FDA Briefing Document

Division of Metabolism and Endocrine Products
and
Office of Surveillance and Epidemiology

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

July 30, 2007

DRAFT Questions for Advisory Committee Members

1. Please comment on the strengths/limitations of the meta-analysis of the 42 controlled clinical studies submitted by GSK to the Agency on defining cardiac ischemic risk for Avandia. Comment on the following areas is of particular relevance:

- types of studies selected (e.g., comparison groups)
- patient populations
- treatment duration of studies
- endpoints (total ischemic events, composite of stroke/MI/CV death) and their ascertainment

2. Please comment on the completed and on-going long-term clinical studies for Avandia with respect to whether cardiac ischemic risk identified in the meta-analysis can be addressed by:

- DREAM
- ADOPT
- RECORD
- BARI-2D

3. Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus (VOTE requested)?

    - If yes, is there evidence that this risk is greater than other available therapies for the treatment of type 2 diabetes mellitus?

4. Does the overall risk-benefit profile of Avandia support its continued marketing in the US (VOTE requested)?

    - If yes, please comment on what FDA should do to maximize the risk-benefit considerations (e.g., limit to certain patients, incorporate a boxed warning….)

FDA Briefing Materials

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TAB 1

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND INTRODUCTORY MEMORANDUM

From: Robert J. Meyer, MD
Director, Office of Drug Evaluation II

Gerald J. DalPan, MD, MHS
Director, Office of Surveillance and Epidemiology

Date: Monday, July 09, 2007

Topic: Introduction of issues for the Advisory Committee meeting on July 30th, 2007 to discuss cardiovascular ischemic events with Avandia (Rosiglitazone)

BACKGROUND

Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is characterized by hyperglycemia and is often accompanied by other conditions, such as dyslipidemia, obesity, and hypertension. The prevalence of T2DM has increased to epidemic proportions in the United States in the past several decades, in part due to the rising rate of obesity in the adult and pediatric population. The chronic complications of diabetes, such as kidney disease, blindness, peripheral vascular disease, and cardio/cerebrovascular disease, further contribute to the public health crisis that is and will result from the rising prevalence of this important disease.

The pathogenic mechanism for T2DM is multifactorial, with impaired glucose tolerance and insulin resistance being an early hallmark of pre-diabetes. The disease process progresses with beta-cell function declining, until the reduced capacity for insulin secretion becomes inadequate to maintain normoglycemia. Derangements in hepatic glucose metabolism are also present, and more recently it has been recognized that gastrointestinal peptides, such as incretin hormones and amylin, play key roles in the regulation of serum glucose levels, particularly in the post-prandial state. The secretion of the incretins also becomes deranged as T2DM progresses.

The differing pathogenic factors in the progression of T2DM have led to the development of therapeutics with different mechanisms of action, each targeted at one or more of the multiple defects contributing to dysglycemia. While preventive measures and lifestyle intervention (e.g., proper diet and exercise) should remain the cornerstone of management, T2DM is a progressive disease with worsening glycemia over time that

makes initiation of drug treatment *and* the use of a combination of different drugs subsequently the rule, more than the exception, as few patients can ultimately be controlled over the long term with diet and exercise alone.

The following table summarizes the currently available agents for the treatment of T2DM.

Table 1. Available Agents for the Treatment of Type 2 Diabetes Mellitus

Drug Class	Route of Administration	Expected HbA1c Reduction (Monotherapy)	Side Effects
Insulin	Subcutaneous injection (inhaled, short-acting insulin recently approved)	> 1.5 to 2.5% (no dose limit)	Hypoglycemia, weight gain
Sulfonylureas (SUs)	Oral	1.5%	Hypoglycemia, weight gain, probable cardiac ischemic risk with certain SUs
Biguanide/Metformin	Oral	1.5%	Rare lactic acidosis, contraindicated in patients with renal impairment
Alpha-glucosidase inhibitors	Oral	0.5 to 0.8%	GI side effects
TZDs/PPAR agonists	Oral	0.5 to 1.5%	Anemia, weight gain, edema, heart failure, cardiac ischemic risk; potential cancer risk (bladder cancer signal with pioglitazone
Glinides	Oral	1 to 1.5%	Hypoglycemia
Amylin analogues	Subcutaneous injection	0.5 to 1.0%	GI side effects
GLP-1 analogues*	Subcutaneous injection	0.4 to 0.8%	GI side effects
DPPIV-inhibitors**	Oral	0.5 to 0.9%	Limited clinical experience; nonclinical safety signals for many in development

*Exenatide is the only approved GLP-1 analogue and is not indicated for use as monotherapy. Efficacy data are for add-on therapy to metformin or SU in T2DM;
**Sitagliptin is the only approved DPP4-inhibitor (approved 10/06).

FDA approves agents for T2DM on the basis of the drug leading to better glycemic control, as manifested by hemoglobin A1c (HgbA1c) determinations, a measure which integrates glycemia over time. Improved glycemic control is of itself a desirable outcome in DM, as elevated blood sugars lead to troublesome symptoms and signs, such as fatigue, polyuria, and polydypsia, and can have more serious immediate consequences, such as an elevated risk of infections and, in extreme instances, hyperosmolar coma. In this sense, utilizing HgbA1c as the endpoint for the approval of drugs to treat T2DM does not represent a surrogate. Improved glycemia over 6 months (the duration of a typical DM trial) is a direct benefit to the patients. Indeed, the labeling claims for oral hypoglycemic agents are specific to improvement in glycemia (e.g., "AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus"), with no wording suggesting a modification in long-term DM sequelae. Nonetheless, long-term improvements in HgbA1c would be expected to decrease the risk of microvascular complications (renal, ophthalmologic, neurologic) and, it is hoped, the macrovascular complications (stroke, MIs, peripheral arterial disease) that are the sequelae of long-standing DM. So, while improved "short-term" glycemic control is a direct benefit to the patient, it would be a significant concern if an agent approved for treating T2DM were to increase the risk of cardiac ischemic events, particularly if there were good evidence that other agents approved to treat T2DM did not do so, especially other agents in the same class.

While new drugs for T2DM have comparatively robust databases at the time of approval, the accumulating clinical experience with each drug and each class of drugs post-arpproval, either as monotherapy or as part of a multiple-drug regimen, has brought to light new safety concerns. This is certainly true with the thiazolidinediones(TZDs), the class that includes rosiglitazone. TZDs are selective ligands of the nuclear transcription factor peroxisome-proliferator-activator-receptor-γ (PPAR-γ). Also referred to as PPAR-γ agonists, these drugs have been developed to target the insulin resistance associated with T2DM. Troglitazone (Rezulin®) was the first TZD approved (in 1997). However, shortly after its approval and marketing, severe cases of hepatotoxicity were observed, with cases necessitating liver transplant and/or resulting in death being reported to FDA post-marketing. In 1999, the FDA approved rosiglitazone (Avandia®) and pioglitazone (Actos®). Clinical trial experience and close post-marketing surveillance of these two compounds have shown much more favorable risk profiles for hepatotoxicity with these agents, compared to troglitazone , which was withdrawn from the market in March 2000. As a class, PPAR agonists are associated with anemia, hemodilution, weight gain, edema, and exacerbation or development of heart failure. The pathogenesis of edema with PPARs appears to be complex, but likely relates to a direct pharmacological action, as it has clearly proven to be a class effect. Indeed, both rosiglitazone and pioglitazone are similarly associated with anemia, weight gain, edema, and risk of heart failure. The risk for significant edema precipitating or exacerbating heart failure was known at the time of approval, but has also led to numerous labeling revisions for both of these drugs as marketing experience and the results of further trials have been reviewed by the agency. This issue will shortly be the subject of a boxed warning for both agents. While this is an important class effect, it is not the subject of the Advisory Committee meeting itself.

While the risk for edema and heart failure has been well-appreciated and described for TZDs, the effect of these drugs on cardiovascular ischemic risk had been less of a known concern. There were early concerns raised by some with regard to the potential for rosiglitazone to have a less favorable effect on long-term macrovascular disease outcomes due to some disadvantageous changes in lipid profiles resulting from rosiglitazone therapy compared to pioglitazone (which has more PPAR-alpha activity, similar to the fibrate class of drugs). In December 2003, the World Health Organization published an analysis of adverse reaction reports from the WHO Database that included a general discussion of thiazolidinediones (TZDs) and a datamining signal for "cardiac disease" overall, which would include both heart failure and ischemic terms. This finding resulted in GSK examining data from the randomized controlled trials (RCTs) with rosiglitazone to further investigate CV risks in general with Avandia. In October 2005, GSK submitted to FDA summary slides showing preliminary results from a pooling of results from RCTs that further raised the concern that rosiglitazone may be associated with ischemic cardiac events. GSK proposed a formal analysis plan to provide a more definitive, formal examination of the pooled data RCTs.

Preceding the receipt of the formal GSK meta-analysis of the phase 2 and 3 RCTs with rosiglitazone, FDA completed a review of a 52-week study performed in patients with pre-existing heart failure. This study was done to examine if rosiglitazone led to decrements in cardiac function as assessed by echocardiography, as an exploration of the mechanism of CHF. In this study, a blinded adjudication committee looked at cardiac events, focusing on CHF events and overall CV deaths and hospitalization. While angina and MIs were not separately adjudicated, they were captured from case report forms. While there were no differences between rosiglitazone and placebo in echocardiographic assessments, there was a numerical disadvantage in cardiac events, both in terms of CHF and ischemic events. FDA considered these findings to be of sufficient importance to place the results of this study with the first WARNING about cardiac adverse effects in the labeling in April of 2006. This was the first specific mention in labeling of a potential association of rosiglitazone with cardiac ischemia, whose risk was in the warning in tabular form.

FDA received the submission detailing the GSK-conducted integrated statistical analysis of 42 phase 2 and 3 randomized controlled clinical trials (RCTs) of rosiglitazone in patients with T2DM in August of 2006 (including the echocardiographic study detailed above). These data were contained in a labeling supplement that also contained the findings from an observational cohort study commissioned by GSK and conducted by i3 Research, a contract research organization. Both these databases focused on characterizing the risk of heart failure as well as the cardiac ischemic events associated with rosiglitazone use. GSK's summary of their meta-analysis showed an apparent imbalance of cardiovascular ischemic events with a hazard ratio of approximately 1.31 (that is, a 31% increase in cardiac ischemic events with rosiglitazone compared to the comparator group). On the other hand, the observational cohort study (Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents) showed no such increased risk of cardiac ischemic risk. On their face, these two studies provided conflicting data on this very important issue. For this reason and because of some significant concerns on

the part of the FDA biometrics staff with the details of how GSK conducted its meta-analysis, FDA believed it was important to conduct its own thorough and complex analysis of these same RCT data, which has only recently been completed. FDA also thoughtfully assessed the results of the observational cohort study. You will see and hear more details on FDA's findings for both studies in this briefing document as well as at the Advisory Committee meeting itself.

Other data relevant to the question of the potential for rosiglitazone to cause cardiac ischemic events became available subsequent to GSK's submission of their RCT meta-analysis in August of 2006. In September 2006, the results from a study of rosiglitazone versus placebo (with a 2x2 factorial design also examining ramipril vs. placebo) used in prediabetic patients to delay the onset of diabetes was published. [1] This study, named DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication), was an independent study (i.e., not conducted by GSK) coordinated by McMaster University. This study will be discussed at the meeting itself and the report as published is contained in this background package.

In December 2006, the results of ADOPT (A Diabetes Outcome Progression Trial) were published. [2] ADOPT was conducted by GSK as a phase 4 commitment made at the time of approval of rosiglitazone. It was a large, long-term diabetes trial comparing the time to failure of monotherapy with rosiglitazone, metformin, or glyburide, as well as assessing relative safety, including CHF. In ADOPT, rosiglitazone performed the best on the primary efficacy outcome of interest (length of time successfully treated with monotherapy), with glyburide having both the highest rate of treatment failure and the highest rates of discontinuation and missing data. For CV ischemic outcomes, rosiglitazone compared favorably to metformin, with both appearing somewhat less favorable than glyburide. Although the results of this study were published in December 2006, the primary data were submitted to FDA by GSK in February 2007 and we do not have a final FDA analysis to present at this time. Ongoing review of cardiovascular events will be presented and are discussed elsewhere in this briefing document.

These various datasets present an array of somewhat inconsistent findings that complicate the interpretation of the available data regarding the effect of rosiglitazone on cardiac ischemic events. Nonetheless, given the findings from the RCT meta-analysis, FDA views this signal with considerable concern.

Following a high level discussion of the issue of the cardiac safety of the PPAR agents (rosiglitazone and pioglitazone) at a Center-wide briefing in April 2007, the following was decided:

1. Because of persistent reports in the spontaneous adverse events reporting system of the PPAR agents being utilized in a manner inconsistent with labeling and what is known about risk of heart failure, the prominent warnings with regard to the risk for heart failure and edema with these agents would be appropriate for a

1 Lancet September 23, 2006; 368: 1096 - 1105
2 NEJM 355;23 December 7, 2006

boxed warning for both rosiglitazone and pioglitazone. (This action is ongoing and is not the subject of this Advisory Committee meeting).

2. With regard to the signal of CV ischemic events with rosiglitazone, FDA was to call in the sponsor (GSK) for a meeting in the near future to discuss their thinking on this risk and to see if they could provide other data or information that would better clarify or quantify the signal of risk. (That meeting took place on May 16th, 2007). In the meantime, FDA was to work on a communication strategy for alerting the public to our ongoing concerns and plans, above and beyond the data already in the rosiglitazone labeling on CV ischemic events.
3. FDA planned to take both the issue of heart failure for both drugs and the CV ischemic signal to an Advisory Committee meeting in the late summer or early fall.

With the publication by Dr. Nissen and Ms. Wolski of their meta-analysis of the risk cardiac ischemic events with rosiglitazone and the accompanying editorials by Drs. Psaty and Furberg,[3] FDA accelerated it public message about its ongoing work with regard to the CV ischemic signal and also moved forward the date for the Advisory Committee meeting, narrowing the focus of the meeting to the CV ischemic issue with rosiglitazone. We should note that while Dr. Nissen's meta-analysis and the editorials engendered considerable public notice and concern, the specific conduct and results of this meta-analysis, performed out of necessity on study level data, will not be a focus of this Advisory Committee meeting nor of this background document. This is because we believe the results of the analysis performed by GSK and subsequently by the FDA on the more granular individual datasets do not greatly differ from that of Dr. Nissen and Ms. Wolski in a qualitative sense. Importantly, though, we believe that the FDA analysis of the data, including patient level data, is more robust than would be possible for an analysis utilizing study-level data alone.

Finally, due to concerns over the findings in the meta-analysis, GSK had the data monitoring committee for its ongoing RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trial perform an interim analysis of cardiovascular safety. This interim analysis was recently published, and a copy of the publication is included in the background package.. RECORD is an ongoing, large, randomized, controlled 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 single-agent therapy with either metformin or a sulfonylurea. While the study is necessarily open label (this being a long-term treatment trial where adjustment of therapy is required), the adjudication of the cardiac events is blinded to treatment assignment. The design of the RECORD study and the results of the interim analysis will be presented at the Advisory Committee meeting and the reports of the interim analysis as published are contained in the background document.

3 NEJM online 10.1056/NEJMoa072761; NEJM online 10.1056/NEJMe078099

Conclusions: Since the prevalence of T2DM is of epidemic proportions in the US, and because the use of rosiglitazone is widespread, it is of high public health importance to characterize and quantify the risk of ischemic CV events with rosiglitazone .. It is also important to place any risk into context of what is known about the risks of other available therapies for T2DM, including the other PPAR agent – pioglitazone. For instance, based on a decades old study with tolbutamide, the sulfonylurea agents all carry a warning about the potential for inducing myocardial ischemia with this class of drugs. Since non-pharmacologic treatment of T2DM is not an option as the disease progresses, one needs to place the data with rosiglitazone into context with what is known and/or not known with alternative therapies, including pioglitazone. In addition, it is necessary to place any risk into context with what is known about the benefits of the drug.

In this document and in the sponsor's and FDA's presentations at the Advisory Committee meeting, along with the public comments, we hope to provide the committee with as complete a set of data as possible to inform the committee's discussion and subsequent recommendations. We look forward to the committee advising FDA on the interpretation of these data, and on any conclusions or actions that should be taken based on them.

We look forward to a thorough and reasoned discussion of this complex, important matter and thank you in advance for the vital public health contribution you are making through your participation in this important meeting.

TAB 2

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. Team Leader Tom Permutt, Ph.D. Division Director
Medical Division:	Division of Drug Risk Evaluation and Division of Metabolic and Endocrine Products
Clinical Team:	Kate Gelperin, M.D. (Reviewer , Division of Drug Risk Evaluation) Karen Mahoney, M.D. (Reviewer, Division of Metabolic and Endocrine Products) Mary Parks, M.D. (Division Director, Division of Metabolic and Endocrine Products)
Project Manager:	Jena Weber (Division of Metabolic and Endocrine Products)

Keywords: Clinical studies, meta-analysis

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.

