risk may differ based on patient populations as well as due to randomized treatment.

Most trials had two rosiglitazone arms; 4 mg and 8 mg. So the first step in the analysis of the pooled dataset was to determine whether there was any evidence of dose response for rosiglitazone. A Cochran-Armitage trend test on any AE (CHF or IHD) and on any serious AE (CHF or IHD) yielded no significant results when looking at individual studies or with studies pooled. Only one study (Study 024, a 6-month monotherapy trial) showed a quantitative trend for serious AEs. Because there was no notable evidence of a dose response, this reviewer pooled rosiglitazone arms, as did the applicant.

Similar to the applicant's analysis, this reviewer named 6 groups as primary units of analysis. These groups are referred to as meta-groups and are defined as follows:

Meta-group	Control	Number of studies	Number of Patients
Monotherapy RSG	PLA or MET or SU	15	4,236
RSG+Background Medications	PLA	3	479
RSG+Sulfonylurea	PLA+SU	14	4,245
RSG+Metformin	PLA+MET or SU+MET	10	3,469
RSG+Insulin	PLA+INS	5	1,530
RSG+Metformin+Sulfonylurea	PLA+MET+SU	1	837

There were a few problems with assigning studies to a meta-group. Both placebo and active treatments were used as controls in these studies and, as will be seen in the results section, this sometimes led to an heterogeneous grouping.

In some studies, there was both a monotherapy arm (RSG) and a rosiglitazone combination arm (RSG+MET or RSG+SU). In order to count all RSG patients (and count each RSG patient once), the combination arm plus the control arm were included in the appropriate meta-group and the monotherapy arm and the same control arm were included in the monotherapy meta-group. This occurred for 4 studies (004, 007, 093, and 079). Two studies had MET arms with an IHD event rate of 1.1% and 2 had SU arms with an IHD event rate of 1.2%. In the overall analysis, studies were pooled within meta-groups and the analysis was stratified by meta-group so these control arms were essentially counted twice in the overall analysis. In analyses to examine covariates, these arms were not counted twice. Overall, one of the goals of the assignment of arms to meta-groups was to maintain the randomization that was used in each trial.; recall in the applicant's analytical models there was no term for study.

Another issue was how to deal with studies where patients remained on their previous diabetic therapy throughout the trial. These patients were randomized to RSG or PLA. In the applicant's analysis, these patients were included in the group that reflected both their randomized treatment and background treatment; this meant that patients from the same trial were used in many comparisons. To avoid this problem and because these trials were unique in other ways as well (unique patient populations and study duration greater than 6 months), this reviewer included the 3 relevant studies in a separate meta-group called RSG+Background Medications.

Forest plots created by this reviewer are presented throughout this review to visually depict the odds ratios and confidence intervals for individual studies. In these plots, the symbol for the OR is sized by the inverse variance (studies with more precise results are given more weight in the computation of the common odds ratio and a symbol proportional to the weight; generally the size of the symbol is related to the sample size of the trial). A log scale is used for the x-axis and a reference line is shown at 1. For trials with 0 events in one or both treatment groups, 0.5 is added to all 4 cells for that individual study in order to be able to compute an OR and to include the study in the graph. The ORs depicted in the graphs are computed using the Mantel-Haenszel test (R software was used to compute and graph the ORs and confidence intervals). Abbreviated names for several trials are used; for example, Study 712753/002 listed in Appendix 1 is referred to as 002 in the forest plots. A letter before the study number indicates the control for those trials not placebo-controlled; an M indicates metformin-controlled and an S indicates sulfonylurea-controlled. An M after the number indicates that the control group was used in the monotherapy analysis and in one other meta-group analysis

The primary analysis was an exact test of 2x2 contingency tables stratified on study (using StatXact via Proc Stratify in SAS). This test yields an exact p-value computed by considering all possible results and the tail probability of results more extreme than the observed results. Heterogeneity among studies was ascertained by Zelen's exact test with a p-value of 0.2 or less indicating possible heterogeneity. The odds ratios are conditional maximum likelihood estimates; a value greater than 1 indicates greater risk due to rosiglitazone. These results are shown in the tables. Usually the conditional maximum likelihood estimates were close to the Mantel-Haenszel common odds ratios shown in the figures; this is primarily due to the fact that there were only four small studies in the whole database with zero IHD events in both treatment groups that were excluded from the exact test computations. The confidence intervals shown are exact 95% confidence intervals. Usually the exact CI is more conservative than the mid-p corrected CI also produced by Proc Stratify but this reviewer found the differences to generally be not different or quite small. It should be noted that the graphs serve as a visual tool to illustrate the results across all the studies while the exact test results in the tables are the results presented for inferring harm or benefit.

A common risk difference was computed using both a random effects model (DerSimonian-Laird) and fixed effects model (Mantel-Haenszel method); these results generally did not differ in any appreciable way. Given that for most meta-groups, the results were homogenous across the trials, a fixed effects model would be appropriate and so only the fixed effects results for the common risk difference are shown. One of the advantages to using a risk difference is that all trials are included so trials with

The forest plots by meta-group depict the odds ratios for serious plus non-serious myocardial ischemic events (IHD) while the tables contain results for total IHD, serious IHD and IHD/CHF (where either an IHD event or CHF event was counted as an event to capture any CHF events that may have been misclassified). Not all endpoints are shown for every meta-group.

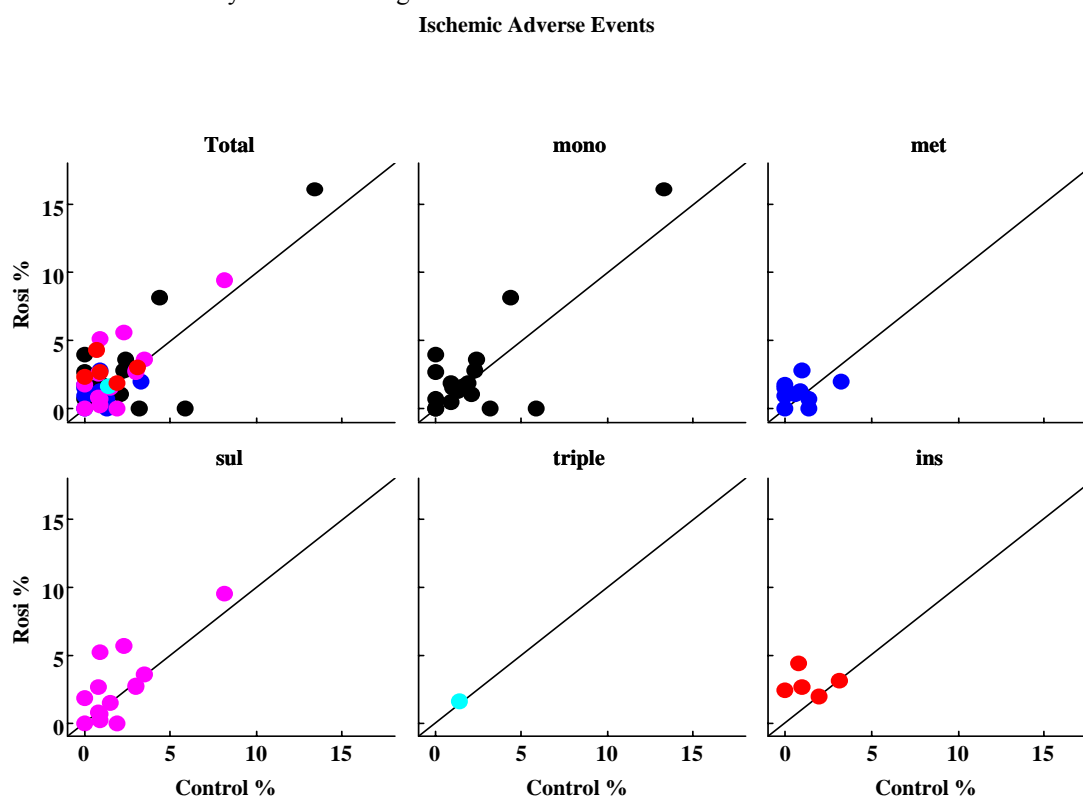
The format of the following sections is first a presentation of the results for each meta-group shown separately and then a discussion of overall results. Additional issues (such as subgroups) are covered last.

Reviewer's Results

The ischemic event rates in the individual studies range from zero to a high of 16% in the CHD study with most trials having rates of 1-2% in one or both treatment groups. A plot of ischemic event rates for the control group against the rosiglitazone group shows that the majority of studies had event rates less than 5% in both groups with a few notable exceptions (Figure 3.3.1 on the following page).

In Figure 3.3.1, the results for all studies are shown in the upper left corner and the results by meta-group are shown in the remaining 5 squares with the 3 studies of patients on background medications included with the monotherapy (mono) studies; values below the identity line favor rosiglitazone. Three studies particularly stand out as different; these are the 2 background medication studies that entered patients with CHD and CHF shown as outliers in the mono graph and the RSG+SU study (Study 135) which was a 2-year study in elderly patients shown in the sulphonylurea (sul) graph. It is clear in every meta-group that more symbols are above the identity line than below suggesting less favorable results for rosiglitazone. What is missing from this group of graphs is a measure of the sample size for each study and hence a means for inferring the contribution of each study to the overall assessment of risk; in the following sections of this review, forest plots where symbols sized to the contribution of a study to the overall estimate will address this issue.

Figure 3.3.1 Percent of patients with ischemic adverse events by study and treatment group graphed by meta-group. Values below the identity line favor rosiglitazone.



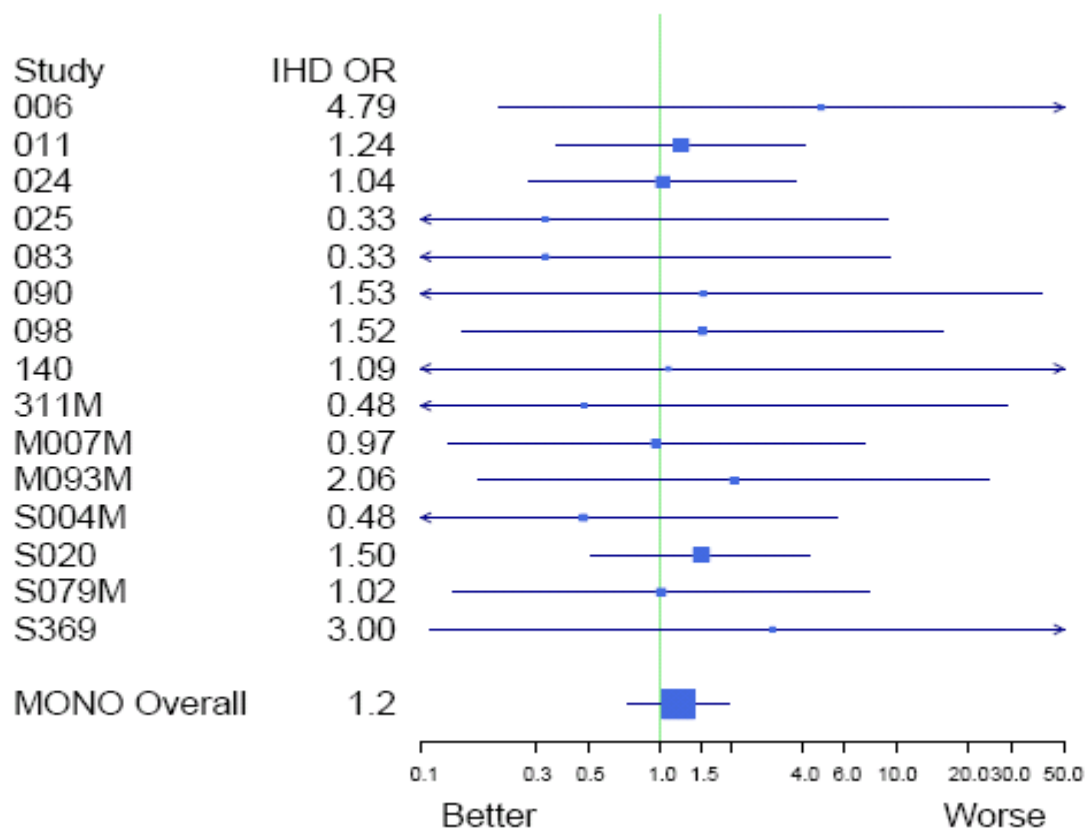
In the forest plots that follow, study numbers preceded by an S or an M were sulphonylurea-controlled or metformin-controlled, respectively. Odds ratios in the figures were computed using the Mantel-Haenszel method where 0.5 was added to each cell of a 2x2 table of outcomes for trials with no events in either or both arms. For some meta-groups, this led to a different common odds ratio estimate than the one computed using the unconditional maximum likelihood estimate shown in the accompanying table. So the plots are tools for illustrating results from all studies while the table results should be considered the source for the statistical evidence of benefit or harm. The source data (sample sizes and numbers of events) by study are provided in Appendix 4.

Monotherapy RSG vs. Placebo or Active Control

There were a total of 15 studies in the database where rosiglitazone was administered as monotherapy at a dose of either 4 mg or 8 mg given in a single daily dose or as divided doses. The control in 9 trials was placebo; in 2, metformin and in 4, sulfonylurea. Seven of the studies were less than 6 months in duration (median exposure of about 3 months) and seven were 6-month studies; one trial (S020) was a one year study (see Appendices 2 and 4 for trial lengths). The patient population of this meta-group comprises about 29% of the patients in the database. The two characteristics that single out this group are the percentage of naïve patients (40% compared to about 20% or less in most of the other groups, Appendix 3) and an average LDL at baseline of 130 mg/dL (~10+ mg/dl above the other groups).

The trials in the forest plot (Figure 3.3.2) are ordered by type of control and then by study number. With about half the studies having a median duration of about 3 months and some with sample sizes of less than 100 in a treatment group, many of the trials make a small contribution to the overall effect. The trials with the most weight were 011, 024 and S020. S020, a one year study against titrated glibenclamide (about half the patients were on a dose of 5mg or 2.5 mg, 17% of patients were at the highest allowed dose of 15 mg), had the highest event rate at 3.6% for rosiglitazone and 2.4% for glibenclamide yielding an OR of 1.5. A time to event analysis (log rank test) of Study 020 yielded a p-value of 0.4 (for a Kaplan-Meier curve, see Figure 3.3.16 on page 31).

Figure 3.3.2 Forest plot of odds ratios ($\pm 95\%$ CI) for IHD; Monotherapy RSG



Analysis of the monotherapy meta-group data yielded an overall IHD estimate of 1.25 and an overall estimate for serious IHD events of 1.51 with confidence intervals ranging from 0.7 to over 2 (Table 3.3.1) and $p>0.4$. The results by various groups of studies are consistent with these overall results.

About 40% of the patients in this meta-group were naïve to diabetes treatment, the highest percentage of all the meta-groups. Most of the trials were a mixture of naïve and previously treated patients; the exceptions were Studies M007M, S004M, and S369 which enrolled all naïve patients and Study M093M which enrolled all previously treated patients. Analyses of subgroups of naïve and previously treated patients suggests there may be a difference in risk (Table 3.3.1); this issue will be explored further later in the review.

Table 3.3.1 Results for monotherapy RSG; odds ratio and risk difference

	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All Trials				
OR	p=0.9	1.25	0.7, 2.2	p=0.5
Risk Difference				
Fixed effects model	p=0.9	+0.4%	-0.5%, +1.2%	p=0.5
Active-controlled trials	p=0.9	1.30	0.6, 2.9	p=0.6
Metformin-controlled	p>0.9	1.32	0.2, 9.1	p>0.9
Sulfonylurea-controlled	p=0.9	1.30	0.5, 3.3	p=0.7
Placebo-controlled trials	p=0.8	1.21	0.6, 2.8	p=0.8
<6 month duration	0.6	1.4	0.3, 8.8	p=0.7
6 months or greater duration	0.9	1.2	0.7, 2.3	p=0.5
Naïve, diet only	p=0.9	0.8	0.3, 2	p=0.7
Previously-treated	p=0.9	1.71	0.8, 3.6	p=0.15
Serious Ischemic events				
All Trials	p=0.9	1.51	0.7, 3.7	p=0.4

Overall this group of 15 monotherapy trials (a total of 2,687 patients treated with rosiglitazone monotherapy) does not provide conclusive evidence of ischemic risk with confidence intervals ranging from a low of 0.2 to a high of 9.1. The data does suggest that previously treated patients may be at higher risk due to rosiglitazone than naïve patients but further data is needed to support this observation.

RSG+Background diabetes therapy vs. PLA+Background diabetes therapy

For three studies in the database, patients who presented on diabetes medications were continued on these background medications and randomized treatment of rosiglitazone or placebo was added on. Study 211 was a one-year study in patients with CHF Class I/II. Study 334 was a one-year atherosclerosis study in patients without significant cardiovascular disorders. Study 352 is a 16-week study in patients with stable coronary heart disease.

The total number of events per randomized treatment group are shown in Appendix 3; the table below breaks down the events by randomized treatment plus background diabetes medication (this is the way the applicant analyzed the data). Most of the events in this group come from Study 211 where groups with sulfonylurea as part of background had the greatest number of patients and events.

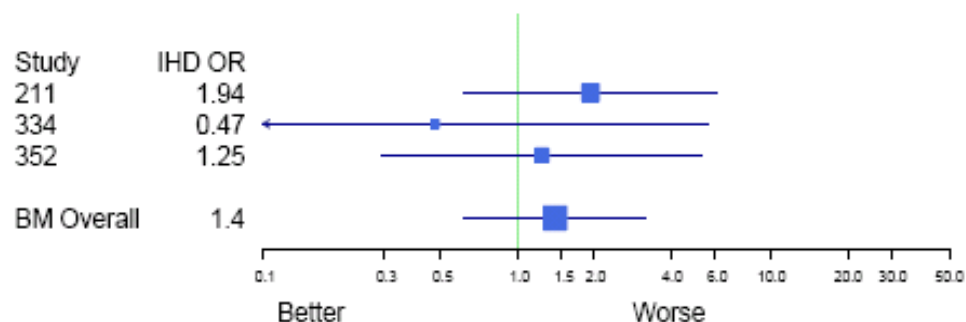
Table 3.3.2 Number of events by study and by randomized treatment + background medication
(S=Sulfonylurea M=Metformin)

Trial	RSG+M	PLA+M	PLA	RSG	RSG+S+M	RSG+S	PLA+S	PLA+S+M
211 N	4	12	19	17	22	67	59	24
IHD	1 (25%)	0	1 (5%)	1 (6%)	2 (9%)	5 (7%)	4 (7%)	0
Ser IHD	1 (25%)	0	0	1 (6%)	1 (5%)	3 (4%)	3 (5%)	0
334 N	35	27	38	45	NA	19	30	NA
IHD	0	0	0	1 (2%)		0	2 (7%)	
Ser IHD	0	0	0	1 (2%)		0	2 (7%)	
352 N	7	7	8	4	14	6	5	10
IHD	1 (14%)	2 (28%)	1 (13%)	1 (25%)	2 (14%)	1 (17%)	1 (20%)	0
Ser IHD	0	0	0	0	1 (7%)	0	0	0

The patient characteristics for patients in each of these trials varied considerably as can be seen from the table in Appendix 3. About half the patients in Study 334 were naïve patients while in Studies 211 and 352, about 20% were naïve. Also only 15% of patients in 334 had a history of CHD. Of all the trials in the database, nitrate use was highest in Studies 211 and 352, 30% and 48%, respectively, as would be expected in CHF and CHD populations. Other CV medication use was high also in these studies.

The forest plot shows that the results for Study 334 (a 1 year study) are inconsistent with the results for the other 2 studies with high risk populations although the results of the test for homogeneity do not statistically indicate a difference ($p=0.5$, Table 3.3.3).

Figure 3.3.3 Forest plot of odds ratios ($\pm 95\%$ CI) for IHD; RSG add-on to background therapy



A higher OR of 1.9 is seen for Study 211 than Study 352 (OR of 1.25) which might be unexpected given that Study 352 patients are patients with stable CHD while only 67% of patients in 211 had a history of CHD. However the length of the trials varied considerably with a mean exposure of about 10 months for Study 211 and mean exposure of about 3 months for Study 352.

The results for IHD/CHF (Table 3.3.3) suggest greater risk from rosiglitazone compared to placebo with borderline significant results; the rest of the results are inconclusive.

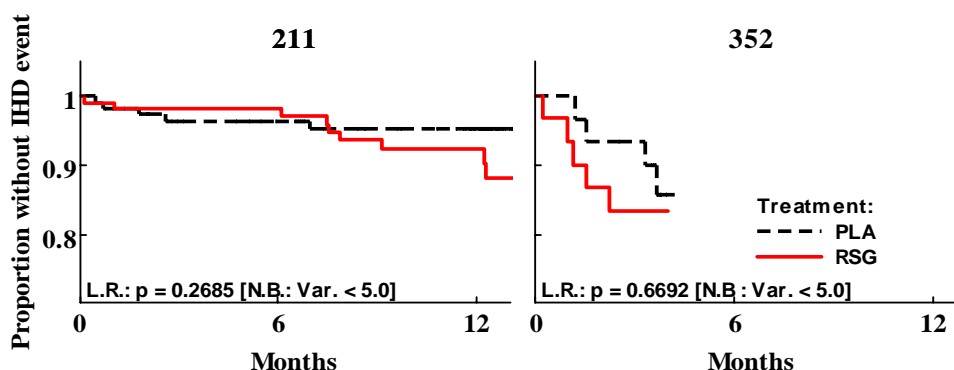
Table 3.3.3 Results for RSG add-on to background therapy; odds ratio and risk difference

	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials				
OR	p=0.5	1.4	0.6, 3.5	p=0.4
Risk Difference	p=0.2	+1.7%	-2.3%, +5.7%	p=0.4
Only 211 and 352	p=0.7	1.6	0.6, 4.5	p=0.3
Only 211		1.9	0.5, 7.7	p=0.4
Serious Ischemic events				
All Trials	p=0.5	1.6	0.47, 6.5	p=0.4
Only 211 and 352	p>0.99	2.5	0.55, 15.1	p=0.2
All Ischemic/CHF events				
All trials	p=0.6	1.5	0.8, 2.9	p=0.18
Only 211 and 352	p=0.7	1.7	0.9, 3.2	p=0.14

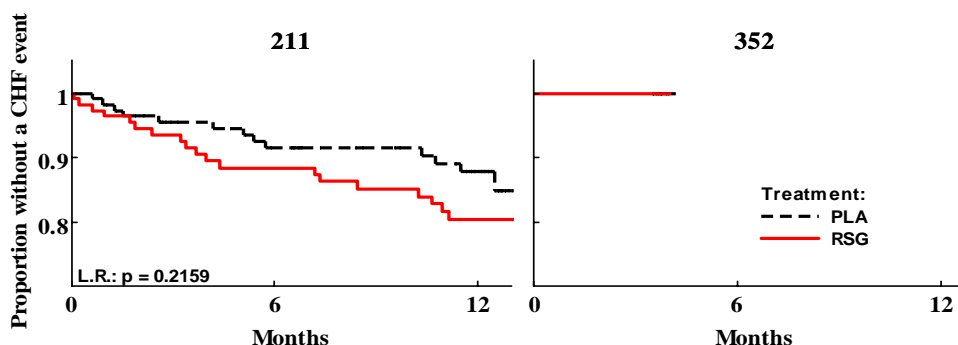
Time to event analyses show no significant treatment effects (log rank test, Figure 3.3.4) in Studies 211 and 352. The early ischemic events seen in study 352 will be examined in an addendum to this review.

Figure 3.3.4 Kaplan-Meier curves for Studies 211 (CHF patients) and 352 (CHD patients)

Ischemic events



CHF events (there were no CHF events in Study 352)

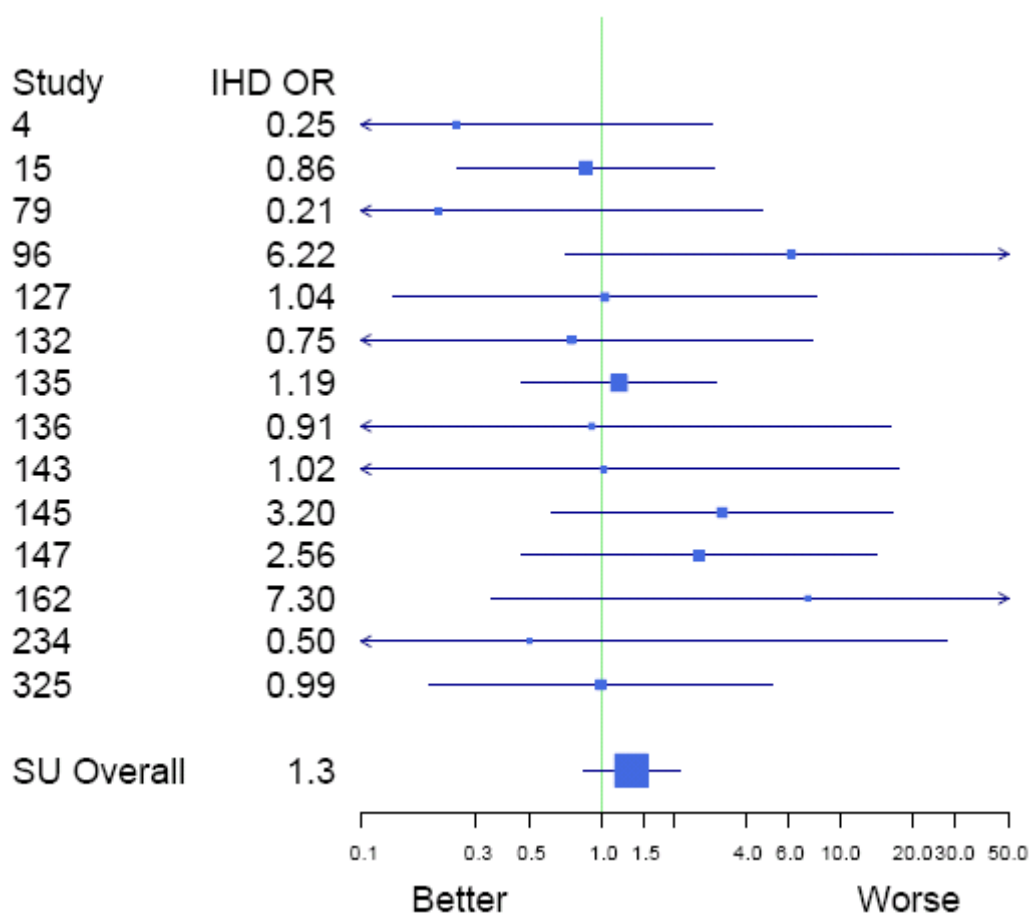


RSG+Sulfonylurea versus Sulfonylurea

The meta-group, RSG+Sulfonylurea, consisting of 14 studies might be considered the most homogeneous meta-group in terms of designs in that (with the exception of Study 135, a 2-year study) all studies were of a 6 month duration and all were placebo-controlled. The population for this group is about 27% of the total sample size. The average patient in these trials were more closely like patients in the monotherapy trials than in the add-on metformin trials in terms of BMI, CV medications including statins and ACE inhibitors and LDL (see Appendix 3) with an important exception being that 98% of the patients had been previously treated with diabetes medications.

Special populations were studied in Study 135; a 2-year trial in elderly patients and Study 136; a 6-month study in patients with chronic renal failure, not on dialysis. All trials except for Study 004 were add-on trials where patients were treated with a sulfonylurea during run-in and then randomized to placebo or RSG. Study 004 was a study of Avandaryl, a fixed dose combination product of RSG plus glimepiride; only naïve patients were enrolled in Study 004.

Figure 3.3.5 Forest plot of odds ratios ($\pm 95\%$ CI) for IHD; RSG add-on to/combination with SU



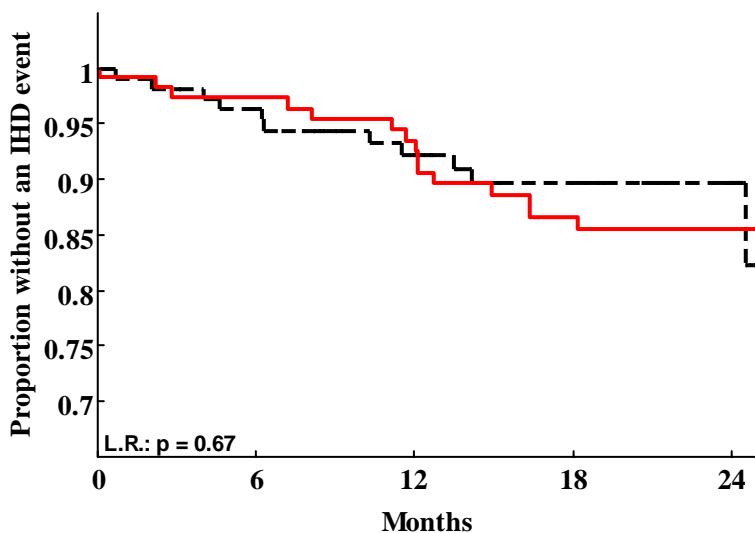
The overall estimate for the sulfonylurea meta-group was 1.4 with a confidence interval of 0.8 to 2.25 (p=0.2); larger than the estimate seen with the monotherapy group but also not statistically significant. However borderline significant results are seen for serious IHD/CHF events with a similar OR. The results in the trials in special populations are consistent with the overall result.

Table 3.3.4 Results for RSG add-on to/combination with SU; odds ratio and risk difference

	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials				
OR	p=0.3	1.4	0.8, 2.25	p=0.2
Risk Difference	p=0.4	+0.6%	-0.3%, +1.5%	p=0.2
Excl. 135	p=0.3	1.4	0.8, 2.6	p=0.2
Excl 135&136	p=0.2	1.5	0.8, 2.65	p=0.2
Combination				
Add-on				
Serious Ischemic events				
All trials	p=0.11	1.5	0.7, 3.2	p=0.3
All Ischemic/CHF events				
All trials	p=0.25	1.5	0.9, 2.3	p=0.09
Excl 135	p=0.2	1.5	0.9, 2.6	p=0.14
Excl 135&136	p=0.1	1.5	0.9, 2.6	p=0.13
Serious Isch/CHF events				
All trials	p=0.06	1.4	0.8, 2.7	p=0.3

The results in Study 135 in 227 elderly patients are of particular interest because this is the longest trial in the database at 2 years (average exposure of 20 months; 51% of SU completed the study while 78% completed on RSG; at Month 18 about 62% of SU and 82% of RSG are on study). The OR for this study is 1.2; the overall event rate in this trial was about 9% with essentially no difference between treatment groups as illustrated in the Kaplan-Meier curve below. A log rank test of time to ischemic event yielded a p-value of about 0.6.

Figure 3.3.6 Study 135 Kaplan-Meier curve of time to ischemic event



There are 10 studies in the metformin meta-group and this is a rather heterogeneous grouping which is reflected in the analyses by significant results for tests of homogeneity (Table 3.3.5 on the following page). Eight studies were placebo-controlled while two were sulfonylurea-controlled. Studies 137 and 282 both have SU+MET as a comparator to RSG+MET while the rest of the trials have PLA+MET. Studies 002, 003 and 007 used the fixed dose combination (FDC) of Avandamet (rosiglitazone plus metformin) while the remaining studies were add-on studies. The median exposure was about 6 months in these trials. The sample size of this group is about 23% of the total database population. About 58% of the patients in these studies were overweight (about 10% higher than in the other meta-groups). About 78% of the patients had been previously treated with diabetes medications; Study 007 was a study of only naïve patients while Study 002 was in only previously treated patients. Six of the studies (002, 003, 007, 284, 137 and 282) were titration studies.

Study	IHD OR
002	10.85
003	9.79
007	0.49
044	1.54
093	3.15
094	1.51
284	2.02
311	0.17
S137	0.60
S282	0.35
MET Overall	1.6

Better **Worse**

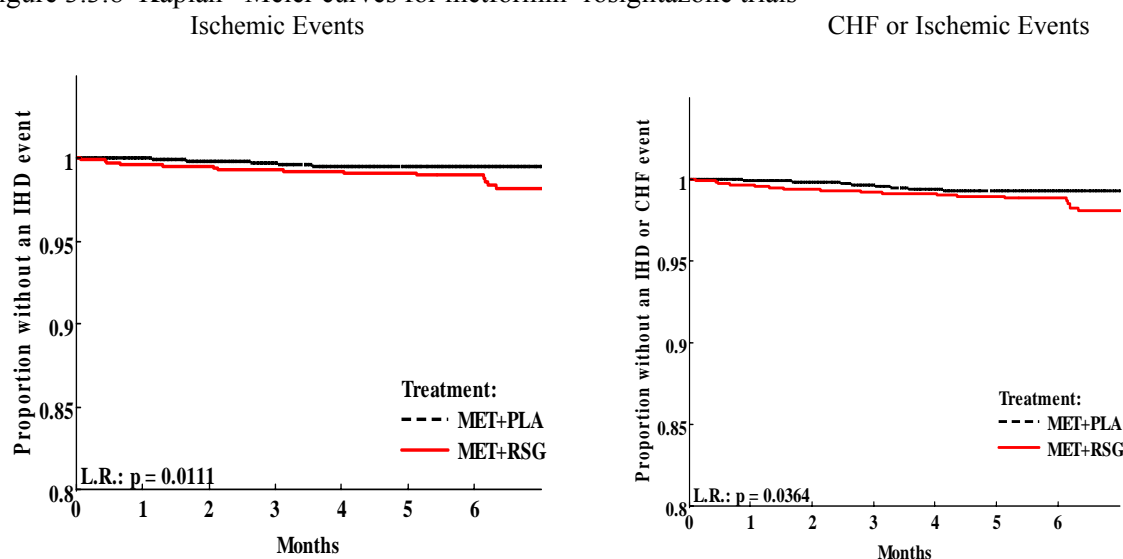
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Heterogeneity (this reviewer considered a p-value of less than 0.2 as a signal of differential treatment effects across studies for this low powered test) was seen when looking at all trials for total and serious ischemic events and serious IHD/CHF events. Excluding the two active-controlled trials reduced the heterogeneity adequately for total events but not for serious events. Taking out the two-active controlled trials changed the OR from 1.8 (p=0.14) to 3.2 (p=0.01) which is a notable change in risk. Given the low event rates seen for this group, the Kaplan-Meier curves are not very impressive though the log-rank test is significant at p=0.01; it is clear that events are seen as early as the first month of therapy.

Table 3.3.5 Results for RSG add-on to/combination with MET; odds ratio and risk difference

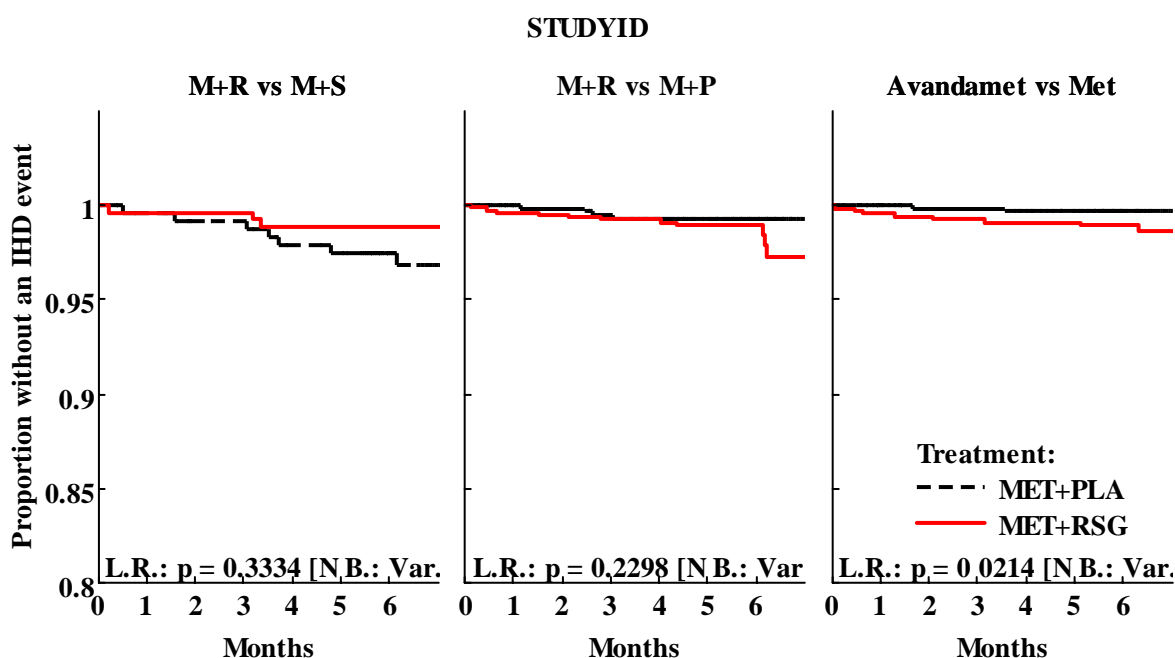
	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials	p=0.12	1.8	0.9, 3.8	p=0.14
OR				
Risk Difference				
Fixed effects model	p=0.60	+0.6%	-0.2%, +1.3%	p=0.12
Placebo-controlled	p=0.30	3.2	1.2, 9.8	p=0.01
Active-controlled (137&282)	p>0.9	0.5	0.1, 2.1	0.4
Studies in FDC Avandamet	p=0.04	5.1	1.1, 48	0.02
Add-on placebo-cont. studies	p=0.8	1.7	0.6, 5.6	0.3
Serious events				
All trials	p=0.09	1.28	0.5, 3.4	p=0.7
Excl 137 and 282	p=0.15	2.9	0.7, 17	p=0.1
All Ischemic/CHF events				
All trials	p=0.30	1.6	0.8, 3.1	p=0.18
Serious Isch/CHF events				
All trials	p=0.04	1.25	0.5, 3.2	p=0.7
Excl 137 and 282	p=0.13	3.3	0.9, 19	p=0.06

Figure 3.3.8 Kaplan –Meier curves for metformin+rosiglitazone trials



Kaplan-Meier curves for the three types of trials seen in the metformin meta-group suggest that most of the risk is seen in the Avandamet trials where patients were randomized to combination therapy (this is supported by the results in Table 3.3.5 where a significant OR of about 5. Two of the Avandamet studies (003 and 007) had no run-in while Study 002 had a metformin run-in like the other studies in this group. It is worth recalling that Study 007 was in a population of all naïve patients.

Figure 3.3.9 Kaplan-Meier curves by type of trial design



The results from this meta-group of rosiglitazone administered with metformin suggests that the combination is particularly adverse when give as Avandamet. There is very limited data specifically for Avandamet though the RECORD study with provide long-term data for the combination of RSG and MET.

RSG+Insulin versus Insulin

There were five trials (1,530 patients, 11% of the whole database) where patients were treated with insulin and then randomized to add-on rosiglitazone or placebo. The median exposure for these trials was about 6 months. Generally these patients would be considered high risk patients with a history of diabetes about twice that of the rest of the database but only 19% of the patients presented with a history of CHD. The ischemic event rate for RSG patients was 2.8% compared to 1.4% in the control group giving an OR of 2. The results are quite consistently borderline significant across all endpoints with a doubling of risk in this relatively small group of patients. Although two trials had ORs of about 1, it is clear from their CIs that the results are not inconsistent with the overall group.

Figure 3.3.10 Forest plot of odds ratios ($\pm 95\%$ CI) for IHD; RSG add-on to insulin

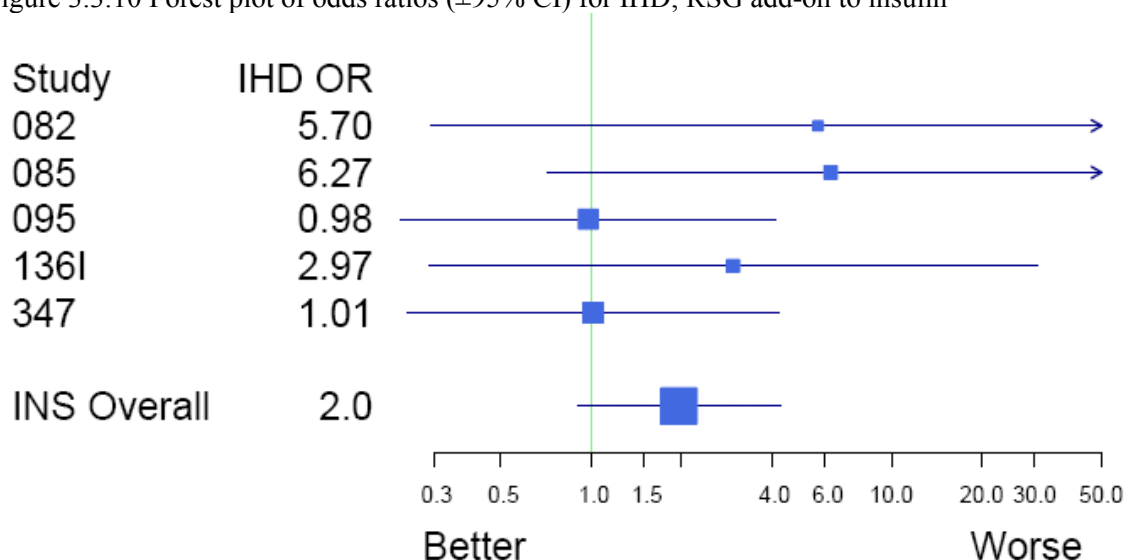


Table 3.3.6 Results for RSG add-on to insulin; odds ratio and risk difference

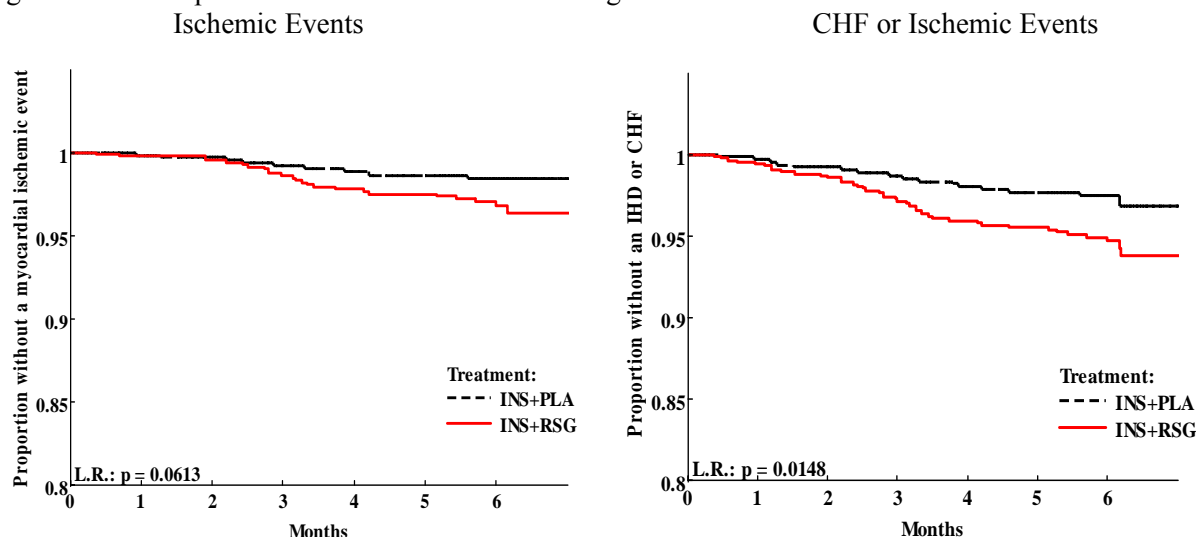
	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials	p=0.4	2.1	0.9, 5.1	p=0.07
Risk Difference				
Fixed effects model	p=0.5	+1.4%	-0.05%, +2.9%	p=0.058
Serious Ischemic events				
All trials	p=0.5	2.6	0.8, 11	p=0.12
Serious Isch/CHF events				
All trials	p=0.7	2.0	0.9, 5.1	p=0.09

One additional study of Avandamet (RSG+MET) plus insulin (Study SB-712753/009 reviewed by FDA in 2006) is not included in the database under review here. In this study, there were 2 serious ischemic events (1 death) in the Avandamet+insulin group (162 patients) and 0 in the insulin alone group (160 patients). Clearly this additional study would render the results for serious ischemic events statistically significant; however one drawback to this study is that the comparison is of the combination of RSG+MET

to placebo whereas most comparisons in the meta-analysis are of RSG versus placebo.

Time to event analyses (log rank test) show a (borderline) significant difference with the proportion of patients without ischemic events illustrated by the Kaplan-Meier curves below.

Figure 3.3.11 Kaplan –Meier curves for insulin+rosiglitazone trials



There were a total of 8 deaths in these 6-month studies; 6 (0.7%, 4 cardiac) on RSG+insulin and 2 (0.3%, 1 cardiac) on insulin alone with an OR of 2.3 (95%CI of 0.5 to 12 and p-value of 0.5, Fisher's exact test). Adding in the additional study (1 death on RSG+MET+INS versus 0 on insulin alone), the OR is 2.8 with p-value of 0.3, Fisher's exact test.

RSG+Sulphonylurea+Metformin versus Sulphonylurea+Metformin

Study 134, a fairly large trial of 561 patients on RSG+SU+MET and 276 patients on SU+MET, showed essentially no statistical difference between the treatment groups. The ischemic event rate was 1.6% for RSG and 1.4% for placebo.

Table 3.3.7 Results for RSG add-on MET+SU; odds ratios

	OR	95% CI	Exact test for OR=1
<u>All</u>			
IHD events	1.11	0.31, 4.97	$p > 0.99$
IHD/CHF events	1.99	0.64, 7.01	$p = 0.24$
<u>Serious only</u>			
IHD events	0.82	0.15, 5.31	$p = 0.72$
IHD/CHF events	1.32	0.31, 7.76	$p > 0.99$

Overall Results

Odds ratios and risk differences by meta-group are summarized in the table below. For this table, the active controlled trials in the metformin group form a separate meta-group (R+M vs S+M). The estimates in the table are weighted by study and p-values are based on an exact test while the ORs depicted on the graphs on the following page are unweighted estimates. The overall estimate of IHD risk is weighted by meta-group; a test for homogeneity of the Ors for IHD yielded a p-value of 0.26.

For total ischemic events, the overall estimate of the odds ratio is 1.38 (95% CI of 1.1 to 1.8 and $p=0.02$) based on this reviewer's meta-analysis (an analysis weighting by study yielded an OR of 1.45 with $p=0.01$). This estimate is consistent with estimates produced by time-to-event and logistics regression analyses of the pooled dataset (see Table 3.2.2). For serious ischemic events, the overall estimate of the odds ratio is also 1.4 (95% CI of 0.98 to 2.1, Table 3.3.9). Forest plots for total and serious ischemic events are shown on the next page.

Table 3.3.8 Summary of the ischemic events results in 7 meta-groups

RSG GROUP	RSG events/N	CONTROL events/N	RD (95% CI)	OR (95% CI)
R+M vs S+M	4/274 (1.5%)	7/260 (2.7%)	-1.3% (-3.8%, +1.2%)	0.5 (0.1, 2.1) [$p=0.37$]
R+M+S	9/561 (1.6%)	4/276 (1.4%)	+0.2% (-1.6%, +1.9%)	1.1 (0.3, 5) [$p>0.99$]
R+S	47/2413 (1.9%)	32/1832 (1.7%)	+0.6% (-0.3%, +1.5%)	1.4 (0.8, 2.3) [$p=0.20$]
R	51/2687 (1.9%)	22/1549 (1.4%)	+0.4% (-0.5%, +1.2%)	1.3 (0.7, 2.1) [$p=0.28$]
R+BM	15/240 (6.2%)	11/239 (4.6%)	+1.7% (-2.3%, +5.7%)	1.4 (0.6, 3.5) [$p=0.42$]
R+I	24/867 (2.8%)	9/663 (1.4%)	+1.4% (-0.1%, +2.9%)	2.1 (0.91, 5.1) [$p=0.07$]
R+M	21/1562 (1.3%)	6/1373 (0.4%)	+0.9% (+0.2%, +1.7%)	3.2 (1.2, 9.8) [$p=0.01$]
Overall Weighted by meta-groups	171/8604 (2.0%)	85/5633 (1.5%)	+0.5% (+0.1%, +1%)	1.4 (1.1, 1.8) [$p=0.02$]

The risk of myocardial ischemia due to rosiglitazone varies, sometimes considerably, though for many of the meta-group estimates, the CIs are wide suggesting a lack of precision in the estimation of the ORs. This reviewer performed additional sensitivity analyses which include subgroup analyses to further explore the risk of ischemia. One of the goals to is understand whether the overall odds ratio of 1.4 is a generalizable estimate of risk or whether this estimate is driven primarily by a high risk group of patients or a particular treatment paradigm.

Figure 3.3.12 Forest plot of odds ratios ($\pm 95\%$ CI) for IHD by meta-group ordered by OR

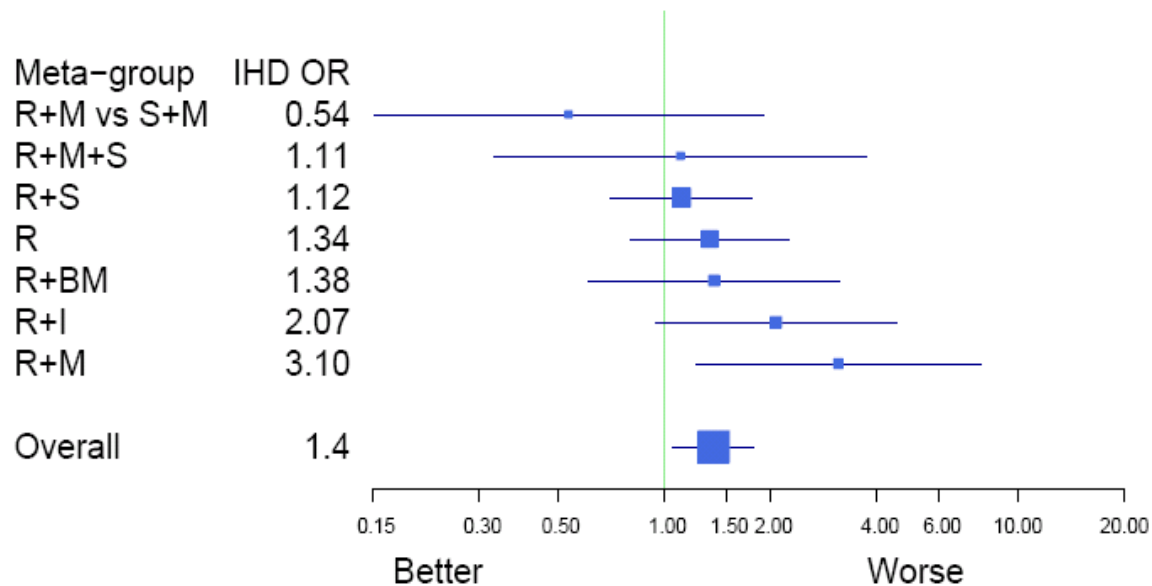


Figure 3.3.13 Forest plot of odds ratios ($\pm 95\%$ CI) for serious IHD by meta-group ordered by OR

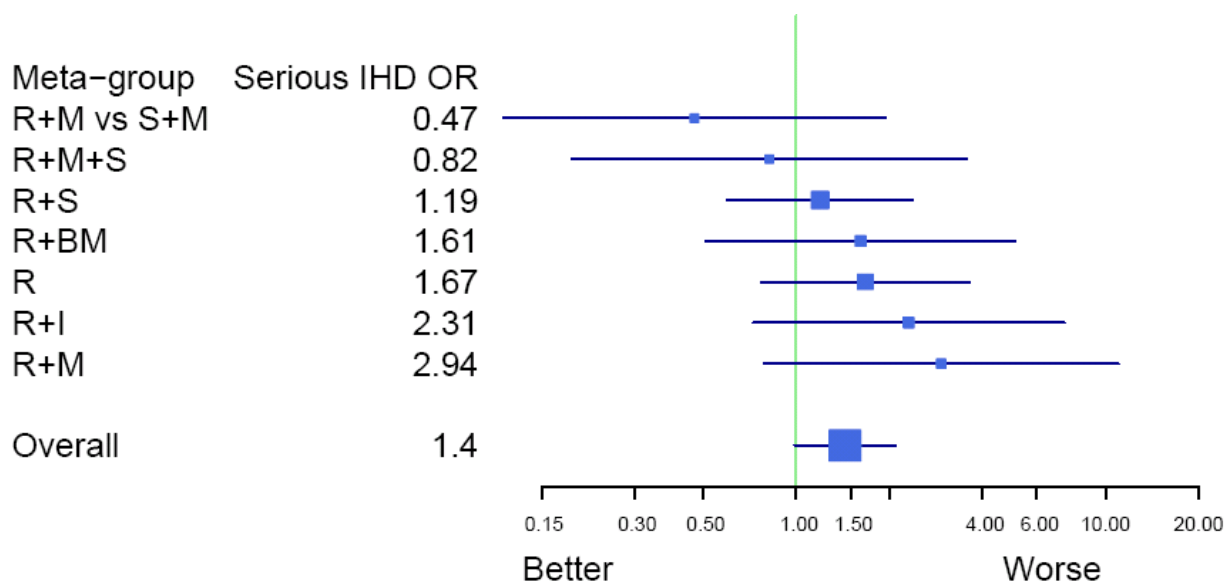


Table 3.3.9 Summary of the serious ischemic events results in 7 meta-groups

RSG GROUP	RSG events/N	CONTROL events/N	OR (95% CI)
R+M vs S+M (Study 137 only) ¹	3/204 (1.5%)	6/185 (3.2%)	0.4 (0.1, 2.1) [p=0.32]
R+M+S	5/561 (0.9%)	3/276 (1.1%)	0.8 (0.2, 5) [p>0.99]
R+S	22/2413 (0.9%)	14/1832 (0.8%)	1.4 (0.8, 2.7) [p=0.3]
R	26/2687 (1%)	9/1549 (0.6%)	1.5 (0.7, 3.7) [p=0.4]
R+BM	8/240 (3.3%)	5/239 (2.1%)	1.5 (0.8, 2.9) [p=0.18]
R+I	12/867 (1.4%)	4/663 (0.6%)	2.6 (0.8, 11) [p=0.12]
R+M	10/1562 (0.6%)	3/1373 (0.2%)	2.9 (0.7, 17) [p=0.1]
Overall Weighted by meta-groups	86/8604 (1.0%)	44/5633 (0.8%)	1.44 (0.98, 2.1) [p=0.06]

¹-There were no serious ischemic events in either treatment arm of Study 282 so only the results of Study 137 are shown here.

The table below summarizes the mortality data; total and due to CHD or CHF. Note that IHD and CHF deaths are included in the analysis of serious events. A more complete description of the mortality data is available in Dr. Mahoney's review (section 7.1.1) and Dr. Gelperin's review (section 4.2.4). As would be expected with predominantly 6-month studies, the mortality data is limited and so the estimates are not precise. Since there were many trials with no deaths, this reviewer computed the unstratified crude rates and a p-value using Fisher's exact test. The long-term datasets of DREAM, ADOPT and particularly, RECORD, should provide more precise estimates of mortality; depending on data availability the mortality results for these large long-term studies will be provided in an addendum to this review.

Table 3.3.10 Mortality results

Mortality	RSG Deaths/N (%)	CONTROL Deaths/N (%)	OR (95% CI)	p-value
Total	28/8605 (0.3%)	11/5633 (0.2%)	1.7 (0.8, 3.4)	0.15
Cardiac (IHD)	12/8605 (0.1%)	6/5633 (0.1%)	1.3 (0.5, 3.5)	0.6
Cardiac (IHD+CHF)	17/8605 (0.2%)	7/5633 (0.1%)	1.6 (0.7, 3.8)	0.4

Sensitivity Analyses

Exclusion of meta-groups

To test the stability of the overall odds ratio, this reviewer removed meta-groups from the analysis with the most extreme effects. Since Studies 211 (CHF) and 352 (CHD) have populations particularly unique to this database, an estimate without those studies is shown also.

Removal of individual meta-groups (Table 3.3.10) has varying effects on the overall estimate. Removing the two groups showing the greatest risk (add-on to insulin and metformin), either together or alone, reduces the OR and renders the results non-significant.

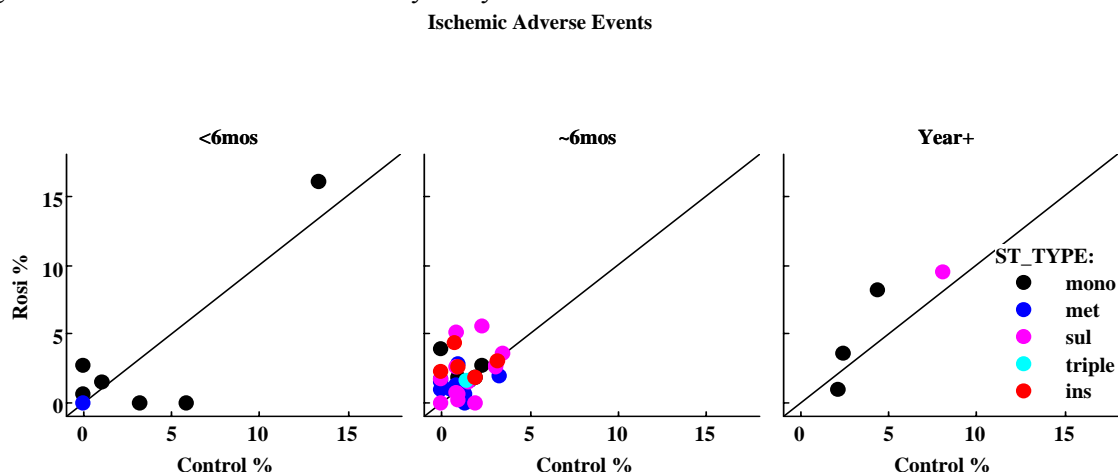
Table 3.3.10 Overall OR excluding meta-groups; exact test stratifying on meta-group

	Odds Ratio	p-value
Overall	1.38	0.02
Overall OR excluding meta-groups		
Minus R+M vs S+M	1.44	0.01
Minus RSG+Insulin	1.31	0.06
Minus RSG+Metformin	1.27	0.09
Minus RSG+Background Meds	1.38	0.02
Minus Ins and Met studies	1.17	0.32
Minus Studies 211 and 352	1.36	0.03

Results by Duration of Study

The majority of the studies in this database were of 6 months duration or less; 7 of the 8 less than 6 months studies were monotherapy studies and the 8th study was Study 352, the CHD study. Three studies were 1-year studies and one was a 2-year study. [See tables in Appendix 4 for notation indicating which studies were included in each grouping.] The event rates for the three groups of studies are shown in Figure 3.3.14.

Figure 3.3.14 Ischemic event rates by study duration



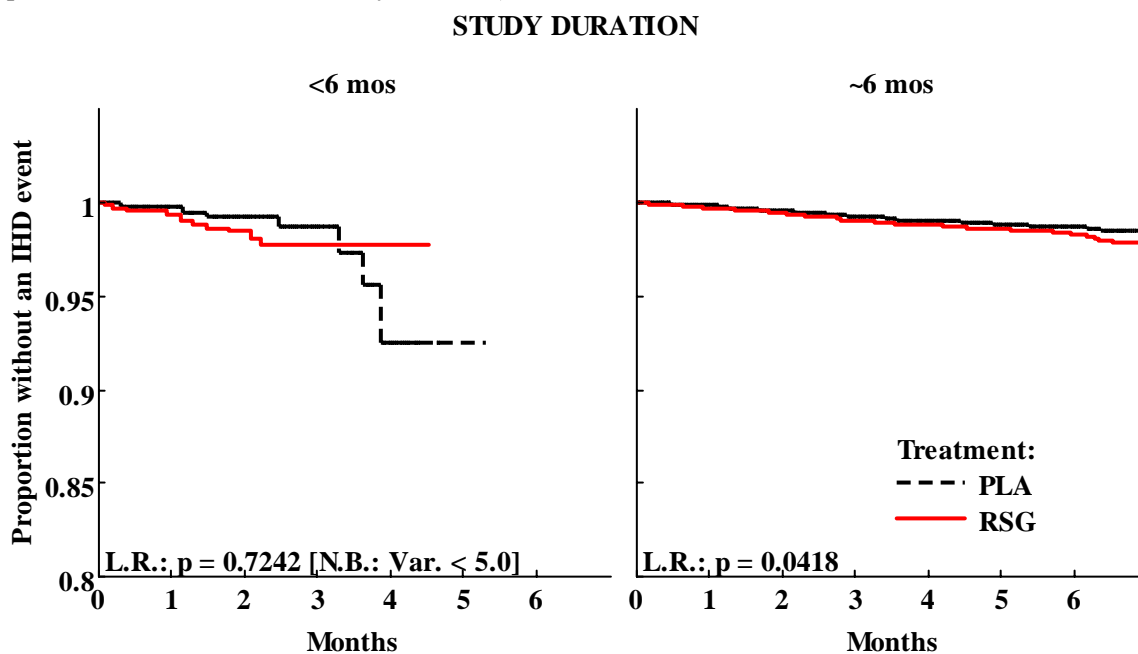
The odds ratios by duration of study (Table 3.3.11) do not vary considerably though the event rates between the short term studies and the 1 year+ studies are notably different. Only the results of the 6-month studies with the majority of the patients show statistically significant evidence of ischemic risk.

Table 3.3.11 Results of IHD and IHD/CHF by duration of study

	RSG	Control	Test of Homogeneity	OR Weighted by study	95% CI	Exact test for Common OR=1
<6 months (8 studies)	n=599	n=396				
IHD	11 (1.8%)	7 (1.8%)	p=0.8	1.3	0.4, 4.2	p=0.6
IHD/CHF	11 (1.8%)	7 (1.8%)	p=0.8	1.3	0.4, 4.2	p=0.6
~6 months (30 studies)	n=6562	n=4562				
IHD	115 (1.8%)	55 (1.2%)	p=0.4	1.5	1.1, 2.2	p=0.01
IHD/CHF	146 (2.2%)	66 (1.5%)	p=0.4	1.6	1.2, 2.2	p=0.001
1 year + (4 studies)	n=716	n=527				
IHD	35 (4.9%)	21 (4.0%)	p=0.8	1.4	0.8, 2.5	p=0.3
IHD/CHF	56 (7.8%)	36 (6.8%)	p=0.7	1.4	0.9, 2.3	p=0.14

Kaplan –Meier curves with results of log-rank tests are shown for the 6 month or less studies (Figure 3.3.15) and on the following page for each of the 4 longer studies.

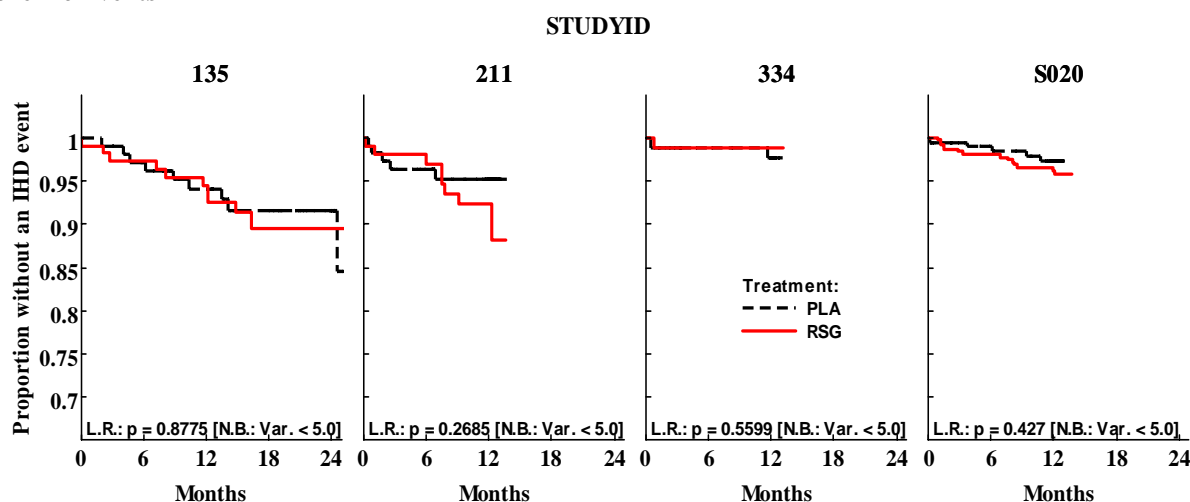
Figure 3.3.15 Kaplan Meier Curves for IHD events for less than 6 month studies and 6 month studies (graphs of IHD/CHF look essentially the same)



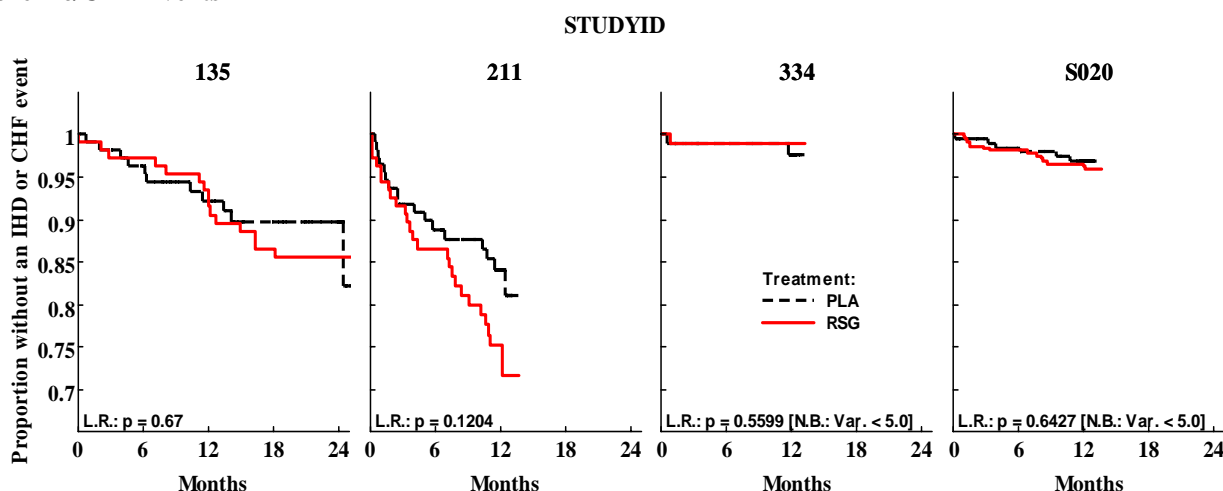
Kaplan-Meier Curves are shown below for one 2-year study (Study 135, a study in 227 elderly patients comparing SU+RSG to SU+PLA) and three 1-year studies (Study 211, a study in 224 CHF patients comparing RSG+background meds to PLA plus background meds; Study 334, a study of 194 patients comparing RSG+background meds to PLA plus background meds and Study S020, a study of 598 patients comparing monotherapy RSG to monotherapy SU (glibenclamide)).

Figure 3.3.16 Kaplan-Meier Curves for 1 year+ studies (note that separation of curves at the end of the trial are usually an artifact of a large drop in the at-risk population)

Ischemic Events



Ischemic/CHF Events



These studies do not individually demonstrate an increased risk of IHD due to rosiglitazone with longer exposure. Study 211 does clearly illustrate an increased risk of CHF events (see Figure 3.3.4 earlier in this review for an illustration of CHD events and CHF events separately).