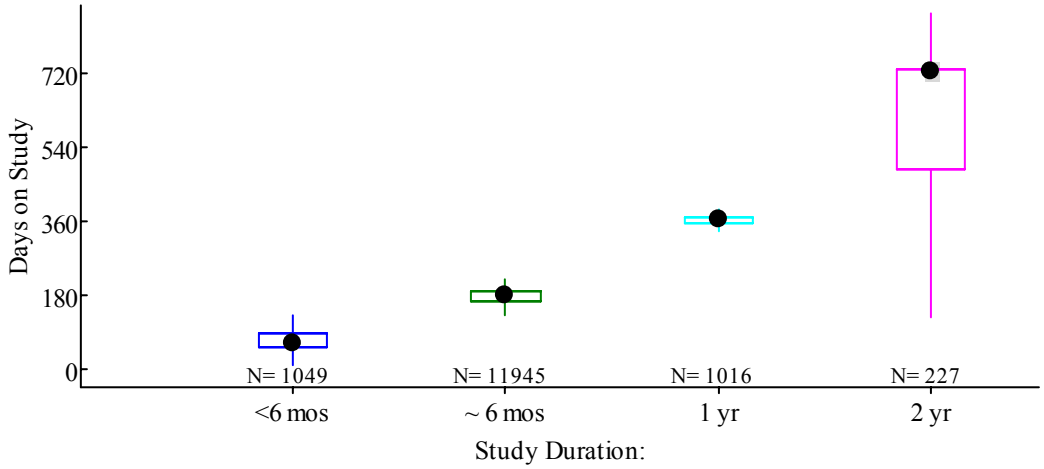
In the 42 studies included in the applicant's database, rosiglitazone was administered as monotherapy, combination therapy or as add-on therapy at the approved doses of 4 mg and 8 mg daily (either once a day or in divided doses, Table 2.2.1). For the add-on trials, patients were treated with metformin, 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/CombinationTrials			
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/cm^2; 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 sulfonlyureas 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-therapy[1] 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

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).

counted in more than one comparison. Therefore an analysis combining the comparison groups would not 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 inhibiter	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 mis-classified). Not all endpoints are shown for every meta-group.

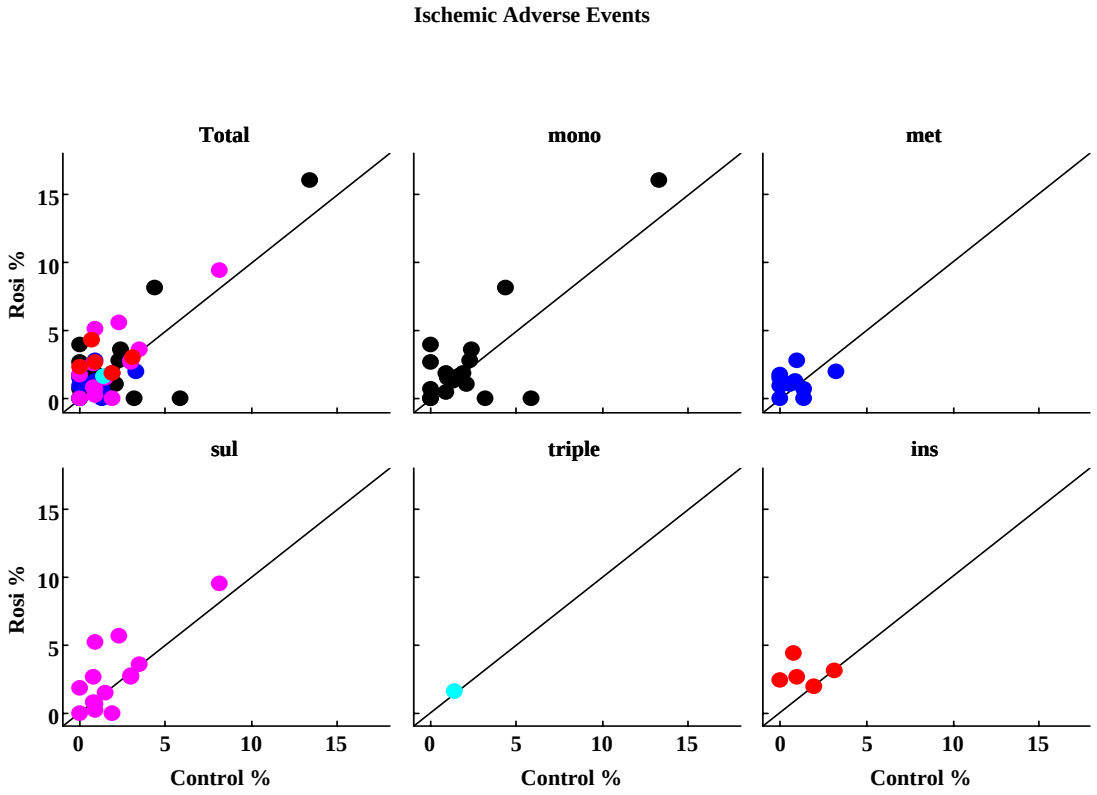
The format of the following sections is first a presentation of the results for each meta-group shown separately and then a discussion of overall results. Additional issues (such as subgroups) are covered last.

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.



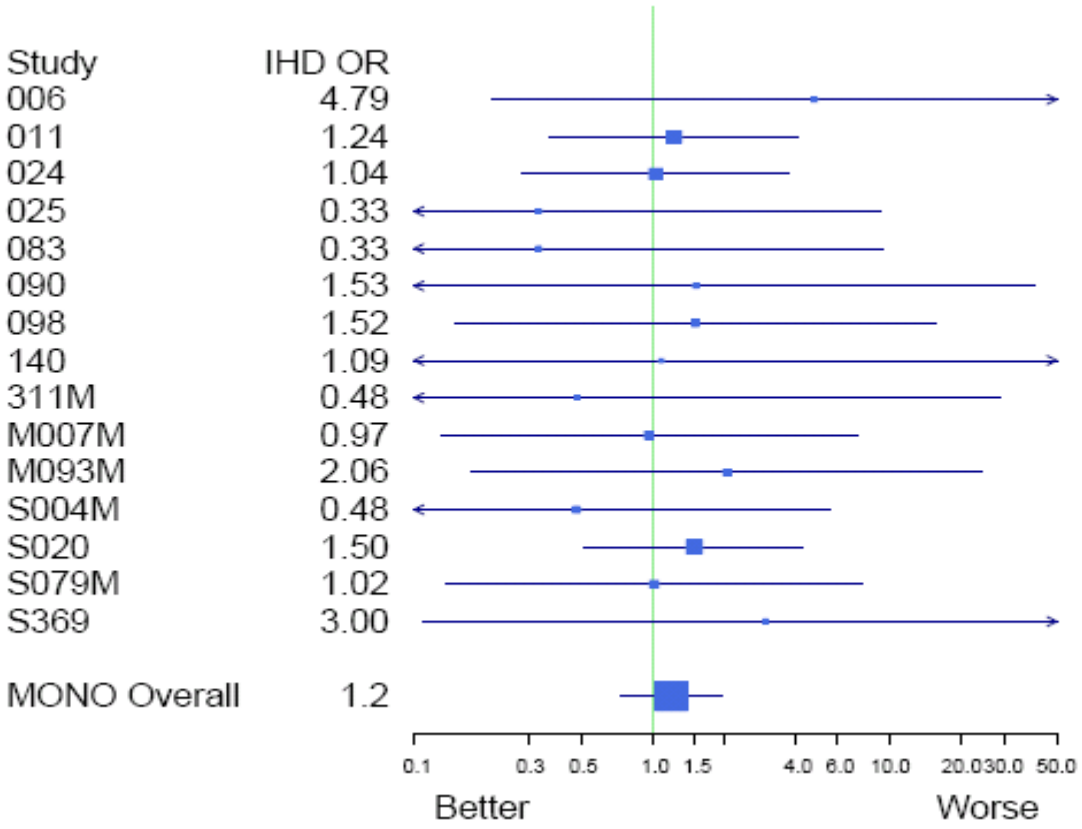
In the forest plots that follow, study numbers preceded by an S or an M were sulfonylurea-controlled or metformin-controlled, respectively. Odds ratios in the figures were computed using the Mantel-Haenszel method where 0.5 was added to each cell of a 2x2 table of outcomes for trials with no events in 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 (±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 naive 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.

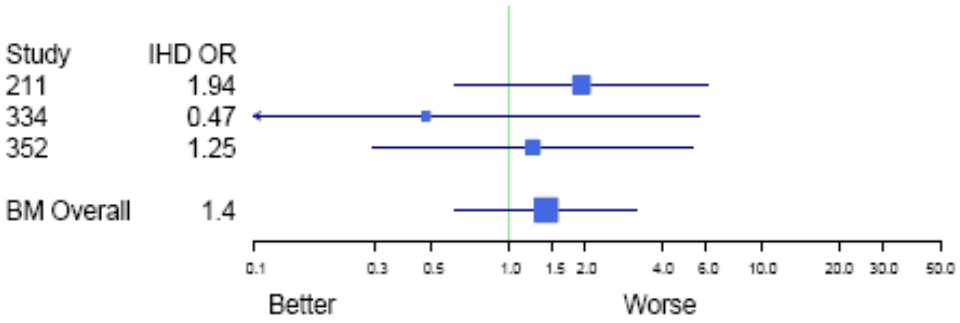
Table 3.3.2 Number of events by study and by randomized treatment + background medication (S=Sulfonylurea M=Metformin)

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 (±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.

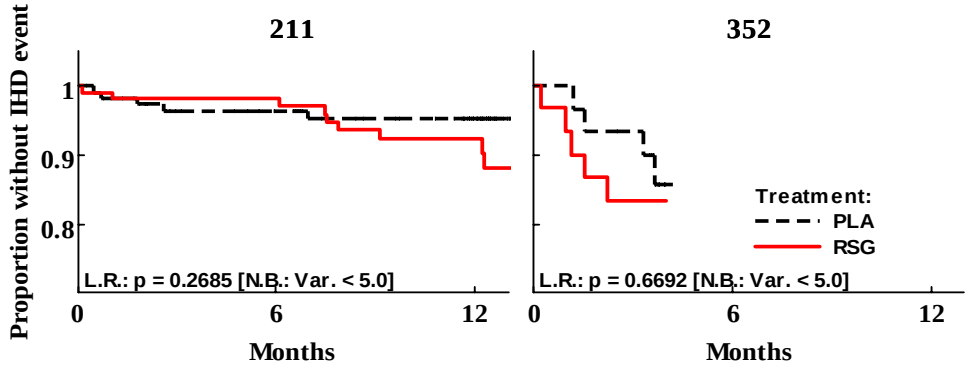
The results for IHD/CHF (Table 3.3.3) suggest greater risk from rosiglitazone compared to placebo with borderline significant results; the rest of the results are inconclusive.

Table 3.3.3 Results for RSG add-on to background therapy; odds ratio and risk difference

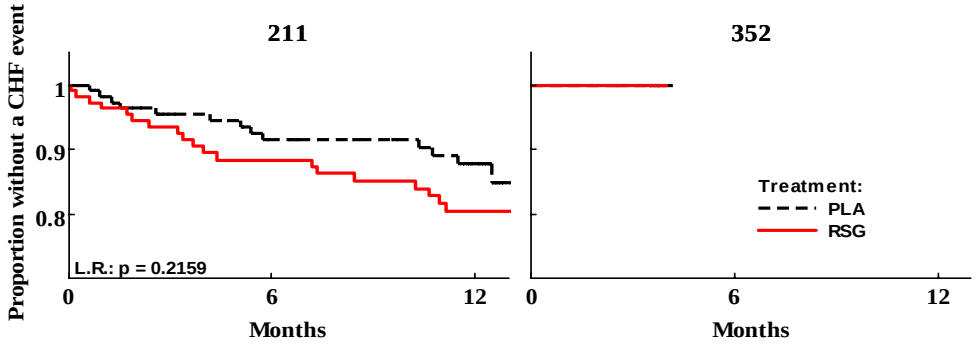
	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials OR Risk Difference	 p=0.5 p=0.2	 1.4 +1.7%	 0.6, 3.5 -2.3%, +5.7%	 p=0.4 p=0.4
Only 211 and 352 Only 211	p=0.7	1.6 1.9	0.6, 4.5 0.5, 7.7	p=0.3 p=0.4
Serious Ischemic events				
All Trials	p=0.5	1.6	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)

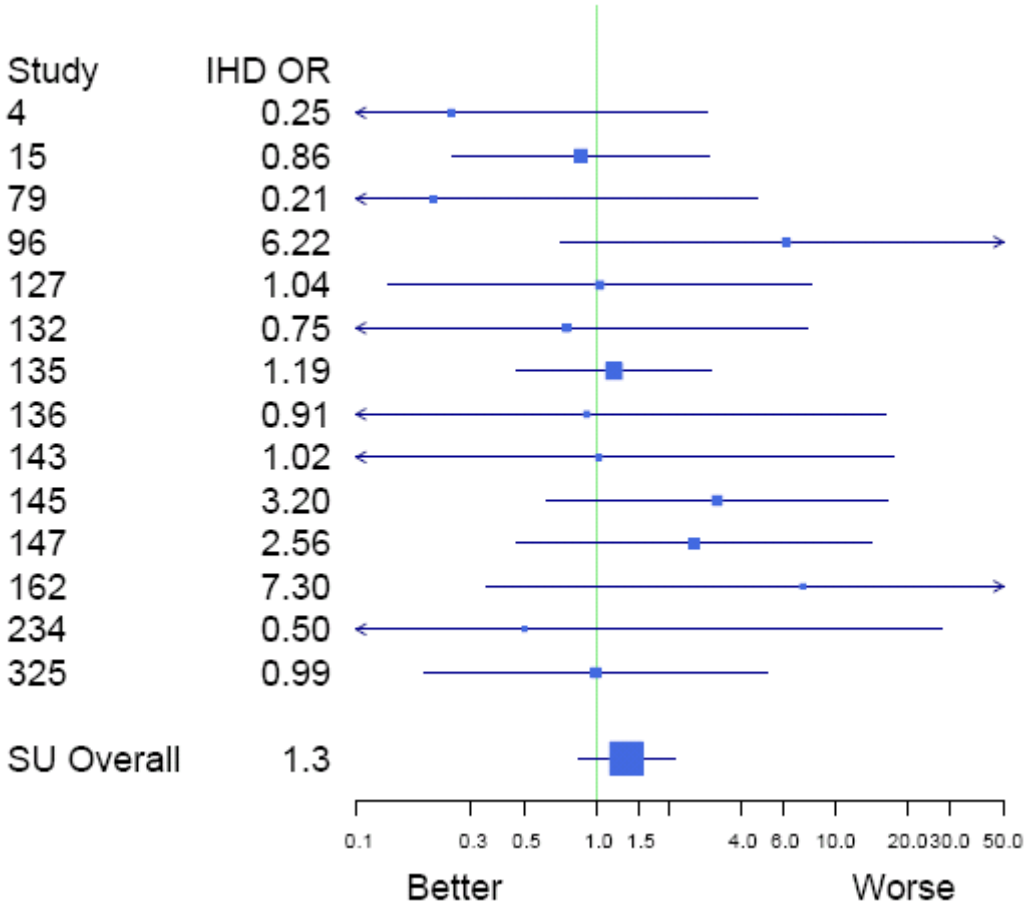


RSG+Sulfonylurea versus Sulfonylurea

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 sulfonlyurea 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 (±95% CI) for IHD; RSG add-on to/combination with SU



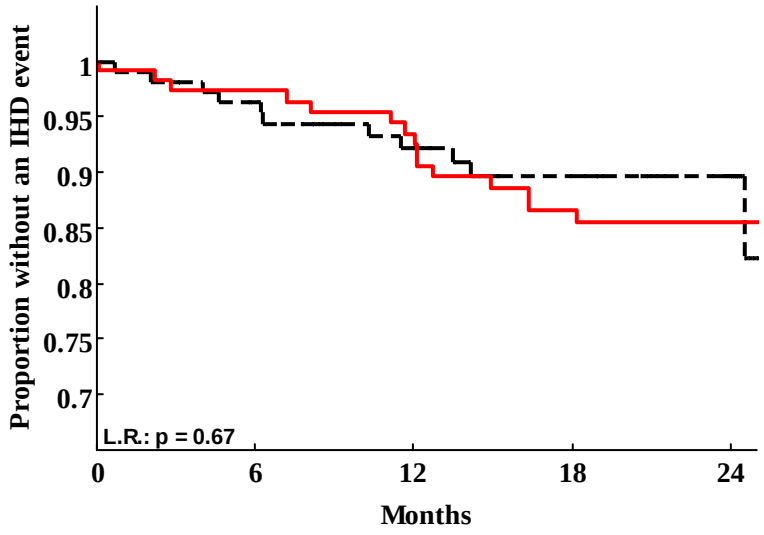
The overall estimate for the sulfonylurea meta-group was 1.4 with a confidence interval of 0.8 to 2.25 (p=0.2); larger than the estimate seen with the monotherapy group but also not statistically significant. However borderline significant results are seen for serious IHD/CHF events with a similar OR. 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 Risk Difference	 p=0.3 p=0.4	 **1.4** **+0.6%**	 **0.8, 2.25** **-0.3%, +1.5%**	 p=0.2 p=0.2
Excl. 135 Excl 135&136	p=0.3 p=0.2	**1.4** **1.5**	**0.8, 2.6** **0.8, 2.65**	p=0.2 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 Excl 135 Excl 135&136	p=0.25 p=0.2 p=0.1	**1.5** **1.5** **1.5**	**0.9, 2.3** **0. 9, 2.6** **0. 9, 2.6**	p=0.09 p=0.14 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.