Results for placebo-controlled and active-controlled 6 month studies presented separately

Differences in results between the placebo-controlled studies and the active-controlled studies has been discussed with the applicant as well as internally at FDA. To address this issue, this reviewer analyzed the placebo-controlled and active-controlled studies separately. In an attempt to make the groups of studies homogenous, only studies of 6 months or less are included; the 3 one-year studies (including 211) and one 2-year study are excluded. Also Study 352, a study in CHD patients, and the insulin studies (all placebo-controlled) are excluded from these analyses. One additional goal of this analysis is to examine risk in a population who are not necessarily at high risk for an ischemic event (as the CHF/CHD patients would be) and where the risk is not as well-defined as in the population of patients taking insulin.

There are a total of 29 placebo-controlled studies included in this analysis. Nine of the studies are monotherapy trials with 5 of those having a duration less than 6 months (median exposure about 3 months). Studies without events (Studies 234 and 140) in both treatment arms are shown in the forest plot by adding 0.5 to each cell; however, these studies are not included in the exact test.

There are a total of 8 studies included in the analysis of the active-controlled studies; 6 studies are comparisons between monotherapy arms (as in ADOPT) and two studies (282 and 137) are add-on arms (as in RECORD).

Opposite results are seen for the two types of trials with a concerning increased risk for rosiglitazone against placebo but a decreased risk against an active control of metformin or sulfonylurea. It should be noted that although the estimate against the active controls is less than 1, the confidence interval is quite wide with an upper limit of 1.9 so the evidence in favor of rosiglitazone is not convincing from this small group of studies.

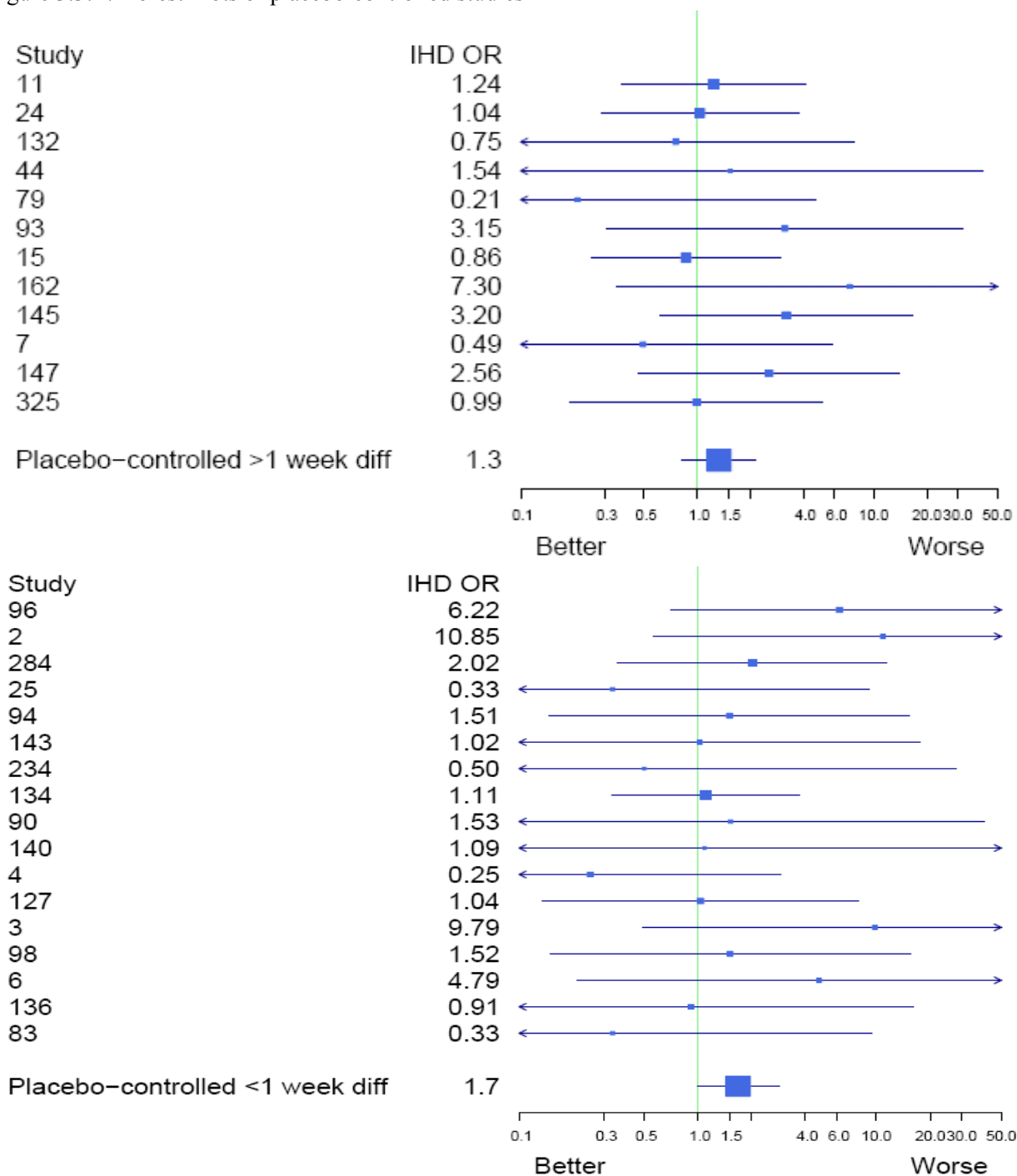
Table 3.3.11 Total (non-serious+serious) and serious IHD results for ~6-month placebo and active controlled studies; studies of 1 year or longer and insulin studies and Studies 211 and 352 in CHF and CHD patients, respectively, are excluded

Event	RSG Events/N (%)	CONTROL Events/N (%)	Test of Homogeneity	OR (95% CI)	p-value
Placebo-controlled					
IHD	95/6033 (1.6%)	43/4083 (1.1%)	0.46	1.6 (1.1, 2.3)	0.02
Serious IHD	48/6033 (0.8%)	17/4083 (0.4%)	0.28	1.9 (1, 3.6)	0.03
Active-controlled					
IHD	12/929 (1.3%)	15/907 (1.7%)	0.80	0.8 (0.3, 1.9)	0.8
Serious IHD	7/929 (0.8%)	10/907 (1.1%)	0.71	0.66 (0.2, 1.9)	0.5

Forest plots of these groupings are shown on the following pages. For the forest plots of the placebo controlled trials this reviewer has additionally addressed the issue of exposure and dropout brought up by the applicant in a meeting with the FDA. According to the applicant, control patients dropped more readily in the placebo controlled trials than in the active controlled trials and so the negative placebo-controlled trial results may be due to a bias against rosiglitazone; i.e. longer exposure in the rosiglitazone group than the placebo group. It is feasible that this is the case in these trials since patients on placebo may reach unacceptable levels of HbA1c and drop due to lack of efficacy. If it is the case then studies with similar dropout rates in both groups should show less negative results than those with differential dropout rates. To look at this issue, this reviewer divided the forest plot into two parts; those studies where the dropout rate difference was more than 10% or where the mean exposure difference was more than 1 week if completion rates were unavailable; the 10% cutoff was used since this was a difference mentioned by the applicant as

being significant. The studies on the plot are ordered by the difference in mean exposure between the placebo and rosiglitazone arm with the largest difference (more rosiglitazone exposure than placebo exposure) at the top of the graph. The mean difference in exposure between the arms ranged from 25 days less on placebo in Study 11 down to 11 days more exposure on placebo in Study 83; the median difference (RSG-PLA) across the trials was about 6 days.

Figure 3.3.17 Forest Plots of placebo-controlled studies



The forest plots above clearly illustrate that longer exposure in the rosiglitazone group than the placebo group did not bias against rosiglitazone; in fact, a larger odds ratio is seen for those trials where the difference in exposure was small (forest plot directly above).

Figure 3.3.18 Forest plot of active-controlled studies; odds ratios for all IHD
An “M” before the study number indicates the control is metformin and an “S” before the study number indicates the control is sulfonylurea.

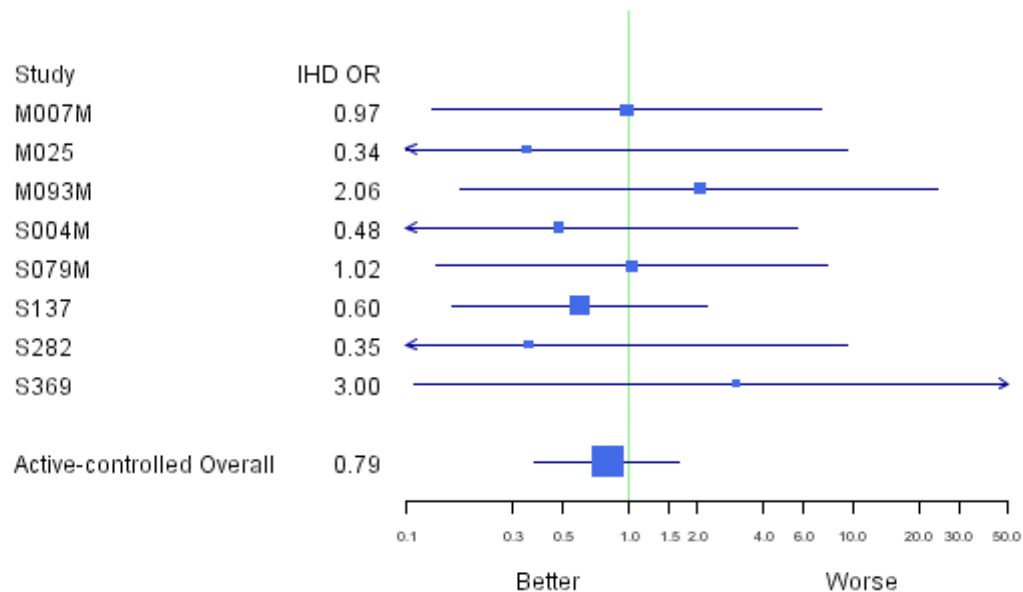
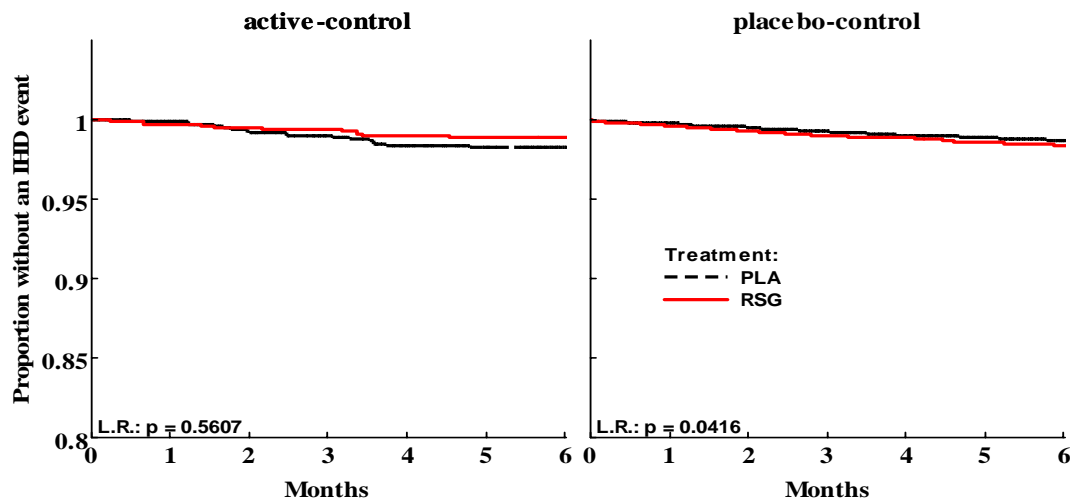


Figure 3.3.19 Kaplan Meier Plots for 6-month active-controlled trials and placebo-controlled trials



Subgroup Analyses

Results for subgroups are shown in the table below. Results are shown for all trials and for trials excluding the insulin trials; insulin trials were excluded so that an additional assessment of risk could be made in the population of studies where the estimate of risk varies by trial types and population characteristics.

Table 3.3.12 All IHD events by subgroups for all trials and excluding the insulin trials

Baseline Characteristic	All Trials			Without Insulin Trials		
	N	OR (95% CI) weighted by study	exact p-value	N	OR (95% CI) weighted by study	exact p-value
Age						
<65	10,537	1.2 (0.9, 1.7)	0.25	9,458	1.2 (0.8, 1.7)	0.4
≥ 65	4,259	2.0 (1.3, 3.2)	0.002	3,808	1.9 (1.1, 3.1)	0.009
Males	8,787	1.4 (1, 2)	0.02	7,981	1.4 (1, 2)	0.04
Females	6,009	1.5 (0.9, 2.7)	0.09	5,285	1.3 (0.8, 2.4)	0.4
BMI						
≤30	7,378	1.2 (0.8, 1.8)	0.4	6,747	1.1 (0.8, 1.7)	0.6
>30	7,418	1.8 (1.2, 2.6)	0.003	6,519	1.8 (1.1, 2.7)	0.008
Ace I						
Y	5,126	1.8 (1.1, 2.8)	0.009	4,401	1.6 (1, 2.6)	0.04
N	9,670	1.3 (0.9, 1.8)	0.18	8,865	1.2 (0.8, 1.8)	0.3
Loop Diuretic						
Y	770	3.7 (1.5, 11)	0.003	599	2.8 (0.99, 9.5)	0.04
N	14,026	1.3 (0.98, 1.7)	0.06	12,667	1.3 (0.97, 1.8)	0.08
Nitrates						
Y	617	2.9 (1.4, 5.9)	0.002	523	3.1 (1.5, 6.8)	0.001
N	14,179	1.3 (0.9, 1.7)	0.14	12,743	1.2 (0.8, 1.6)	0.3
Hx of CHD						
Y	2,118	1.5 (1.0, 2.2)	0.03	1,834	1.5 (1, 2.3)	0.03
N	12,678	1.5 (0.98, 2.3)	0.06	11,432	1.3 (0.9, 2.1)	0.18
CHD+Nitrates						
Y	557	3.0 (1.5, 6.2)	0.001	474	3.3 (1.6, 7.3)	0.0006
N	14,239	1.3 (0.9, 1.7)	0.14	12,792	1.2 (0.8, 1.6)	0.3
Hx of CHF						
Y	450	3.2 (1.1, 10)	0.02	401	2.8 (0.98, 9.2)	0.04
N	14,346	1.3 (1, 1.8)	0.05	12,865	1.3 (0.9, 1.7)	0.12
Prev. Treated	11,448	1.6 (1.2, 2.1)	0.002	9,918	1.5 (1.1, 2.1)	0.01
Naive	3,348	0.97 (0.5, 1.9)	p>0.9	3,348	0.97 (0.5, 1.9)	p>0.9
# CV Meds						
≤ 2	11,109	1.3 (0.9, 1.8)	0.2	10,090	1.2 (0.8, 1.8)	0.3
> 2	3,687	1.7 (1.1, 2.7)	0.007	3,176	1.6 (1, 2.5)	0.03
Major CV risk Condition						
0	11,702	1.5 (0.98, 2.4)	0.06	10,603	1.4 (0.9, 2.2)	0.2
1	2,319	1.4 (0.9, 2.1)	0.15	2,020	1.4 (0.9, 2.3)	0.15
≥ 2	775	1.7 (0.9, 3.4)	0.09	643	1.7 (0.8, 3.5)	0.2

The objectives of the subgroup analyses are to identify potential risk factors and generate hypotheses that may be tested with data from the long-term studies (DREAM, ADOPT and RECORD). Differential treatment effects seen in the meta-analysis (such as nitrates and ace inhibitors) should be verified in these large randomized trials.

The results for nitrates are particularly concerning considering that a highly significant treatment effect with an OR of about 3 is seen in a very small subgroup of patients. These patients on nitrates would in general be a high risk population (the majority had an history of CHD at baseline) but the interaction with treatment is of particular interest. Also it should be noted that patients with a history of CHD and no nitrate use show essentially no risk (applicant computed HR of 1.1).

An interaction with ramapril and rosiglitazone was seen for MI and for a composite CV endpoint ($p=0.09$ and $p=0.07$, respectively) in the DREAM study where higher rates were seen with the combination of rosiglitazone plus ramapril than with either monotherapy or placebo. [DREAM had not been reviewed by FDA at the time of the completion of this review.] Coupled with the results seen for ace inhibitors in a subgroup analysis of the studies in the pooled dataset, there is sufficient evidence to suggest further examination of this potential interaction.

The inconsistencies across the subgroups (particularly without the insulin trials) suggest that the ischemic effect of rosiglitazone varies considerably and that confirmation of these effects is needed to ascertain whether the overall effect is primarily driven by effects in identifiable subgroups.

In an addendum to this review, the subgroup issues will be further examined in the context of the large, long-term studies.

Appendix 1. Trials Included in Analyses											
Treatment groups were defined by the applicant based on randomized treatment and concomitant medication use; this table shows the treatment assignments used by the applicant											
	Treatment Group Sample Sizes										
Trial	I+R	INS	M+R	MET	PLA	RSG	S+M+R	S+R	SU	S+M	Total
006	0	0	0	0	69	74	0	0	0	0	143
011	0	0	0	0	176	357	0	0	0	0	533
015	0	0	0	0	0	0	0	190	198	0	388
020	0	0	0	0	0	391	0	0	207	0	598
024	0	0	0	0	185	774	0	0	0	0	959
025	0	0	0	32	31	30	0	0	0	0	93
044	0	0	101	51	0	0	0	0	0	0	152
079	0	0	0	0	0	104	0	99	106	0	309
082	212	107	0	0	0	0	0	0	0	0	319
083	0	0	0	0	17	16	0	0	0	0	33
085	138	139	0	0	0	0	0	0	0	0	277
090	0	0	0	0	75	149	0	0	0	0	224
093	0	0	106	109	0	107	0	0	0	0	322
094	0	0	232	116	0	0	0	0	0	0	348
095	196	96	0	0	0	0	0	0	0	0	292
096	0	0	0	0	0	0	0	116	115	0	231
098	0	0	0	0	96	191	0	0	0	0	287
127	0	0	0	0	0	0	0	56	58	0	114
132	0	0	0	0	0	0	0	437	110	0	547
134	0	0	0	0	0	0	561	0	0	276	837
135	0	0	0	0	0	0	0	116	111	0	227
136	112	109	0	0	0	0	0	36	33	0	290
137	0	0	204	0	0	0	0	0	0	185	389
140	0	0	0	0	71	65	0	0	0	0	136
143	0	0	0	0	0	0	0	121	124	0	245
145	0	0	0	0	0	0	0	231	242	0	473
147	0	0	0	0	0	0	0	89	88	0	177
162	0	0	0	0	0	0	0	168	172	0	340

Appendix 1. Trials Included in Analyses											
Treatment groups were defined by the applicant based on randomized treatment and concomitant medication use; this table shows the treatment assignments used by the applicant											
	Treatment Group Sample Sizes										
Trial	I+R	INS	M+R	MET	PLA	RSG	S+M+R	S+R	SU	S+M	Total
211	0	0	4	12	19	17	22	67	59	24	224
234	0	0	0	0	0	0	0	116	58	0	174
282	0	0	70	0	0	0	0	0	0	75	145
284	0	0	382	384	0	0	0	0	0	0	766
311	0	0	43	7	7	15	0	0	0	0	72
325	0	0	0	0	0	0	0	196	195	0	391
334	0	0	35	27	38	45	0	19	30	0	194
347	209	212	0	0	0	0	0	0	0	0	421
352	0	0	7	7	8	4	14	6	5	10	61
369	0	0	0	0	0	25	0	0	24	0	49
712753/002	0	0	289	280	0	0	0	0	0	0	569
712753/003	0	0	254	272	0	0	0	0	0	0	526
712753/007	0	0	155	154	0	159	0	0	0	0	468
797620/004	0	0	0	0	0	230	0	442	222	0	894
Total	867	663	1882	1451	792	2753	597	2505	2157	570	14237

I+R=Insulin+Rosiglitazone

INS=Insulin

M+R=Metformin+Rosiglitazone

MET=Metformin

PLA=Placebo

RSG=Rosiglitazone

S+M+R= Sulfonlyurea+Metformin+Rosiglitazone

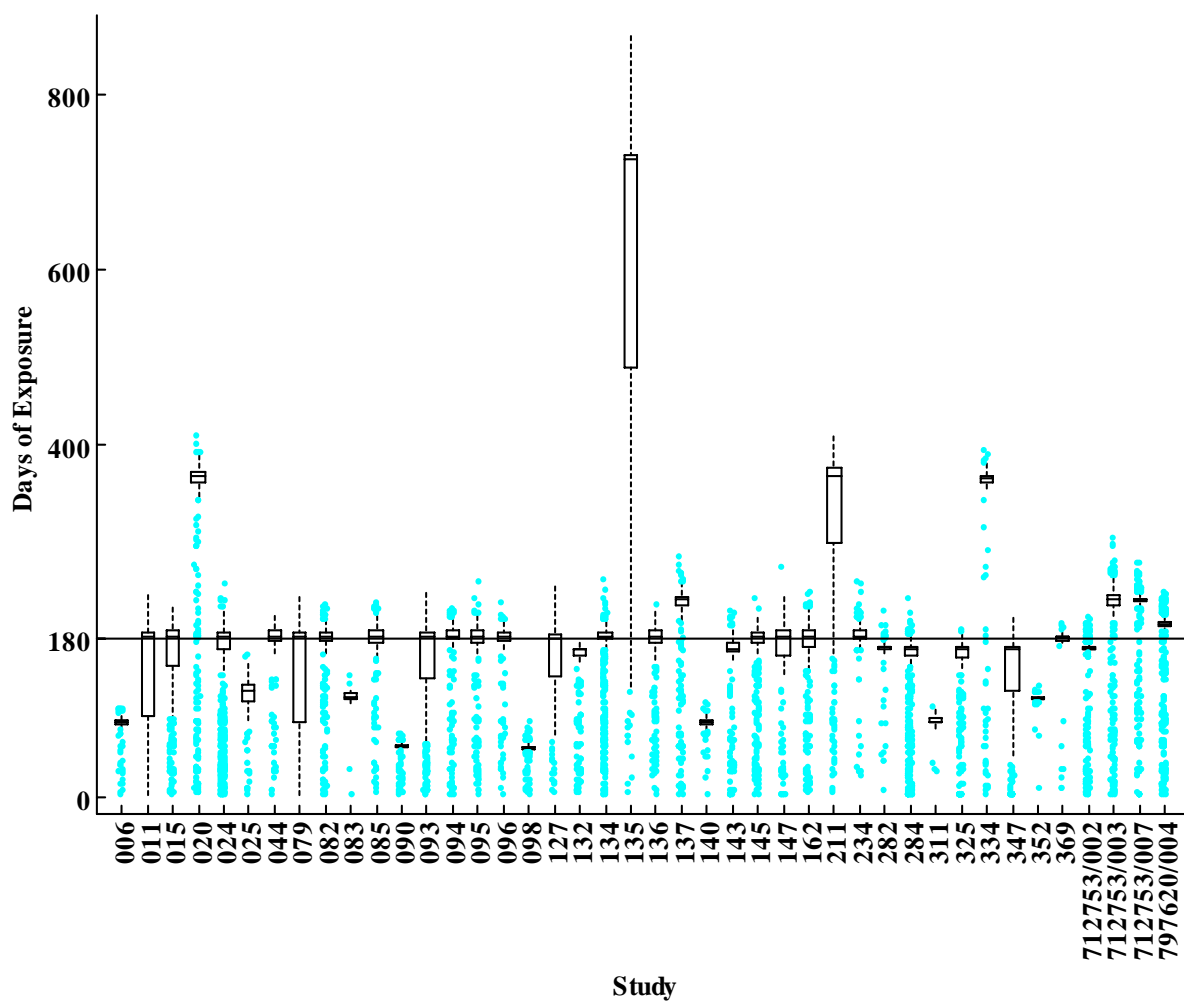
S+R= Sulfonlyurea+ Rosiglitazone

Su= Sulfonlyurea

S+M= Sulfonlyurea+Metformin

Studies 334, 712753/002, 712753/003, 712753/007 and 797620/004 were the 5 studies added to the original dataset to comprise the updated dataset.

Appendix 2. Boxplots of days of exposure by study



Appendix 3. Patient characteristics by meta-group

Meta-groups shown here were defined by the reviewer

	RSG (n=4236)	RSG+BM			RSG+SU		RSG+MET (n=3469)	RSG+INS (n=1530)	TRIPLE (n=837)
		211 (n=224)	334 (n=194)	352 (n=61)	All w/o 135 (n=4018)	135 (n=227)			
<u>Age</u>									
Mean (SD)	58 (10)	64 (9)	67 (7)	64 (7)	58 (10)	68 (6)	57 (10)	58 (9)	56 (9)
Range	33-78	42-78	35-78	48-77	33-78	59-78	33-78	33-78	33-78
<u>Gender</u>									
% males	63%	81%	56%	74%	57%	73%	57%	53%	60%
<u>BMI</u>									
Mean (SD)	30 (5)	29 (4)	29 (5)	30 (4)	30 (5)	31 (5)	32 (6)	32 (5)	33 (6)
%>30	48%	34%	40%	49%	41%	48%	58%	59%	63%
%>40	3%	0%	4%	2%	5%	4%	10%	9%	13%
<u>Dur Diab (yrs)</u>									
Mean (SD)	5 (6)	6 (6)	4 (4)	8 (7)	7 (6)	7 (6)	6 (5)	13 (8)	8 (6)
<u>Trt Exp (mos)</u>									
Mean (SD)	5.4 (3)	10.3 (4)	10.7 (4)	3.6 (1)	5.4 (2)	20.1 (7)	5.7 (2)	5.3 (2)	5.6 (1)
<u>CV Meds</u>									
0	42%	0%	25%	2%	42%	22%	33%	26%	28%
1	24%	0.5%	28%	15%	22%	21%	23%	21%	24%
2	16%	4%	18%	16%	16%	19%	18%	20%	20%
>2	18%	95.5%	29%	67%	20%	38%	26%	33%	28%
<u>CV Major Risk Cond</u>									
0	83%	0%	75%	0%	82%	60%	83%	72%	79%
1	14%	31%	24%	95%	15%	29%	13%	20%	15%
≥2	3%	69%	1%	5%	3%	11%	4%	9%	6%
Hx CHF	1%	100%	2%	0%	1%	5%	2%	3%	1%
Hx CHD	11%	67%	15%	100%	13%	29%	11%	19%	16%
Prev trt diab	60%	83%	53%	80%	98%	100%	78%	100%	100%
<u>Baseline meds</u>									
Nitrates	3%	30%	6%	48%	4%	10%	2%	6%	3%
Statin	13%	43%	32%	48%	15%	31%	25%	26%	28%
Loop diuretic	3%	60%	8%	5%	3%	7%	3%	11%	6%
Alpha blocker	3%	2%	2%	3%	4%	5%	4%	5%	3%
Beta blocker	12%	70%	28%	59%	13%	20%	15%	12%	13%
CCB	14%	10%	14%	23%	15%	22%	15%	19%	14%
Ace inhibitor	25%	98%	30%	52%	28%	41%	43%	47%	41%
<u>HbA1c</u>									
Mean (SD)	8.5 (1)	8 (1)	7 (1)	7 (1)	9 (1)	8 (1)	8 (1)	9 (1)	9 (1)
<u>HDL</u>									
Mean (SD)	45 (11)	42 (11)	47 (12)	43 (11)	46 (12)	44 (11)	47 (12)	48 (13)	50 (13)
<u>LDL</u>									
Mean (SD)	131 (36)	113 (32)	120 (32)	97 (25)	125 (34)	113 (30)	117 (33)	122 (34)	112 (33)
<u>HCT</u>									
Mean (SD)	44 (4)	43 (4)	41 (3)	42 (3)	43 (4)	43 (4)	42 (4)	42 (4)	42 (6)
<u>DBP</u>									
Mean (SD)	81 (9)	78 (8)	82 (8)	85 (8)	81 (9)	78 (9)	80 (8)	79 (9)	80 (8)

Appendix 4. Sample size and number of events by study for each meta-group

The tables on the following pages are labeled by these meta-groups:

- **Monotherapy rosiglitazone versus placebo or active control**
- **RSG+Background diabetes therapy vs. PLA+Background diabetes therapy**
- **RSG+Sulphonylurea versus Sulphonylurea**
- **RSG+Metformin versus Metformin**
- **RSG+Insulin versus Insulin**
- **RSG+Sulphonylurea+Metformin versus Sulphonylurea+Metformin**

Monotherapy RSG vs Placebo or Active Control

Study	RSG					CONTROL				
	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF
006 < 6 mos	74	2 (2.7%)	1 (1.4%)	2 (2.7%)	1 (1.4%)	69	0	0	0	0
011	357	10 (2.8%)	5 (1.4%)	11 (3.1%)	6 (1.7%)	176	4 (2.2%)	3 (1.7%)	5 (2.8%)	4 (2.2%)
024	774	13 (1.7%)	9 (0.5%)	13 (1.7%)	9 (0.5%)	185	3 (1.6%)	1 (0.5%)	3 (1.6%)	1 (0.5%)
025 < 6 mos	30	0	0	0	0	31	1 (3.2%)	0	1 (3.2%)	0
083 < 6 mos	16	0	0	0	0	17	1 (5.9%)	0	1 (5.9%)	0
090 < 6 mos	149	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	75	0	0	0	0
098 < 6 mos	191	3 (1.6%)	1 (0.5%)	3 (1.6%)	1 (0.5%)	96	1 (1%)	0	1 (1%)	0
140 < 6 mos	65	0	0	0	0	71	0	0	0	0
311M < 6 mos	15	0	0	0	0	7	0	0	0	0
M007M	159	2 (1.3%)	1 (0.6%)	2 (1.3%)	1 (0.6%)	154	2 (1.2%)	1 (0.6%)	2 (1.2%)	1 (0.6%)
M093M	107	2 (1.9%)	1 (0.9%)	2 (1.9%)	1 (0.9%)	109	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
S004M	230	1 (0.4%)	0	2 (0.9%)	1 (0.4%)	222	2 (0.9%)	1 (0.5%)	2 (0.9%)	1 (0.5%)
S020 1 yr	391	14 (3.6%)	5 (1.3%)	14 (3.6%)	5 (1.3%)	207	5 (2.4%)	1 (0.5%)	6 (3.3%)	1 (0.5%)
S079M	104	2 (1.9%)	2 (2.9%)	3 (0.7%)	2 (1.9%)	106	2 (1.9%)	1 (0.9%)	2 (1.9%)	1 (0.9%)
S369	25	1 (4%)	0	1 (4%)	0	24	0	0	0	0
Overall	2687	51 (1.9%)	26 (1%)	54 (2%)	28 (1%)	1549	22 (1.4%)	9 (0.6%)	24 (1.5%)	10 (0.6%)

RSG+Background diabetes therapy vs. PLA+Background diabetes therapy

Study	RSG Events					CONTROL Events				
	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF
BM211 1 yr CHF	110	9 (8.2%)	6 (5.5%)	26 (24%)	13 (12%)	114	5 (4.4%)	3 (2.6%)	17 (15%)	10 (8.8%)
BM334 1 yr	99	1 (1%)	1 (1%)	1 (1%)	1 (1%)	95	2 (2%)	2 (2%)	2 (2%)	2 (2%)
BM352 <6 m. CHD	31	5 (16%)	1 (2.8%)	5 (16%)	1 (2.8%)	30	4 (13%)	0	4 (13%)	0
Overall	240	15 (6.2%)	8 (3.3%)	32 (13.3%)	15 (6.2%)	239	11 (4.6%)	5 (2.1%)	23 (9.6%)	12 (5.0%)

RSG+Sulphonylurea versus Sulphonylurea

Study	RSG Events					CONTROL Events				
	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF
004	442	1 (0.2%)	0	2 (0.5%)	0	222	2 (0.9%)	1 (0.5%)	2 (0.9%)	1 (0.5%)
015	190	5 (2.6%)	1 (0.5%)	5 (2.6%)	1 (0.5%)	198	6 (3%)	2 (1%)	7 (3.5%)	2 (1%)
079	99	0	0	0	0	106	2 (1.9%)	1 (0.9%)	2 (1.9%)	1 (0.9%)
096	116	6 (5.2%)	2 (1.7%)	7 (6%)	4 (3.4%)	115	1 (0.9%)	0	2 (1.7%)	1 (0.9%)
127	56	2 (3.6%)	1 (1.8%)	2 (3.6%)	1 (1.8%)	58	2 (3.4%)	0	2 (3.4%)	0
132	437	3 (0.7%)	1 (0.2%)	3 (0.7%)	1 (0.2%)	110	1 (0.9%)	0	1 (0.9%)	0
135 2 yrs	116	11 (9.5%)	6 (5.2%)	15 (12.9%)	8 (6.9%)	111	9 (8.1%)	7 (6.3%)	11 (9.9%)	10 (9%)
136	36	1 (2.8%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	33	1 (3%)	0	1 (3%)	0
143	121	1 (0.8%)	1 (0.8%)	2 (0.8%)	2 (0.8%)	124	1 (0.8%)	0	1 (0.8%)	0
145	231	6 (2.6%)	3 (1.3%)	7 (3%)	3 (1.3%)	242	2 (0.8%)	0	2 (0.8%)	0
147	89	5 (5.6%)	3 (3.4%)	5 (5.6%)	3 (3.4%)	88	2 (2.3%)	0	2 (2.3%)	0
162	168	3 (1.8%)	2 (1.2%)	5 (3.0%)	3 (1.8%)	172	0	0	0	0
234	116	0	0	0	0	58	0	0	0	0
325	196	3 (1.5%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	195	3 (1.5%)	3 (1.5%)	4 (2.1%)	4 (2.1%)
Overall	2413	47 (1.9%)	22 (0.9%)	57 (2.4%)	28 (1.2%)	1832	32 (1.7%)	14 (0.8%)	37 (2%)	19 (1%)

RSG+Metformin versus Metformin

Study	RSG Events					CONTROL Events				
	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF
002	289	5 (1.7%)	2 (0.7%)	5 (1.7%)	2 (0.7%)	280	0	0	1 (0.4%)	0
003	254	4 (1.6%)	1 (0.4%)	5 (2%)	2 (0.8%)	272	0	0	0	0
007	155	1 (0.6%)	0	1 (0.6%)	0	154	2 (1.3%)	1 (0.8%)	2 (1.3%)	1 (0.8%)
044	101	1 (1%)	0	1 (1%)	0	51	0	0	0	0
093	106	3 (2.8%)	1 (0.9%)	3 (2.8%)	1 (0.9%)	109	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
094	232	3 (1.3%)	2 (0.9%)	3 (1.3%)	2 (0.9%)	116	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
284	382	4 (1%)	4 (1%)	5 (1.3%)	4 (1%)	384	2 (0.5%)	0	4 (1%)	0
311 < 6 mos	43	0	0	0	0	7	0	0	0	0
S137	204	4 (2%)	3 (1.5%)	5 (2.5%)	3 (1.5%)	185	6 (3.2%)	6 (3.2%)	7 (3.8%)	7 (3.8%)
S282	70	0	0	1 (1.4%)	0	75	1 (1.3%)	0	1 (1.3%)	0
Overall	1836	25 (1.4%)	13 (0.7%)	29 (1.6%)	14 (0.8%)	1633	13 (0.8%)	9 (0.6%)	17 (1%)	10 (0.6%)

RSG+Insulin versus Insulin

Study	RSG Events					CONTROL Events				
	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF
082	212	5 (2.4%)	1 (0.5%)	9 (4.2%)	3 (1.4%)	107	0	0	1 (0.9%)	0
085	138	6 (4.3%)	5 (3.6%)	10 (7.2%)	8 (5.8%)	139	1 (0.7%)	1 (0.7%)	2 (1.4%)	2 (1.4%)
095	196	6 (3.1%)	2 (1%)	11 (5.6%)	5 (2.6%)	96	3 (3.1%)	1 (1%)	4 (4.2%)	2 (2.1%)
136I	112	3 (2.7%)	2 (1.8%)	8 (7.1%)	4 (3.6%)	109	1 (0.9%)	0	5 (4.6%)	3 (2.7%)
347	209	4 (1.9%)	2 (1%)	4 (1.9%)	2 (1%)	212	4 (1.9%)	2 (0.9%)	4 (1.9%)	2 (0.9%)
Overall	867	24 (2.8%)	12 (1.4%)	42 (4.8%)	22 (2.5%)	663	9 (1.4%)	4 (0.6%)	16 (2.4%)	9 (1.4%)

RSG+Sulphonylurea+Metformin versus Sulphonylurea+Metformin

Study	RSG Events					CONTROL Events				
	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF	N	IHD	Ser IHD	IHD/CHF	Ser IHD/CHF
134	561	9 (1.6%)	5 (0.9%)	16 (2.9%)	8 (1.4%)	276	4 (1.4%)	3 (1.1%)	4 (1.4%)	3 (1.1%)

Appendix 5 Long-term rosiglitazone studies

	TRT ARMS (Sample size)	Duration	Population	Primary outcome
DREAM	Placebo (1321) Ramapril (1313) Rosiglitazone (1325) RAM+RSG (1310)	Completed Median 3 years	Impaired FPG or impaired glucose tolerance No pts with hx of T2DM, or CV disease	Time to incident diabetes or death
ADOPT	Rosiglitazone (1456) Metformin (1454) Sulfonylurea (1441)	Completed Median 4 years	T2DM diagnosed w/i last 3 years No NYHA CHF Class 3&4 nor CHF requiring meds	Time to monotherapy failure
RECORD (OL due to added insulin therapy)	MET+RSG (1117) MET+SU (1105) SU+RSG (1103) SU+MET (1122)	On-going Minimum 5 years Median 6 years	T2DM No Hospitalization for CV event in last 3 mos No CHF requiring meds	Time to CV death or CV hospitalization

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/s/

Joy Mele
6/4/2007 06:33:19 PM
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S. Edward Nevius
6/4/2007 06:39:43 PM
BIOMETRICS
Signing for Todd Sahlroot.