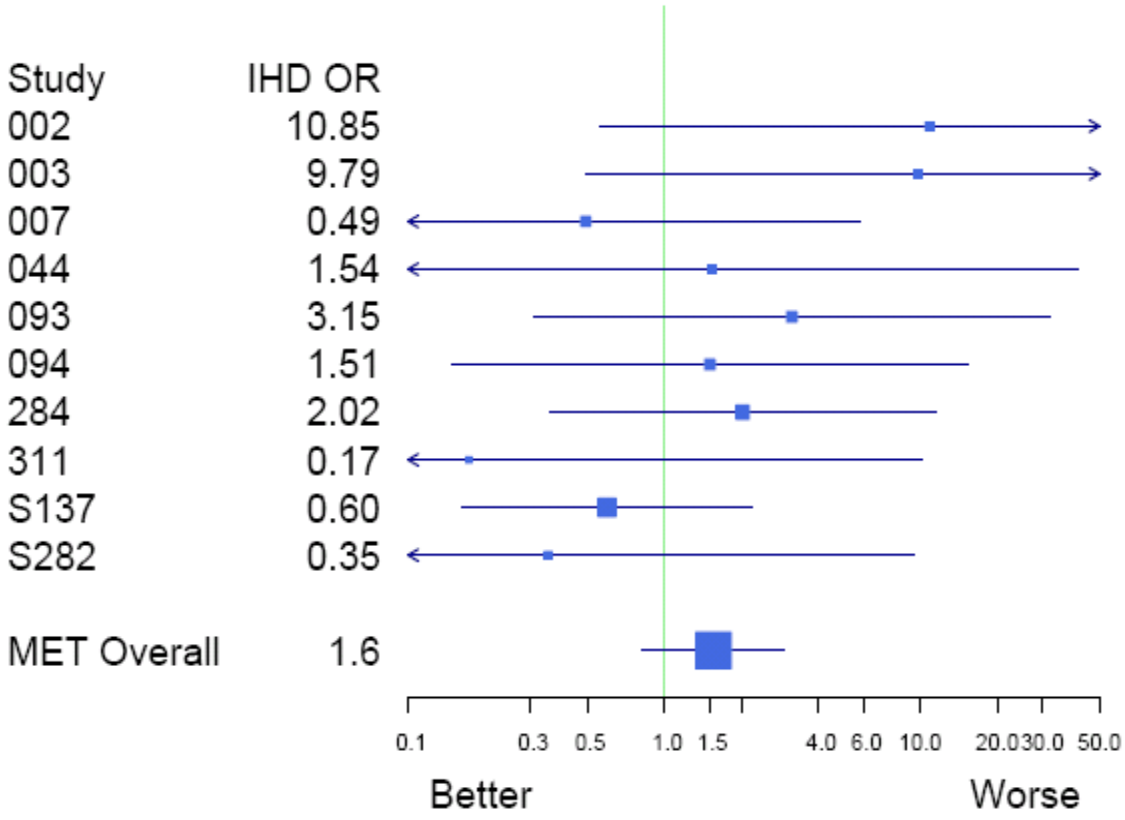
Figure 3.3.6 Study 135 Kaplan-Meier curve of time to ischemic event



RSG+Metformin versus Metformin

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.

Figure 3.3.7 Forest plot of odds ratios (±95% CI) for IHD; RSG add-on to/combination with MET



Note that Study 311 is a small trial of 50 patients (43 on RSG and 7 on PLA) with no events in either arm; this study contributes very little to the overall estimate depicted in the graph above and is excluded from the exact test results in the following table.

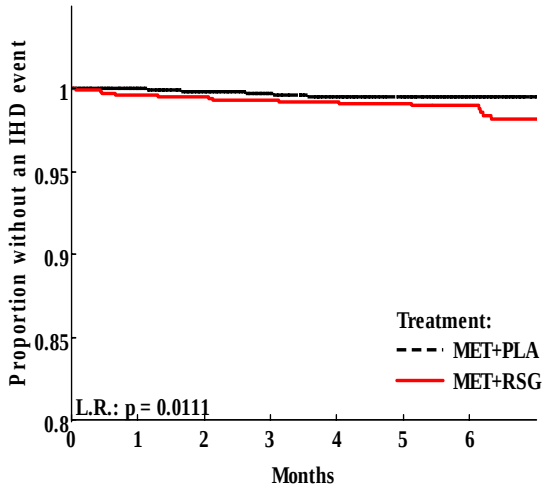
Heterogeneity (this reviewer considered a p-value of less than 0.2 as a signal of differential treatment effects across studies for this low powered test) was seen when looking at all trials for total and serious ischemic events and serious IHD/CHF events. Excluding the two active-controlled trials reduced 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

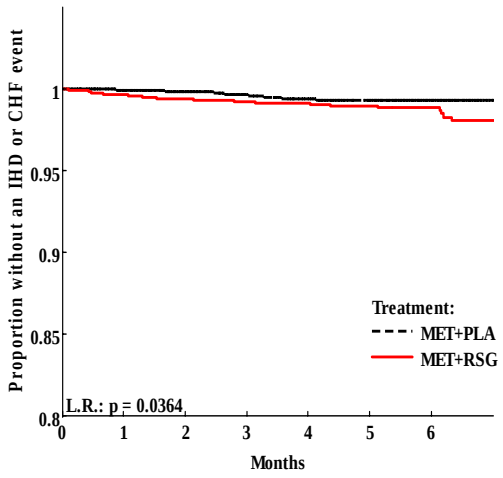
	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials OR Risk Difference Fixed effects model	p=0.12 p=0.60	**1.8** **+0.6%**	**0.9, 3.8** **-0.2%, +1.3%**	p=0.14 p=0.12
Placebo-controlled Active-controlled (137&282)	p=0.30 p>0.9	**3.2** **0.5**	**1.2, 9.8** **0.1, 2.1**	p=0.01 0.4
Studies in FDC Avandamet Add-on placebo-cont. studies	p=0.04 p=0.8	**5.1** 1.7	**1.1, 48** 0.6, 5.6	0.02 0.3
Serious events				
All trials Excl 137 and 282	p=0.09 p=0.15	1.28 **2.9**	0.5, 3.4 **0.7, 17**	p=0.7 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 Excl 137 and 282	p=0.04 p=0.13	1.25 **3.3**	0.5, 3.2 **0.9, 19**	p=0.7 p=0.06

Figure 3.3.8 Kaplan –Meier curves for metformin+rosiglitazone trials

Ischemic Events

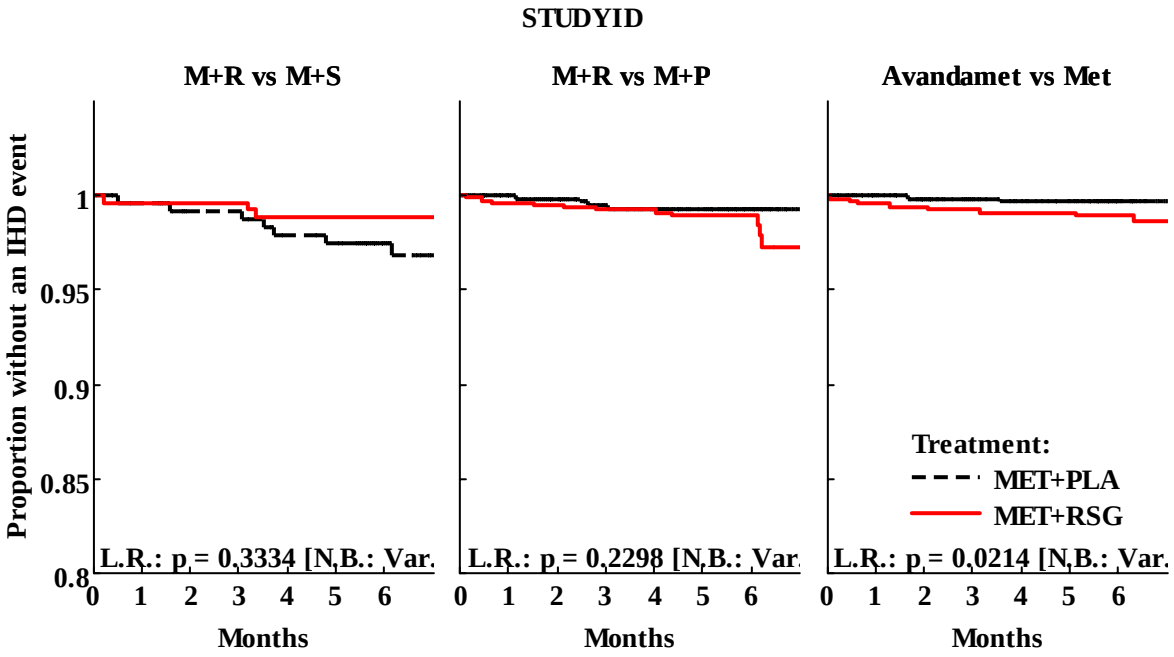


CHF or Ischemic Events



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 (±95% CI) for IHD; RSG add-on to insulin

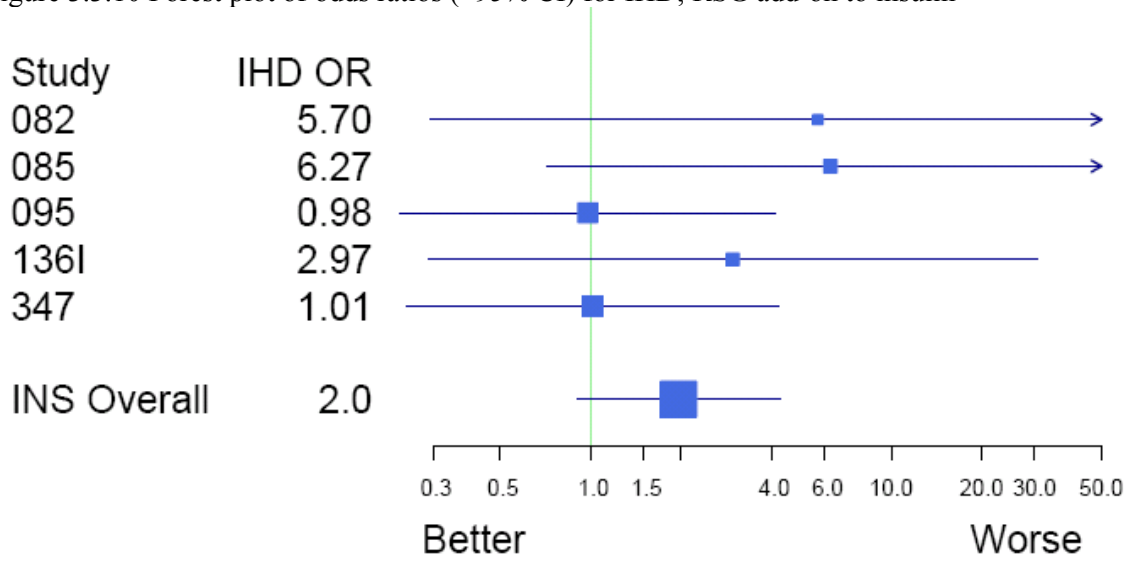


Table 3.3.6 Results for RSG add-on to insulin; odds ratio and risk difference

	Test of Homogeneity	Estimate	95% CI	Exact test for Common OR=1 or RD=0
All Ischemic events				
All trials OR	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

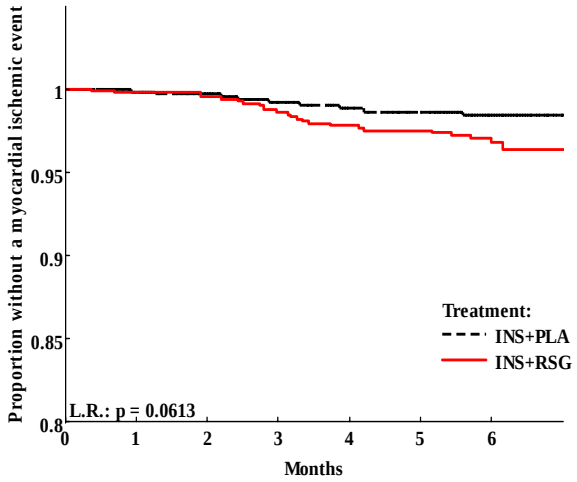
One additional study of Avandamet (RSG+MET) plus insulin (Study SB-712753/009 reviewed by FDA in 2006) is not included in the database under review here. In this study, there were 2 serious ischemic events (1 death) in the Avandamet+insulin group (162 patients) and 0 in the insulin alone group (160 patients). 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.

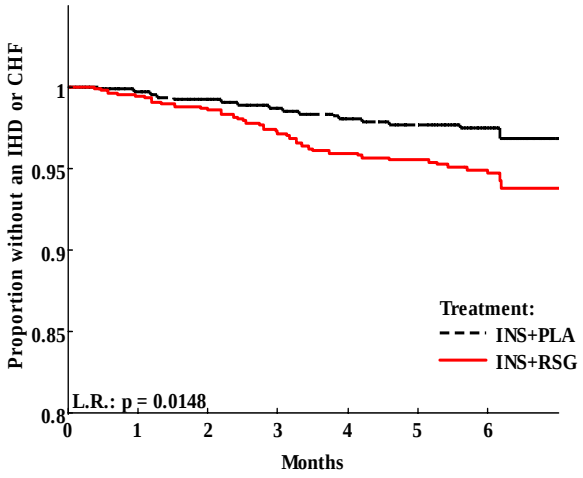
Time to event analyses (log rank test) show a (borderline) significant difference with the proportion of patients without ischemic events illustrated by the Kaplan-Meier curves below.

Figure 3.3.11 Kaplan –Meier curves for insulin+rosiglitazone trials

Ischemic Events



CHF or Ischemic Events



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 (±95% CI) for IHD by meta-group ordered by OR

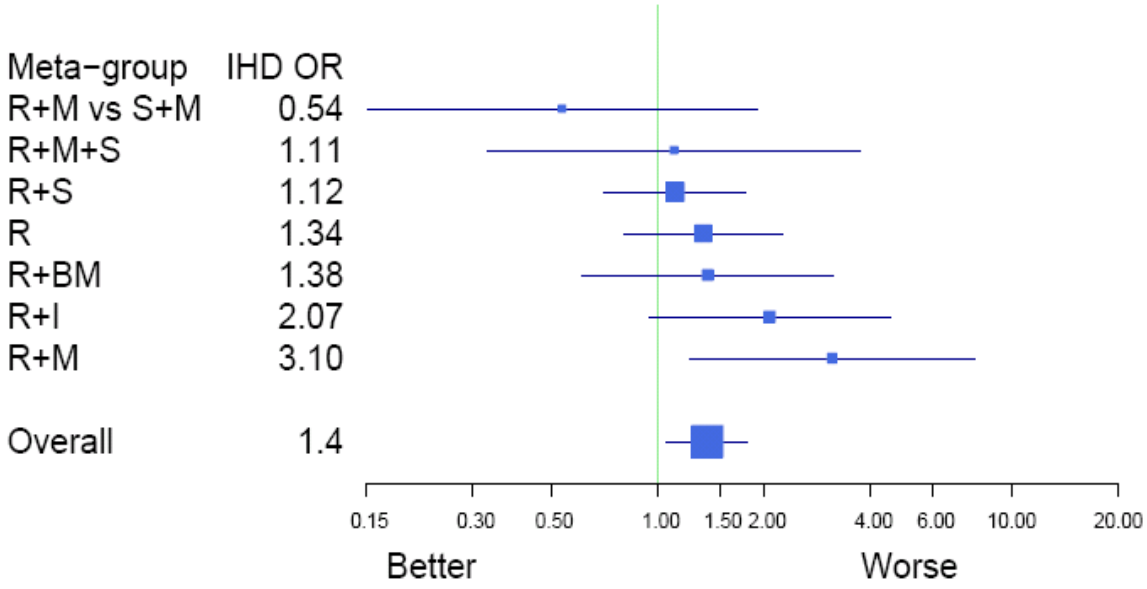


Figure 3.3.13 Forest plot of odds ratios (±95% CI) for serious IHD by meta-group ordered by OR

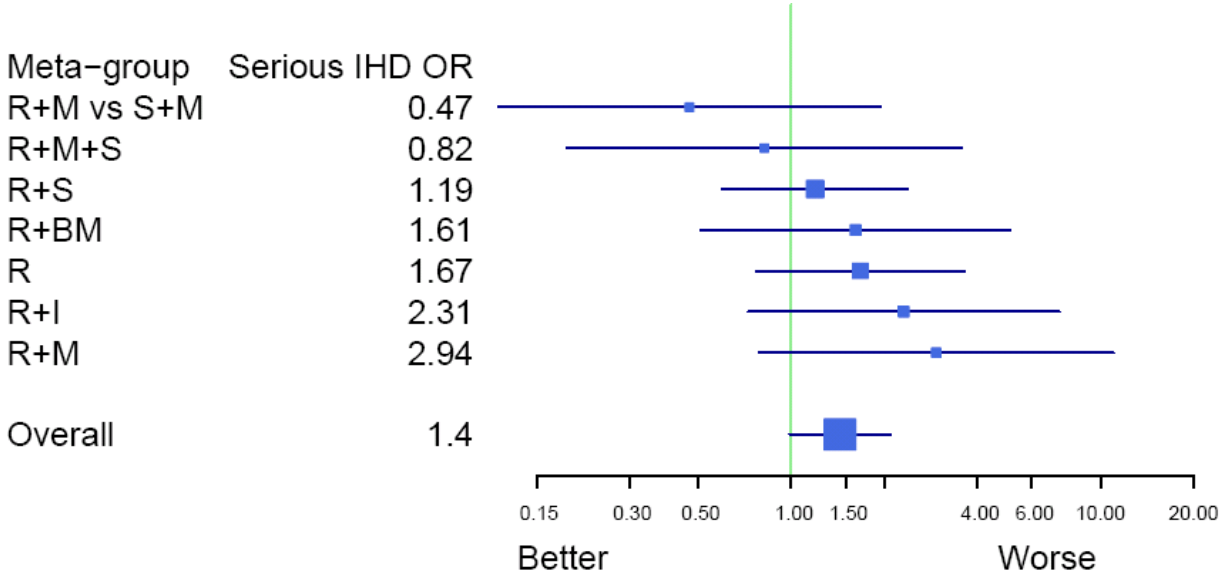


Table 3.3.9 Summary of the serious ischemic events results in 7 meta-groups

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.

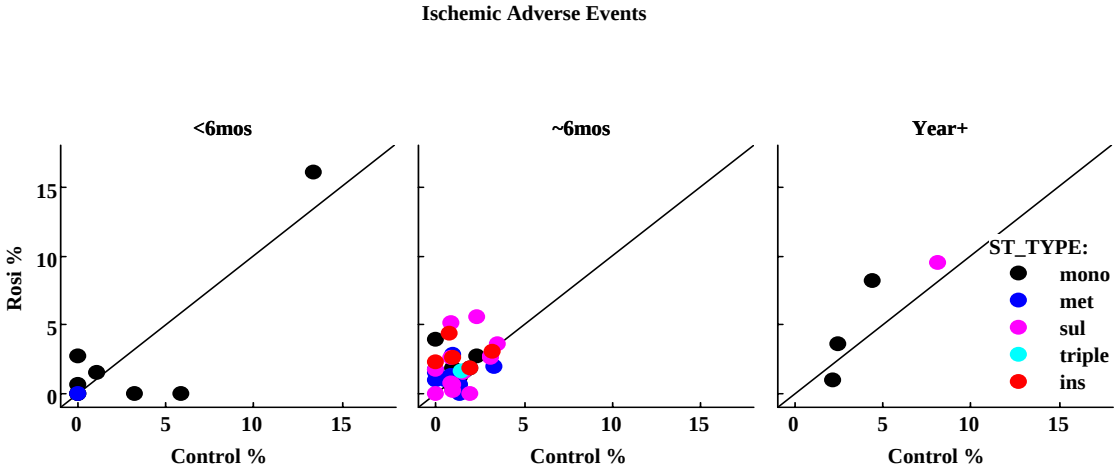
Table 3.3.10 Overall OR excluding meta-groups; exact test stratifying on meta-group

	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



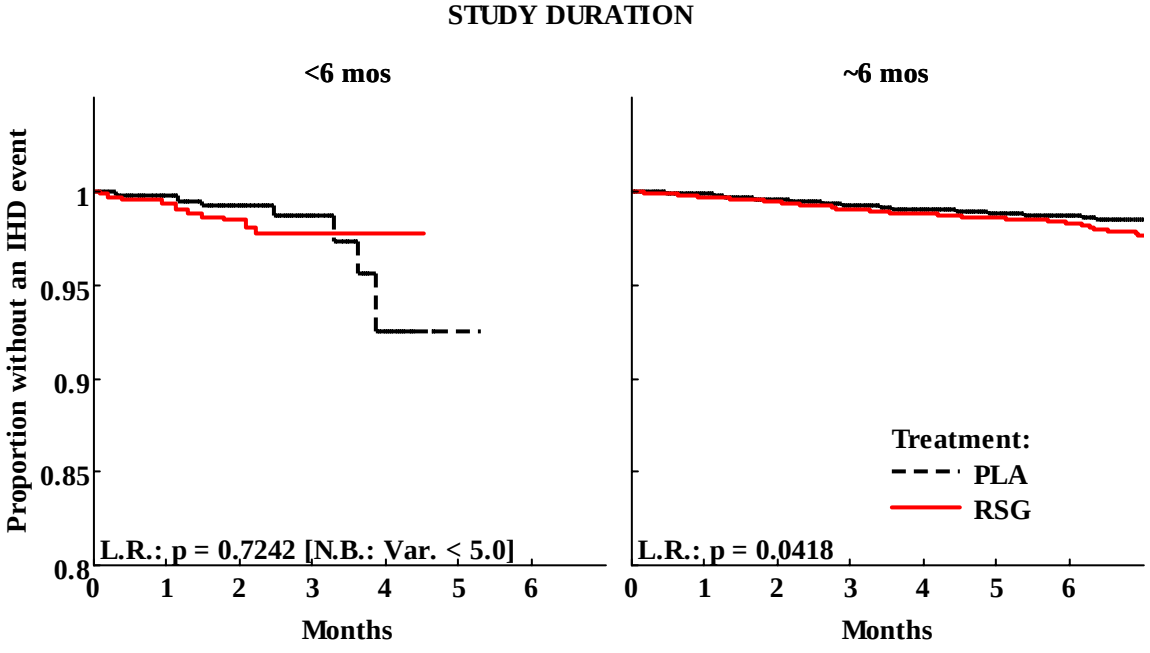
The odds ratios by duration of study (Table 3.3.11) do not vary considerably though the event rates between the short term studies and the 1 year+ studies are notably different. Only the results of the 6-month studies with the majority of the patients show statistically significant evidence of ischemic 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.

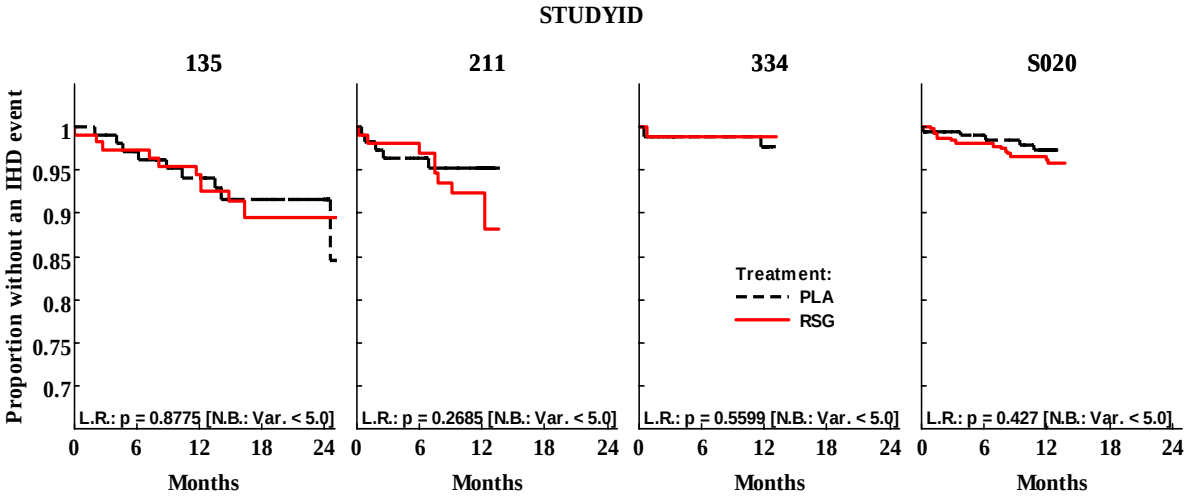
Figure 3.3.15 Kaplan Meier Curves for IHD events for less than 6 month studies and 6 month studies (graphs of IHD/CHF look essentially the same)



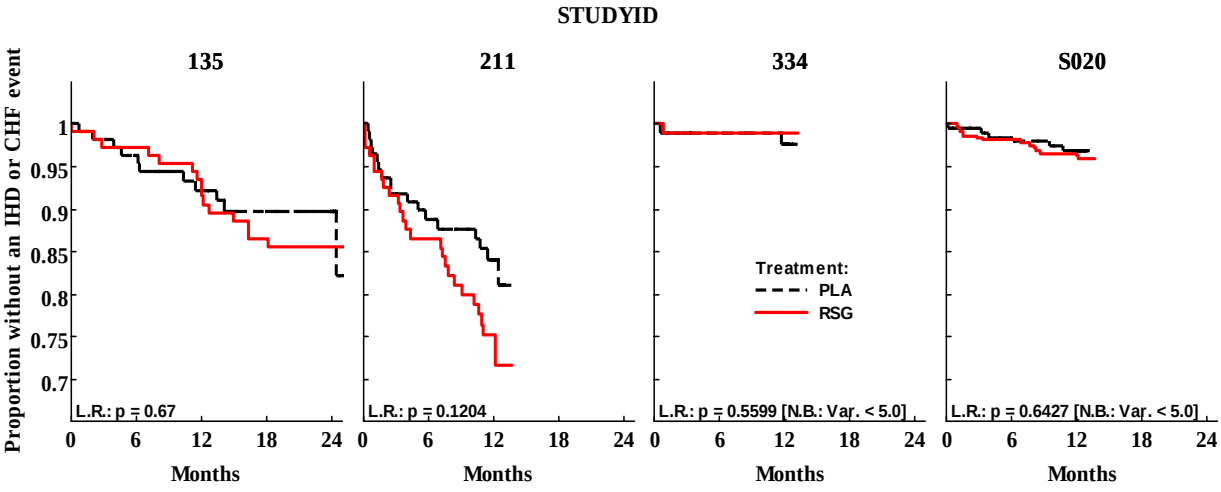
Kaplan-Meier Curves are shown below for one 2-year study (Study 135, a study in 227 elderly patients comparing SU+RSG to SU+PLA) and three 1-year studies (Study 211, a study in 224 CHF patients comparing RSG+background meds to PLA plus background meds; Study 334, a study of 194 patients comparing RSG+background 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.

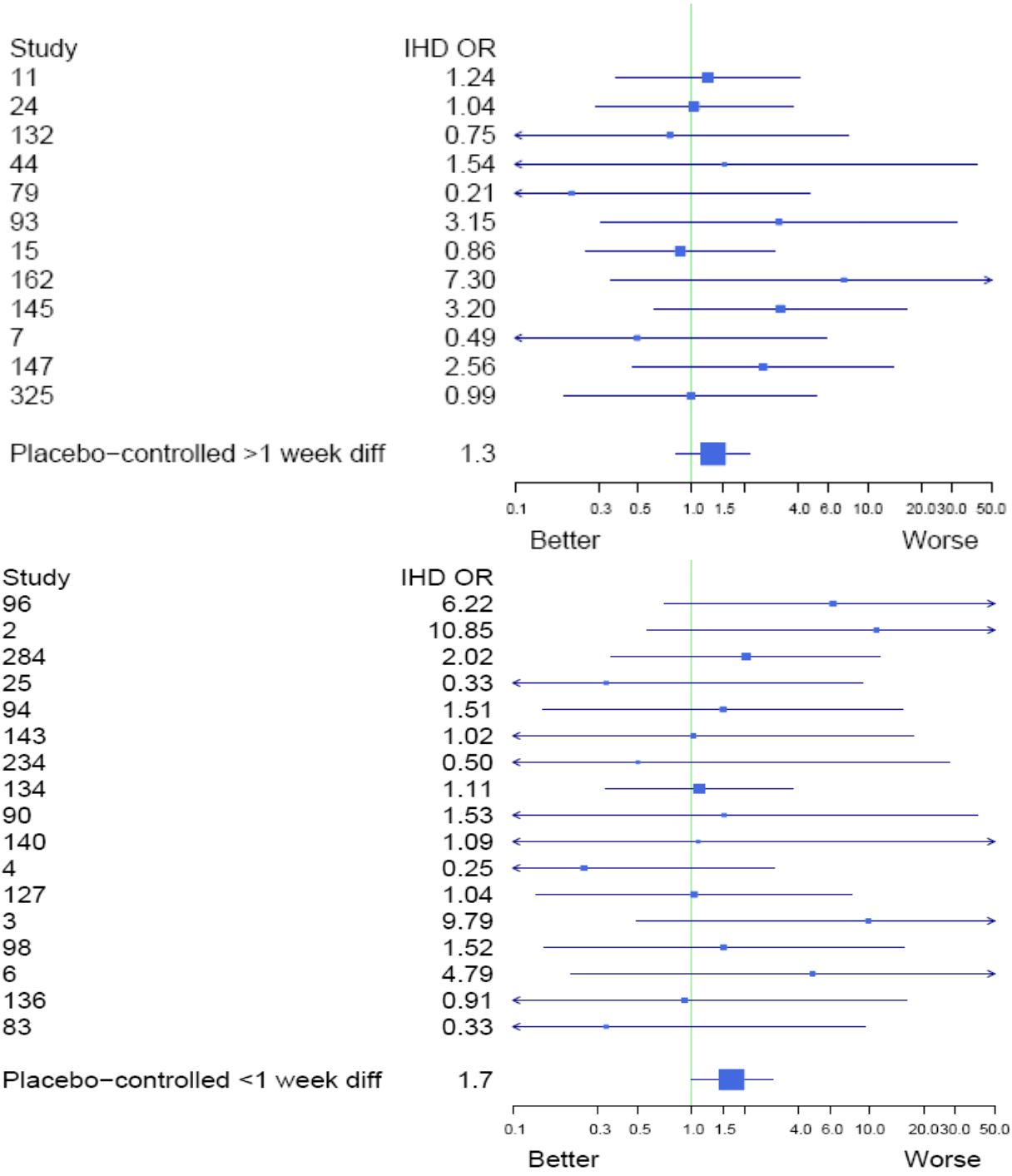
Table 3.3.11 Total (non-serious+serious) and serious IHD results for ~6-month placebo and active controlled studies; studies of 1 year or longer and insulin studies and Studies 211 and 352 in CHF and CHD patients, respectively, are excluded

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 then 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.