Advisory Committee Nonclinical Briefing Document NDA 21-071**Drug:** Avandia (rosiglitazone maleate)**Drug Class:** PPAR gamma agonist**Clinical Indication:** Type II Diabetes**Reviewer:** Todd Bourcier, Ph.D., Division of Metabolism and Endocrinology Products**Re:** Tumor findings in animals associated with rosiglitazone and pioglitazone

Animal studies with pioglitazone identified carcinoma, papilloma, and hyperplasia of urinary bladder transitional cells in male rats. The bladder tumors occurred at a dose that approximates human exposure from a 45mg clinical dose. This finding is disclosed in the Carcinogenesis section of the Actos label. Rosiglitazone did not produce bladder tumors from similar studies in animals, although the incidence of adipose hyperplasia and lipomas were increased at clinically relevant exposures.

Experience subsequent to approval of pioglitazone and rosiglitazone revealed that bladder tumors commonly occur in rats exposed for long periods to PPAR agonists with alpha and gamma activity (i.e., 'dual' PPAR agonists, none approved by FDA). Pioglitazone and rosiglitazone activate PPAR gamma with approximate potencies (EC50s) of 600nM and 86nM, respectively. Of interest, pioglitazone also activates PPAR alpha, at least partially, at clinically relevant plasma drug concentrations, whereas rosiglitazone does not. Thus, it is thought that bladder tumors observed with pioglitazone and with subsequent PPAR dual agonists might occur via a common mechanism.

A hypothesis has emerged that dual PPAR-induced changes in urinary pH and solute composition predispose male rats to forming urinary crystals that would persistently damage the bladder epithelium and, over time, result in transitional cell hyperplasia and neoplasms. Aspects of this hypothesis are supported by experimental evidence with some though not all PPAR dual agonists known to produce bladder tumors, including pioglitazone. Hyperplastic lesions found in the bladder of non-human primates exposed to some dual PPAR agonists and tumor promoter activity of pioglitazone in a rodent model of bladder cancer represent additional findings that are not explained by the crystalluria hypothesis. The weight of evidence suggests that rats are more susceptible to dual PPAR agonist-induced bladder tumors than other species (including humans), but that the risk of patients developing bladder tumors with chronic exposure to a PPAR dual agonist cannot be entirely excluded.

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

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/s/

TODD M BOURCIER

06/18/2010

Nonclinical comments regarding carci findings for 2010 AC meeting



Date: July 6, 2010

From: Center for Drug Evaluation and Research
U.S. Food and Drug Administration

To: Advisory Committee Panel Members for July 13 and 14, 2010 public
meeting on Avandia® (rosiglitazone)

Subject: Addendum to FDA Advisory Committee Meeting Background Package

The following addendum contains FDA decisional memos on the issue of cardiovascular safety of Avandia® (rosiglitazone). These documents are being made available to the advisory committee panel members and released to the public to provide insight on decisions made over the past three years as new data became available.



**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: September 27, 2007

To: Paul Seligman, MD, MPH
Director, Safety Policy and Communications Staff

From: Gerald Dal Pan, MD, MHS
Director, Office of Surveillance and Epidemiology

Subject: Office Director Memorandum for Drug Safety Board Meeting

Drug Name(s): Rosiglitazone

Application Type/Number: NDA 21-071

Submission Number: S-022

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2006-331

1 INTRODUCTION

Over the past several months, there has been intense discussion of the risk of myocardial ischemia associated with rosiglitazone in FDA, in the medical literature, in the media, and at a joint meeting of the Endocrine and Metabolic Drug Advisory Committee (EMDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). The purpose of this memorandum is to explain my views regarding the risk of myocardial ischemic events related to rosiglitazone (Avandia), and the basis for my recommendation that the product be withdrawn from the market. While many staff in the Office of Surveillance and Epidemiology (OSE) have worked closely with me on this issue, this memorandum will explain my own views.

This memorandum does not address adding a boxed warning for congestive heart failure (CHF) to the labels of rosiglitazone and pioglitazone products, which OSE recommended in a review on February 22, 2006,¹ and which we reiterated in our review of myocardial ischemic events on February 6, 2007.² In addition, this memorandum does not address risk management strategies that the Agency might consider, should it decide that rosiglitazone will remain on the market.

2 MATERIAL REVIEWED

Sponsor Submissions

GlaxoSmithKline Submissions:

Supplement 022: submitted Aug 4, 2006: includes (a) Final Study Report for the integrated clinical trials analysis (“AVANDIA Cardiovascular Event Modeling Project”); (b) Final report for the observational balanced cohort study (“Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents”); (c) proposed labeling that provides a description of these studies; and, (d) response to FDA safety data request regarding cardiovascular serious adverse events (SAEs) in rosiglitazone (RSG)-treated subjects in the pooled safety analysis.

ADOPT (A Diabetes Outcomes Progression Trial) Final Study Report and datasets; submitted by GSK Feb 28, 2007.

¹ Green, L. DDRE Review of Macular Edema with Rosiglitazone and Pioglitazone. PID Number D050735. February 22, 2006.

² Gelperin, K and Green, L.. Thiazolidinediones and Cardiovascular Adverse Effects. February 6, 2007. RCM #2006-331.

RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) interim analysis results; submitted by GSK May 18, 2007.

Walker AM, Landon J, and Ziyadeh N (for i3 Drug Safety). Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents in the Pharmetrics Data base – Preliminary Report. June 27, 2007.

Takeda Submissions (Not directly reviewed by OSE staff):

PROactive Clinical Study Report. NDA 21073 SE8-026, Actos (pioglitazone), Takeda; Report date Jan 24, 2006.

Cardiovascular Events and Deaths Reported During Double-Blind, Randomized, Comparator-controlled Clinical Trials of Pioglitazone HCl (ACTOS): A Time-to-Event Meta-analysis. Final Report. Study #01-06-TL-OPI-526; Report date Oct 6, 2006.

FDA Reviews

Cooper C and Wu Y. Division of Biometrics VI. Statistical review. NDA 21-071. Coronary heart disease outcomes in patients receiving antidiabetic agents (HM2006/00497/00). GlaxoSmithKline; Submitted Aug 4, 2006. Review date Jan 31, 2007.

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Graham DJ. Review of interim analysis for RECORD. Avandia (rosiglitazone) NDA 21-071. RCM #2006-331. Review date July 6, 2007.

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Lawrence J. Statistical review and evaluation of RECORD protocol and interim analysis. Avandia (rosiglitazone) NDA 21-071. Review date July 3, 2007.

Levenson M. Statistical review of the study report: An assessment of the Effect of Thiazolidinedione Exposure on the Risk of Myocardial Infarction in Type 2 Diabetic Patients. July 11, 2007.

Mahoney KM. Clinical Review (draft). NDA 21071 SE8-022, Avandia (rosiglitazone), GlaxoSmithKline; Retrospective integrated analysis of randomized controlled trials with rosiglitazone and retrospective observational balanced cohort study. Submitted Aug 4, 2006; Review date June 4, 2007.

Mahoney KM. Clinical Review. NDA 21073 SE8-026, Actos (pioglitazone), Takeda; PROactive cardiovascular outcome study; Submitted Jan 24, 2006; Review date Aug 24, 2006.

Mahoney KM. Addendum to Clinical Review NDA 21073 SE8-026, Actos (pioglitazone), Takeda; Major amendment, CHICAGO (Carotid Intima Media Thickness Trial Comparing Pioglitazone to Glimepiride) and Meta-analysis of Cardiovascular Events in Pioglitazone Controlled Trials; Submitted Oct 10, 2006; Review date January 4, 2007.

Mahoney KM and Parks M. DMEP. Briefing document for TZD / Rosiglitazone Public Advisory Committee Meeting. July 9, 2007.

Mele J. Division of Biometrics 2 (HFD-715) Statistical Review and Evaluation, Clinical Studies; NDA 21-071/S-022 Avandia (rosiglitazone); Submitted Aug 4, 2006; Review date June 4, 2007.

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Misbin RI. Medical Officer Review. Actos (pioglitazone) Study H6E-US-GLAI Takeda, NDA 21073; Submitted Feb 1, 2005; Review date April 23, 2007.

Parks M. Division Director's Memo. NDA 21-071/Supplement 022; Avandia (rosiglitazone) GlaxoSmithKline. June 4, 2007.

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Dormandy JA, Charbonnel B, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 2005; 366:1279-1289.

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Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007 Sep 12; 298(10):1189-95.

3 DISCUSSION

There is a vast amount of clinical data that has been used to address the issue of an association between myocardial ischemic events and rosiglitazone. Data from individual clinical trials, meta-analyses of clinical trials, and observational studies have contributed to the body of information that has been the basis of our discussions. Much of these data have been reviewed in detail by Dr. Kate Gelperin of the Office of Surveillance and Epidemiology. In addition, reviews by the Office of New Drugs and the Office of Biostatistics have also provided detailed analyses of the available data. I will therefore not provide specific detailed critiques of each of the studies or analyses. Rather, I will highlight certain points that are relevant to my thinking on this issue.

One challenge in the review of the available data is that the results of some studies or analyses, on their face, are not consistent with the results of other studies or analyses. Given the relatively small size of the effect on the relative risk scale (about 1.4, though on a population basis this effect size is important³), it is thus not surprising that different people, looking at the same data, have arrived at different conclusions regarding the risk of myocardial ischemia with rosiglitazone. Because there are different views on the nature of this risk, there are, not surprisingly, different views on the most appropriate regulatory action.

The analysis that has been at the center of the discussion on the risk of myocardial ischemia with rosiglitazone is a pooled clinical trial analysis performed by the sponsor, GlaxoSmithKline

³ The relative risk of 1.4 implies a 40% increase in the rate of myocardial ischemic events in diabetic patients taking rosiglitazone, compared to those not taking rosiglitazone. If the background rate of myocardial infarction in the diabetic population is between 2% and 4% per year, the excess absolute risk in diabetic patients taking rosiglitazone (ie, the risk difference between diabetic patients who take rosiglitazone and those who do not) is between 0.8 and 1.6% per year. Given the large number of diabetic patients on oral agents, the population burden of this increased risk is significant.

(GSK). The GSK pooled clinical trial analysis yields an overall hazard ratio for cardiac ischemia of 1.31 (95% CI: 1.01-1.70).

A major issue in the review of the pooled clinical trial data is whether the overall increased risk of cardiac ischemia is explained by a particularly elevated risk in an identifiable subgroup of patients, or whether the risk is uniform across all patients. Using recursive partitioning analysis, the sponsor's pooled analysis suggests that this risk is particularly high in patients with pre-existing coronary heart disease (CHD) on nitrates at baseline. However, the data for patients without known CHD, the largest of the three patient subgroups based on the sponsor's recursive partitioning analysis, shows an association with a hazard ratio of 1.42, with a lower bound of the 95% CI (0.96) that, while below 1.0, is not far from it.

A specific methodological issue with the GSK pooled clinical trial analysis is that it may not have preserved the randomization of the original trials. FDA's re-analysis of these data, which employed a statistical technique to preserve the randomization of the original trials, has found a hazard ratio (1.4, 95% CI: 1.1, 1.8) that is statistically significant and similar in magnitude to that of the sponsor.

The FDA review⁴ noted that the qualitative heterogeneity of study designs and patient populations made interpretation of a single, overall risk estimate difficult. In sub-analyses, the following risk estimates were obtained:

- In placebo-controlled studies of rosiglitazone+metformin versus metformin alone, the odds ratio was 3.2 (95% CI: 1.2, 9.8, p=0.01). Of note, a variety of study designs and patient populations contributed to this meta group, complicating the interpretation of the findings.

⁴ Mele J. Division of Biometrics 2 (HFD-715) Statistical Review and Evaluation Clinical Studies NDA 21-071/S-022 Avandia (rosiglitazone) Submitted 8/4/2006; UFGD 6/4/2007.

- The risk of ischemic events was doubled in patients taking rosiglitazone in combination with insulin, compared to patients taking insulin alone (OR 2.1, 95% CI: 0.9, 5.1, p=0.07).
- Data on direct comparisons of rosiglitazone to either metformin or a sulfonylurea were limited. The odds ratio for these active-controlled trials was 0.8 (p=0.8). In contrast, the odds ratio for placebo-controlled trials was 1.6 (p=0.02), driven in large part by trials of rosiglitazone + metformin versus metformin alone.. The data are summarized in Table 3.3.11, reprinted below, of the FDA statistical review.

Table 3.3.11 Total (non-serious+serious) and serious IHD results for ~6-month placebo and active controlled studies; studies of 1 year or longer and insulin studies and Studies 211 and 352 in CHF and CHD patients, respectively, are excluded

Event	RSG Events/N (%)	CONTROL Events/N (%)	Test of Homogeneity	OR (95% CI)	p-value
Placebo-controlled					
IHD	95/6033 (1.6%)	43/4083 (1.1%)	0.46	1.6 (1.1, 2.3)	0.02
Serious IHD	48/6033 (0.8%)	17/4083 (0.4%)	0.28	1.9 (1, 3.6)	0.03
Active-controlled					
IHD	12/929 (1.3%)	15/907 (1.7%)	0.80	0.8 (0.3, 1.9)	0.8
Serious IHD	7/929 (0.8%)	10/907 (1.1%)	0.71	0.66 (0.2, 1.9)	0.5

- Subgroup analyses of studies in which insulin was not administered demonstrated that patients taking nitrates had a higher risk of ischemic events (OR 3.1, 95% CI: 1.5, 6.8, p=0.001) compared to patients not on nitrates.

Thus, the FDA re-analysis of the sponsor's pooled clinical trial data confirmed an overall elevated risk of ischemic cardiac events with rosiglitazone. This analysis also identified patients on nitrates and patients on insulin therapy as groups that were at particularly high risk for ischemic cardiac events. The combination of rosiglitazone and metformin carried a higher risk of ischemic cardiac events than did metformin alone. Of note, the pooled population of the placebo-controlled trials was much larger than that of the active-controlled trials.

The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study used a 2x2 factorial design to determine whether treatment with ramipril and/or rosiglitazone

prevents diabetes in patients with impaired glucose tolerance or impaired fasting glucose.⁵ In the rosiglitazone group, 2.9% of patients experienced the cardiovascular composite outcome, while 2.1% of patients in the non-rosiglitazone group experienced this outcome (hazard ratio 1.37, 95% CI: 0.97, 1.94, P=0.08). In the manuscript describing these results, the authors note that terms for interactions were not statistically significant. Review of additional outcome data for each of the four arms of the trial, however, suggests that patients treated with the combination of rosiglitazone and ramipril, relative to those treated with ramipril alone, are at increased risk for ischemic cardiac events (3.4% vs. 1.8%, RR = 1.9 for the composite cardiovascular outcome), while patients treated with rosiglitazone alone are not at an increased risk for these events, compared to patients treated with placebo (2.4% vs. 2.4%, RR = 1.0 for the composite cardiovascular outcome). In any event, the data from the DREAM trial suggest that some patients treated with rosiglitazone are at increased risk of myocardial ischemic events, even if the available data do not allow for a precise specification of these patients. These findings are particularly concerning, as patients enrolled in the DREAM trial were pre-diabetic at the time of study entry, and thus suggest that the risk imparted by rosiglitazone is not unique to diabetic patients. Furthermore, the potential interaction with ramipril resulting in an increased frequency of myocardial infarction is also important to note, since a large portion of the diabetic population is on an angiotensin-converting enzyme inhibitor.

A Diabetes Outcome Progression Trial (ADOPT) was a GSK-sponsored study designed to study three oral anti-diabetic agents (rosiglitazone, metformin, and glyburide) as initial monotherapy in 4360 patients recently diagnosed with type 2 diabetes.⁶ The primary outcome measure was monotherapy failure, defined as a fasting plasma glucose of more than 180 mg/dL. The median duration of treatment was 4.0 years for patients on rosiglitazone and metformin and 3.3 years for patients on glyburide. The rates of any cardiovascular adverse event and investigator-reported CHF were generally similar between the rosiglitazone and metformin groups, but were lower in the glyburide group. Edema was notably higher in the rosiglitazone group. In their discussion, the ADOPT study authors noted that their study was not designed to assess cardiovascular risk. They also comment that “[o]verall, the proportions of patients with cardiovascular events were

⁵ The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial, *Lancet* 2006; 368:1096-1105.

⁶ Kahn SE, Haffner SM, Heise MA et al. ADOPT study group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; 355:2427-2443.

similar in the rosiglitazone and metformin groups but were lower in the glyburide group. This observation differs from the UKPDS findings, which suggested that metformin reduces overall mortality and may reduce coronary events.”⁷ They note that the length of follow-up in ADOPT was shorter than that in the UKPDS, and that patients entering ADOPT were younger and had better glycemic control. Finally, they remark that the lower rate of cardiovascular events in the glyburide group is not consistent with epidemiologic findings that have suggested that patients taking sulfonylureas have an increase in deaths and myocardial infarction. The reason for this observation is not clear, though it does raise questions about the generalizability of findings in ADOPT. The lack of a placebo in ADOPT allows only comparisons to other treatments. While there is certainly clinical relevance to these comparisons, an independent effect of rosiglitazone (or any of the other agents) can not be discerned.

GSK is currently sponsoring the RECORD study to assess the cardiovascular risk associated with rosiglitazone. In a separate memorandum⁸ that was part of the background package for the advisory committee meeting, I expressed my concern that the RECORD study would not satisfactorily resolve the uncertainty over the cardiovascular risk of rosiglitazone. My concerns center around the low power of the study (given the data observed to date), the open-label design, the lack of justification for selection of a 20% increase in relative risk (ie, an upper limit of the 95% confidence interval of hazard ratio equal to 1.2) as the magnitude of excess cardiovascular risk that is to be excluded, and the composite cardiovascular outcome, which includes cardiovascular events beyond those of interest for the present discussion. In addition, I noted that careful execution of a non-inferiority study is essential for a valid conclusion from such a study. The data available to date from the RECORD study are from an interim analysis. As such, FDA has not had the opportunity to analyze the primary data, nor has FDA had the opportunity to examine the conduct of the study. Given these limitations, I am hesitant to base any regulatory decisions on the RECORD study. In addition, the final results of the RECORD study will not be available for about 18 months, too long a time for FDA to delay any regulatory action.

⁷ Ibid.

⁸ Dal Pan, G. Supervisory Memo for Review of RECORD Study. July 6, 2007. OSE RCM #2006-331.

Two observational studies were commissioned by GSK and conducted by i3 Drug Safety. The first, a propensity score matched cohort study using claims data from enrollees of United Healthcare, identified new cases of myocardial infarction or coronary revascularization in diabetics prescribed rosiglitazone, metformin, sulfonylureas, or insulin, in monotherapy or combination.⁹ The study found increased cardiovascular risk for new users of sulfonylureas compared to metformin monotherapy; however, the risk for new users of rosiglitazone was not significantly different from either of the other groups. The second study from GSK is a cohort study that was also conducted by i3 Drug Safety but uses claims data from a different source, PharMetrics (study report was submitted to FDA, but has not been published). The study population is much larger than that of the United Healthcare study and included a pioglitazone group. The overall results were consistent with the initial study. However, both studies were limited by poor representation of patients older than age 65, and a definition of outcome that was not sufficiently inclusive to capture the adjudicated events from the rosiglitazone meta-analysis, including sudden cardiac death. Other weaknesses include potentially poor ascertainment of study drug exposure, since unknown compliance, poor adherence, and switching among diabetic study cohorts can lead to misclassification bias. In addition, questions remain on unmeasured confounding. For instance, major risk factors for cardiac disease such as smoking and aspirin use were not captured. These methodological problems with the two observational studies preclude, in my view, reliance on them for decision making.

Rosiglitazone is not the only currently marketed thiazolidinedione. Pioglitazone (Actos), another member of this class, is also marketed in the US. It is important to note that while both agents can lead to heart failure, the available data do not seem to indicate that the risk of ischemic cardiac disease with rosiglitazone exists with pioglitazone. One relatively small clinical trial, the GLAI study¹⁰ directly compared rosiglitazone to pioglitazone in patients with type 2 diabetes and dyslipidemia over a 12-week period. In this study, 2/369 (0.6%) of pioglitazone-treated patients and 6/366 (1.6%) of rosiglitazone-treated patients experienced cardiac serious adverse events. Apart from the GLAI study, however, all other comparisons of clinical trial data between these two thiazolidinediones are generally indirect. Such an approach must be viewed with caution.

⁹McAfee AT, Koro C, Landon J, Yiyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents, *Pharmacoepidemiol Drug Saf* 2007; 16(7): 711-725.

¹⁰Goldberg RG, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005; 28:1547-1554.

Nonetheless, the data summarized below do not suggest that pioglitazone is associated with a risk of myocardial ischemia.

Two observational cohort studies include direct comparisons of rosiglitazone and pioglitazone. The PharMetrics study sponsored by GSK showed no difference in risk for the two drugs. The other, a retrospective cohort study conducted by Takeda, showed a 22% relative risk reduction of hospitalization for acute myocardial infarction with pioglitazone, compared to rosiglitazone.¹¹

There is one published long-term study examining macrovascular endpoints in patients with type 2 diabetes treated with pioglitazone. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) study was a study that enrolled patients with type 2 diabetes with an elevated HbA1c despite treatment with diet alone or oral glucose-lowering agents, with or without insulin, who also had evidence of extensive macrovascular disease before study entry.¹³ Though the study did not meet its primary endpoint (time from randomization to: all-cause mortality, non-fatal myocardial infarction [including silent myocardial infarction], stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankles), the results suggest that pioglitazone does not have a long-term adverse cardiovascular effect, as assessed by the primary endpoint. The hazard ratio was 0.90 (95% CI: 0.80-1.02, P=0.095). The study's main secondary endpoint (death from any cause, myocardial infarction [excluding silent myocardial infarction], or stroke) did reach statistical significance in favor of pioglitazone (hazard ratio=0.84, 95% CI: 0.72-0.98, P=0.027).

A meta-analysis of 19 randomized placebo- or active controlled clinical trials enrolling 16,390 patients treated with pioglitazone or comparator for periods ranging from four months to 3.5

¹¹ Gerrits CM, Bhattacharya M, Manthena S, et al. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. *Pharmacoepidemiol Drug Saf*; published online Aug 3, 2007.

¹³ Dormandy JA, Charbonnel B, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 2005; 366:1279-1289.

years was recently published.¹⁴ Using patient-level time-to-event data, the study indicated that the hazard ratio for the primary outcome (death, myocardial infarction, or stroke) was 0.82 (95% CI: 0.72, 0.94, P=0.005). The study authors report that this favorable effect of pioglitazone on ischemic events was homogeneous across trials, comparators, and durations of treatment. The authors also found that pioglitazone increased the rate of CHF (HR= 1.41, 95% CI: 1.14, 1.76, P=0.002), an effect seen across trials, comparators, and durations of treatment. The patient populations studied in these trials, and the relative use of the various comparators, are somewhat different from those in the rosiglitazone meta-analysis. Thus, while caution must be exercised in comparing these data to the data from the rosiglitazone meta-analysis, the available data do not suggest that pioglitazone is associated with a risk of myocardial ischemia. FDA staff has not yet analyzed the data from the pioglitazone meta-analysis to the same extent that the rosiglitazone data have been analyzed.¹⁵ Such review and statistical analysis, which FDA should undertake as a priority to confirm the published findings, will be an important step in making conclusions about the risk of ischemic cardiac disease with pioglitazone. It is also important to note that pioglitazone, like any other agent to treat diabetes, has its own side effects.

Although questions regarding the risk of myocardial ischemia with rosiglitazone remain unanswered, it is unlikely that ongoing clinical trials, for the reasons mentioned above, will provide answers with sufficient certainty to assure that the risk of myocardial ischemia is less than that suggested by current estimates. In addition, given the risks already identified with rosiglitazone in higher risk patients (e.g. those on nitrates or taking insulin), as well as the apparent lack of an increased risk of myocardial ischemia with pioglitazone, a head-to-head comparison with pioglitazone in such patients would likely face challenges on ethical grounds.

The advisory committee voted 20-3 that rosiglitazone was associated with an increased frequency of myocardial ischemic events, and further voted 22-1 that the drug should continue to be marketed, albeit with a change in the product's labeling to reflect this risk. There was a wide

¹⁴ Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus – a meta-analysis of randomized trials. JAMA 2007; 298(10): 1180-88.

¹⁵ Mahoney KMM. Clinical Reviewer. Addendum to Clinical Review NDA 21073 SE8-026, Major amendment submitted 10 OCT 06, CHICAGO Carotid Intima Media Thickness Trial Comparing Pioglitazone to Glimepiride and Meta-analysis of Cardiovascular Events in Pioglitazone Controlled Trials, January 4, 2007.

range of opinions amongst the advisory committee members regarding the nature and certainty of the risk of myocardial ischemia, and a simple tally of the votes does not reflect the diversity of these opinions. Many advisory committee members felt that the available data did not provide strong or definitive evidence of a risk of myocardial ischemia. Some qualified their “yes” vote on the risk of myocardial ischemia by changing the words “support a conclusion” to “suggest” in the question “Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus?” Most felt that the risk of myocardial ischemia was not sufficiently established to justify market withdrawal.

Data from FDA’s meta-analysis point to an increased risk of ischemic myocardial events in patients taking rosiglitazone. This effect is most pronounced when rosiglitazone is compared to placebo, and is even more pronounced in certain subgroups, such as those on concomitant insulin therapy and those on nitrates. A broader ischemic cardiovascular risk can not be excluded. Meta-analysis data and data from individual clinical trials comparing rosiglitazone to other active comparators are less clear about a risk of myocardial ischemia. However, the available data, in my view, do not provide convincing evidence that such a risk does not exist.

Since most of the data in the rosiglitazone meta-analysis comes from trials with a median duration of six months, some have argued that the results of the meta-analysis are not relevant to the assessment of the long-term risk-benefit balance of rosiglitazone, or even to the regulatory decisions at hand. However, population-based data suggest that short-term data are, in fact, highly relevant. An analysis from Ingenix shows that by nine to eleven months of use, 50% or fewer of patients started on rosiglitazone are still using the drug.¹⁶ The long-term data on the risk of myocardial ischemia with rosiglitazone have not been as carefully reviewed at FDA as have been the short-term data. Nonetheless, a recently published meta-analysis¹⁷ of long term trials with rosiglitazone (ADOPT, RECORD, -211, DREAM) shows significantly increased risk of myocardial infarction (relative risk 1.42, 95% CI: 1.06-1.91, P=0.02), without a significantly increased risk of cardiovascular mortality. As with the meta-analysis of the short-term

¹⁶ Walker AM (for i3Drug Safety). Additional analyses for the study “Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents” requested by Dr. David Graham of the FDA. August 22, 2007. Submitted by GSK.

¹⁷ Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone – a meta-analysis. JAMA 2007; 298(10):1189-1195.

rosiglitazone clinical trials, the meta-analysis of the long-term clinical trials is complicated by variations across trials in patient populations, study designs, and outcome ascertainment. Nonetheless, the relative risk estimate in this meta-analysis of long-term studies is similar in magnitude to that in the short-term studies.

The variability in results across the different studies and analyses precludes a precise estimate of the relative risk of myocardial ischemia with rosiglitazone. There are differences across trials with regard to patient populations studied, duration of treatment, severity of diabetes, presence of underlying cardiovascular disease, cardiovascular risk factors, and method of cardiovascular outcome ascertainment. In addition, there are recognized limitations of meta-analyses, which is complicated by the fact that the studies were not designed with the primary objective of quantifying cardiovascular risk in patients taking rosiglitazone. In combination, these factors lead to uncertainty concerning the ischemic cardiovascular risk of rosiglitazone. Nonetheless, several analyses point to a relative risk of approximately 1.4. Specifically, meta-analyses of both short-term and long-term studies suggest a relative risk of 1.4 for myocardial ischemic events. In addition, the DREAM study in pre-diabetics (which was part of the meta-analysis of the long-term studies) also suggests a relative risk of about 1.4. This 40% relative increase in the risk of myocardial ischemic events is extremely consequential on a population basis, given the high background rate (about 2-4%/year) of myocardial infarctions in diabetic patients. Moreover, one of the primary reasons for attempting to achieve euglycemia in diabetic patients is to prevent complications, which are primarily cardiovascular in nature. Yet here, the very complication that we are trying to prevent appears to be increased.

The uncertainty of the risk measurement must be weighed against the public health implications of such risk. Definitive proof of a causal effect is rarely, if ever, achieved in postmarketing safety analyses. From a public health standpoint, in my view, it is neither necessary nor appropriate to demand definitive statistical proof of a causal effect before taking regulatory action. In this case, the public health impact of an approximately 40% relative increase in the frequency of myocardial infarction in patients taking rosiglitazone outweighs the uncertainty that exists about the risk assessment, especially since myocardial ischemia is such an important cause of morbidity and mortality in diabetic patients.

At the July 30, 2007, joint advisory committee meeting, I supported Dr. David Graham's conclusion that rosiglitazone be removed from the market. While I disagree with some of Dr. Graham's methods and other technical points, I support the overall conclusion that rosiglitazone be removed from the market. My conclusion is based on a public health approach, not a statistical one. In reaching this conclusion, I am aware of the growing burden of diabetes, especially Type 2 diabetes, in the US. I am also aware of the need for better treatments for diabetes. I am aware of the need for good glycemic control in patients with Type 2 diabetes, and that no treatment is not an option for most patients. Finally, I am aware that another widely used class of oral antidiabetic agents used in the treatment of Type 2 diabetes, the sulfonylureas, may also carry a cardiovascular risk. However, when I consider the data before me, they point to a consequential risk of myocardial ischemia that is not counterbalanced by data that convincingly refute that risk. While rosiglitazone does provide glycemic control, which is important in the treatment of diabetes, it is my understanding that rosiglitazone has no unique qualities in this area. Finally, there are no data that demonstrate that rosiglitazone favorably impacts the long-term micro- and macrovascular complications of Type 2 diabetes. Given this information, I believe that the balance of risks and benefits does not favor rosiglitazone.