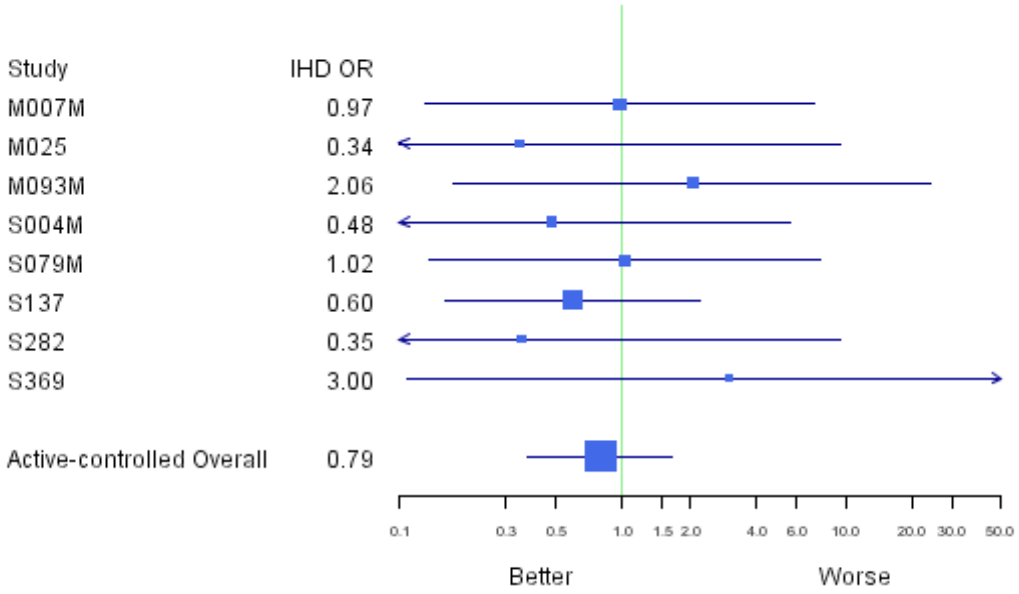
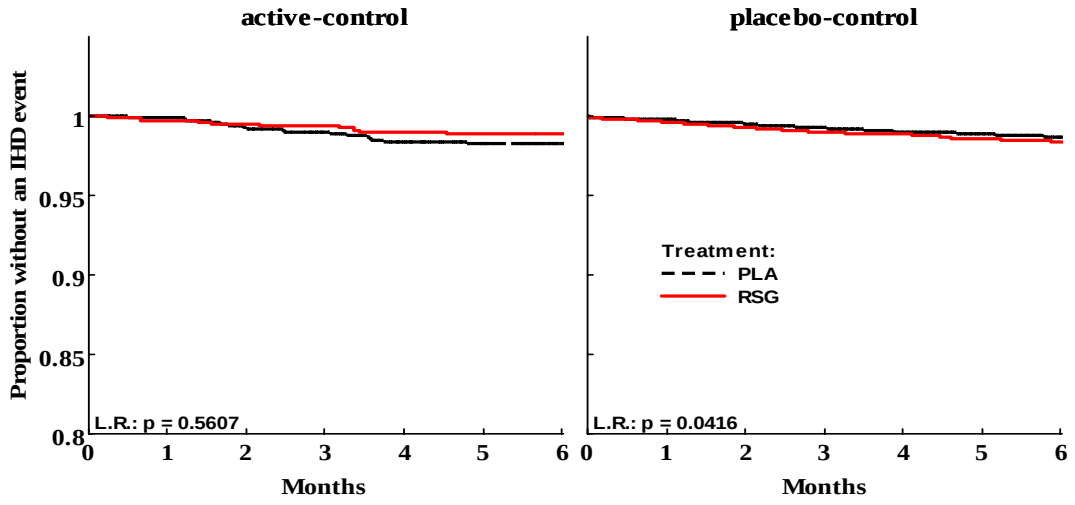


Figure 3.3.19 Kaplan Meier Plots for 6-month active-controlled trials and placebo-controlled trials



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

	All Trials			**Without Insulin Trials**		
Baseline Characteristic	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

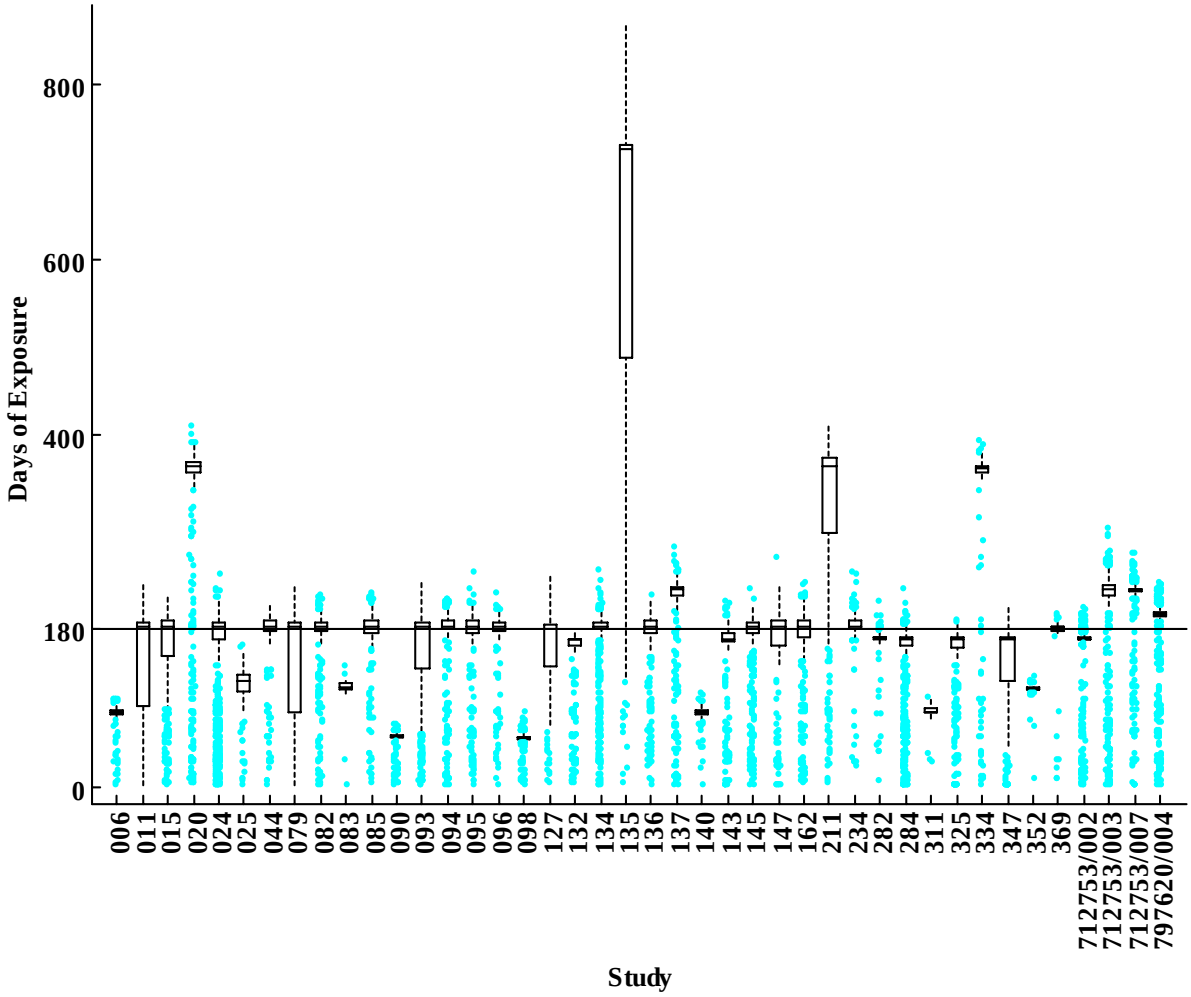
Treatment groups were defined by the applicant based on randomized treatment and concomitant medication use; this table shows the treatment assignments used by the applicant

	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= 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. 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)			
Age									
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
Gender									
% males	63%	81%	56%	74%	57%	73%	57%	53%	60%
BMI									
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%
Dur Diab (yrs)									
Mean (SD)	5 (6)	6 (6)	4 (4)	8 (7)	7 (6)	7 (6)	6 (5)	13 (8)	8 (6)
Trt Exp (mos)									
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)
CV Meds									
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%
CV Major Risk Cond									
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%
Baseline meds	3%	30%	6%	48%	4%	10%	2%	6%	3%
Nitrates	13%	43%	32%	48%	15%	31%	25%	26%	28%
Statin	3%	60%	8%	5%	3%	7%	3%	11%	6%
Loop diuretic	3%	2%	2%	3%	4%	5%	4%	5%	3%
Alpha blocker	12%	70%	28%	59%	13%	20%	15%	12%	13%
Beta blocker	14%	10%	14%	23%	15%	22%	15%	19%	14%
CCB	25%	98%	30%	52%	28%	41%	43%	47%	41%
Ace inhibitor									
HbA1c									
Mean (SD)	8.5 (1)	8 (1)	7 (1)	7 (1)	9 (1)	8 (1)	8 (1)	9 (1)	9 (1)
HDL									
Mean (SD)	45 (11)	42 (11)	47 (12)	43(11)	46 (12)	44(11)	47 (12)	48 (13)	50 13)
LDL									
Mean	131	113	120	97	125	113	117	122	112
(SD)	(36)	(32)	(32)	(25)	(34)	(30)	(33)	(34)	(33)
HCT									
Mean (SD)	44 (4)	43 (4)	41 (3)	42 (3)	43 (4)	43 (4)	42 (4)	42 (4)	42 (6)
DBP									
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

	RSG Events					CONTROL Events				
Study	**N**	**IHD**	**Ser IHD**	**IHD/CHF**	**Ser IHD/CHF**	**N**	**IHD**	**Ser IHD**	**IHD/CHF**	**Ser IHD/CHF**
BM211	110	9	6	26	13	114	5	3	17	10
1 yr CHF		(8.2%)	(5.5%)	(24%)	(12%)		(4.4%)	(2.6%)	(15%)	(8.8%)
BM334	99	1	1	1	1	95	2	2	2	2
1 yr		(1%)	(1%)	(1%)	(1%)		(2%)	(2%)	(2%)	(2%)
BM352	31	5	1	5	1	30	4	0	4	0
<6 m. CHD		(16%)	(2.8%)	(16%)	(2.8%)		(13%)		(13%)	
Overall	**240**	**15**	**8**	**32**	**15**	**239**	**11**	**5**	**23**	**12**
		(6.2%)	**(3.3%)**	**(13.3%)**	**(6.2%)**		**(4.6%)**	**(2.1%)**	**(9.6%)**	**(5.0%)**

RSG+Sulphonylurea versus Sulphonylurea

	RSG Events					CONTROL Events				
Study	**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

	RSG Events					CONTROL Events				
Study	**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

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

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
	S-026 Submitted 2/28/07
	S-022 Additional datasets submitted 5/31/07
	Original review of S-022 completed and filed 6/4/07
	Completion date for this review 7/3/07
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Division of Drug Risk Evaluation and Division of Metabolic and Endocrine Products
Clinical Team:	Kate Gelperin, M.D. (Reviewer , Division of Drug Risk Evaluation)
	Karen Mahoney, M.D. (Reviewer, Division of Metabolic and Endocrine Products)
	Mary Parks, M.D. (Division Director, Division of Metabolic and Endocrine Products)
Project Manager:	Jena Weber (Division of Metabolic and Endocrine Products)

Keywords: Clinical studies, meta-analysis, safety

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 the results of the short-term studies. 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 stroke[1]. 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.

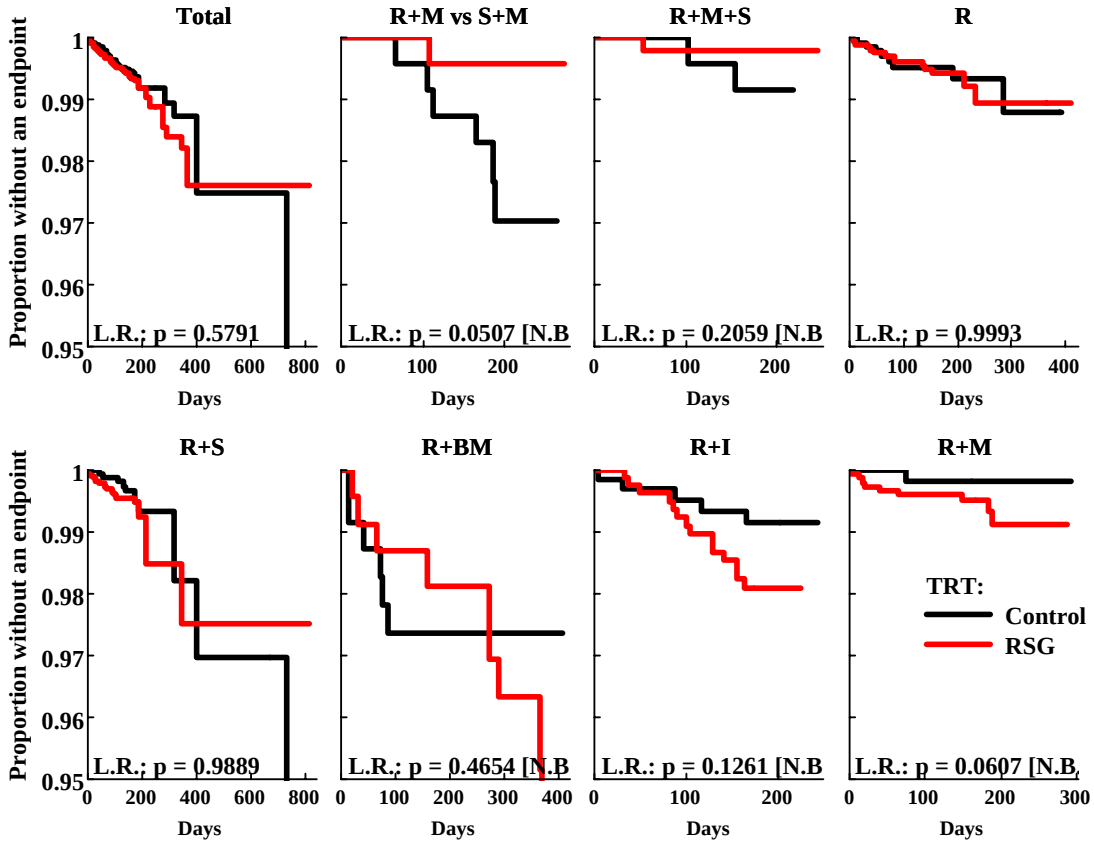
Table 3.1.3 Odds ratios (95% CI) by meta-group for all myocardial ischemic events, serious myocardial ischemic events and composite of CV death, MI or stroke. The results in the first 3 columns are from an exact test with conditional maximum likelihood estimates where studies with zeros in both arms 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).

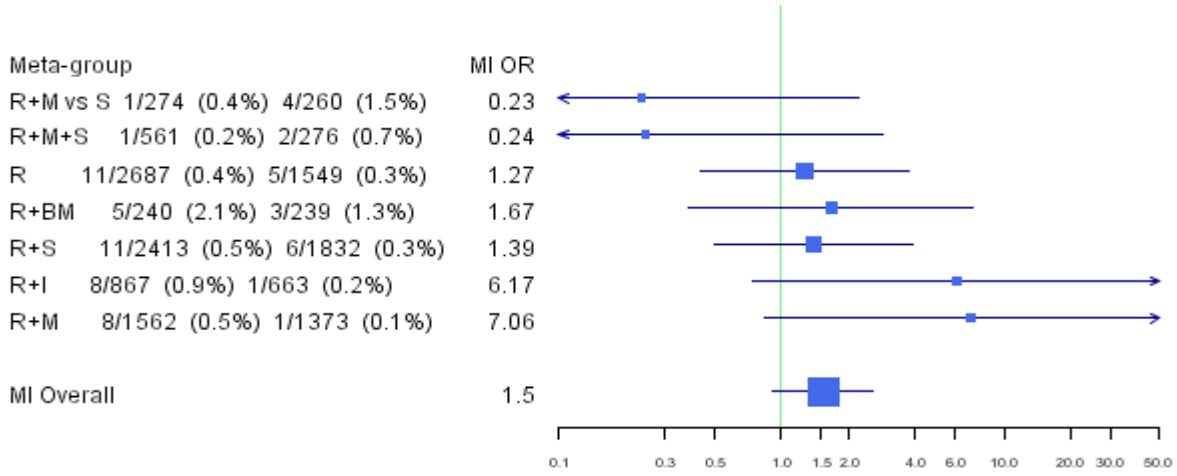
Table 3.1.2 Results for components of MI, stroke and CV death

	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

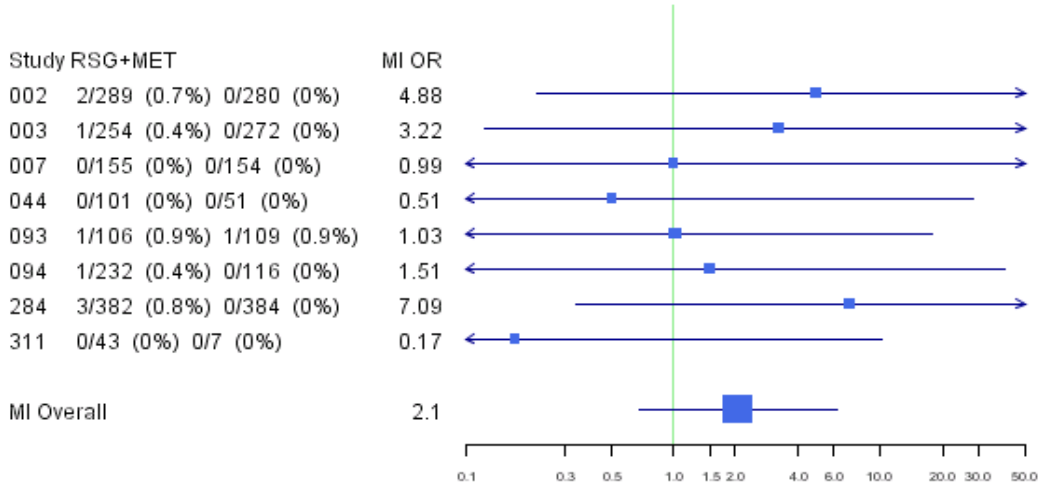
The heterogeneity across meta-groups for MI is illustrated by the forest plot below.

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



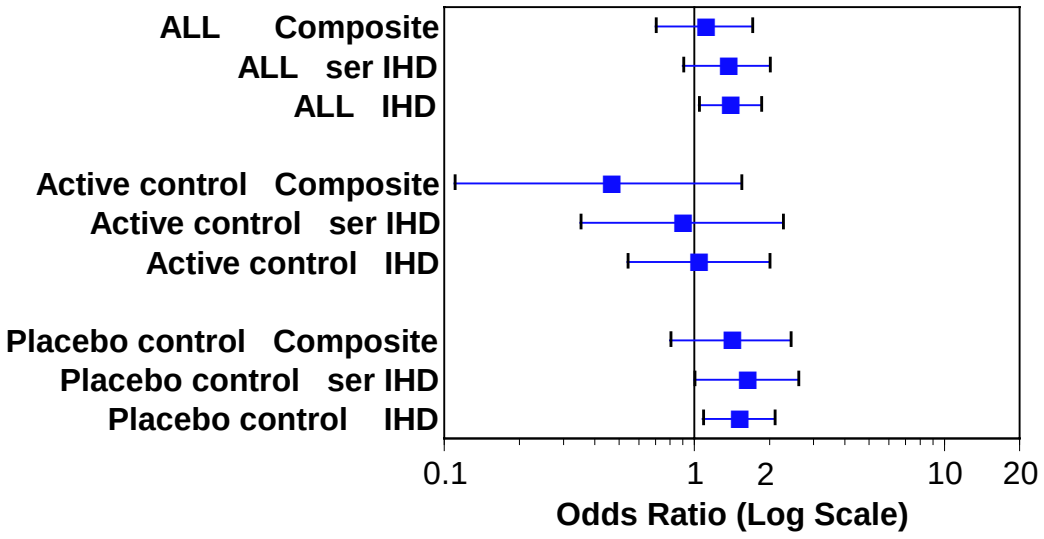
The rare events for the components of the composite present some analytical problems and no approach appears to be satisfactory for the case where there are numerous studies with no events in either one arm or in both arms. Use of a continuity correction appears to move estimates of risk towards one 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.

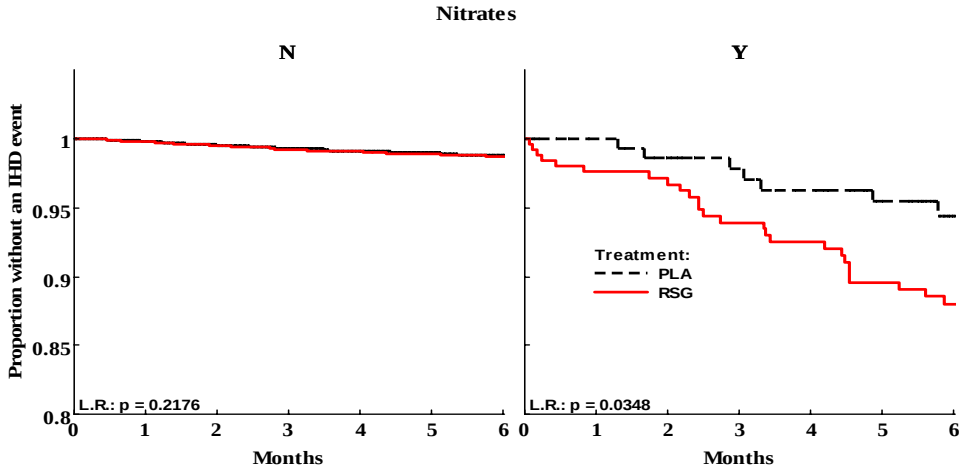
Table 3.3.1 OR (95% CI) using exact test stratifying on meta-group excluding the insulin studies

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≤FPG≤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:

- FPG>180 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 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.

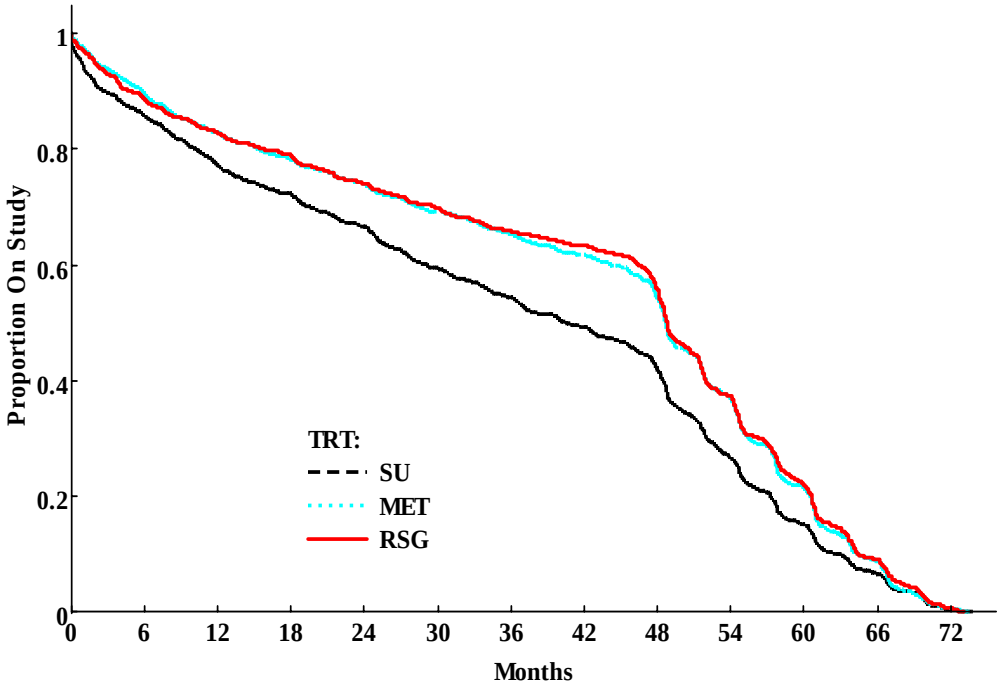
Of 6385 patients who were enrolled in the run-in period, 4351 (68%) were randomized. The disposition of patients by analysis populations show higher numbers for the RSG group than the comparators, particularly SU, though clearly completion rates are low in all groups with less than 60% of the patients 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.

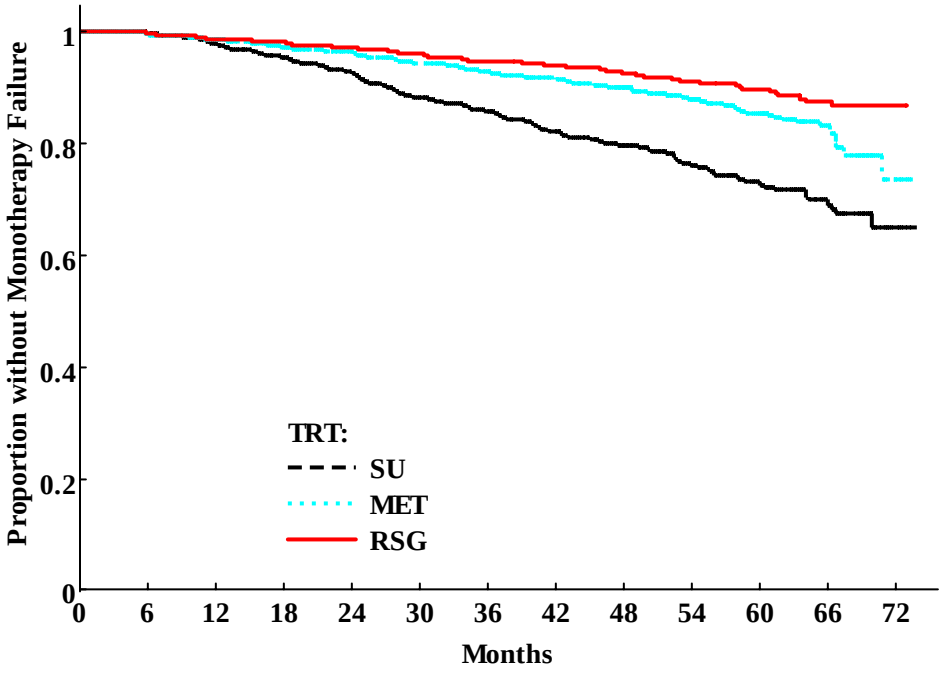
Table 4.1.4 ADOPT patient characteristics

	RSG (n=1456)	SU (n=1441)	MET (n=1454)
Age			
Mean (SD)	56 (10)	56 (10)	57 (10)
Range	30-76	26-75	29-76
%>65	23%	24%	25%
Gender			
% males	56%	58%	59%
% Smokers	16%	13%	15%
BMI			
Mean (SD)	32 (7)	32 (6)	32 (6)
Median	31	31	31
Dur Diab			
<2 years	79%	78%	78%
2 years or more	11%	12%	12%
Hx CV	16%	17%	19%
Hx hypertension	51%	52%	51%
Baseline meds			
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≤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

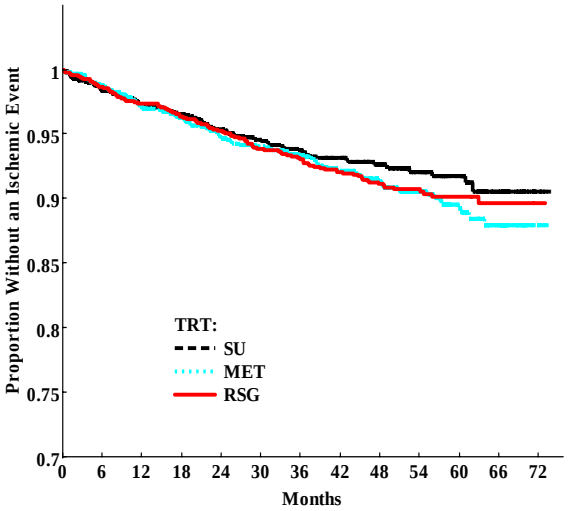
1-Applicant's results, OR greater than 1 indicates higher risk on MET compared to SU

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.

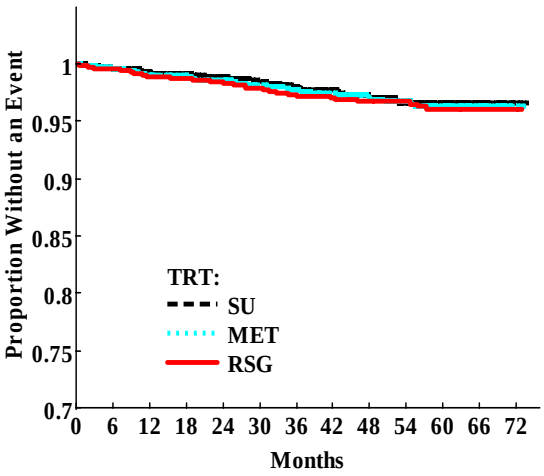
The Kaplan-Meier curves (Figure 4.1.3) illustrate the lack of a difference among the treatment groups for the two outcome variables of total IHD and the composite of MI, CV death or stroke. A separation of the curves for total IHD is seen late in the trial when the risk set is notably smaller with about 60% of the patients on study during Year 4.

Figure 4.1.3 ADOPT Kaplan-Meier Curves

Time to Myocardial Ischemic Event

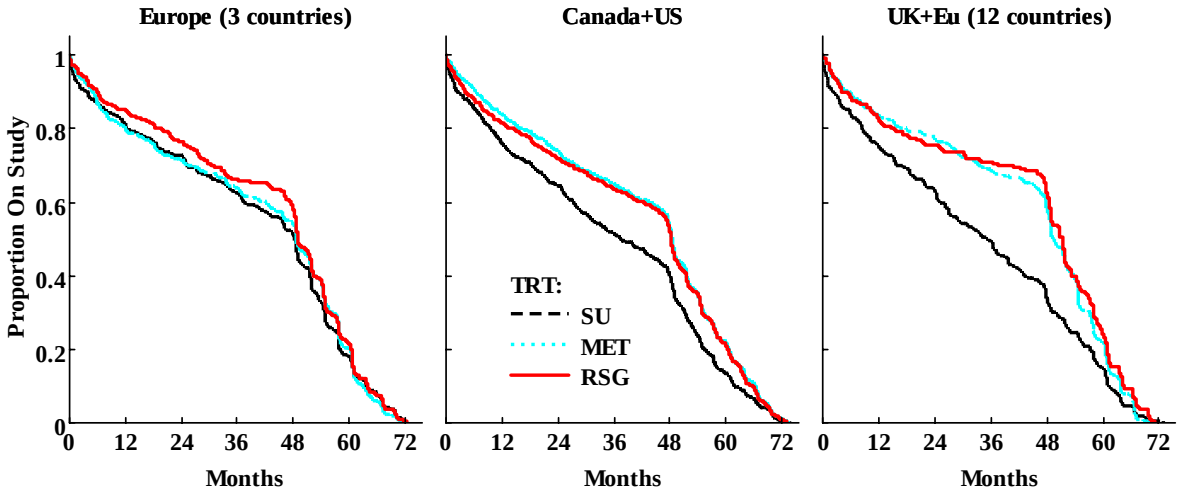


Time to MI, CV death or Stroke



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)

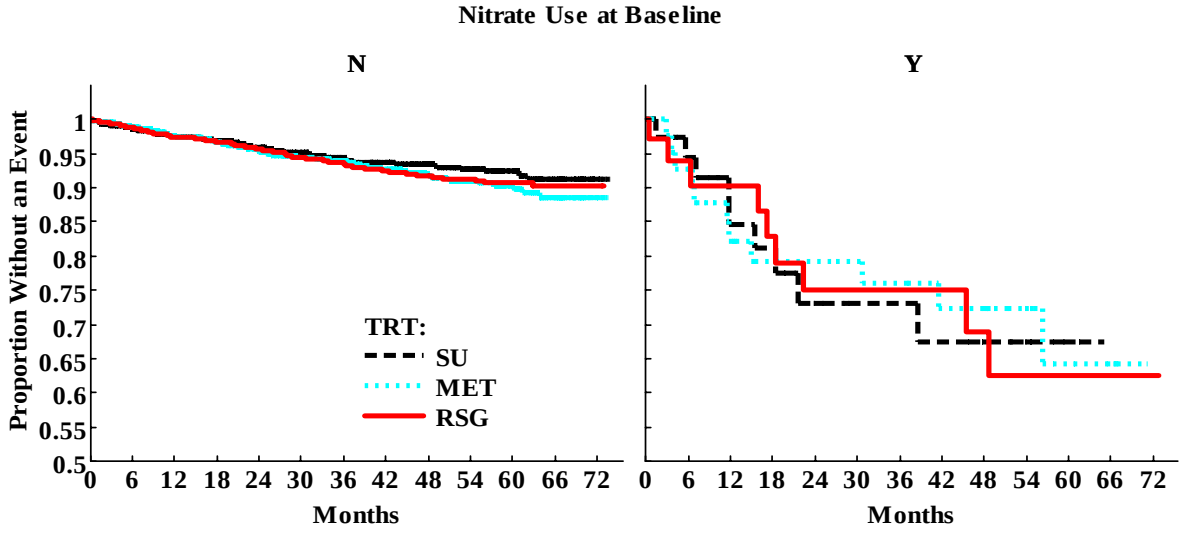
This reviewer performed analyses by subgroups identified in the analysis of the 42 short-term studies and found no higher risk in the RSG group over either comparator.