Market withdrawal of any pharmaceutical product is not an action to be taken lightly. The one group of patients who would be most acutely affected by such an action are those who are already taking rosiglitazone and whose blood glucose is well-controlled, in the absence of significant side effects. Market withdrawal would result in treatment disruption for these patients. If a subset of patients for whom rosiglitazone were uniquely beneficial could be identified, then an alternative to market withdrawal could be considered. However, the identification of such patients would have to be prospective and based on data, rather than on anecdote. Such patients should not be those for whom FDA's analysis has indicated a high risk of myocardial ischemia, such as those on insulin therapy or those with cardiac disease on nitrates. Although it is possible that some individual patients may do well on rosiglitazone and not experience increased cardiac risk, such patients have not been identified in clinical trials.

It is important to note that the assessment of regulatory and public health options regarding rosiglitazone can not be based simply on the estimate of risk of myocardial ischemia. Rather, it is based on a balance of the risks and benefits of the drug, in the context of current treatment options. There are certainly many serious and life-threatening conditions for which treatment

options are limited, and for which available treatments are justified, even when such treatments carry a serious risk. For this reason, each decision must be handled on a case-by-case basis.

4 CONCLUSIONS AND RECOMMENDATIONS

In considering the overall risk of a drug, it is important to weigh the magnitude of the relative and absolute risk, the clinical importance of the risk, the public health implications of the risk, and the certainty of the evidence. In assessing the benefit of a drug, it is important not only to consider the salutary effects, but the availability of alternative therapies and whether the drug has any unique beneficial properties. With regard to the use of rosiglitazone in the treatment of type 2 diabetes, the magnitude, importance, and public health implications of the estimated cardiovascular risk are consequential beyond question. Legitimate questions have been raised regarding the certainty of the risk; however, multiple analyses point to a relative risk of 1.4. In terms of benefit, rosiglitazone provides glycemic control but has no unique properties and no demonstrated beneficial effects on the long-term macro- and microvascular complications of diabetes. Data regarding an alternative thiazolidinedione, pioglitazone, do not suggest that this agent has an increased risk of myocardial ischemia.

For the reasons stated above, I believe that currently available data do not support a favorable risk-benefit balance for rosiglitazone, and that the product should be removed from the market.

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/s/

Gerald DalPan
10/1/2007 06:22:28 PM
MEDICAL OFFICER



From: Mary H. Parks, M.D.
Director, Division of Metabolism and Endocrinology
Products

Through: Curtis Rosebraugh, M.D., M.P.H.
Deputy Director, Office of Drug Evaluation II

To: John Jenkins, M.D.
Director, Office of New Drugs

Introduction

On July 30, 2007, the cardiovascular safety concerns associated with Avandia® (rosiglitazone) were discussed before a joint public advisory committee involving members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) and Drug Safety and Risk Management Committee (DSARM). The committee was also comprised of experts in cardiovascular disease from the Cardiorenal Drugs Advisory Committee and diabetologists from the National Institutes of Health. The manufacturer, GlaxoSmithKline (GSK), and reviewers from the FDA presented clinical data from the following different sources for rosiglitazone:

Integrated Clinical Trials (ICT) Database – comprised of 42 controlled clinical trials involving rosiglitazone 4 to 8 mg daily use in patients with Type 2 diabetes mellitus (T2DM). These studies were included in a meta-analysis performed by GSK and the FDA.

Long-term Controlled Clinical Trials (LCCT) Database which included:

1. DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) - a large, double-blind, randomized, 2x2 factorial design study in 5269 patients with impaired glucose tolerance or impaired fasting glucose designed to assess the effect of 4 different treatment groups (placebo, rosiglitazone monotherapy, ramipril monotherapy, and rosiglitazone + ramipril) on the composite endpoint of incident diabetes or all-cause mortality.
2. ADOPT (A Diabetes Outcomes Progression Trial) - a randomized, double-blind, parallel group study in 4351 subjects recently diagnosed with T2DM who were previously managed with diet and exercise only. The study evaluated the following treatment groups: rosiglitazone monotherapy, metformin monotherapy, and SU monotherapy. The primary endpoint was time to monotherapy failure defined as having either a FPG > 180 mg/dL on consecutive assessments following at least 6 weeks of therapy at the maximum tolerated dose of study medication or as judged by an independent adjudication committee.
3. RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) - an ongoing, open-label, randomized trial of rosiglitazone as add-on therapy to either metformin or sulfonylurea in comparison to metformin and a sulfonylurea in patients not adequately controlled on their prior therapy. This trial was designed as a non-inferiority trial on the primary endpoint of CV death and CV hospitalization, including CHF.

Observational Studies

1. Balanced cohort study utilizing data from the United Healthcare health plans from July 2000 through December 2004 conducted by Ingenix. This database was comprised of 11,000 enrollees.

2. Observational study from Pharmetrics Database comprised of 80 US health plans from June 2000 through March 2007
3. Data from a Takeda commissioned study comparing pioglitazone to rosiglitazone were presented with the caveat that the study was just published and not yet reviewed by FDA.

Additional studies presented by FDA included:

- PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) – a clinical outcomes trial involving pioglitazone
- GLA-I – a 24-week lipid-altering efficacy trial comparing pioglitazone and rosiglitazone

Additional data were presented at the open public hearing including two observational cohort studies conducted by WellPoint and the Department of Defense.

At the conclusion of the data presentation and after extensive discussion, the advisory committee voted 22 to 1 in favor of keeping rosiglitazone on the market. This vote was preceded by a 20 to 3 vote in which the majority of members voiced concern that Avandia was associated with an increased risk for myocardial ischemia, although this was with the proposal that the question be re-worded to state that the available data *suggest* not *support* this conclusion. Members declined to discuss whether this risk was greater than other available anti-diabetic therapies while several qualified that the risk was increased when compared to placebo or in certain patient subgroups or drug combinations (see transcripts of advisory committee meeting, starting page 432).

The Division of Metabolism and Endocrinology Products (DMEP) is recommending to uphold the majority recommendation from the advisory committee to maintain market availability of rosiglitazone. This memo will discuss the basis for this recommendation and subsequent sections will delve further into the ICT and LCCT databases, including their strengths and limitations. The observational studies are not relied upon extensively in this decision given the greater limitations of these studies. Furthermore, the data from the observational studies presented at the advisory committee did not reveal an increased risk of myocardial ischemia across the different oral anti-diabetic therapies marketed.

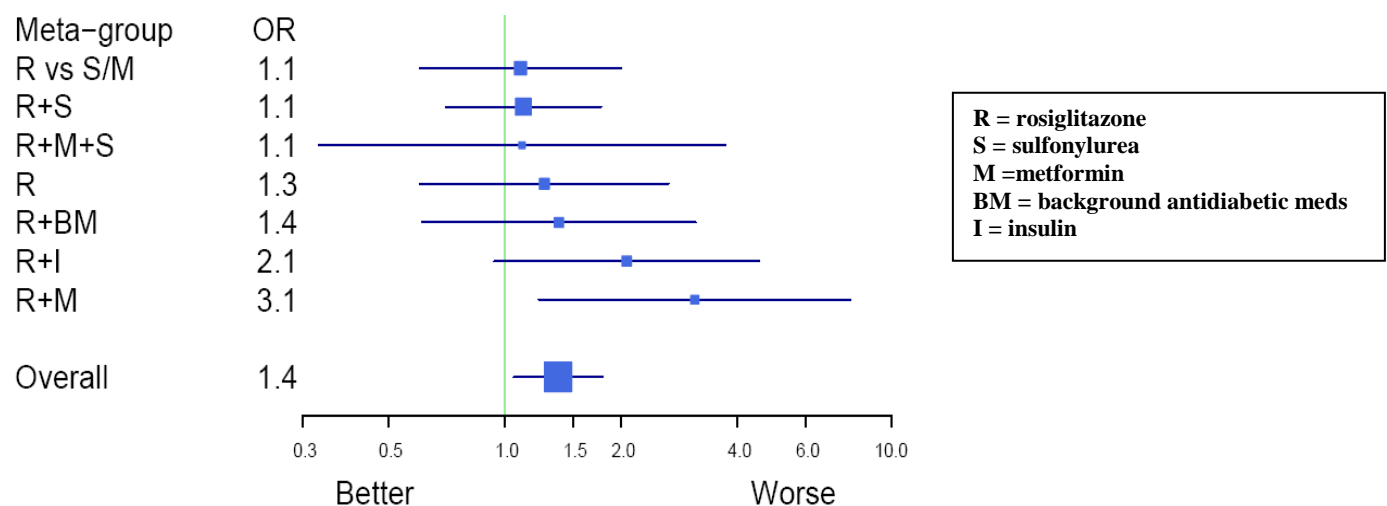
Integrated Clinical Trial Database

This database was comprised of 42 studies selected by GSK based on the following criteria:

- randomized, double-blind, controlled trials in adults with T2DM
- utilized the 4 or 8 mg dose of rosiglitazone
- cut-off period of December 2005

This database has served as the signal of cardiac ischemic risk associated with rosiglitazone. Different analyses have been performed by GSK and FDA, yielding similar estimates for ischemic risk. From Joy Mele's analysis, the odds ratio for non-serious or serious myocardial ischemia was 1.4 (95% CI: 1.1-1.8) with an associated p-value of 0.02 based on 171/8604 (2.0%) RSG events vs. 85/5633 (1.5%) control events. The following figure from Ms. Mele's advisory committee presentation summarizes the overall risk estimates and the risk estimates from the individual meta-groups (studies with similar treatment regimens).

Figure 1. Findings from FDA Meta-analysis



The strengths of this database included:

1. large number of patients - 14,237 patients (8604 on RSG/RSG-containing regimen vs 5633 non-RSG containing regimen)
2. all the studies were randomized, blinded and controlled studies

The limitations of this database included:

1. majority of trials were of 6 months duration (38 were 6 months or less; 3 were 1 year in duration; one 2-yr trial)
2. studies were not designed to evaluate cardiovascular endpoints; only one study had a blinded adjudication committee for CV endpoints, all other studies had endpoints adjudicated retrospectively
3. heterogeneous population (treatment-naïve, multiple-drug regimen, long-standing vs early diabetes, established heart disease, heart failure)
4. control group varied (placebo, different active controls – sulfonylurea/metformin/insulin)
5. treatment regimen for rosiglitazone varied (monotherapy, combination therapy, add-on)

While the overall risk estimate exceeded 1.0, this result was not robust and further analyses by certain subgroups, which highlight the heterogeneity of the database, revealed that this overall risk estimate was

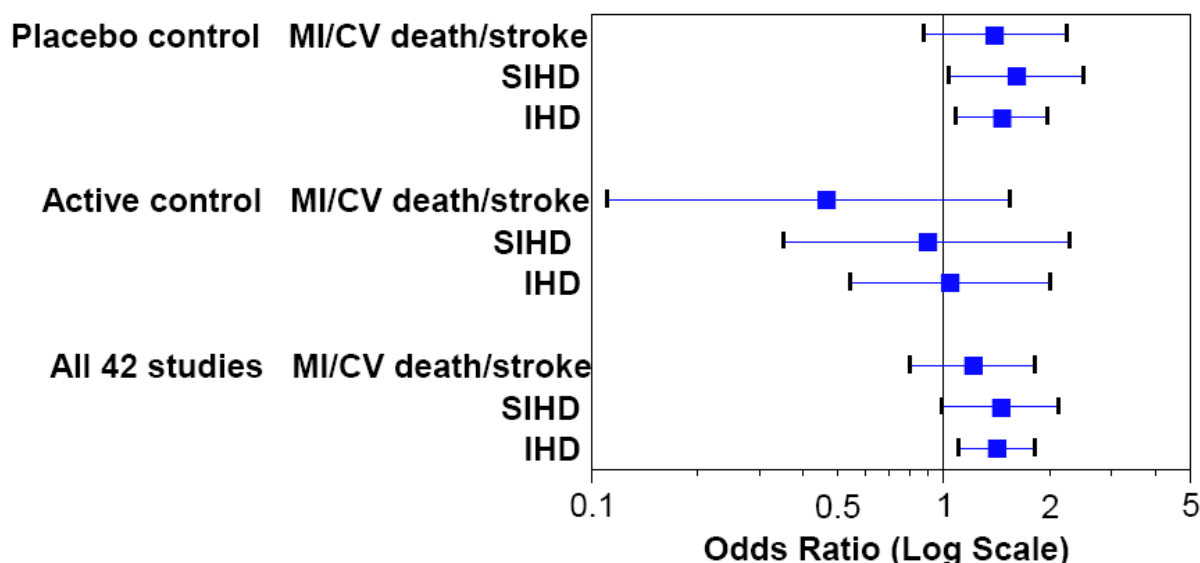
predominantly driven by certain factors described below. When these factors were excluded, the risk estimates were no longer statistically significant or in some cases, fell below 1.0. While statistical significance at a p-value of 0.05 is not necessary to take regulatory action for safety concerns, exploring the level of significance and how fragile the result is when certain sub-groups are added or removed may indicate whether the overall risk estimate is driven predominantly by a particular patient characteristic(s).

Placebo vs. Active Controlled Trials

The ICT database was comprised primarily of placebo-controlled trials (85% of the studies were placebo-controlled). These studies could have been monotherapy trials in which rosiglitazone was compared directly to placebo with no other background medications or rosiglitazone added-on to other anti-diabetics was compared to placebo added-on to other anti-diabetic therapies.

Compared to placebo, rosiglitazone was associated with a significant increase in risk of myocardial ischemia (OR 1.6, 95% CI of 1.1 to 2.3). Analysis of active-controlled trials did not reveal an increased risk for ischemia associated with rosiglitazone compared to other oral anti-diabetic agents (OR 0.8, 95% CI of 0.3 to 1.9). The following forest plot from Ms. Mele's review illustrates these findings.

Figure 2. Ischemic Risk Associated RSG Use in Placebo vs Active-controlled Studies



SIHD = serious ischemic heart disease events; IHD = serious and nonserious ischemic heart disease events

This finding suggests that the risk of myocardial ischemia is similar between rosiglitazone and other oral anti-diabetic agents that it was compared against; however, this will require further evaluation as the number of active-controlled trials is small and the confidence interval around the lower point estimate is wide. While an increased risk is observed in the subset of placebo-controlled studies, a practical question is how this observed risk can be applied to clinical practice as the majority of diabetics require drug therapy. One could not avoid a potential risk by treating diabetics with placebo.

Early Diabetes vs. Long-standing Diabetes

This analysis is relevant as the absolute risk for a cardiac ischemic event may be greater in a patient with long-standing diabetes. This was noted by Dr. Peter Savage at the advisory committee (page 393 of transcript) where he discussed the large spectrum of risk between a pre-diabetic or early diabetic and the patient with a 20-year history of diabetes. He stated that the benefit of preventing diabetes or delaying the

progression of disease with rosiglitazone may offset the slight increase in absolute risk of CVD in this population whereas the addition of rosiglitazone to a patient already requiring insulin therapy may represent an unjustifiable risk.

To evaluate any difference in risk in this subgroup of diabetic patients, Ms. Mele compared the treatment-naïve (which often represents early diabetics) population to the previously-treated population. For treatment-naïve patients (n=3348) the OR for an ischemic event was 0.97 (95% CI of 0.5 to 1.9) compared to an OR of 1.5 (95% CI of 1.1 to 2.1) in previously treated patients (11,109). Although the CI for the treatment-naïve subgroup is wide, these findings do suggest that the risk for myocardial ischemia may be higher in diabetics with long-standing disease as speculated by Dr. Savage.

Combination Therapies

In her separate analyses of meta-groups, Ms. Mele noted a greater risk of myocardial ischemia in the studies where rosiglitazone was combined with metformin (10 studies) or insulin (5 studies). For rosiglitazone + metformin, the overall OR for ischemic events was 1.8 (95% CI of 0.9 to 3.8). This was a heterogeneous meta-group (2 studies included a sulfonylurea comparator) and limiting the analysis to only the placebo-controlled studies increased this risk to an OR 3.2 that reached statistical significance (p=0.01). Evaluation of only those studies employing the fixed-dose combination of Avandamet also resulted in a significant increased risk (OR 5.1, p=0.02). It is uncertain why selected use of rosiglitazone in combination with metformin results in markedly difference risk estimates. However, this safety concern might be better addressed in the long-term study, RECORD, which includes a rosiglitazone + metformin treatment group.

For rosiglitazone + insulin, the overall OR was 2.1 (95% CI of 0.9 to 5.1) across 5 studies involving 1530 patients. This patient population was comprised of patients with long-standing disease (mean duration of diabetes was 13 years versus 4 to 8 years across the other meta-groups (monotherapy, RSG + background meds, RSG + SU, RSG + met, or triple combination therapy). Interestingly, when Ms. Mele evaluated the overall risk of myocardial ischemia in the ICT excluding these 5 RSG + insulin studies, the OR remained 1.4 but this was no longer statistically significant (p=0.06) suggesting that this patient population (only ~10% of the ICT cohort) contributed markedly to the overall risk estimate.

Other Baseline Characteristics

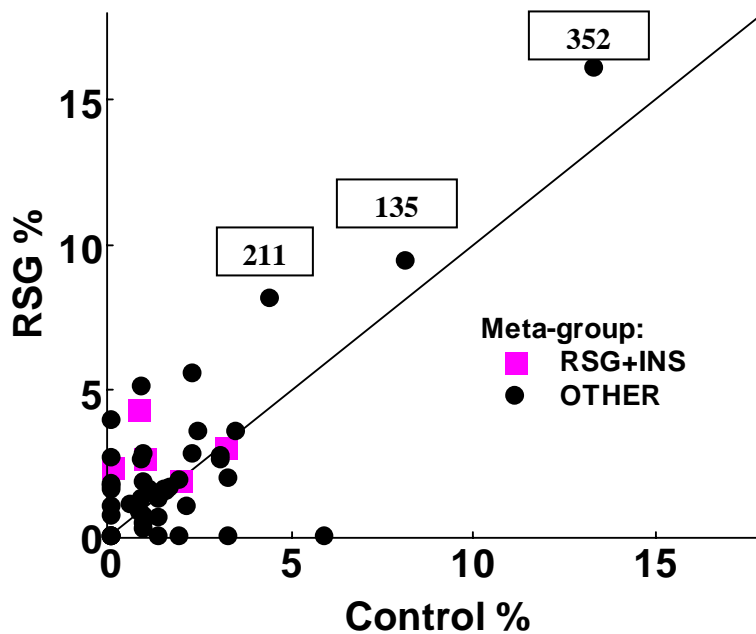
Other baseline characteristics that appeared to affect the overall risk estimate included nitrate use. There were only 557/14,237 patients in the ICT who were classified as using nitrates at Baseline. Despite this small number of patients, analysis by use or non-use of nitrates showed a significant interaction as summarized below.

Table 1. Effect of Nitrate Use at Baseline on Risk Estimate in ICT Database

Nitrate Use	N	OR (95% CI)	Exact p-value
Yes	557	3.0 (1.5, 6.2)	0.001
No	14,346	1.3 (0.9, 1.7)	0.14

Similar to insulin use, this baseline characteristic may represent a high risk population for CVD. In fact, three studies in this database wherein nitrate use was prevalent had the highest event rates (>8%) for CVD. Study 211 was a 1-year study in patients with Class I/II heart failure. Study 135 was a 2-year study in elderly patients. Study 352 was a 16-week study in patients with coronary artery disease. The following plot presented by Ms. Mele illustrates the contribution of these studies to the overall incidence of ischemic events in the ICT database.

Figure 3. Incidence Ischemic Event in 42 ICT Database



Mortality

As noted above, a limitation of the ICT database is the absence of a blinded adjudication committee in the setting of studies not conducted with the goal of capturing CV endpoints. An endpoint that would not be subject to ascertainment bias would be mortality, especially all-cause mortality. In the ICT database, there was no statistically significant difference between rosiglitazone and the control groups for these events although the short duration of evaluation (6 mos or less) would have limited information on this outcome.

Table 3.3.10 Mortality results

Mortality	RSG Deaths/N (%)	CONTROL Deaths/N (%)	OR (95% CI)	p-value
Total	28/8605 (0.3%)	11/5633 (0.2%)	1.7 (0.8, 3.4)	0.15
Cardiac (IHD)	12/8605 (0.1%)	6/5633 (0.1%)	1.3 (0.5, 3.5)	0.6
Cardiac (IHD+CHF)	17/8605 (0.2%)	7/5633 (0.1%)	1.6 (0.7, 3.8)	0.4

Conclusion

While the meta-analysis of these 42 controlled clinical trials yields an overall significant increased risk for myocardial ischemia with an upper limit of the CI being 1.8, the finding is not robust as inclusion or exclusion of certain subgroups affects the p-value or point estimate. Notwithstanding the limitations of the studies comprising this database and the method of ascertaining CV events, further evidence of the uncertainty of this risk estimate includes the observation that:

- the risk is increased only in placebo-controlled studies
- the risk appears to be predominantly driven by high-risk patient populations (e.g., insulin use, CHD, longstanding diabetes)

Given these findings, it is important to evaluate the long-term controlled clinical database to determine if similar results are observed, as meta-analyses have inherent methodologic limitations not shared by independent, large, randomized trials.

Long-term Controlled Clinical Trials (LCCT) Database

The LCCT database is comprised of three randomized, controlled studies of minimum 3 years duration. Overall, this database involves over 14,000 patients – comparable to the ICT database. Each of these three studies has been extensively reviewed already in the division memo for the Avandia supplement 022 and the background materials for the advisory committee meeting. The different patient populations, treatment regimens, and study designs address several of the questions raised in the meta-analysis of the 42 controlled clinical trials.

DREAM

This study was a double-blind, randomized, placebo-controlled clinical trial of patients with impaired fasting glucose or impaired glucose tolerance. A total of 5269 patients were randomized to ramipril 15 mg/day or placebo and rosiglitazone 8 mg/day or placebo in a 2x2 factorial design and assessed semi-annually for the primary composite endpoint of incident diabetes or death. The numbers of patients in each factorial group were as follows: placebo (n=1321); rosiglitazone monotherapy (n=1325); ramipril monotherapy (n=1313); and rosiglitazone + ramipril (n=1310).

The median duration of follow-up in this trial was 3.0 years. Although the primary objective of this study was not a CV outcomes trial, CV events were adjudicated prospectively by a blinded endpoints committee.

The following table from the *Lancet* September 2006 publication summarizes the primary and secondary outcomes of this trial.

The rosiglitazone-containing treatment group had a significantly lower incidence of developing either diabetes or experiencing death compared to the placebo group (primary outcome measure). The predominant event in this primary composite endpoint was incidence of diabetes with 10.6% of rosiglitazone-treated patients developing diabetes compared to 25.0% of placebo-treated patients. There was essentially no difference between the two treatment groups in overall mortality (1.1% rosiglitazone vs. 1.3% placebo; HR 0.9 at $p=0.7$).

Concern has been raised regarding the secondary composite of CV events. There was a non-significant increase in the composite endpoint of MI, stroke, CV death, heart failure, angina, or revascularization (HR 1.37; 95% CI: 0.97-1.94) with a statistically significant difference in the incidence of heart failure (HR 7.03; 95% CI: 1.60-30.9). Heart failure is a known, dose-related side-effect of thiazolidinediones (TZD). It is therefore important to note that DREAM studied the highest approved dose of rosiglitazone *“to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose.”* For the commonly combined cardiovascular endpoints of MI, stroke, and CV death, there was a non-significant increase associated with rosiglitazone treatment (1.2%) compared to placebo (0.9%) (HR 1.39; 95% CI: 0.81-2.37). This HR is very similar to that seen in the meta-analysis.

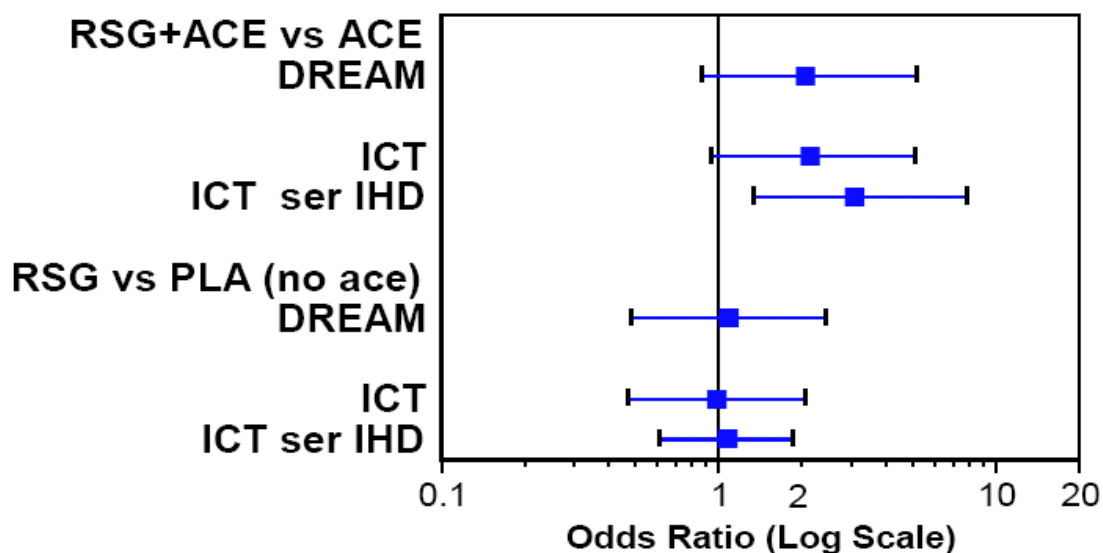
However, these results combined the factorial groups into rosiglitazone- versus non-rosiglitazone-containing treatment groups. As stated earlier, the trial was a 2x2 factorial design with four different treatment groups. The following table summarizes the CV outcomes by factorial group, as provided by the DREAM investigators to the FDA.

Table 2: CV Outcomes in DREAM Presented by Factorial Groups								
	Ramipril+Rosiglitazone N=1310		Ramipril Only N=1313		Rosiglitazone Only N=1325		Placebo N=1321	
CV Composite	N	%	N	%	N	%	N	%
MI	45	3.4	24	1.8	32	2.4	32	2.4
Stroke	11	0.8	3	0.2	5	0.4	6	0.5
All Death	2	0.2	2	0.2	5	0.4	3	0.2
CV Death	15	1.1	16	1.2	15	1.1	17	1.3
Revasc	7	0.5	5	0.4	5	0.4	5	0.4
New Angina	18	1.4	10	0.8	19	1.4	19	1.4
CHF	15	1.1	9	0.7	9	0.7	11	0.8
	11	0.8	1	0.1	3	0.2	1	0.1

In this analysis, the incidences of the CV composite and the individual components of this composite are similar between patients treated with rosiglitazone and placebo-treated patients. Ramipril-only treated patients had an overall lower rate of CV events compared to both rosiglitazone- and placebo-groups (a finding reflective of the CV prevention indication for ramipril). An unexpected finding was an increased risk of CV events in the treatment group receiving *both* ramipril and rosiglitazone. The DREAM investigators stated that no statistical interaction between the two interventions were observed ($p=0.11$). In the information provided to the FDA, tests for interaction between the two treatments were significant for the CV composite ($p=0.066$) and MI ($p=0.09$). As discussed in Ms. Mele's review of the meta-analysis, there were 5,126 reported users and 9,670 non-users of ACE-inhibitors across the 42 controlled clinical trials. The odds ratio for ischemic heart disease was statistically significantly increased among the users (1.8; $p=0.009$) whereas the increase among non-users was not significant (1.3; $p=0.18$). In Figure 4.2.3 of Ms. Mele's memo for the advisory committee meeting, she further compares the DREAM cohort to the subgroup of placebo-controlled studies from the meta-analysis (selection of placebo-only was because DREAM was a placebo-controlled study) with respect to use or non-use of ACE-inhibitor. Although this is an exploratory analysis, the point estimates and the CIs around these estimates for the composite of CV death, MI, and stroke and the serious ischemic heart disease are nearly superimposable between these two clinical databases, and would argue that further investigation in the combined effects of rosiglitazone (and perhaps all TZDs) and ACE-inhibitors are warranted.

The following figure is obtained from Ms. Mele's briefing memo to the advisory committee.

Figure 4.2.3 Plot of odds ratios for the combination of RSG with an ACE inhibitor in DREAM and in the database of short-term studies for the composite endpoint of CV death, MI or stroke and for serious ischemic (IHD) events



ADOPT

This study was an active-controlled study comparing rosiglitazone 4 to 8 mg daily to metformin or sulfonylurea in patients diagnosed with T2DM ≤ 3 years and who were treatment-naïve. The study endpoint was time to monotherapy failure. A total of 4351 patients were randomized in a 1:1:1 fashion to the three different treatment regimens. The comparison of rosiglitazone to metformin or sulfonylurea in this trial is relevant to the findings of the ICT database as no increased risk of myocardial ischemia was noted between rosiglitazone and metformin or SU in the meta-analysis.

The median duration of treatment was 4 years; however, there was a disproportionate number of patient withdrawals and discontinuations from the SU group secondary to monotherapy failure and hypoglycemia that did impact interpretability of comparison between rosiglitazone and SU. However, the patient-yrs exposure between the rosiglitazone and metformin groups was comparable.

A criticism of this study was the non-prospective collection of CV events. CV events were collected as adverse events and not adjudicated prospectively by a blinded endpoint committee. It should be repeated that CV events in the ICT database were also not prospectively identified by an endpoint committee. The criteria for selecting CV events were reviewed by DMEP and Dr. Ellis (acting deputy director in OSE) and no evidence of systematic bias was detected.

Supporting the finding from the ICT analysis of active-controlled trials, CV event rates were comparable between rosiglitazone and the active comparators, metformin and sulfonylureas.

Table 11 On-Therapy Cardiovascular-Related Adverse Events, Serious Non-Fatal Adverse Events and Withdrawals (All Randomized Subjects)

Preferred Term / Lower Level Term	Number of Subjects, n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	100 PY	n (%)	100 PY	n (%)	100 PY
Subjects with AE	201 (13.8)	4.1	170 (11.8)	4.0	237 (16.3)	4.8
Myocardial ischemia	106 (7.3)	2.1	82 (5.7)	1.9	111 (7.6)	2.3
Angina	64 (4.4)	1.3	45 (3.1)	1.1	69 (4.8)	1.4
Coronary artery disease	39 (2.7)	0.8	33 (2.3)	0.8	48 (3.3)	1.0
Myocardial infarction	27 (1.9)	0.6	18 (1.3)	0.4	23 (1.6)	0.5
Arrhythmia/Conduction	79 (5.4)	1.6	71 (4.9)	1.7	85 (5.9)	1.7
CHF/Pulmonary edema	22 (1.5)	0.4	9 (0.6)	0.2	19 (1.3)	0.4
Other	63 (4.3)	1.3	46 (3.2)	1.1	73 (5.0)	1.5
Subjects with SAE	82 (5.6)	1.7	54 (3.7)	1.3	86 (5.9)	1.8
Myocardial ischemia	55 (3.8)	1.1	43 (3.0)	1.0	60 (4.1)	1.2
Angina	16 (1.1)	0.3	15 (1.0)	0.4	26 (1.8)	0.5
Coronary artery disease	18 (1.2)	0.4	17 (1.2)	0.4	21 (1.4)	0.4
Myocardial infarction	24 (1.6)	0.5	14 (1.0)	0.3	20 (1.4)	0.4
Arrhythmia/Conduction	14 (1.0)	0.3	9 (0.6)	0.2	19 (1.3)	0.4
CHF/Pulmonary edema	12 (0.8)	0.2	3 (0.2)	0.1	12 (0.8)	0.2
Other	7 (0.5)	0.1	4 (0.3)	0.1	1 (0.1)	<0.1
Withdrew due to AE	26 (1.8)	-	13 (0.9)	-	18 (1.2)	-
Myocardial ischemia	13 (0.9)	-	9 (0.6)	-	12 (0.8)	-
Angina	3 (0.2)	-	3 (0.2)	-	2 (0.1)	-
Coronary artery disease	2 (0.1)	-	2 (0.1)	-	4 (0.3)	-
Myocardial infarction	8 (0.5)	-	6 (0.4)	-	6 (0.4)	-
Arrhythmia/Conduction	1 (0.1)	-	4 (0.3)	-	2 (0.1)	-
CHF/Pulmonary edema	10 (0.7)	-	4 (0.3)	-	5 (0.3)	-
Other	4 (0.3)	-	0	-	0	-

Note: Sorted by frequency of adverse events in RSG group.
Data Source: Table 8.2.4.3, Table 8.2.3.3, and Table 8.5.1

There was no difference across the three treatment groups in incidence of death. The incidence was 0.8%, 1.5%, and 1.0% in the rosiglitazone, SU, and Metformin groups, respectively.

RECORD

This is an ongoing, multi-center, randomized, open-label study comparing rosiglitazone in combination with either metformin or a SU to the combination of metformin and a SU in patients with type 2 diabetes. Patients on background metformin who are inadequately treated will be randomized to receive, in addition to metformin, rosiglitazone or a SU in a 1:1 ratio. Patients on background SU who are inadequately treated will be randomized to receive, in addition to the SU, rosiglitazone or metformin in a 1:1 ratio. Treatment allocation schedule was computer generated in blocks and stratified according to background treatment with either metformin or SU.

The open-label design of this trial has been cited by some, including reviewers in FDA, as a reason for concern as it could introduce bias. Bias could include intentional or unintentional decisions regarding selection of patients for study enrollment, management of glycemia once enrolled, reporting of events, or management of ischemic events (e.g., outpatient management versus hospitalization). Notwithstanding these concerns which would have to be considered in the review of the final study results, several features of the study design may minimize such biases including:

- a central randomization process and multi-center (327 centers across 25 countries) enrollment with approximately 10-20 patients per center
- treatment algorithm for additional glycemic control
- blinded endpoint committee adjudication process

It is also important to point out in a long-term diabetes trial where titration and addition of medications is necessary, true blinding of study drug assignment may be impractical.

The primary objective of RECORD is to compare the time to experiencing the primary combined endpoint of CV death and/or CV hospitalization between the rosiglitazone-containing treatment groups

(RSG+SU/Met) and the non-rosiglitazone-containing treatment group (Met+SU). Secondary efficacy endpoints include: all cause mortality; definite heart failure; microvascular endpoints and combined CV hospitalizations or CV death endpoint plus microvascular endpoints. An independent Clinical Endpoint Committee (CEC) reviews and adjudicates all potential CV hospitalization and CV death endpoints in a blinded fashion. The CEC is comprised of at least one diabetologist, five cardiologists, and other experts as required.

All deaths are analyzed under the all-cause mortality endpoint. Deaths are further classified by the CEC as “CV” or “non-CV”. CV deaths are defined as deaths for which an unequivocal non-cardiovascular cause cannot be established. CV deaths will include the following:

- death from heart failure
- death following acute MI
- sudden death
- death due to acute vascular event
- unknown deaths (cannot be categorized under the aforementioned terms) are counted as CV deaths in the primary analysis

CV hospitalizations include hospital admissions involving a change in date and include the following:

- hospitalization for acute MI
- hospitalization for definite CHF
- hospitalization for stroke
- hospitalization for unstable angina
- hospitalization for TIA
- hospitalization for invasive CV procedure or amputation of extremities due to diabetes complication (trauma-related amputations not included)
- hospitalization for other CV or undefined CV reason

The design of this trial also answers an important question regarding choice of therapy for patients with T2DM. While the American Diabetes Association recommended in its 2006 Consensus Treatment Guidelines that metformin be the first-line drug therapy for the majority of patients, there was no agreement from the panel as to which agent should be added to metformin when glycemic control is inadequate. For the majority of diabetics, progressive deterioration in glycemic control often requires multiple drug therapy. RECORD may inform prescribers which agent should be initiated as second-line therapy.

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 is below 1.20. A sample size of 4000 patients followed for a median of 6 years was estimated to provide 99.2% power to confirm this non-inferiority margin, given the estimated event rate was 11% per year (3% CV deaths and 8% CV hospitalizations) with an estimated 2% loss to follow-up per year.

As a result of Dr. Nissen's meta-analysis and Congressional inquiries on the safety of rosiglitazone, the RECORD investigators published an interim analysis of this study in the *New England Journal of Medicine* in June 2007. For the 4447 patients randomized and treated, mean follow-up is approximately 3.75 years. For the primary endpoints, 217 events have been adjudicated in the rosiglitazone group versus 202 in the control group yielding a HR 1.08 (95% CI: 0.89-1.31). The following interim results were submitted to the FDA and have been published in the NEJM.

Table 3: Interim Analysis from RECORD					
		RSG+MET or SU N=2220	MET+SU N=2227	HR	99.9% CI 95% CI
Adjudicated or pending	CV Death/CV hospitalization	267 (12.0%)	243 (10.9%)	1.11	(0.83, 1.48) (0.93, 1.32)
Adjudicated	CV Death/CV hospitalization (primary endpoint)	217 (9.8%)	202 (9.1%)	1.08	(0.78, 1.49) (0.89, 1.31)
	Acute MI	43 (1.9%)	37 (1.7%)	1.16	(0.56, 2.43) (0.75, 1.81)
	CV Death	29 (1.3%)	35 (1.6%)	0.83	(0.36, 1.9) (0.51, 1.36)
	CV Death/Stroke/MI¹	93 (4.2%)	96 (4.3%)	0.97	(0.60, 1.56) 0.73, 1.29)
	Stroke	29 (1.3%)	38 (1.7%)	0.76	(0.34, 1.71) (0.47, 1.23)
	Heart Failure	38 (1.7%)	17 (0.8%)	2.24	(0.86, 5.85) (1.27, 3.97)
	CV Death/Stroke/MI/UA	109 (4.9%)	110 (4.9%)	0.99	(0.64, 1.55) (0.76, 1.29)
Adjudication not required	All-cause mortality	74 (3.3%)	80 (3.6%)	0.925	(0.54, 1.57) (0.67, 1.27)
1 MACE or APTC composite					

Notwithstanding that these are interim results and the study was designed as a non-inferiority study with an upper bound of the 95% CI of 1.2, these results show no conclusive evidence that rosiglitazone has a statistically significant increase risk for ischemic events compared to metformin or sulfonylurea, again upholding the findings from the ICT meta-analysis of the active-controlled trials. It is reassuring, given the findings of the meta-analysis of shorter term trials, that the point estimate of the upper bounds of the 95% CI for the combined CV death/MI/Stroke excludes HR higher than 1.3. It is also important to note that for certain adjudicated events, rosiglitazone added to metformin appears to have a lower HR than metformin plus sulfonylurea for CV death, MACE, and stroke. This finding is relevant as the meta-analysis of the ICT raised concerns for the combination of rosiglitazone and metformin.

Dr. John Lawrence from the Office Biometrics has evaluated the conditional power of RECORD based on these interim results. From his review, this trial with its current enrollment status still has adequate power to exclude the risk observed in the meta-analyses (GSK's, FDA's, and Nissen's). There is low power to exclude the originally proposed non-inferiority margin of 20% which may warrant amendment to the protocol to be event-driven which would extend the trial duration.

From Dr. Lawrence's review, the following power calculations have been performed based on the current results from the interim analysis of RECORD:

True hazard Ratio (HR) ^a	Conditional power to exclude HR = 1.2 ^b	Conditional power to exclude HR = 1.3	Conditional power to exclude HR = 1.4
Primary endpoint			
1.00	46%	94%	>99%
1.08 ^c	22%	80%	99%
Composite endpoint of CV death, MI and stroke (secondary endpoint)			
1.00	43%	82%	97%
0.97 ^c	50%	87%	98%

^a Hazard ratio (HR) for data following the interim analysis

^b Non-inferiority margin specified in the protocol

^c Assumes HR for data after the interim analysis is equal to the HR at interim analysis

Conclusions

All told, these three studies provide over 3 years of treatment exposure to rosiglitazone in a database that is comparable in size to the ICT. Two of these studies collected CV events in a prospective, pre-defined, blinded fashion. ADOPT and RECORD confirm the findings from the ICT meta-analysis in that no difference in risk of myocardial ischemia between rosiglitazone and other anti-diabetic agents was observed. There was a non-significant increased risk in myocardial infarction in DREAM where rosiglitazone was compared to the combination of placebo and ramipril in pre-diabetics. This risk was not evident when the results were analyzed by factorial groups which isolated the results of rosiglitazone compared to placebo. The results of the combination of rosiglitazone and ramipril compared to placebo merit further investigation on the combined effects of ACE-inhibitors and TZD use.

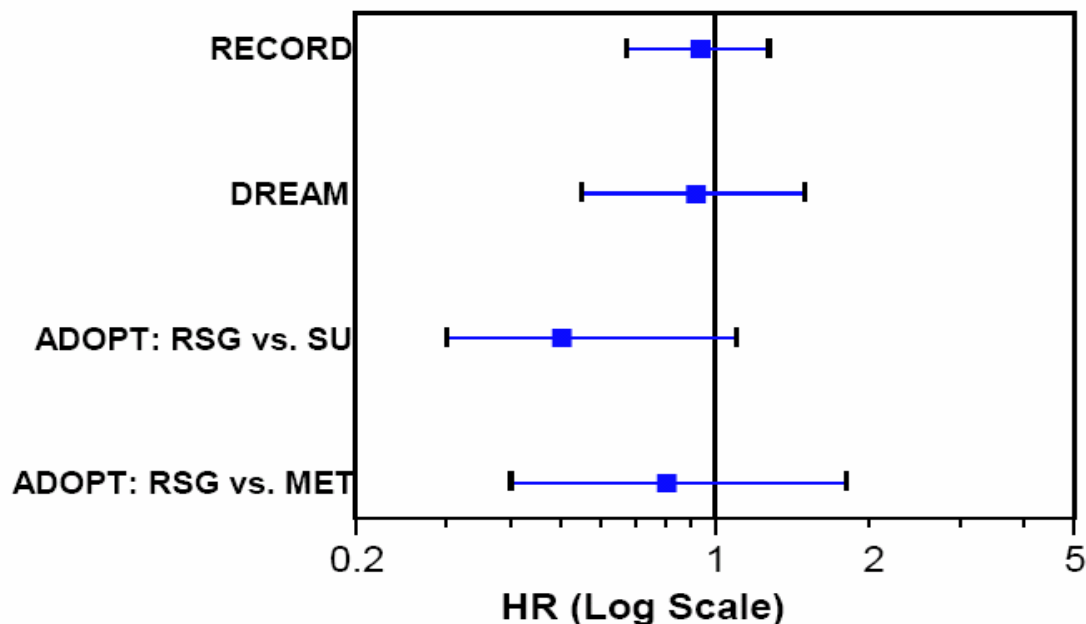
Some of the arguments raised by critics of these long-term controlled clinical trials include the non-prospective adjudication of CV events in ADOPT and the open-label design of RECORD. While there is little one can do at this point regarding the study designs for both these trials, it should be re-emphasized that the ICT also included retrospective adjudication of CV events in predominantly 6-month trials.

A finding that has not received much attention is the total mortality and CV mortality findings from these long-term clinical trials. While there has been considerable debate over a 40% excess risk of myocardial ischemia of marginal significance from different meta-analyses, it is interesting to note that there is no evidence of excess all-cause mortality in any of the three long-term trials. In fact, mortality findings favor rosiglitazone. Some have stated that there may be a meaningful increased risk for myocardial infarction in DREAM without evidence of an effect that counterbalance that risk. This conclusion seems to be made without viewing the cardiovascular mortality or all cause mortality where rosiglitazone seems to have an advantage. While this possible advantage is not evident in the meta-analysis, it may reflect that only studies of long enough duration can detect the favorable trend.

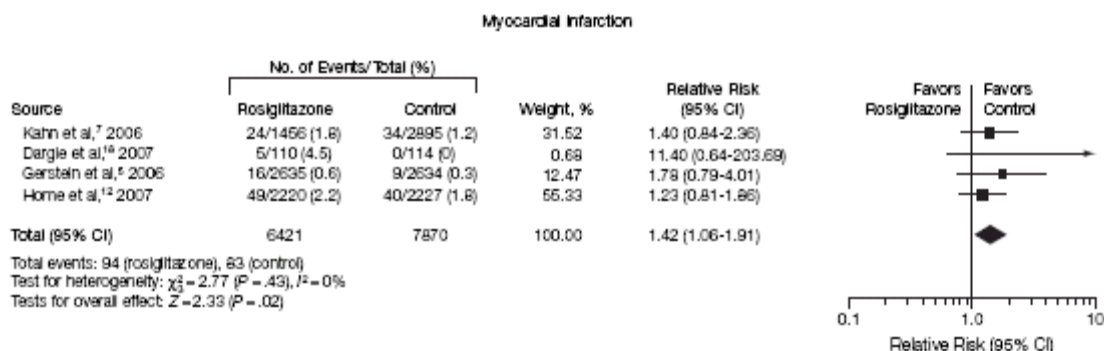
The following forest plots display mortality findings in the LCCT database.

Figure 4. Total mortality in long-term trials of rosiglitazone

Total Mortality OR = 0.87 95% CI (0.68, 1.12)



In a recent *JAMA* publication by Singh et al., the authors reported findings from another meta-analysis of 4 long-term studies (≥ 1 yr duration). All four of these studies have been discussed in the preceding sections of this memo and the meta-analysis does not raise any finding not already identified by the agency. The studies were: Study 211, a one-year study in patients with Class I/II heart failure whose results were included in a labeling supplement approved in April 2006; ADOPT; DREAM; and RECORD. This database was comprised of 14,291, of which 14,067 (98%) were from the LCCT database. The authors evaluated the risks for MI, heart failure, and cardiovascular mortality. Unlike the review of these trials by the FDA, the authors did not appear to have access to patient level data but retrieved and tallied events based on publicly available data. This may explain some differences in the event rates reported in the article versus what has been summarized in FDA reviews. For example, the authors did not report any event of MI in the control group in Study 211 whereas the FDA noted 5 events categorized as serious and nonserious ischemic events and three serious ischemic events. The authors presented the following forest plot for MI in their meta-analysis:



In this analysis, Singh et al. combined the two different control groups in ADOPT as a single comparator group (in figure above, Kahn et al. represent ADOPT results). The FDA has evaluated serious ischemic events in ADOPT comparing rosiglitazone to metformin and rosiglitazone to sulfonylurea separately with the following results:

ADOPT : RSG vs SU: OR 1.3 (95% CI 0.8-2.0) ; p=0.26

ADOPT : RSG vs Met : OR 0.9 (95% CI 0.6-1.3) ; p=0.6

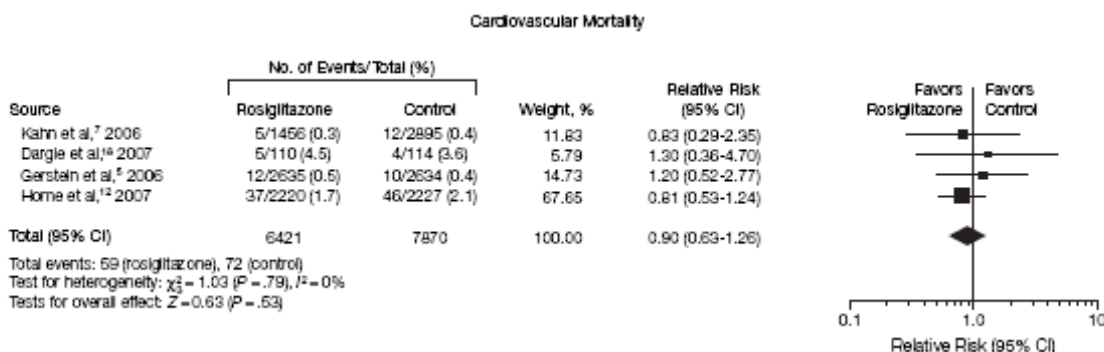
Regardless, we acknowledge that the OR for MI in the meta-analysis by Singh et al. is very similar to FDA's findings:

Singh et al.: 1.42 (95% CI 1.06-1.91)

FDA: 1.4 (95% CI: 1.1-1.8)

The finding of a significant increased risk of heart failure by Singh et al. is not an unexpected finding. As has been extensively discussed in FDA reviews and published literature, TZDs can cause and exacerbate heart failure. Recently, the labels for both pioglitazone and rosiglitazone were updated to emphasize these known side-effects of TZD therapy in a boxed warning.

As has been stated earlier, an increased risk of all-cause mortality has not been observed with rosiglitazone in any of the three long-term controlled clinical trials. Similarly, Singh et al. did not observe an increase in risk of cardiovascular mortality in their pooled analysis of the 4 studies as summarized below. Again, Singh et al. did not evaluate the metformin and SU group separately in their analysis of CV mortality in ADOPT. Furthermore, the authors do not discuss the results in DREAM when the CV event rates were analyzed by factorial treatment groups (See Table 2 of this memo).



In summary, while the meta-analysis of 42 randomized controlled clinical trials has noted a potential signal for myocardial ischemia, the finding is not robust and other data, particularly from 3 long-term controlled clinical trials, have not replicated findings from the meta-analysis. Instead, the long-term studies have revealed a non-significant increase in risk of ischemia accompanied by a consistent finding of lower total mortality and no consistent evidence of increase in CV mortality.

Cardiovascular Safety with Other Available Anti-diabetic Agents

As non-treatment of diabetes is not an acceptable option, the decision regarding the market availability of rosiglitazone should take into consideration the CV safety profile of other available agents. No anti-diabetic agent has conclusively established a benefit for reducing cardiovascular mortality/morbidity. In fact, CV safety concerns have been associated with the sulfonylureas based on the University Group Diabetes Program (UGDP) study from 1970 which has resulted in a warning for all drugs in this class as follows:

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 supp. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of AMARYL (glimepiride tablets) and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Some have questioned the validity of these findings as the United Kingdom Prospective Diabetes Study (UKPDS), initiated in 1977, found no difference in the incidence of MIs or CV death between the SU and insulin treatment groups. Hypotheses generated from the UGDP study included increased risk associated with those SUs whose mechanism of action included inhibition of ATP-K⁺ channels.

In the UKPDS, a 10-year study evaluating whether tight glycemic control with either SU or insulin would reduce diabetes-related complications in T2DM over conventional treatment with diet alone, significant risk reductions in diabetes-related complications were observed with tight glycemic control that were predominantly microvascular-related, including photocoagulation for retinopathy. This trial also illustrated the progressive nature of T2DM with many patients requiring the addition of pharmacotherapy. An amendment to the protocol allowed the early addition of metformin when fasting plasma glucose exceeded 6 mmol/L while on maximum doses of SU. Although no significant reductions in cardiovascular morbidity and mortality were observed in the original UKPDS cohort, there was a trend favoring intensive treatment. However, in a subgroup of overweight patients, treatment with metformin was associated with significant reductions in all-cause mortality and stroke over treatment with chlorpropamide, glibenclamide or insulin. This finding forms one of the reasons for recommending metformin as initial therapy for T2DM by many medical organizations.

The PROactive trial was a cardiovascular outcomes trial comparing pioglitazone to placebo added on to current anti-diabetic therapies in patients with T2DM who had significant risk for cardiovascular disease. The primary endpoint was a composite of all-cause mortality, nonfatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, cardiac intervention including coronary artery bypass graft or percutaneous coronary intervention, major leg amputation (above the ankle), or bypass surgery or revascularization in the leg. There was no statistically significant difference between pioglitazone and placebo for this endpoint. A total of 514/2,605 (19.7%) of pioglitazone group patients

experienced one or more of these events, compared to 572/2,633 (21.7%) of placebo group patients ($p = 0.0954$). For individual components of the primary endpoint, there was no statistically significant difference between treatment groups for any component; numerically fewer events occurred in the pioglitazone group for all components except major leg amputation and leg revascularization. A late amendment to the protocol designated the composite of CV death, nonfatal MI (excluding silent) and stroke as a "main" secondary endpoint for which a significant treatment difference favoring pioglitazone was observed. Upholding the original pre-specified analysis, the main conclusion from this trial is that pioglitazone is not associated with an increased risk of cardiac ischemic events. Such a finding is reassuring, as pioglitazone was associated with a significant increased risk of heart failure similar to other TZDs. The agency approved similar language in the pioglitazone label in February 2006. There is no implied claim of CV benefit in the label based on the nonsignificant results of the primary composite endpoint. It should also be noted that the pioglitazone-treated group had an approximately 0.5% greater HbA1c reduction and lower systolic blood pressure levels than the placebo-treated group. To the extent that several clinical studies have shown that lowering blood pressure and improving glycemic control lowers CV risk, it is difficult to discern whether the favorable trend in PROactive is attributed entirely to pioglitazone or the better control of established CV risk factors relative to the placebo group.

Some have turned to the PROactive results as evidence of no CV harm which supports the removal of rosiglitazone from the market. The conclusion that pioglitazone is better than rosiglitazone is, however, being made in the absence of a direct head-to-head comparison. Instead, this comparison is using two vastly different databases: one single long-term, controlled CV outcomes trial (pioglitazone) vs 42 heterogenous clinical trials primarily of 6 mos duration (rosiglitazone). The duration of evaluation is relevant since a look at CV event data in PROactive at the 6 month time point does not favor pioglitazone. The following Kaplan-Meier curves and table might even suggest that the risk is higher in the pioglitazone group compared to placebo.

Figure 5. Kaplan-Meier Curve of Time to Primary Composite Endpoint in PROactive

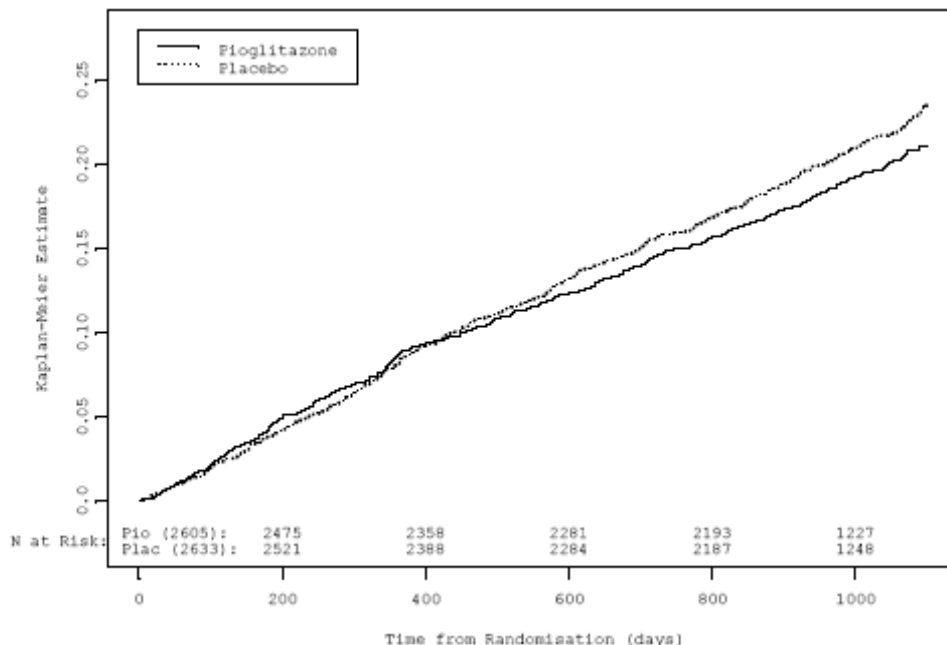


Table 4 Results for Predefined Secondary Endpoints for PROactive (Measured at 6 Months)			
Endpoint	Pio N=2605 n (%)	Pbo N=2633 N (%)	HR¹
Cardiovascular mortality	20 (0.8)	27 (1.0)	0.8
All-cause mortality	25 (1.0)	30 (1.1)	0.9
Nonfatal myocardial infarction	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	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			

Finally, a pioglitazone meta-analysis has been conducted recently by Dr. Nissen and published in JAMA. Takeda has provided the FDA with a summary of the 19 studies contributing to this meta-analysis. More than half of these studies (10) were of 1 yr duration or greater with one of these studies being the PROactive study described above. Recall that only 4/42 (9.5%) studies in the rosiglitazone ICT database were of a duration greater than 1 year. The longest rosiglitazone trial was two years. Other notable differences included:

- In the rosiglitazone database, about **85%** of the database is placebo-controlled while in pioglitazone only approximately **18%** are against placebo
- In the rosiglitazone database, about **15%** of the database is head to head against SU while in pioglitazone about **63%** is against SU
- In the rosiglitazone database, about **23%** of the database is add-on to metformin/placebo controlled compared to 6% in the pioglitazone group
- In the rosiglitazone database, about **26%** of the patients were naïve to therapy compared to 48% in the pioglitazone database

Given the differences in the databases comprising the meta-analyses of these two drugs (with some of these differences potentially spuriously skewing results in favor of pioglitazone), caution should be applied in making a conclusion that one drug is superior to, or safer than, the other.

RECOMMENDATIONS

Although a relative risk for myocardial ischemia of 1.4 in several different analyses of the integrated controlled trials is a concern, the totality of data at present does not provide sufficient evidence to withdraw rosiglitazone from the market. The upper bound of the CI for the estimate of risk is 1.8, which when derived from a meta-analysis with the limitations described in this memo, is not considered a robust finding.

Prior recommendations for market withdrawal of drugs have been based on more robust data, including Zelnorm® which was associated with a 5 to 8-fold CV risk from a meta-analysis of 29 clinical studies. The agency recommended market withdrawal of Baycol 0.8 mg dose based on reporting odds ratio for spontaneous postmarketing adverse event reports of fatal rhabdomyolysis. Baycol was associated with a

42-fold excess risk of fatal rhabdomyolysis relative to Lipitor. The undeniable evidence of harm here resulted in the complete withdrawal of Baycol worldwide. In both these examples of drug withdrawal, there were no data from completed or ongoing long-term controlled studies, as exists for rosiglitazone, for the Agency to question the safety signals from meta-analyses or postmarketing reports.

Our recommendation to not suspend marketing of rosiglitazone should not be construed as dismissal of a potential risk for myocardial ischemia. Indeed, we find that the consistent findings of a 40% increased risk for ischemia by GSK, FDA, and a meta-analysis by Nissen and Wolski very concerning and if real, unacceptable for a drug where the intended population carries an elevated baseline risk for heart disease. When considering all data available at this time, however, the overall evidence of increased myocardial ischemic event risk with rosiglitazone is weak. We do conclude that the myocardial ischemia safety concern is sufficient enough to warrant substantial, but accurate, changes to the label for rosiglitazone. In addition, the issuance of a Medication Guide and other forms of risk communication will be necessary to ensure that prescribers can carefully weigh the evidence of risk and benefits of initiating or continuing rosiglitazone in their patients.

Finally, we recommend that GSK undertake a cardiovascular outcome study to more definitively address the concerning findings from the meta-analysis. Such a study could either evaluate the CV benefit of rosiglitazone over other available therapies (superiority design) or establish within an acceptable margin that rosiglitazone has no evidence of increased CV risk over other available therapies. GSK should immediately discuss with the FDA their plans for this CV outcomes trial and commit to time lines for protocol submission, initiation of trial, completion of trial, and submission of data.

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this page is the manifestation of the electronic signature.**

/s/

Mary Parks
10/2/2007 03:55:19 PM
MEDICAL OFFICER

Curtis Rosebraugh
10/2/2007 04:00:51 PM
MEDICAL OFFICER

John Jenkins
10/22/2007 08:12:54 AM
MEDICAL OFFICER

Date: January 2, 2008

From: Janet Woodcock, MD
Acting Director
Center for Drug Evaluation and Research

To: Paul Seligman, MD
Associate Director, Safety, Policy and
Communication

Gerald Dal Pan, MD, MS
Director, Office of Surveillance and Epidemiology

John Jenkins, MD
Director, Office of New Drugs

Re: Decisional Memo - Rosiglitazone

Background

I have reviewed the detailed memoranda from Drs. Dal Pan and Parks, their presentations before the October 2nd meeting of the Drug Safety Oversight Board and the summary of the discussion from the meeting that presents the reasons for and against withdrawing rosiglitazone from the market, as well as multiple reviews of the controlled trials and the observational data. I have also weighed carefully the issues and concerns presented to me at our October 9th meeting. My findings and conclusion as relayed in my October 13, 2007 e-mail (attached) are stated below.

Findings

Rosiglitazone is associated with an increased risk of acute MI in certain patient populations with type 2 diabetes. The at-risk populations are not well defined; however, some of the long term trials have indicated certain populations where the risk does not appear to be significantly elevated compared to either placebo or the other mainstay treatment options, MET or SU (e.g., people who were 'prediabetic' (DREAM-rosiglitazone vs placebo arm) and those previously not treated with pharmacologic therapy (ADOPT)). While for those maintained on monotherapy until randomization (RECORD) the hazard ratio for acute MI is about 1.2 as an add on versus no add on, other serious permanent CV events (CV death and stroke) go the other way. In these fairly long term trials, overall mortality was not different among the groups (and was numerically lower for rosiglitazone, suggesting no trend in the other direction). In the ICT database, there is an increase in the hazard of MI in trials where patients are randomized to rosiglitazone versus placebo that correlates roughly with how much underlying cardiovascular risk exists in the population studied (e.g. use of nitrates or maintenance on insulin or multiple antidiabetic agents). There is no similar finding of an increased risk in the active controlled studies. These active controlled studies in the ICT are not large/long enough to provide confidence that longer term use in these populations might not reveal an excess risk for rosiglitazone. However, except for the lower risk groups discussed above, no therapy is not an option in these populations and the studies also do not shed light on the question of whether any of the available treatments are safer or superior in other ways in this population. So the question is still open about the relative safety of these agents in higher risk people.

The PROactive study of pioglitazone was a longer term add-on study against placebo in significantly high risk people. This study had a large number of events and did not uncover a excess risk of AMI over the length of the study; there were also numerically fewer other serious

CV events in the treatment arm. Therefore, pioglitazone has had a placebo controlled evaluation in a fairly long term study of higher risk people and has not been associated with excess cardiovascular risk.

There is a serious issue of an interaction of rosiglitazone with ACE inhibitors (or at least with ramipril) that has been surfaced by the results of the DREAM trial and the exploratory analysis performed by Joy Mele in the ICT database (p.10 of Dr. Park's memo).

Conclusion

Based on these findings, I do not believe that rosiglitazone should be withdrawn from the market.

It needs to have a black box warning about the risk of MI in higher risk individuals, including those at risk by virtue of duration of their diabetes. There should also be a Medguide. (If high risk people need to take a drug in this class, pioglitazone has evidence to support the safety of this use.)

The warnings section of the label should go into some detail about the risk factors. Whether or not the drug should be indicated for use with insulin is open for discussion.

It is fair to indicate that comparative risk against metformin or SUs is not known.

The firm should be required to begin and promptly execute a study comparing their drug to pioglitazone as add-on therapy. They also should be asked to immediately query their existing databases about any interactions between the drug and ACE inhibitors in general or ramipril in particular, for risk of cardiovascular events. If they don't find a lot, then this should be studied in the clinic. If they do, we need to look at the data.

I do not think that consent or restricted distribution measures should be implemented. The drug use should be directed in the label to those populations where evidence from controlled trials support its safety.

CC:

Mary Parks, MD
Robert Temple, MD
Robert O'Neill, PhD

Date: October 23, 2009

From: Gerald Dal Pan, MD, MHS
Director, Office of Surveillance and Epidemiology

To: Mary Parks, MD
Director, Division of Metabolic and Endocrine Products

Jennifer L. Stevens, Esq.
Regulatory Counsel, Office of Regulatory Policy

Re: NDA 21-071/S-022 (rosiglitazone)
a) Office Director Memorandum
b) Response to Request for Consultation from Office of Regulatory Policy
Regarding Citizen Petition (Docket FDA 2008-P-0580)

Introduction

This memorandum serves as a cover memorandum to two documents generated by the Office of Surveillance and Epidemiology (OSE): 1) a memorandum by Drs. David Graham and Kate Gelperin on the risk-benefit balance of rosiglitazone, dated October 7, 2008,¹ and 2) OSE's response² to a consultation request from CDER's Office of Regulatory Policy (ORP) regarding a Citizen Petition filed by Public Citizen requesting that FDA remove rosiglitazone from the market.³

Background

Since late 2006, the cardiovascular safety of rosiglitazone⁴ has been the subject of intense discussion within FDA, in the medical community, and in the policy arena. Multiple FDA documents provide the details of the data, analyses, and regulatory actions that have occurred over the past three years. I will briefly summarize the highlights of the data and actions, but will refer to other documents, as needed, for details.

¹ Graham DJ, Gelperin K. Benefit-risk assessment of rosiglitazone versus pioglitazone. OSE RCM #: 2007-1945, 2008-278. Review date October 7, 2008.

² Rosiglitazone OSE Citizen Petition Response Team. OSE RCM #s: 2006-331, 2007-1945, 2008-278. Review date October 23, 2009.

³ Public Citizen Health Research Group. Citizen's Petition dated October 30, 2008. Docket Number FDA 2008-P-0580: Petitions FDA to immediately ban the diabetes drug, Avandia (rosiglitazone; GlaxoSmithKline) based on multiple serious risks.

⁴ 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.

In late 2006, rosiglitazone's manufacturer, GlaxoSmithKline (GSK), submitted to FDA the results of a pooled analysis of 42 randomized controlled clinical trials in which cardiovascular adverse events, specifically myocardial ischemia, were evaluated *post hoc* by an expert panel convened by GSK.⁵ Myocardial ischemia included both angina and myocardial infarction. Most (30) of these studies had a duration of six months, eight studies had a duration of less than six months, and four studies had a duration of one year or more. In these trials rosiglitazone was administered as monotherapy, as combination therapy, or as add-on therapy. In the trials in which rosiglitazone was administered as add-on therapy, patients were treated with metformin, sulfonylurea or insulin during a run-in period and then randomized to add-on rosiglitazone or placebo. For the trials in which rosiglitazone was administered in combination with other antidiabetic agents, patients were randomized to a fixed dose combination of rosiglitazone with metformin or sulfonylurea. Results of GSK's pooled analysis suggested that there was an overall 30% increase in ischemic myocardial adverse events in persons treated with rosiglitazone compared to persons treated with comparator agents. Because this was a pooled analysis that did not maintain within-study randomization schemes, FDA initiated its own patient-level analysis of the data to address this limitation in the GSK analysis.⁶ While FDA was conducting its analysis, a study-level meta-analysis of 42 clinical trials (not the exact set of 42 clinical trials used in the GSK and FDA meta-analyses), was published in the *New England Journal of Medicine*.⁷ This analysis indicated an approximately 40% increase in the risk of myocardial infarction with rosiglitazone. Publication of this study led to intense public interest in the potential cardiovascular risks of rosiglitazone, especially myocardial ischemia.⁸ In reaction to this interest, GSK published the results of an unscheduled interim analysis of the RECORD study⁹ (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes), which had been initiated in 2001 in the European Union to address potential cardiovascular safety issues. The primary endpoint of the RECORD study was cardiovascular hospitalization or cardiovascular death. The results of this interim analysis indicated a slightly elevated risk of the composite primary endpoint (HR=1.08, 95% CI =0.89 – 1.31) in rosiglitazone-treated patients, though the level did not reach statistical significance. GSK and its Data and Safety Monitoring Board interpreted these findings as “inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes”,¹⁰ but sufficiently reassuring to allow continuation of the trial as planned.