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/m^2 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 component[1]

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

	MET+RSG (n=1117)	*MET*+SU (n=1105)	*SU*+RSG (n=1103)	*SU*+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

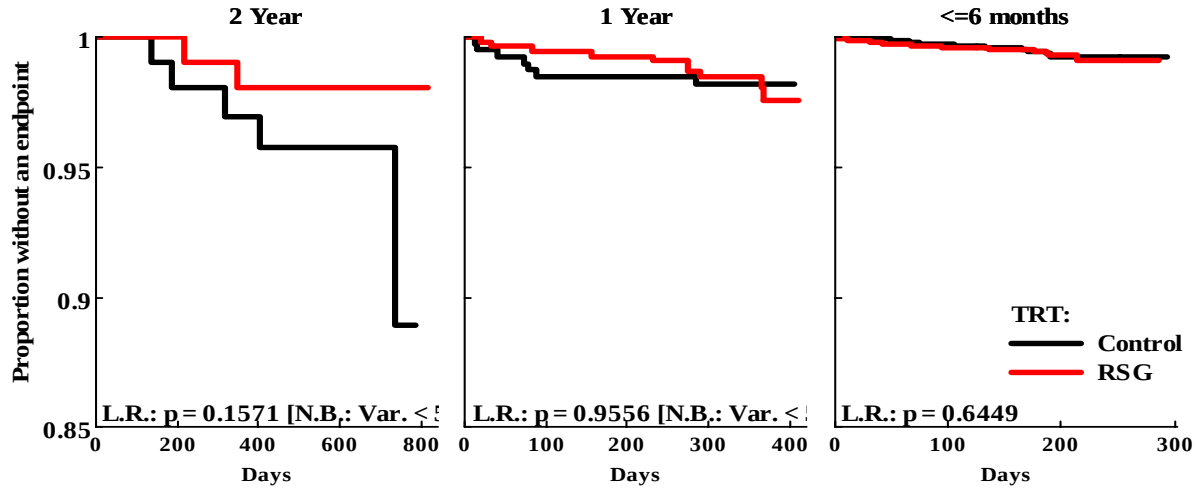
There is no endpoint where the incidence of events is consistently higher (or lower) for rosiglitazone compared to control across the pooled studies and the long-term studies.

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.

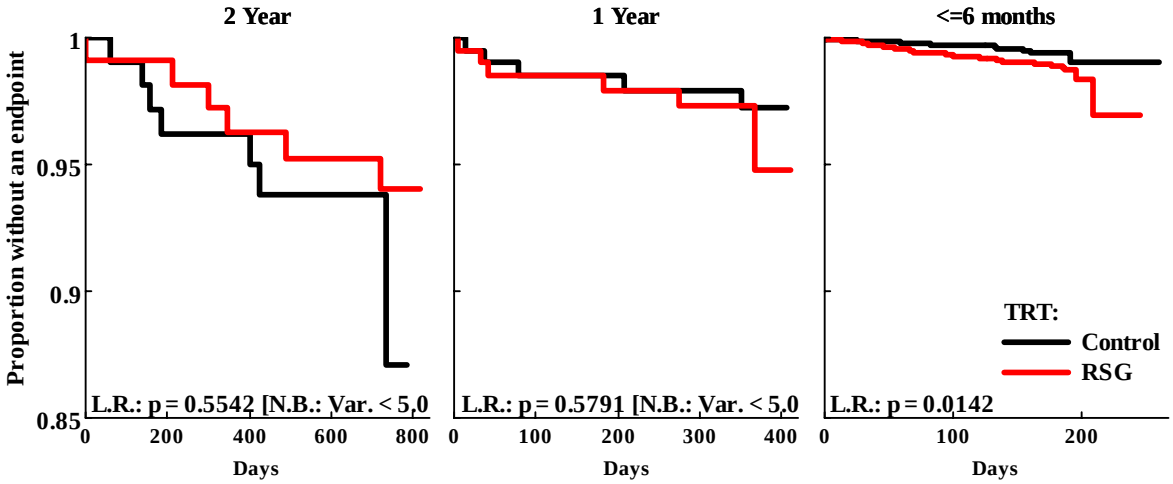
Figure 4.2.1 Kaplan-Meier curves for time to first event of the composite endpoint of CV death, MI or stroke and for serious ischemic events for the short term studies by length of study. One study *(Study 135; RSG+SU vs PLA+SU, 227 pts over 60 years old)* was 2 years in length, 3 studies *(Studies 211: 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



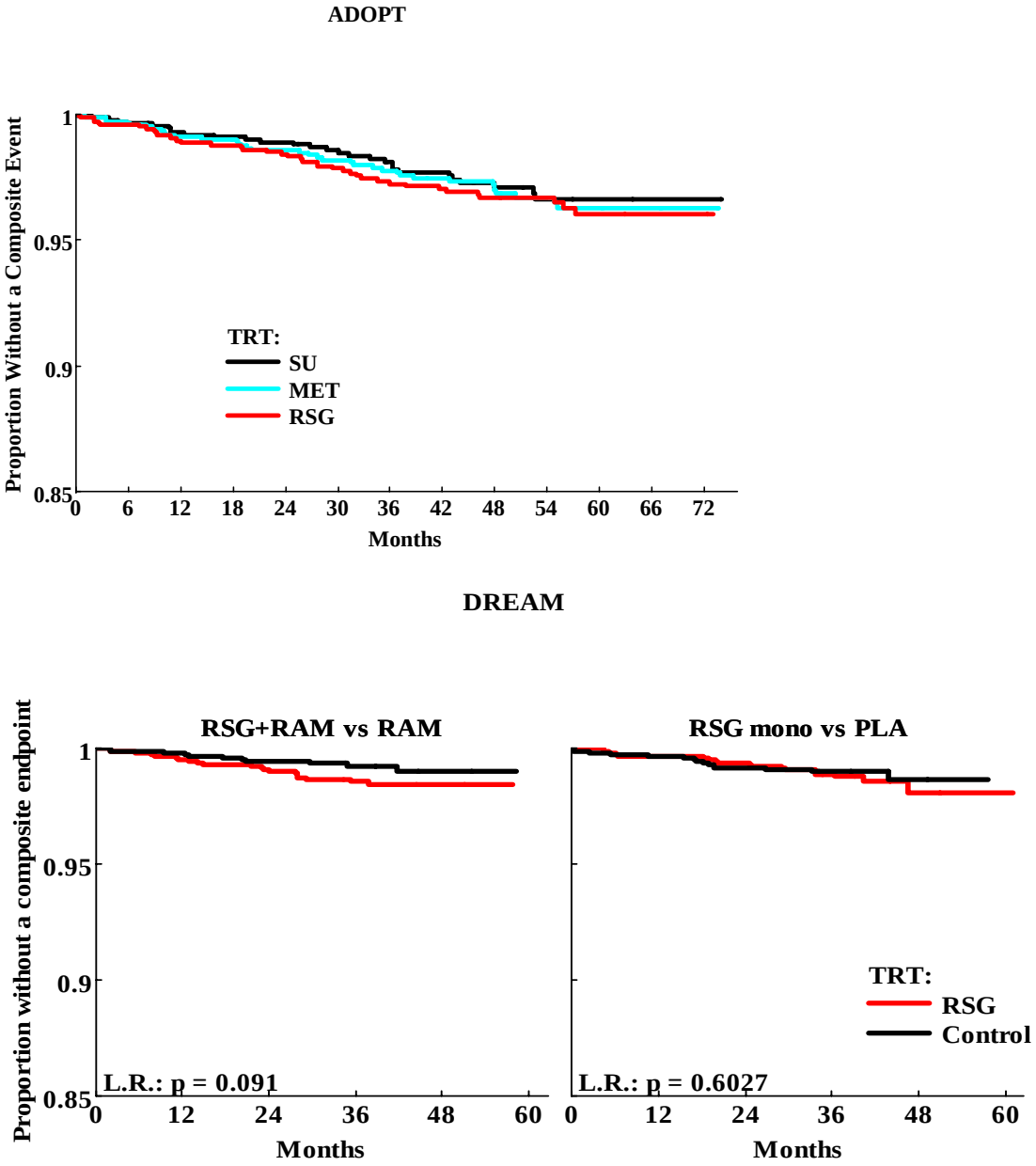
Serious Myocardial Ischemic events



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.



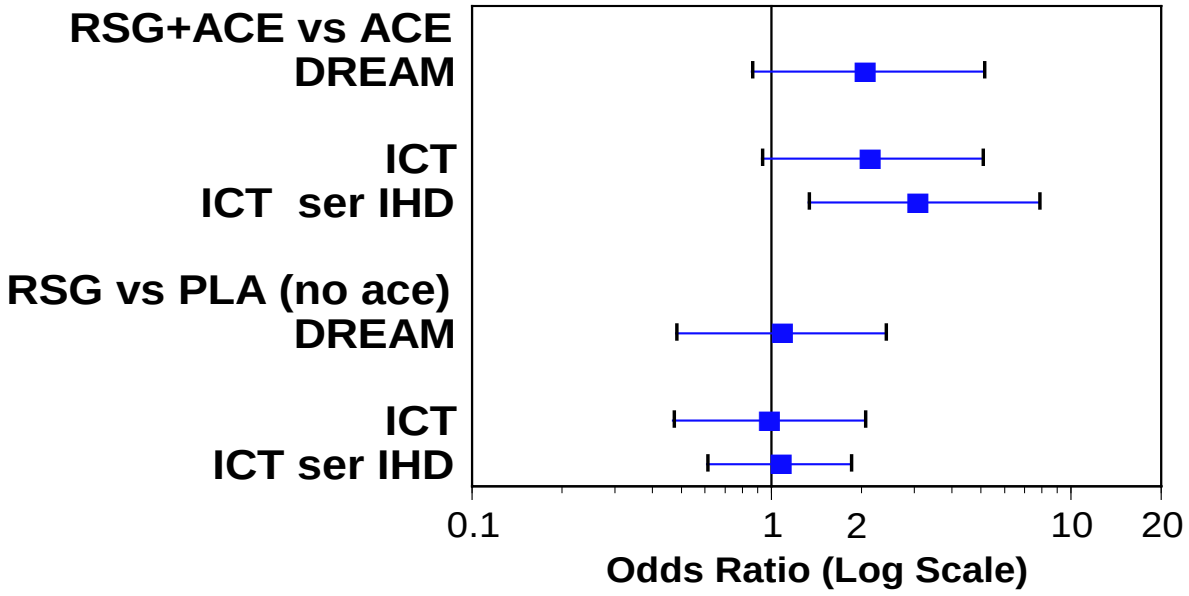
The Kaplan-Meier curves above illustrate the lack of a difference among the three treatment groups in ADOPT and, for DREAM, the difference in treatment effects between monotherapy versus placebo and combination therapy versus ramipril.

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).

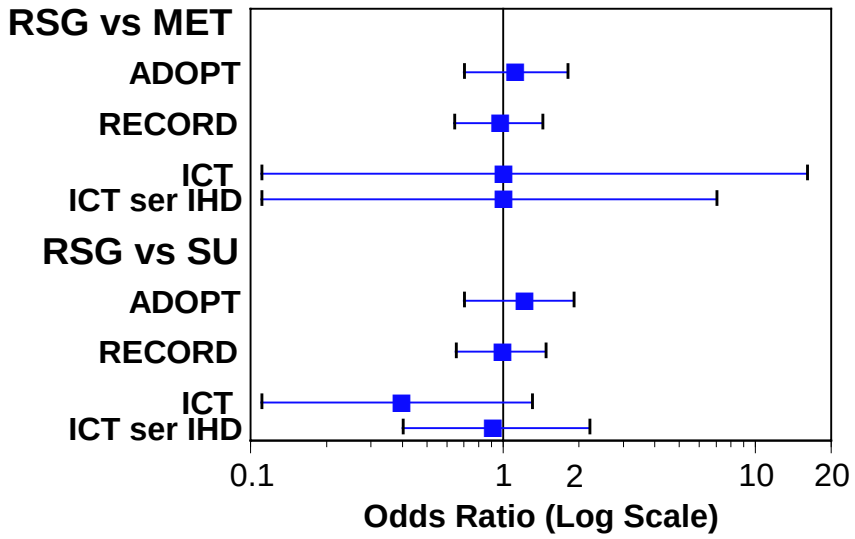
Figure 4.2.3 Plot of odds ratios for the combination of RSG with an ACE inhibitor in DREAM and in the database of short-term studies for the composite endpoint of CV death, MI or stroke and for serious ischemic (IHD) events



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 (third row of Table 3.1.2). 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.

	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; data for these individual studies is available in Appendix 4 of the FDA statistical review dated 6/4/07.

	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

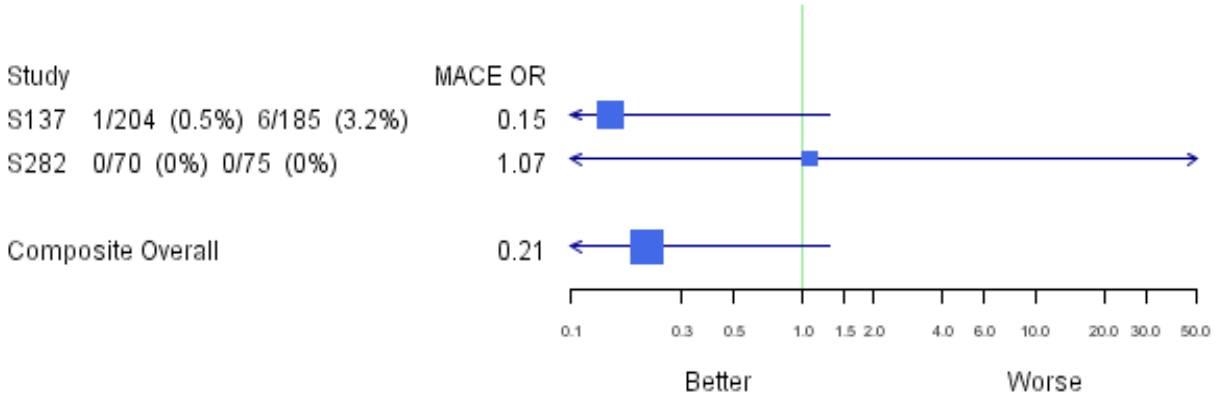
I+R=Insulin+Rosiglitazone
INS=Insulin
M+R=Metformin+Rosiglitazone
MET=Metformin
PLA=Placebo
RSG=Rosiglitazone
S+M+R= Sulfonlyurea+Metformin+Rosiglitazone
S+R= Sulfonylurea+ Rosiglitazone
Su= Sulfonylurea
S+M= Sulfonylurea+Metformin

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.

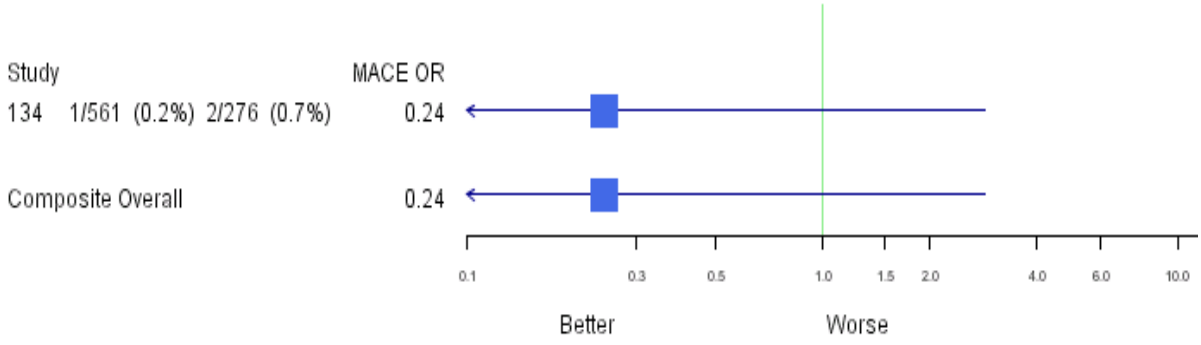
Appendix 2 Forest plots of composite endpoint by meta-groups

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.