⁵ GlaxoSmithKline. NDA 21-071/Supplement 022. Avandia® (rosiglitazone maleate). “Cardiovascular Event Modeling Project” final study report. Date of Submission: August 4, 2006.

⁶ 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. Accessed August 5, 2009.

⁷ 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.

⁸ Heart failure is a recognized cardiovascular complication of both rosiglitazone and the other currently marketed thiazolidinedione, pioglitazone. The labels of both products contain Boxed Warnings. Heart failure and myocardial ischemia are both addressed in this memorandum, though in different sections.

⁹ 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.

¹⁰ *Ibid*.

The results of FDA's patient-level meta-analysis of myocardial ischemic adverse events from the same 42 trials evaluated by GSK, but using a method that preserved randomization of groups, showed a statistically significant increased risk of myocardial ischemia with rosiglitazone (OR 1.4, 95% CI 1.1-1.8). FDA's analysis also suggested that rosiglitazone-treated patients receiving concomitant nitrate therapy may be at substantially higher risk of myocardial ischemia than those not receiving nitrates (OR 2.9, 95% CI 1.4-5.9), consistent with findings from the GSK pooled analysis.¹¹

Against this background of multiple meta-analyses and pooled analyses, the results of two long-term studies of rosiglitazone had been published and were available for consideration. The first study, ADOPT¹² (A Diabetes Outcome Progression Trial) was conducted by GSK at FDA's request at the time of approval to examine the safety of rosiglitazone, though it was not focused on myocardial ischemia, *per se*. ADOPT compared rosiglitazone to two other oral antidiabetic agents, metformin and the sulfonylurea glyburide. The primary outcome was the time from randomization to treatment failure, which was defined as confirmed hyperglycemia. Published safety data from the ADOPT study suggested that proportions of patients with cardiovascular events were similar in the rosiglitazone and metformin groups but were lower in the glyburide group (4.3%, 4.0%, and 2.8%, respectively).¹³ FDA staff has reviewed this study, and have determined that several features of the study design and conduct limited any ability to conclude that the signal of myocardial ischemia with rosiglitazone seen in FDA's meta-analysis was no longer a concern. These features included: 1) a study population at relatively low risk of cardiovascular events yielded low cardiovascular event rates, 2) no systematic ascertainment or adjudication of cardiovascular events other than heart failure, and 3) very high drop-out rate (overall >40%) with no follow-up for outcomes after drop-out. The rate of withdrawal of patients from ADOPT was highest in the glyburide treatment group, with 47% dropouts. Total person-years of exposure follow-up in ADOPT were 4,954 for rosiglitazone, 4,906 for metformin, and 4,244 for glyburide. The FDA statistical reviewer concluded that "exposure to glyburide is significantly lower than exposure to either of the other two drugs, rosiglitazone and metformin, with the differences occurring as early as the first year...The significant difference in exposure...needs to be considered when assessing event rates since [this difference] may bias the adverse event rates in favor of glyburide and against both metformin and rosiglitazone." To address this concern the FDA statistical reviewer analyzed time to cardiovascular adverse events in ADOPT using a proportional hazards model. Results showed that the risk of myocardial infarction was non-statistically significantly increased for rosiglitazone vs. metformin (OR=1.3; 95% CI 0.7-2.3) and for rosiglitazone vs. glyburide (OR=1.6; 95% CI 0.8-3.1). The wide confidence intervals may be due to the

¹¹ Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US FDA background package. Op cit.

¹² Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. for the ADOPT study group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355(23):2427-43.

¹³ Ibid.

small event rates in this population of patients at relatively low risk of cardiovascular disease.¹⁴

A second long-term study, the DREAM¹⁵ (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) study, was an international, randomized, double-blind, 2x2 factorial design trial involving 5,269 participants with impaired glucose tolerance and/or impaired fasting glucose (pre-diabetes).¹⁶ Patients were randomized to rosiglitazone or placebo and independently randomized to ramipril or placebo. The published results of this study suggested that rosiglitazone significantly reduced progression to diabetes. The initial publication combined the factorial groups into RSG- versus non-RSG treatment groups. A between-group comparison for the composite outcome of cardiovascular death, nonfatal AMI, or nonfatal stroke showed a hazard ratio of 1.39 (95% CI 0.81-2.37). A comparison for the composite of all cardiovascular events showed a hazard ratio of 1.37 (95% CI 0.97-1.94, p=0.08) which approached statistical significance.

A concern was raised about the possibility of an interaction between rosiglitazone and ramipril, though the authors reported that a statistical interaction was not present (p=0.07). Subsequently, data on cardiovascular outcomes for the four factorial groups were requested by FDA. Based on these data, a comparison of rosiglitazone+ramipril versus ramipril suggested a risk for any cardiovascular event (OR = 1.91, 95% CI 1.13 – 3.30), as well as for myocardial infarction (OR = 3.70, 95% CI 0.97 – 20.7). Conversely, a comparison of rosiglitazone monotherapy versus placebo did not suggest an elevated risk for any cardiovascular event (OR 1.00, 95% CI 0.59-1.68). These results show an increased risk of CV events in patents treated with the combination of rosiglitazone plus ramipril compared to those treated with ramipril alone.¹⁷ This finding raised the possibility of drug-drug interaction between rosiglitazone and ACE inhibitors, a finding of potential considerable clinical importance given the recommended use of ACE inhibitors in the management of diabetes.¹⁸

Also, in conjunction with the above data, FDA staff¹⁹ reviewed the results of the PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) Study,²⁰

¹⁴ Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US FDA background package. Op cit. page 22.

¹⁵ The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet* 2006; 368: 1096-1105

¹⁶ Gerstein HC, Yusuf S, Holman R, Bosch J, Pogue J; DREAM Trial Investigators. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. *Diabetologia*. 2004 Sep;47(9):1519-27.

¹⁷ Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US FDA background package. Op cit. Appendix 5 table, page 103 of background document.

¹⁸ American Diabetes Association. Standards of Medical Care in Diabetes - 2009. *Diabetes Care* (2009) Jan 32 (Suppl 1):S13-S61.

¹⁹ Mahoney KM. Clinical Review. NDA 21073 SE8-026, Actos (pioglitazone), Takeda; PROactive cardiovascular outcome study; Submitted Jan 24, 2006; Review date Aug 24, 2006.

²⁰ 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* 366: 1279-1289, 2005.

²¹ which assessed secondary prevention of cardiovascular outcomes in diabetics with significant macrovascular disease treated with pioglitazone, another member of the thiazolidinedione class of oral antidiabetic agents.²² The PROactive study was a prospective, multicenter, double-blind, placebo-controlled trial of 5,238 patients with type 2 diabetes and macrovascular disease. Patients were randomized to either pioglitazone or placebo in addition to their other glucose-lowering and cardiovascular medication. The primary end point was the time to first occurrence of macrovascular events or death. 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0.90, 95% CI 0.80-1.02, p=0.095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (0.84, 0.72-0.98, p=0.027). With regard to heart failure: 6% (149 of 2605) and 4% (108 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups. The findings of this study suggested that pioglitazone is not associated with any excess risk of myocardial ischemia, although there is an increased risk of heart failure.²³

Lincoff and colleagues²⁴ conducted a patient-level meta-analysis of 19 randomized controlled trials of pioglitazone (n=8,554) vs. comparator (n=7,836), including PROactive.²⁵ The primary outcome was a composite of death, myocardial infarction, or stroke, and results for individual components were also presented. There were 825 primary outcome events (pioglitazone: 375, control: 450). The hazard ratio for myocardial infarction with pioglitazone vs. control was 0.81 (95% CI 0.64- 1.02), for stroke, 0.80 (95% CI 0.62-1.04), and for all-cause mortality, 0.92 (95% CI 0.76-1.11). For the composite outcome of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke, the hazard ratio was statistically significantly reduced (HR=0.82, 95% CI 0.72-0.94). Similar results were obtained when stratified by PROactive (HR=0.84, 95% CI 0.72-0.98) and all other trials (HR=0.75, 95% CI 0.56-1.02). The hazard ratio for serious heart failure with pioglitazone was increased (HR=1.41, 95% CI 1.14-1.76).

As one part of its process to address these data, FDA convened a joint meeting of the Endocrine and Metabolic Drugs and the Drug Safety and Risk Management Advisory Committees on July 30, 2007.²⁶ The focus was an assessment of the cardiovascular risks

²¹ Erdmann E, Dormandy JA, Charbonnel B, et al., PROactive Investigators. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction. Results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007;49 (17): 1772-80.

²² Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med*. 351:1106-1118, 2004.

²³ Dormandy et al. 2005, op.cit.

²⁴ Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis of randomized trials. *JAMA* 2007; 298(10):1180-8833

²⁵ This meta-analysis was not available at the time of the Advisory Committee meeting on 30 July 2009.

²⁶ Transcript of the Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety Management Advisory Committee, July 30, 2009, available at <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#DrugSafetyRiskMgmt>

of rosiglitazone, with particular attention to myocardial ischemia, using the available data, described above, from studies of rosiglitazone. Studies of pioglitazone were not considered. The Advisory Committee members voted (20-3) that there was a signal of a risk of myocardial ischemia with rosiglitazone, though most advisory committee members did not judge the available data sufficient to constitute definitive evidence of such a risk. The committee then voted 22-1 that rosiglitazone should remain on the market.

Following the Advisory Committee meeting, there were substantial differences of opinion within CDER regarding the appropriate regulatory actions for rosiglitazone. Differences within CDER were largely along organizational lines, with Office of New Drugs (OND) staff supporting continued marketing, while most OSE staff, myself included, supported market withdrawal. To address this difference of opinion, CDER convened a meeting of its Drug Safety Board, which considered arguments on both sides of the issue. The Board voted 8-7 (with one abstention) to recommend continued marketing of rosiglitazone. The Board's recommendation was forwarded to the Center Director, who agreed that the product should remain marketed, with the addition of new warnings of risk of myocardial ischemia added to the label. On Nov 14, 2007, the label of rosiglitazone-containing products was updated with a new Boxed Warning and changes to the Warnings and Precautions section of the package insert to describe a risk of myocardial ischemia.²⁷

In my memorandum²⁸ to the Drug Safety Board, I made the following arguments for removing rosiglitazone from the market:

- The signal of a risk of myocardial ischemia was clear, and available data did not mitigate it.
- The point estimate of the relative risk (1.4) for myocardial ischemia corresponds to a substantial absolute attributable risk. Assuming a background rate of myocardial infarction in the diabetic population between 2% and 4% per year, the excess absolute risk in diabetic patients taking rosiglitazone (ie, the risk difference between diabetic patients who take rosiglitazone and those who do not) is between 0.8 and 1.6% per year. Given the large number of diabetic patients on oral agents, the population burden of this increased risk is significant.
- The available data did not point to a unique benefit of rosiglitazone. For persons needing therapy with a thiazolidinedione, pioglitazone appears to be equally efficacious and appears not to have concerning signals of myocardial ischemic risk.

Since FDA's regulatory actions, there have been numerous publications of observational studies addressing the cardiovascular risks of rosiglitazone and, to a lesser degree, pioglitazone. There has also been a publication of a meta-analysis of clinical trials of

²⁷ AVANDIA USPI. FDA approval date November 14, 2007.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021071s031lbl.pdf. Accessed August 6, 2009.

²⁸ Dal Pan, G. Office Director Memorandum for Drug Safety Board Meeting. RCM #2006-331; Review date September 27, 2007.

pioglitazone. Finally, GSK has launched a clinical trial to meet the requirement that FDA imposed to study the risk of myocardial ischemia. This study, known as TIDE²⁹ (Thiazolidinedione Intervention with vitamin D Evaluation), uses a 2x2 factorial design to study the cardiovascular effects of rosiglitazone, and an unrelated question regarding the effects of Vitamin D on diabetes.

In October 2008, Drs. Graham and Gelperin reviewed the accumulated body of data on the cardiovascular risks of rosiglitazone.³⁰ In particular, many of the observational studies were published in the interval between FDA's regulatory actions and the date of their memorandum. They concluded that rosiglitazone should not remain marketed. Because the final results of the RECORD study were to be available in early spring 2009, I deferred writing a memorandum addressing their concerns until the data for RECORD were available. Additionally, at about the time OSE staff completed their memorandum, Public Citizen Health Research Group filed a Citizen Petition requesting FDA to remove rosiglitazone from the market, citing: "multiple, serious risks, including one just documented by our new analysis of 14 cases of liver failure, of which 12 resulted in death. In addition, there is clear previous evidence of increased risk of heart attacks, heart failure, bone fractures, anemia and macular (retinal) edema with vision loss. The evidence for this unique combination of toxicities is compounded by the accompanying lack of evidence of any clinical benefit, compared to other approved drugs for diabetes."³¹

For the reasons I will articulate below, I continue to maintain that rosiglitazone should no longer be marketed.

Risks Other than Myocardial Ischemia

OSE staff has reviewed the claims in the Citizen Petition.³² For safety issues other than myocardial ischemia, the available evidence suggests that these risks do not occur at a sufficient rate, or are not sufficiently serious, to warrant market withdrawal of rosiglitazone.

OSE staff has concluded that liver failure with rosiglitazone occurs at a rate that is similar to that seen with pioglitazone, and that is substantially less than that observed with troglitazone.³³ This risk can be managed by appropriate labeling.

²⁹ GlaxoSmithKline. IND 43,468, AVANDIA® (rosiglitazone maleate) Tablets; REQUIRED POSTMARKETING PROTOCOL UNDER 505(o); Serial No.650 submitted on July 30, 2008.

³⁰ Graham DJ, Gelperin K. Benefit-risk assessment of rosiglitazone versus pioglitazone. OSE RCM #: 2007-1945, 2008-278. Review date October 7, 2008.

³¹ Public Citizen Health Research Group. Citizen's Petition dated October 30, 2008. Docket Number FDA 2008-P-0580. op.cit.

³² Rosiglitazone OSE Citizen Petition Response Team. OSE RCM #s: 2006-331, 2007-1945, 2008-278. Review date October 23, 2009. Op.cit.

³³ Troglitazone was the first oral antidiabetic member of the thiazolidinedione drug class to be marketed in the United States. Postmarketing surveillance indicated that it was associated with severe hepatotoxicity. It was withdrawn from the US market in 2000, following the introductions of rosiglitazone and pioglitazone.

The risk of heart failure with rosiglitazone is well recognized and is included in a Boxed Warning. The risk of heart failure also exists for pioglitazone, though some data suggest that the frequency is higher with rosiglitazone.³⁴ In any case, this risk can be managed by appropriate labeling, which is currently in place for both rosiglitazone and pioglitazone.

Increased risk of fractures with thiazolidinedione drugs has been reported. The ADOPT study³⁵ showed a hazard ratio of 1.8 (95% CI 1.2-2.8) for fractures in patients treated with rosiglitazone compared to those treated with metformin, and 2.1 (95% CI 1.3-3.5) compared to glyburide. Similarly, increased risk of fractures has been reported with pioglitazone.³⁶

We have largely deferred analysis of the causative mechanism for the observed risk of anemia with thiazolidinediones to OND staff, as to whether this effect is caused by hemodilution or another mechanism. The current approved labeling for rosiglitazone³⁷ states that “decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA (mean decreases in individual studies as much as 1.0 g/dL hemoglobin and 3.3% hematocrit).” In any event, the severity of this phenomenon does not appear to justify market withdrawal.

Thus, risks other than myocardial ischemia cited in the Citizen Petition do not support market withdrawal of rosiglitazone.

Myocardial Ischemia

As I will elaborate below, the signal of risk of myocardial ischemia, taken together with other factors, constitutes a sufficient reason to remove rosiglitazone from the market.

Myocardial Ischemia – Data from Clinical Trials

The principal source of data giving rise to a signal of myocardial ischemia risk with rosiglitazone comes from analysis of 42 clinical trials, first in the form of GSK’s pooled analyses, and later in the form of FDA’s patient-level meta-analysis. FDA’s analysis of the data suggests that the risk of myocardial ischemia is about 40% higher in rosiglitazone-treated patients than in patients not treated with rosiglitazone.

One argument of those who advocate for the continued marketing of rosiglitazone is that further analysis of the data seems to indicate that this excess risk is seen largely in those clinical trials in which rosiglitazone was compared to a placebo, both in monotherapy trials as well as in add-on therapy trials. This argument is based on a *post hoc* analysis

³⁴ Graham DJ, Gelperin K. Benefit-risk assessment of rosiglitazone versus pioglitazone. Op.cit.

³⁵ Kahn SE, Zinnari B, Lachin 3M, Haffner SM, Herman WH, Holman RR, Kravitz BG, Yu D, et al, for the ADOPT Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008 May;31(5):845-51.

³⁶ Takeda. Observation of an increased incidence of fractures in female patients who received long-term treatment with Actos® (pioglitazone HCl) tablets for type 2 diabetes mellitus. March 2007. Available at: <http://www.fda.gov/medwatch/safety/2007/Actosmar0807.pdf>.

³⁷ USPI for AVANDIA available at <http://www.fda.gov/cder/foi/label/2006/021071s019s0211bl.pdf>.

which, upon further examination, does not support continued marketing of rosiglitazone. The comparison of rosiglitazone monotherapy to placebo monotherapy is instructive, because it establishes the fact that rosiglitazone is an agent that can cause (or worsen) myocardial ischemia. While a comparison of rosiglitazone monotherapy to placebo monotherapy may not inform practical clinical decision-making (diabetics who need to be on an oral antidiabetic agent would not be well served by placebo monotherapy), it does serve to establish this risk of myocardial ischemia with rosiglitazone. Data from the ADOPT study suggest (though certainly do not prove) that there may be differential risk of myocardial ischemia across classes of oral antidiabetic agents. Differential dropout among the treatment groups in ADOPT, driven by preferentially early dropout of patients assigned to glyburide, limits the inferences one can make to address this issue in the ADOPT study.

Some who maintain that rosiglitazone should remain marketed have argued that most of the trials in the 42-study meta-analysis conducted by FDA were short-term studies and that short-term studies are not as relevant as long-term studies for a chronic illness. Most (30) of the included studies were six months in duration, and only a few studies followed patients for up to one year. It is important to note that many medications intended for chronic conditions, such as hypertension³⁸ and hypercholesterolemia,³⁹ are often not taken chronically (i.e., a several year period), but rather are used for less than a year by a substantial proportion of patients. In fact, 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.⁴⁰ Thus, amongst diabetic patients in the United States prescribed rosiglitazone, a substantial proportion take the medication for six months or less. For this reason, risks estimated at the six-month time point are important to persons taking rosiglitazone.

Data from short-term studies are informative, and important for a second reason. It is possible (though available data are not sufficient to address this question) that rosiglitazone confers a risk over a short term (e.g., 6-12 months), but that this risk is attenuated over the long term. It is possible that substantial long-term follow-up may dilute a signal of a clinically important cardiovascular risk if such risk occurs early, but not later, in the course of treatment.

³⁸ 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.

³⁹ Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, and Platt R. Discontinuation of antihypertensive drugs – Do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med* 1995 April;332(17):1125-1131.

⁴⁰ 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.

Another argument put forth for maintaining rosiglitazone on the market is that many of the events under the term “myocardial ischemia” were angina and not myocardial infarction. Along the spectrum of myocardial ischemic events, it would not be surprising to find numerically more episodes of angina than of myocardial infarction in a population of diabetics followed over time. Because the number of observed events of myocardial infarctions and events of angina, considered separately, are lower than the sum of the two, separate estimates of relative risks for angina and myocardial infarction would be less precise than the estimate for the overall term “myocardial ischemia.” It is important to note that the FDA statistical reviewer’s analysis⁴¹ of the 42 trials found the overall estimate of the odds ratio was also 1.4 (95% CI of 0.98 to 2.1) when limited to serious ischemic events alone. Because angina and myocardial infarction both fall along the clinical spectrum of myocardial ischemia, it is not unreasonable to apply the observed relative risk (1.4) to each of the two component events angina and myocardial infarction. Thus, the relative risk of 1.4 is applicable to myocardial infarction for public health decision making in the absence of more precise data.

Another argument put forth by those who argue for the continued marketing of rosiglitazone is that the clinical trials and the associated meta-analyses fail to show a mortality disadvantage for rosiglitazone. They further argue that the signal of risk of myocardial ischemia is thus attenuated by the lack of a concomitant increase in mortality. In the demonstration of efficacy for a treatment of myocardial infarction, it would clearly be useful to demonstrate a reduction not only in myocardial infarction, but also in cardiovascular mortality. In the evaluation of a safety signal, a finding of excess mortality along with a finding of excess myocardial ischemia would clearly strengthen the signal. However, in the evaluation of the signal of myocardial ischemia with rosiglitazone, the lack of a mortality finding does not mitigate in any substantial way the signal of myocardial ischemia. Because some of the rosiglitazone clinical trials were conducted in persons at relatively low risk for myocardial infarction, it is not surprising that the rates of myocardial infarction and death are low. In this setting, it would not be surprising to fail to detect a cardiovascular mortality signal, even if one existed.

Thus the data from the meta-analyses of the short-term clinical trials provide an important signal of myocardial ischemia in diabetics taking rosiglitazone. As discussed above, the fact that the meta-analysis was composed mainly of short-term studies, the observation that many of the myocardial ischemic events were angina and not myocardial infarction, the lack of an adverse cardiovascular mortality finding, and the fact that many of the clinical trials compared rosiglitazone to placebo do not mitigate the importance of the finding.

As frequently occurs in the postmarketing setting, the data available to answer an important safety concern are often not the most relevant or the best suited to address the issue. The data from the meta-analysis provide the signal, but are not able to address the issue definitively. As I have noted above, and have described in more detail in my

⁴¹ Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US FDA background package. Op cit. page 26 of statistical review (see Table 3.3.9).

September 2007 memorandum,⁴² data from the ADOPT and DREAM trials are not sufficient to provide a robust answer to the issue of myocardial ischemia with rosiglitazone. As I will describe below, the published final results of the RECORD studies also do not provide sufficient evidence to resolve the issue.

OSE has previously reviewed the design and published interim findings of the RECORD study.^{43 44 45} OSE noted several issues with the design of the study that limit its utility to address the issues of risk of myocardial ischemia; the most notable one was the open-label design, which could compromise objective end-point ascertainment as well as overall adverse event reporting. In consultation with CDER biostatisticians, we also concluded that the study was underpowered to reach its primary endpoint.

RECORD 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 include: 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.

We have reviewed the publication of the final RECORD study⁴⁶ results, and remain concerned that these data do not adequately address the question. 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). The overall cardiovascular event rate in RECORD was lower than the study authors

⁴² Dal Pan, G. Office Director Memorandum for Drug Safety Board Meeting. RCM #2006-331; Review date September 27, 2007

⁴³ Dal Pan, G. Supervisory Memo for Review of RECORD Study. RCM #2006-331; Review date July 6, 2007.

⁴⁴ Graham DJ. Review of protocol for RECORD. Avandia (rosiglitazone) NDA 21-071. RCM #2006-331. Review date July 6, 2007

⁴⁵ Graham DJ. Review of interim analysis for RECORD. Avandia (rosiglitazone) NDA 21-071. RCM #2006-331. Review date July 6, 2007.

⁴⁶ 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.

anticipated at the time of trial design.⁴⁷ The study investigators anticipated an 11% per year event rate for the primary composite outcome in the active-control group; the observed rate was 28 per 1,000 person-years. This observation raises the possibility that the sensitivity of the study to ascertain cardiovascular events was not adequate.

Although the RECORD study reached its primary endpoint, several features of the study design limit any ability to make meaningful conclusions based in these findings. First, the open-label design may allow for biased ascertainment of adverse cardiovascular outcomes that favor rosiglitazone. Until the Agency can formally review the RECORD study's underlying data, the extent, if any, of this potential misclassification bias will not be known. While RECORD did detect an elevated rate of heart failure in rosiglitazone-treated patients compared to patients not treated with rosiglitazone (HR=2.0, 95% CI=1.35-3.27), the rate of reported hospitalized or fatal heart failure for rosiglitazone-treated patients in RECORD (61/12, 338 person-years=0.49/100 person-years) was lower than expected given the baseline cardiovascular risk factors of patients treated in RECORD. By contrast, the rate of hospitalized heart failure in the placebo group in the PROactive study was 1.4/100 person-years.⁴⁸ This finding raises the possibility that at least some cardiovascular adverse events were not completely ascertained in RECORD.

In addition, post-baseline factors could account for the apparent lack of a signal of cardiovascular adverse events in rosiglitazone-treated patients in the RECORD study. For example, the proportion of patients using statins at baseline was similar between rosiglitazone-treated and comparator-treated patients (18.0 % and 19.2%, respectively)⁴⁹, but it was notably higher during follow up in the rosiglitazone-treated patients compared to comparator-treated patients (55.2% and 46.0%, respectively).

Further, a detailed Agency review of the RECORD study has not been done. Issues such as completeness of cardiovascular adverse event ascertainment and determination of the extent to which study participants actually took the assigned medication remain in question.⁵⁰ If study participants did not take the assigned medication, this non-adherence could have biased the study results toward one of no between-group difference.

Despite these potential shortcomings of the RECORD study, and despite the study authors' finding of no excess risk of cardiovascular risk or cardiovascular mortality amongst rosiglitazone-treated patients compared to comparator-treated patients, the RECORD study still raises concerns about the cardiovascular safety of rosiglitazone. In

⁴⁷ Ibid. page 9.

⁴⁸ Based on a) 108 placebo-treated patients experiencing at least one hospitalization for heart failure, and b) 2,633 placebo-treated patients followed for a mean duration of 34.5 months. See 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* 366: 1279-1289, 2005.

⁴⁹ 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.

⁵⁰ At this point, FDA has access to the published report of the RECORD study, but a formal study report has not been submitted to the Agency.

RECORD, amongst patients with prior ischemic heart disease, rosiglitazone treatment resulted in a higher rate of cardiovascular hospitalization or cardiovascular death (HR=1.26, 95% CI=0.95-1.68) compared to those not treated with rosiglitazone (HR=0.91, 95% CI=0.75-1.09).⁵¹ This finding of increased cardiovascular risk with rosiglitazone amongst patients with prior ischemic heart disease is consistent with the findings in FDA's meta-analysis that amongst patients treated with nitrates (presumably a marker for severe ischemic heart disease), rosiglitazone conferred an increased risk of ischemic cardiovascular adverse events.⁵²

Thus, rather than mitigating the prior signal of ischemic cardiovascular risk with rosiglitazone, the findings of the RECORD study continue to suggest an increased rate of ischemic cardiovascular adverse events at least in certain patients treated with rosiglitazone.

Myocardial Ischemia – Data from Observational Studies

Against the backdrop of a strong suggestion of ischemic cardiovascular risk of rosiglitazone assessed in clinical trials, several observational studies have been conducted and published. Across these studies, there was variability in terms of patient populations, study design, comparator groups, methods to adjust for potential confounders, and outcome measures. In view of this study-to-study variability, it is hard to summarize succinctly the results of these studies. Drs. Graham and Gelperin have summarized many of these studies in their memorandum, though several more have been published since that time. Appendix 1 to this document summarizes the meta-analyses and systematic reviews of clinical trials, as well as the observational studies published since October 2008, that have examined the adverse cardiovascular effects of rosiglitazone and pioglitazone.

Despite the heterogeneity of these observational studies, a few patterns emerge. First, no observational study noted a statistically significant protective cardiovascular effect of rosiglitazone. Second, most observational studies suggested that there is an adverse cardiovascular effect of rosiglitazone that goes beyond the known adverse effect of heart failure. The point estimates for these effects were similar to those observed in meta-analyses of clinical trials, ranging from slightly above unity to generally less than 2.0, although point estimates were higher in dialysis patients.⁵³ In some studies, the results were statistically significant; in others, they were not.

⁵¹ See Figure 4 in 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.

⁵² Mele J. Statistical review and evaluation of rosiglitazone clinical trials (meta-analysis). US FDA background package. Op cit.

⁵³ Ramirez SP, Albert JM, Blayney MJ, Tentori F, Goodkin DA, Wolfe RA, Young EW, Bailie GR, Pisoni RL, Port FK. Rosiglitazone is associated with mortality in chronic hemodialysis patients. *J Am Soc Nephrol*. 2009 May;20(5):1094-101.

There have also been some observational studies examining the adverse cardiovascular effects of pioglitazone. Like the observational studies involving rosiglitazone, these studies vary amongst themselves in terms of patient populations, study design, comparator groups, methods to adjust for potential confounders, and outcome measures. However, a few patterns again emerge. First, no study demonstrated a statistically significant adverse cardiovascular effect of pioglitazone. Second, many of the point estimates for adverse cardiovascular effects are below one, consistent with findings of the ProActive study and the meta-analysis of pioglitazone clinical trials. Three of the eight trials have point estimates above one. None of the pioglitazone observational studies is statistically significant due perhaps, in part, to the relatively small number of patients.

Two observational studies have directly compared rosiglitazone to pioglitazone. In one study,⁵⁴ the findings suggested a statistically significant decreased composite cardiovascular risk for pioglitazone relative to rosiglitazone (HR 0.83, 95% CI: 0.76-0.90), while in the other study⁵⁵ the findings suggested a statistically significant increased all-cause mortality risk with rosiglitazone relative to pioglitazone (Incidence rate ratio [IRR] 1.15, 95% CI 1.05-1.26). In each of the two cases, the point estimates for acute myocardial infarction, though not statistically significant, also pointed to an increased risk with rosiglitazone relative to pioglitazone. In the former study, pioglitazone was associated with a statistically significantly lower risk of heart failure than rosiglitazone (HR 0.77, 95% CI 0.69-0.87), and in the later study rosiglitazone was associated with a higher risk of hospitalization for heart failure compared to pioglitazone (IRR 1.13, 95% CI 1.01-1.26).

Observational pharmacoepidemiologic studies are often criticized because treatment is not randomly assigned to patients. While this is true, observational studies can assess the safety profile of a medicine as it is actually being used. Data from such studies can thus complement the findings from clinical trials. A major criticism of pharmacoepidemiologic studies of drug safety is that patients who are prescribed a particular medicine may be different from those prescribed an alternative medicine, in ways that may relate to the safety outcome of interest. This phenomenon is known as channeling bias. It is not possible to measure the extent of channeling bias in these studies. However, it is unlikely that such channeling bias contributed to the observed findings from studies using data collected prior to 2007 (when the data from the meta-analysis suggesting increased cardiovascular risk with rosiglitazone were released). Prior to 2007, roughly half of the thiazolidinedione prescriptions were for rosiglitazone, while the other half were for pioglitazone.⁵⁶ Indeed, examination of baseline characteristics from the two observational studies that compared rosiglitazone to pioglitazone indicates that the two groups were well matched with regard to baseline characteristics that could

⁵⁴ Juurlink DN, Gomes T, Lipscombe L, Austin PC, Jux JE, Mamdani M. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population base cohort study. *BMJ* 2009;339:b2942.

⁵⁵ Winkelmayer WC, Setoguchi S, Levin R, Solomon DH. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med* 2008;168:2368-2375.

⁵⁶ SDI, Vector One®: National (VONA), calendar months January 2007 through April 2008. Data extracted 6-3-08. in Borders-Hemphill V. FDA/OSE/DEPI Drug Utilization review. OSE RCM #2008-278.

influence cardiovascular outcomes.⁵⁷ Thus, channeling bias is unlikely to explain the results of the observational studies.

Assessing the Evidence

There is a reasonably large body of evidence examining the cardiovascular effects of rosiglitazone. As is often the case in the analysis of complex postmarketing drug safety issues, the individual pieces of data do not yield a clear, consistent answer. The data on rosiglitazone are no exception. However, certain patterns emerge. The meta-analysis of clinical trials suggests an increased risk of myocardial ischemia, with a point estimate indicating an approximate 40% relative increase in the incidence of myocardial ischemic events. Larger individual clinical trials appear not to show this signal, though, for the reasons mentioned above, the lack of this finding does not mitigate the concerns raised by the meta-analyses. Taken as a whole, the clinical trials data do not definitively quantify the cardiovascular risk of rosiglitazone, though they do raise an important signal that remains unresolved.

Like the clinical trials, the observational studies do not provide a consistent estimate of the cardiovascular risk of rosiglitazone. However, the available data from these studies constitute an additional signal of cardiovascular risk that is at least as strong as that from the clinical trials. Of note, the magnitude of the cardiovascular risk in these observational studies is similar to that in the clinical trials.

A reasonably consistent finding of the available data has been the observation that trials and studies of pioglitazone have not yielded the same signal of cardiovascular risk as has been seen with rosiglitazone.

Taken as a whole, the data indicate a clear signal of a risk of myocardial ischemia with rosiglitazone. The apparently conflicting nature of some pieces of data does not mitigate this suggestion; rather, they contribute to the uncertainty surrounding the body of data. These findings, and the accompanying uncertainty, are reflected in the revisions to the Boxed Warning of rosiglitazone-containing products that went into effect in November 2007.⁵⁸

- **AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)**
- **A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)**

⁵⁷ See Table 1 in Juurlink et al, and Table 1 in Winkelmayr et al.

⁵⁸ Substantial additions to the Warnings section of the label regarding the risk myocardial ischemia were also instituted at the same time.

While much of the evidence cited by Drs. Graham and Gelperin in their memorandum was available when CDER staff recommended and approved the above labeling changes, additional observational studies have become available since that time. In particular, several observational studies have become available since CDER's Fall 2007 regulatory decision. More recently (ie, after Drs. Graham and Gelperin wrote their memorandum) the publication of the RECORD trial results became available.

In all, since the time that CDER made its decision in Fall 2007 to require stronger language in a Boxed Warning regarding the risks of myocardial ischemia of rosiglitazone, the overall body of evidence continues to point to a signal of such a risk. Specifically, the observational studies that point to this risk strengthen the signal. For the reasons mentioned above, the published results of the RECORD study do not mitigate these findings.

Regulatory Actions in the Face of Uncertainty

As noted above, there continues to be a clear signal of risk of myocardial ischemia with rosiglitazone, though there is uncertainty around it. The issue at hand is what actions, if any, should be taken in response to the Citizen Petition seeking removal of rosiglitazone from the market, in the face of this uncertainty.

Uncertainty about drug safety is an inherent part of the drug regulatory system. Indeed, the entire premise for a postapproval drug safety surveillance system is that there is residual uncertainty about drug product safety at the time of approval. The drug safety surveillance system seeks to identify safety signals of previously unrecognized, or underappreciated, safety concerns. These safety signals are then evaluated, and appropriate regulatory and public health recommendations are then made.

Uncertainty about the risk of a drug product is not a reason, *per se*, to remove a product from the market. Indeed, under appropriate circumstances, drugs can remain marketed even when there is uncertainty about important, clinically significant adverse events. For example, after the market withdrawal of rofecoxib because of the finding of excessive myocardial infarctions, there was general concern about the cardiovascular risk of all non-steroidal anti-inflammatory drugs (NSAIDs), with a particular focus on those that are selective cyclooxygenase-2 (COX-2) inhibitors. Available evidence at the time that rofecoxib was withdrawn suggested that celecoxib did not have the same degree of cardiovascular risk as rofecoxib, though selective COX-2 inhibitors were thought to have more cardiovascular risk than other NSAIDs.⁵⁹ However, relative to other NSAIDs, COX-2 selective NSAIDs result in fewer gastrointestinal bleeds, a desired effect of this

⁵⁹ A third selective COX-2 inhibitor, valdecoxib, was removed from the market on 07 April 2005 because of serious skin reactions (eg, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme), the potential risk for serious cardiovascular adverse events shared by all non-steroidal anti-inflammatory drugs, and the fact that valdecoxib had not been shown to offer any unique advantages over the other available NSAIDs. See www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124648.pdf.

class of drugs. For this reason, celecoxib remains marketed while the cardiovascular effects of this agent relative to other NSAIDs is being tested in a clinical trial.^{60 61}

The fact that a drug product can result in serious adverse events is also not, *per se*, a reason for market withdrawal. For example, the long-acting beta agonists (LABAs), when used to treat asthma, have been shown to increase asthma-related hospitalizations, intubations, and deaths. Nonetheless, there are benefits to using these medicines in other dimensions of treatment, such as symptom control, that justify their continued use in appropriately selected patients.⁶² In other cases, products may cause serious adverse events when not used according to the conditions of safe use recommended in the product's approved labeling. In these instances, risk management programs can be put into place to minimize the occurrence of adverse events. In yet other circumstances, misuse and abuse of medicines can cause substantial harm, yet products are kept on the market because the benefits outweigh the risks under conditions of use recommended in the label. In this last case, FDA must work with manufacturers and healthcare professionals to develop and implement measures to minimize misuse and abuse.

The question of the risk of myocardial ischemia with rosiglitazone is not an isolated question. There is concern that other oral antidiabetic agents, such as the sulfonylureas, may also carry an excessive cardiovascular risk. This is an area of active interest at FDA, though it is beyond the scope of this memorandum.⁶³ In order to approach assessment of the cardiovascular risk of new antidiabetic agents, FDA issued *Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.⁶⁴ This guidance document provides a systematic approach to assessing cardiovascular risk of antidiabetic agents prior to approval, and further outlines the circumstances under which that assessment could continue into the post approval period. Amongst other considerations, the guidance document notes that as part of the submission for marketing approval, manufacturers “should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence

⁶⁰ Pfizer, the manufacturer of celecoxib, has launched the PRECISION (the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen) study to address the cardiovascular effects of celecoxib relative to other NSAIDs that are not COX-2 selective.

⁶¹ Becker MC, Wang TH, Wisniewski L, Wolski K, Libby P, Lüscher TF, Borer JS, Mascette AM, Husni ME, Solomon DH, Graham DY, Yeomans ND, Krum H, Ruschitzka F, Lincoff AM, Nissen SE; PRECISION Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal anti-inflammatory agents in patients with arthritis. *Am Heart J*. 2009 Apr;157(4):606-12.

⁶² For a full discussion of this issue, see, for example, Transcript of the Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee. 10-11 December 2008.

⁶³ For an overview of this issue, and its implications for development of antidiabetic agents, see Joffe HV and Parks MH. Background Introductory Memorandum – The role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus, July 1-2, 2008 (available at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4368b1-01-FDA.pdf>), a document prepared by FDA staff as background material for a meeting of the Endocrinologic and Metabolic Drugs Advisory committee meeting on July 1-2, 2008 to discuss cardiovascular assessment of antidiabetic agents.

⁶⁴ This guidance document is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>

of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8... Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.” When the upper bound of the 95% confidence interval for the estimated risk ratio is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, the guidance document suggests that a postmarketing trial would generally be necessary to demonstrate definitively that the upper bound of the 95% confidence interval of the estimated risk ratio is less than 1.3. Finally, when the upper bound of the 95% confidence interval of the estimated risk ratio from the premarketing data is less than 1.3, a postmarketing clinical trial would generally not be necessary. This document was written several years after the approval of rosiglitazone, and the implementation of this approach is relatively recent. Applying the approach to the data from the rosiglitazone meta-analysis suggests that rosiglitazone would not be approved using these standards. The estimated risk ratio and associated 95% confidence interval from the FDA meta-analyses was OR 1.4, 95% CI 1.1-1.8. The upper bound of the 95% confidence interval is 1.8, the cutoff in the guidance document below which further study in the post-approval period could be considered. The point estimate of this nominally significant increased risk ratio (1.4) is “not...reassuring”, and suggests that the product would not be approved without further study and demonstration of cardiovascular safety.

Given the amount of uncertainty regarding the extent of risk of myocardial ischemia with rosiglitazone and the amount of risk that can be appropriate for marketed medicines, what is the appropriate regulatory action regarding rosiglitazone? There is no simple way to answer this question, as many factors must be considered. Factors to consider include the nature and magnitude of the risk, the beneficial effects of the drug, the conditions of safe use (if any) of the drug, the ability to identify persons who may be at increased risk, interventions that could mitigate risk, and the availability and risk-benefit profile of alternative therapies.

The public health significance of the observed increased risk of myocardial ischemia, if real, is unacceptably high. Though there is uncertainty about the degree of risk of myocardial ischemia with rosiglitazone, the current estimate centers around a relative risk of 1.4, which represent a 40% increase in events of myocardial ischemia in rosiglitazone-treated patients compared to those not treated with rosiglitazone. 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. 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.

A regulatory decision based on a risk-benefit analysis can not consider only data on risk. It must incorporate and consider information on both risk and benefit. In the case of rosiglitazone, the drug is an effective antidiabetic agent, though it is no more effective than the other marketed thiazolidinedione, pioglitazone. Rosiglitazone, to the best of my knowledge, has no unique advantage over pioglitazone. As discussed above, the available data do not suggest an adverse cardiovascular profile for pioglitazone. Rather, both direct and indirect comparisons between these two agents suggest that rosiglitazone is notably more cardiotoxic than pioglitazone.

In considering the risk of myocardial ischemia with rosiglitazone, it is important to note that these adverse effects occur at recommended doses and under recommended conditions of use. While there are clearly identifiable subgroups of patients who have a higher risk of myocardial ischemia (e.g., patients on nitrate therapy), there is no way to identify other patients who may be at risk of myocardial ischemia. Thus, there is no way to define conditions of safe use. Furthermore, there is no way to mitigate the effects of myocardial ischemia. For these reasons, education of patients and prescribers, and other attempts at risk management, could not be used to ensure that the benefits of the drug outweigh its risks.

In light of the above considerations, the magnitude of the observed risk and its public health consequences outweigh the uncertainty that the risk may not be real, or at least as large as the estimates suggest. While it is possible to examine each clinical trial, meta-analysis, and observational study critically and identify potential factors in the data sources or study design that would render suspect the finding of increased cardiovascular risk in individual instances, the totality of the evidence simply does not support the conclusion that the observed findings are not real. If the cardiovascular findings were the result of chance, I would expect the studies and trials of rosiglitazone to show cardioprotection as often as they show cardiotoxicity. This is not the case, as the data do not in any way suggest a cardioprotective effect of rosiglitazone. Rather, they point to a significant risk of myocardial ischemia. These findings come both from the meta-analysis of clinical trials as well as from observational studies. While clinical trials are usually considered a higher level of evidence than observational studies,⁶⁵ this approach has recently been questioned for drug safety research.⁶⁶ The findings of the observational studies can not be dismissed simply because they are not randomized clinical trials. At a minimum, the findings of the observational studies strengthen the signal of cardiovascular risk generated by the meta-analysis of the randomized clinical trials, and further support the notion that the cardiovascular risks of rosiglitazone and pioglitazone are different. Though the observational studies and clinical trials, either individually or collectively, do not definitively demonstrate the cardiovascular toxicity of rosiglitazone from a statistical point of view, such definitive proof of causality is rarely, if ever, achieved in postmarketing safety analyses.

⁶⁵ Russell RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Current Methods of the U.S. Preventive Services Task Force: A Review of the Process. *Am J Prev Med* 2001;20(3S):21-35.

⁶⁶ van Staat TP, Smeeth L, Persson I, Parkinson J, Leufkens HGM. Evaluating drug toxicity signal: is a hierarchical classification of evidence useful or a hindrance? *Pharmacoepidemiol and Drug Safety* 2008;17:475-484.

My views are similar to those echoed by others outside of FDA. For example, the American Diabetes Association, in its recommendations on the medical management of hyperglycemia in Type 2 diabetes,⁶⁷ has acknowledged the uncertainty around the cardiovascular data on rosiglitazone, and has concluded that, “Although the meta-analyses discussed above are not conclusive regarding the potential cardiovascular risk associated with rosiglitazone, given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone.”

As I mentioned in my September 2007 memorandum, market withdrawal of a pharmaceutical product is not an action to be taken lightly. I maintain that position today. However, in view of the public health considerations I note above, I conclude, after review of the available data, that the benefits of rosiglitazone do not outweigh its risks.

Conclusions and Recommendations

The benefits of rosiglitazone do not outweigh its risks. I recommend granting the Citizen Petition’s request that FDA remove rosiglitazone from the market.

⁶⁷ Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. 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 Jan;32(1):193-203. Epub 2008 Oct 22.

APPENDIX

TABLE 1: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008

Published observational studies of rosiglitazone versus pioglitazone

	Outcome	Study Design	<u>Exposed Patients</u>		<u>Events</u>		<u>Relative Risk (95% CI)</u>
			RSG	PIO	RSG	PIO	
Winkelmayer et al ¹	All-cause mortality	Cohort	14,101	14,260	984	885	1.15 (1.05-1.26) ^a
	AMI				374	363	1.08 (0.93-1.25)
Juurlink et al ²	CV hosp or death	Cohort	22,785	16,951	1563	895	0.83 (0.76-0.90) ^b
	AMI				425	273	0.95 (0.81-1.11)
Pantalone et al ³	CAD ^c	Cohort	1,079	1,508	NR	NR	1.15 (0.87-1.53) ^e
	All-cause mortality _d						0.81 (0.52-1.27) ^f

^a Adjusted incidence rate ratio; On-drug exposure model; results favor pioglitazone (elderly population)

^b Adjusted hazard ratio; Cox proportional hazards model; results favor pioglitazone (elderly population)

^c “CAD” in this study was defined as “documentation of coronary artery bypass grafting, PTCA, MI, or a diagnosis of CAD via ICD-9 documentation under encoded diagnosis or problem list in the EHR after baseline.”

^d Mortality in this study was defined as “documentation in the EHR or SSDI.”

^e Adjusted hazard ratio; Multivariable Cox proportional hazards model; results favor rosiglitazone but were not statistically significant (p=0.32).

TABLE 2: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008
Meta-analyses of randomized controlled trials with rosiglitazone

	Outcome	Number of studies		Incidence (%)		Odds Ratio (95% CI)
				RSG	Comparator	
Cobitz et al (GSK) ⁴	Myocardial ischemia ^g	^h		172/8604 (2.00%)	86/5633 (1.53%)	1.30 (1.004-1.69) ⁱ
	CV morbidity ^j	42	5	NR/1338	NR	1.68 (0.92-3.06) ^k
Selvin et al ⁵	CV mortality		5	NR/3202	NR	1.03 (0.30-3.53)
	All-cause mortality		6	NR/2927	NR	1.21 (0.39-3.77)

^f Adjusted hazard ratio; Multivariable Cox proportional hazards model; results favor pioglitazone but were not statistically significant (p=0.36).

^g Definition: cases of myocardial ischemia were selected based on post hoc adjudication by an expert panel

^h Data from 14,237 patients in 42 double-blind RCTs of RSG versus placebo or active diabetes medications

ⁱ Exact logistic regression analysis

^j Definitions of cardiovascular morbidity and mortality were as defined in the respective studies

^k For comparisons with 4 or more independent trials, results were pooled quantitatively using the Mantel-Haenszel method

TABLE 3: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008
Published observational studies of rosiglitazone versus other non-TZD anti-diabetic agents
Nested Case Control Studies

	<u>Outcome</u>	<u>Exposure Category</u>	<u>Cases</u> <u>No. (%)</u>	<u>Controls</u> <u>No. (%)</u>	<u>Adjusted Odds Ratio</u> <u>(95% CI)</u>
Dore et al ⁶	AMI ^l	prevalent RSG exposure	240 (10.4%)	1016 (10.5%)	0.87 (0.71-1.06)
		recent RSG initiation ^m	54 (2.3%)	150 (1.6%)	1.29 (0.85-1.94)
Dormuth et al ⁷	AMI ⁿ	overall RSG exposure	51 (2.3%)	184 (2.1%)	1.14 (0.90-1.43)
		current RSG exposure ^o	18 (0.8%)	64 (0.7%)	1.71 (1.19-2.46)
Stockl et al ⁸	AMI ^p	any RSG exposure	219 (13.0%)	820 (12.3%)	1.09 (0.90-1.32)
		recent RSG exposure ^q	52 (3.1%)	141 (2.1%)	1.69 (1.18-2.44)

^l Risk of AMI with RSG exposure compared to patients who used MET plus SU; base cohort of 307,121 patients from the Medicaid Analytic Extract database

^m Definition of recent = start of RSG within 90 days before index date

ⁿ Within-drug exposure in AMI cases and matched controls (compared to no RSG exposure); base cohort of 189,563 residents of British Columbia with T2DM who used MET as first line drug therapy

^o Definition of current = cumulative RSG exposure 1-6 months

^p Risk of AMI with RSG exposure compared to no TZD exposure; base cohort of 230,858 patients with OHA or exenatide prescription in a large US PBM

^q Definition of recent = days supply for last RSG prescription before the index date ended between 1 and 60 days before the index date.

TABLE 4: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008
Published observational studies of rosiglitazone versus other non-TZD anti-diabetic agents
Cohort Studies

	<u>Outcome</u>	<u>Exposed Patients</u>		<u>Events</u>		<u>Relative Risk (95% CI)</u>
		RSG	comparator	RSG	comparator	
Habib et al ⁹	AMI			NR	NR	1.06 (0.66–1.70) ^s
	CHF hosp			NR	NR	1.65 (1.25-2.19)
	Combined CHD	1056	15,647 ^r	NR	NR	1.22 (0.91–1.63)
	All-cause mortality			NR	NR	0.91 (0.57-1.48)
Hsiao et al ¹⁰	AMI	2093	97,651 ^t 46,444 ^u	266	1678 464	1.49 (0.99-2.24) ^v 2.09 (1.36-3.24)
	AMI			NR	NR	3.49 (1.21-10.04) ^x
Ramirez et al ¹¹	CV mortality	177	2050 ^w	29	273	1.59 (1.14-2.22)
	All-cause mortality			NR	NR	1.38 (1.05-1.82)

^r Comparator group = patients taking non-TZD oral hypoglycemic agents (OHAs); study population from large HMO in Michigan (Henry Ford)

^s Adjusted hazard ratio plus propensity score modeling probability of being treated with RSG

^t Comparator group = “sulfonylurea-based therapy without TZD”; study population from Taiwan National Health Insurance database

^u Comparator group = “metformin-based therapy without TZD”; study population from Taiwan National Health Insurance database

^v Adjusted hazard ratio using Cox proportional hazards model

^w Comparator group = patients taking non-TZD OHAs; study population from US hemodialysis facilities (DOPPS)

^x Adjusted (Model 2) hazard ratio using multivariable Cox models

TABLE 5: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008
Meta-analyses of randomized controlled trials with pioglitazone

	<u>Outcome</u>	<u>Number of studies</u>	<u>Incidence (%)</u>		<u>Relative Risk (95% CI)</u>
			PIO	Comparator	
Mannucci et al ¹²	All-cause mortality	94	NR	NR	0.30 (0.14-0.63)
	AMI	5	143/4969 (2.9%)	168/4996 (3.4%)	0.86 (0.69-1.07)
Nagajothi et al ¹³	Revascularization	3	200/2861 (7.0%)	264/2889 (9.1%)	0.40 (0.13-1.23)
	CV mortality	5	130/4969 (2.6%)	143/4996 (2.9)	0.92 (0.73-1.16)
	All-cause mortality	5	185/4969 (3.7%)	198/4996 (4.0%)	0.94 (0.78-1.15)
Selvin et al ¹⁴	CV morbidity ^y	6	NR/9287	NR	0.88 (0.78-1.00) ^z
	CV mortality	2	NR/5566	NR	NR ^{aa}
	All-cause mortality	4	NR/7507	NR	0.96 (0.78-1.18)

^y Definitions of cardiovascular morbidity and mortality were as defined in the respective studies

^z For comparisons with 4 or more independent trials, results were pooled quantitatively using the Mantel-Haenszel method

^{aa} Data were pooled only for comparisons with 4 or more trials

TABLE 6: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008
Published observational studies of pioglitazone versus other non-TZD anti-diabetic agents
Nested Case Control Studies

	<u>Outcome</u>	<u>Exposure Category</u>	<u>Cases</u> <u>No. (%)</u>	<u>Controls</u> <u>No. (%)</u>	<u>Adjusted Odds Ratio</u> <u>(95% CI)</u>
Dore et al ¹⁵	AMI ^{bb}	prevalent PIO exposure	198 (8.6%)	783 (8.1%)	0.99 (0.80-1.23)
		recent PIO initiation ^{cc}	37 (1.6%)	130 (1.3%)	1.15 (0.73-1.81)
Dormuth et al ¹⁶	AMI ^{dd}	Overall PIO exposure	51 (2.3%)	184 (2.1%)	1.21 (0.82-1.57)
		Current PIO exposure ^{ee}	18 (0.8%)	64 (0.7%)	1.21 (0.72-2.04)
Stockl et al ¹⁷	AMI ^{ff}	any PIO exposure	52 (3.1%)	242 (3.6%)	0.78 (0.56-1.09)
		recent PIO exposure ^{gg}	13 (0.8%)	55 (0.8%)	1.18 (0.61-2.28)

^{bb} Risk of AMI with PIO exposure compared to patients who used MET plus SU; base cohort of 307,121 patients from the Medicaid Analytic Extract database

^{cc} Definition of recent = start of PIO within 90 days before index date

^{dd} Within-drug exposure in AMI cases and matched controls (compared to no RSG exposure); base cohort of 189,563 residents of British Columbia with T2DM who used MET as first line drug therapy

^{ee} Definition of current = cumulative RSG exposure 1-6 months

^{ff} Risk of AMI with PIO exposure compared to no TZD exposure; base cohort of 230,858 patients with OHA or exenatide prescription in a large US PBM

^{gg} Definition of recent = days supply for last PIO prescription before the index date ended between 1 and 60 days before the index date.

TABLE 7: CARDIOVASCULAR OUTCOMES STUDIES PUBLISHED AFTER OCTOBER 2008
Published observational studies of pioglitazone versus other non-TZD anti-diabetic agents
Cohort Studies

	Outcome	<u>Exposed Patients</u>		<u>Events</u>		<u>Relative Risk (95% CI)</u>
		PIO	Comparator	PIO	Comparator	
Habib et al ¹⁸	AMI			NR	NR	0.91 (0.69–1.21) ⁱⁱ
	CHF hosp	3217	17,808 ^{hh}	NR	NR	1.14 (0.96-1.37)
	Combined CHD			NR	NR	0.86 (0.69–1.06)
	All-cause mortality			NR	NR	0.60 (0.42-0.96)
Hsiao et al ¹⁹	AMI	495	97,651 ^{jj}	44	1678	0.72 (0.19-2.77) ^{ll}
			46,444 ^{kk}	464	464	1.00 (0.26-3.89)
Ramirez et al ²⁰	CV mortality	118	2050 ^{mm}	NR	NR	1.37 (0.77-2.42) ⁿⁿ
	All-cause mortality			NR	NR	1.14 (0.79-1.64)

^{hh} Comparator group = patients taking non-TZD oral hypoglycemic agents (OHAs); study population from large HMO in Michigan (Henry Ford)

ⁱⁱ Adjusted hazard ratio plus propensity score modeling probability of being treated with PIO

^{jj} Comparator group = “sulfonylurea-based therapy without TZD”; study population from Taiwan National Health Insurance database

^{kk} Comparator group = “metformin-based therapy without TZD”; study population from Taiwan National Health Insurance database

^{ll} Adjusted hazard ratio using Cox proportional hazards model

^{mm} Comparator group = patients taking non-TZD OHAs; study population from US hemodialysis facilities (DOPPS)

ⁿⁿ Adjusted (Model 2) hazard ratio using multivariable Cox models

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- ¹ Winkelmayer WC, Setoguchi S, Levin R, Solomon DH. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch Intern Med.* 2008 Nov 24;168(21):2368-75.
 - ² Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ.* 2009 Aug 18;339:b2942. .
 - ³ 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 Jun;46(2):145-54.
 - 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.
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- ¹⁹ Hsiao FY, Huang WF, Wen YW, Chen PF, Kuo KN, Tsai YW. 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 Saf*. 2009;32(8):675-90.
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/s/

GERALD J DALPAN
10/23/2009

MEMORANDUM

DATE: November 18, 2009

FROM: John K. Jenkins, MD
Director, Office of New Drugs

TO: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

SUBJECT: Reassessment of the benefit/risk profile for Avandia (rosiglitazone)

On October 23, 2009, Dr. Dal Pan, Director of the Office of Surveillance and Epidemiology, completed a review related to the potential for increased cardiovascular risk associated with rosiglitazone. In that review, Dr. Dal Pan reiterated his view that "The benefits of rosiglitazone do not outweigh its risks. I recommend granting the Citizen Petition's request that FDA remove rosiglitazone from the market."

In 2007, CDER concluded that the benefits of rosiglitazone as a treatment for patients with type 2 diabetes mellitus were greater than its risks and that marketing as a prescription drug should continue. The package insert was amended to include a boxed warning regarding the potential for an increased risk of cardiovascular adverse events (e.g., myocardial infarction) and a Medication Guide was required. FDA also exercised its new authority under FDAAA to require the sponsor to conduct a prospective cardiovascular outcomes trial comparing rosiglitazone to pioglitazone, another member of the same class of anti-diabetic agents. That study, commonly referred to as TIDE, is currently ongoing.

Dr. Dal Pan notes that several observational studies have been published in the medical literature since CDER's 2007 decision. Recently GSK, the sponsor of the rosiglitazone NDA, submitted two efficacy supplements that included new data relevant to the evaluation of the potential increased cardiovascular risk of rosiglitazone. These supplements include:

- The final results of RECORD, a large, randomized clinical trial evaluating prospectively adjudicated cardiovascular events in patients with type 2 diabetes mellitus randomized to rosiglitazone in combination with either metformin or sulfonylurea versus metformin in combination with a sulfonylurea. An interim analysis of the RECORD trial was considered as part of CDER's 2007 decision.
- An updated meta-analysis of rosiglitazone trials, which includes 10 additional controlled clinical trials other than RECORD that were not included in the original meta-analysis submitted by the sponsor.

Based on the results of these new clinical trial data, GSK is proposing to remove the boxed warning language related to a potential increased risk of myocardial ischemia and recommendations against use of rosiglitazone by patients receiving nitrates.

Before Dr. Dal Pan's review was completed, OND had made plans to conduct a comprehensive review of the results of RECORD and the new clinical trial meta-analysis and to present the issue for discussion at a public advisory committee meeting next spring. As part of the review, consults were issued to the Division of Cardio-renal Products and plans were made to engage independent expert cardiologists and clinical trialists as SGEs to conduct a review of the study. The Office of Biostatistics will also be reviewing the updated meta-analysis of controlled clinical trials.

I believe it is premature to reach a new Center decision on the cardiovascular safety of rosiglitazone and its marketing status before a full review of RECORD, and all other new data that have become available since the Center's 2007 decision, is completed and discussed at a public advisory committee meeting. Therefore, I recommend that we convene a review team to include representatives from OND, OSE, OB, and other appropriate offices to plan for a comprehensive re-evaluation of the cardiovascular risk of rosiglitazone as well as the overall assessment of whether the benefits of rosiglitazone continue to be greater than its risks. As part of this review, we would plan to also assess how the benefits and risks of rosiglitazone compare to other available anti-diabetic agents. We would plan to present our findings for discussion at an advisory committee meeting in late spring/early summer 2010 that would include members from the Endocrine and Metabolic, Cardio-renal, and Drug Safety and Risk Management Advisory Committees. Following the advisory committee meeting, the review team would develop recommendations on how to proceed with regard to regulatory action and discuss these plans with you for your concurrence.

I request your concurrence with this plan.

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
NDA-21071	SUPPL-37	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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/s/

JENA M WEBER
11/18/2009

JOHN K JENKINS
11/19/2009

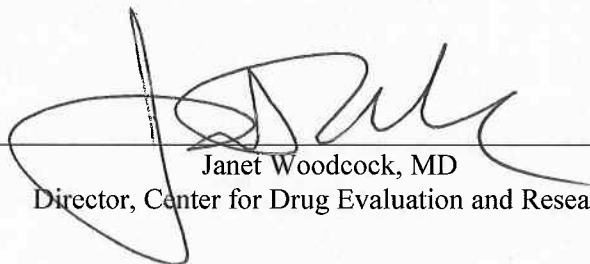


Memorandum

Date: December 7, 2009
From: Director, Center for Drug Evaluation and Research
Subject: Avandia Safety Review
To: Gerald Dal Pan and John Jenkins

This is a decisional memo on next steps in the safety review of Avandia. I have evaluated Dr. Dal Pan's memo of October 23, 2009, which was written in response to a consultation on a Citizen Petition requesting removal of Avandia from the market. I have also evaluated Dr. Jenkin's November 18, 2009 memo on the assessment of the benefit/risk profile of the drug.

It is clear that new data are available, including the observational studies cited by OSE, as well as the RECORD study results and a meta-analysis of controlled trials of the drug. It is also obvious that there are multiple conflicting opinions on the data. I request that OSE and OND work together with other appropriate Center offices to rapidly evaluate the new data with the aim of presenting to an FDA advisory committee in the spring of 2010. To assure an orderly process, I would like to be briefed during the ongoing analyses and on the Center position(s) prior to the Advisory Committee meeting.



Janet Woodcock, MD
Director, Center for Drug Evaluation and Research

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/

JENA M WEBER
12/10/2009

JANET WOODCOCK
12/10/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Date: March 8, 2010

From: Director, Center for Drug Evaluation and Research

Subject: Cardiovascular Safety of Rosiglitazone

To: For the Record

This memorandum provides further details on my decision in November 2009 to bring the question of the cardiovascular safety of rosiglitazone to an FDA Advisory Committee meeting.

In October 2007, soon after becoming Acting CDER Director, I was required to make a decision on the continuing marketing of rosiglitazone because of a disagreement between the Office of New Drugs and the Office of Surveillance and Epidemiology over its cardiovascular safety. This matter had been presented to an Advisory Committee in July 2007, which voted 22-1 to recommend continued marketing of the drug. Additionally, CDER's Drug Safety Oversight Board had considered the issue in October 2007 and voted 8-6 in favor of continued marketing, with one abstention. I decided that the data were insufficient to warrant withdrawal, and stipulated that a boxed warning on the potential risk of myocardial ischemia be added along with further warnings, and that the sponsor be required to conduct additional studies of cardiovascular risk. The drug label was changed in November 2007 and a revised MedGuide approved by FDA in February 2008. In May 2008, FDA required a postmarketing trial under the authority of FDAAA to compare cardiovascular outcomes among rosiglitazone, pioglitazone and placebo as add-ons to standard anti-diabetic agents.

In December 2008 the advocacy group Public Citizen submitted a Citizen Petition to FDA calling for the market withdrawal of rosiglitazone, citing an increased risk of hepatotoxicity and other toxicities, as well as an increased rate of myocardial ischemia compared to pioglitazone. Various center staff were assigned to analyze the data pertaining to these issues.

In late October 2009 I became aware that Gerald Dal Pan, the OSE Office Director, had completed a memorandum summarizing OSE's position on the issues raised in the Citizen Petition. Dr. DalPan's memorandum recommended granting the Citizen Petition on the grounds of inferior cardiovascular safety compared to pioglitazone. I first learned of this recommendation from Ms. Jane Axelrad, and then from Dr. Dal Pan. I promptly discussed the issues with Dr. Dal Pan and with Dr. John Jenkins, Director of the Office of New Drugs. After consulting with these individuals, in November 2009 I decided that an analysis of all available data (any new observational studies, meta-analyses and clinical trials) should be undertaken and the results presented at a public Advisory Committee meeting as soon as

possible. I met with Drs. Dal Pan and Jenkins and they agreed with this plan. The reasons for this decision are as follows.

Dr. Dal Pan's memorandum explained that OSE had evaluated the potential hepatotoxicity of rosiglitazone, as well as other organ toxicities raised in the Citizen Petition, and had concluded that there was not evidence of an increased risk. However, OSE's position on the risk of myocardial ischemia of rosiglitazone was unchanged from 2007. Dr. Dal Pan's primary point was that not only the original meta-analyses and other studies presented at the 2007 Advisory Committee, but also some (but not all) subsequent meta-analyses and some additional observational studies, suggested an increased risk of myocardial ischemia in users of rosiglitazone compared to either either users of older oral hypoglycemic agents or pioglitazone. In contrast, no such body of evidence existed for pioglitazone, given that a controlled trial (PROactive), several meta-analyses of controlled trials, and some, but not all, published observational studies did not suggest increased risk. (See Tables 1-7 in the Appendix of Dr. Dal Pan's October 23, 2009 memorandum.) Therefore, he concluded that pioglitazone had greater comparative safety, with equivalent efficacy, and thus should be the drug of choice in the class. Dr. Dal Pan discussed the results of the RECORD study, but did not weigh them very strongly in his analysis for several reasons, including the fact that FDA had not had the opportunity to evaluate the study data in detail.

The Office of New Drug staff did not agree with the recommendation to withdraw rosiglitazone from the market on the basis of these data.

In considering next steps, I evaluated what new data were available since the 2007 Advisory Committee meeting, and to what extent these data could impact on a regulatory decision. Many of the new observational studies and meta-analyses cited by Dr. Dal Pan were published but had not been made available to FDA for detailed analysis. The pioglitazone meta-analyses had the most consistent results, but making conclusions about superior performance (on a safety issue) of one drug over another by comparing one set of meta-analyses with another is fraught with severe methodological problems, and conclusions based on such procedures should only be made after broad scientific input, unless the findings are clear-cut. Although the degree of rigor needed to take regulatory steps regarding safety findings is much lower than would be needed for efficacy, some degree of scientific confidence in the conclusions is needed. In fact, Dr. Dal Pan was making a "weight of the evidence" argument, taking all the evidence as a whole, and new results most pertinent to this question, from the RECORD study, had recently been submitted to the FDA for analysis. RECORD, a randomized, controlled clinical trial of the cardiovascular safety of rosiglitazone, had been conducted by the drug's sponsor at the request of the European authorities. The results had been published in June 2009 with a conclusion by the study authors that "rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs". (Lancet, 373; June 2009) FDA does not ordinarily accept assertions such as these without a careful review of the patient-level study data and, frequently, clinical site audits. RECORD, as published, did not suggest a signal of overall increased cardiovascular risk but was inconclusive on myocardial infarction and did not rule out some increased risk in individuals with pre-existing ischemic heart disease. RECORD had some shortcomings: it was quite small (4447 patients) for a cardiovascular outcome trial—although there were more than five years of patient follow up—and the observed event rate was much lower than projected at the trial start, so that there were

fewer than 700 events contributing to the primary composite endpoint. Nevertheless, RECORD is the largest and longest study extant that was designed to explicitly evaluate the cardiovascular safety of rosiglitazone, and thus, had the potential to add significant information to the problem at hand. However, the study would have to be thoroughly reviewed by an FDA team to determine whether the results were robust. Therefore, a complete review of all new data followed by public presentation and scientific discussion seemed to be the appropriate course of action. Additionally, rosiglitazone was clearly labeled with a boxed warning about the potential for myocardial ischemic risk with an updated alert posted on FDA MedWatch. Therefore, no urgent new information needed to be put before the public. For these reasons, I determined that holding an FDA Advisory Committee as soon as possible after the data review was the right decision.

A handwritten signature in red ink, appearing to read "J. Woodcock", is positioned above the printed name.

Janet Woodcock, M.D.

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
SAFETY-141	ORIG-1	NO FIRM	Thiazolidinediones

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JANET WOODCOCK
03/08/2010