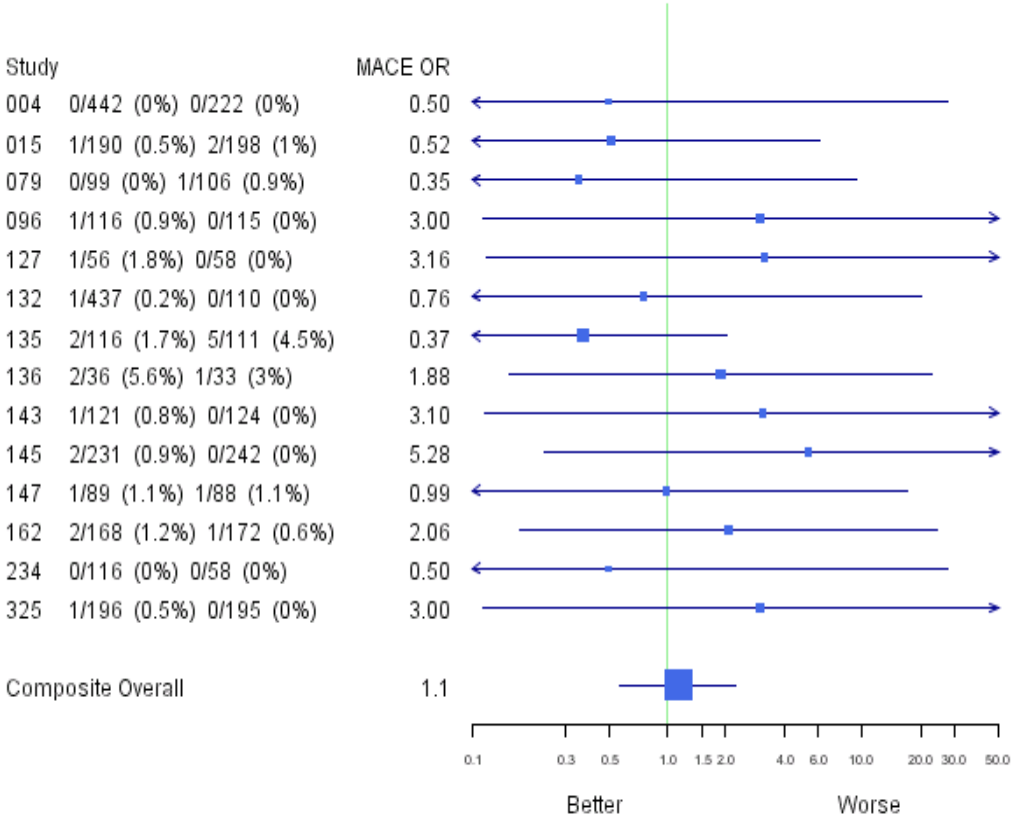
RSG+MET vs SU+MET



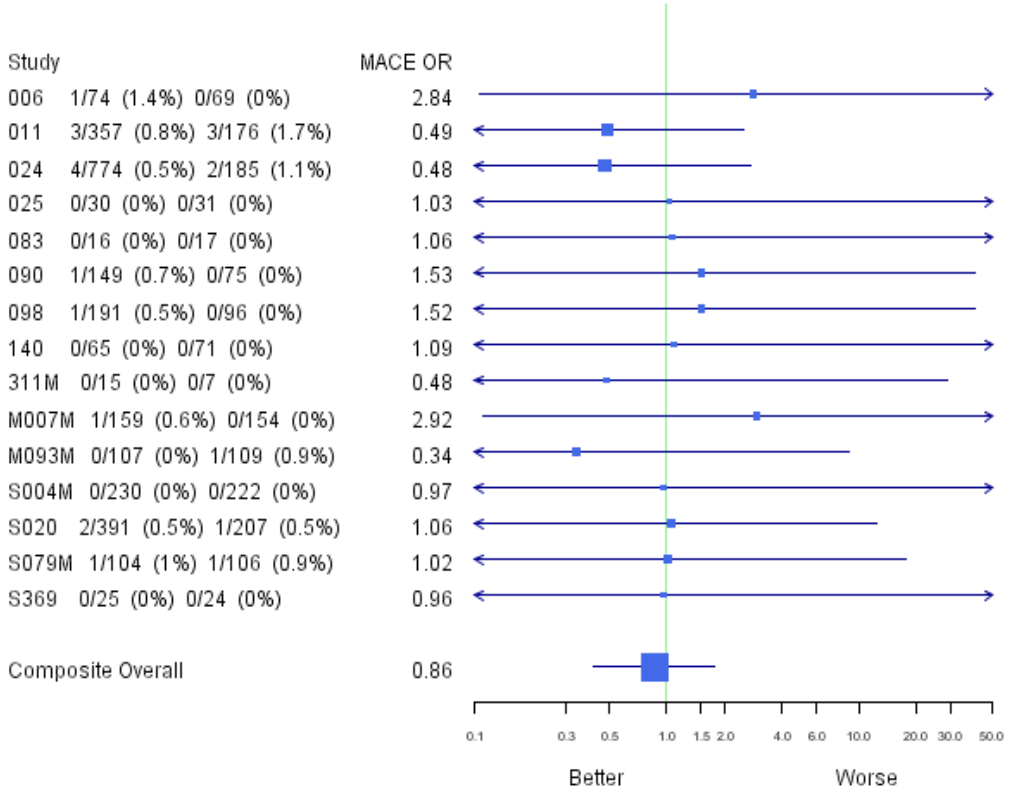
Triple therapy (RSG+MET+SU vs MET+SU) (axis upper limit reduced to 10)



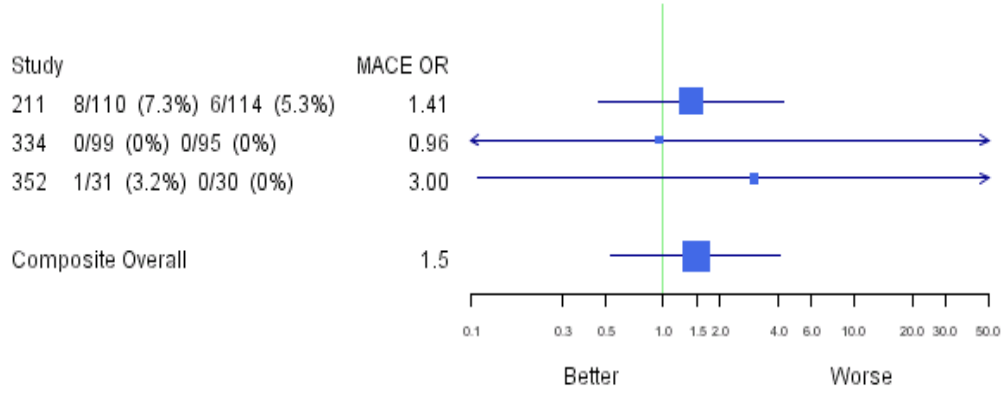
RSG+SU vs PLA+SU



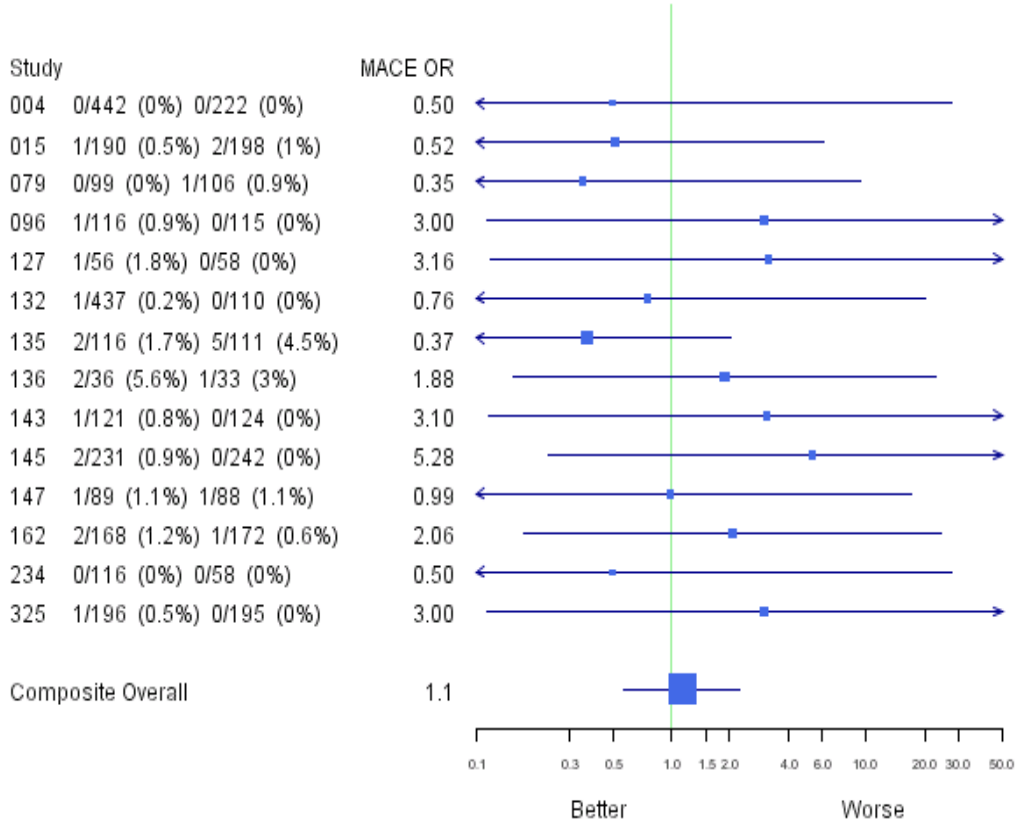
RSG Monotherapy vs placebo or MET (M) or SU (S)



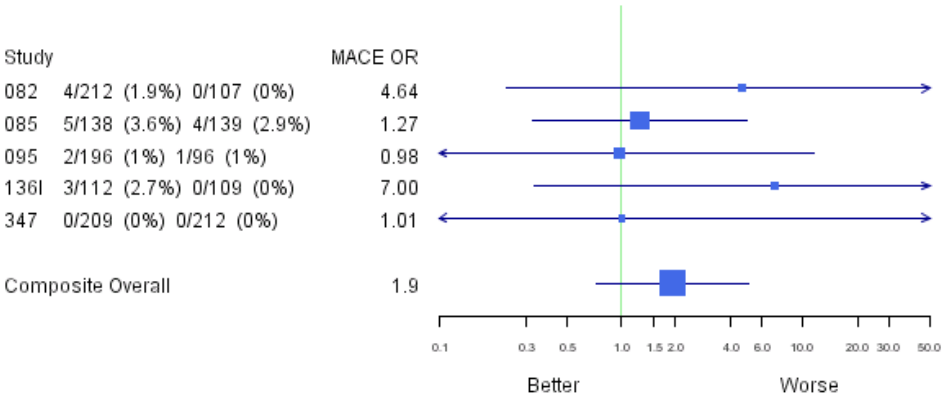
RSG+Background Medication vs PLA+ Background Medication (211-CHF pts & 352-CHD pts)



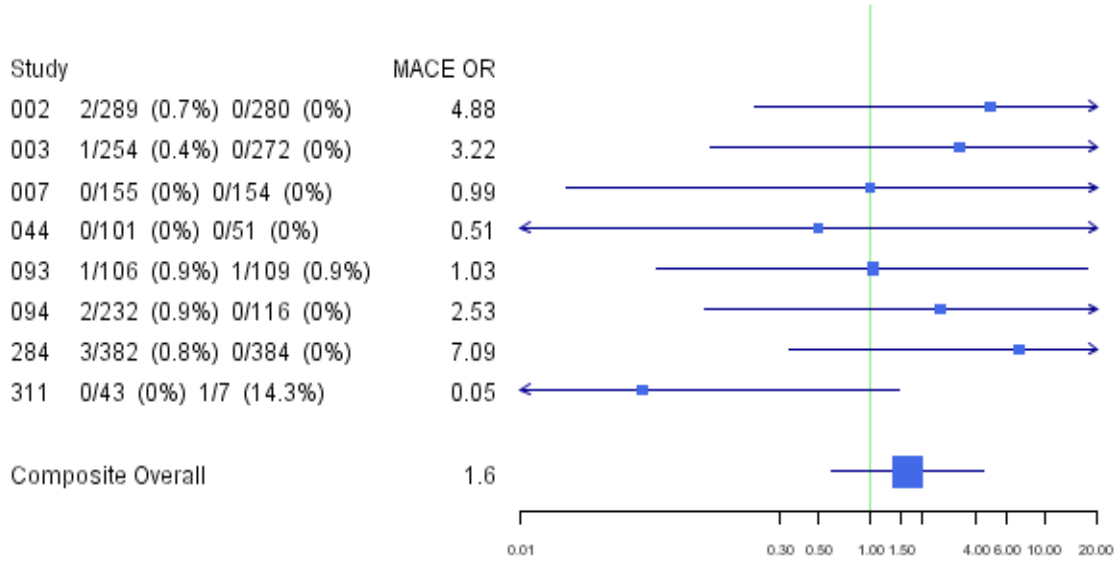
RSG+SU vs PLA+SU



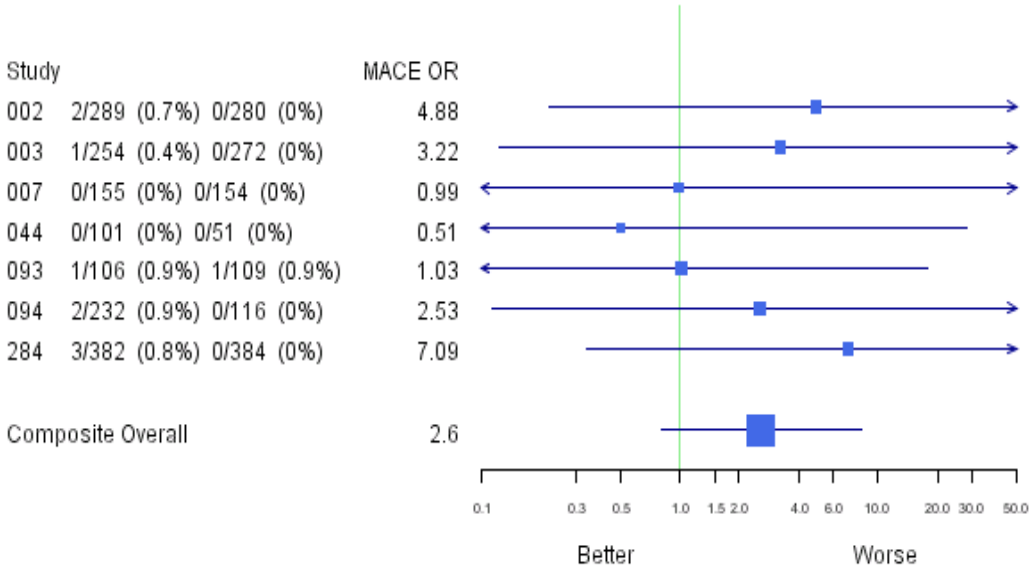
RSG+INS vs PLA+INS



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)			
Age									
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
Gender									
% males	63%	81%	56%	74%	57%	73%	57%	53%	60%
BMI									
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%
Dur Diab (yrs)									
Mean (SD)	5 (6)	6 (6)	4 (4)	8 (7)	7 (6)	7 (6)	6 (5)	13 (8)	8 (6)
Trt Exp (mos)									
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)
CV Meds									
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%
CV Major Risk Cond									
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%
Baseline meds	3%	30%	6%	48%	4%	10%	2%	6%	3%
Nitrates	13%	43%	32%	48%	15%	31%	25%	26%	28%
Statin	3%	60%	8%	5%	3%	7%	3%	11%	6%
Loop diuretic	3%	2%	2%	3%	4%	5%	4%	5%	3%
Alpha blocker	12%	70%	28%	59%	13%	20%	15%	12%	13%
Beta blocker	14%	10%	14%	23%	15%	22%	15%	19%	14%
CCB	25%	98%	30%	52%	28%	41%	43%	47%	41%
ACE inhibitor									
HbA1c									
Mean (SD)	8.5 (1)	8 (1)	7 (1)	7 (1)	9 (1)	8 (1)	8 (1)	9 (1)	9 (1)
HDL Mean (SD)	45 (11)	42 (11)	47 (12)	43(11)	46 (12)	44(11)	47 (12)	48 (13)	50 13)
LDL Mean (SD)	131 (36)	113 (32)	120 (32)	97 (25)	125 (34)	113 (30)	117 (33)	122 (34)	112 (33)
HCT									
Mean (SD)	44 (4)	43 (4)	41 (3)	42 (3)	43 (4)	43 (4)	42 (4)	42 (4)	42 (6)
DBP									
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}

Appendix 6 References

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TAB 3

BRIEFING DOCUMENT FOR THIAZOLIDINEDIONE/ROSIGLITAZONE PUBLIC ADVISORY COMMITTEE MEETING

From:	Karen M. Mahoney, M.D. Mary H. Parks, M.D. Division of Metabolism and Endocrinology Products
Through:	Robert J. Meyer, M.D. Director Office of Drug Evaluation II
To:	Endocrine Metabolic Drugs Advisory Committee members Drug Safety and Risk Management Advisory Committee Invited Panelists
Date:	July 9, 2007

INTRODUCTION

In August 2006, GlaxoSmithKline (GSK) submitted to the FDA a completed meta-analysis of 42 controlled clinical trials involving rosiglitazone (RSG) use in patients with type 2 diabetes mellitus (T2DM). This analysis was undertaken by GSK as a result of a 2003 World Health Organization report of a data mining signal for increased cardiac risk, including heart failure, for the thiazolidinedione (TZD) drug class. The overall findings from the meta-analysis, as conducted by GSK, suggested an increased risk for myocardial ischemia. Submitted in the same application as the meta-analysis was an observational cohort study, which did not confirm a signal of concern associated with rosiglitazone for the risk of MI or coronary revascularization relative to other anti-diabetic therapies. This application has undergone extensive review by the agency with an internal Center-level briefing in April 2007 resulting in a recommendation for a public advisory committee meeting that was initially planned for the Fall 2007 that would cover cardiovascular risks in general with the TZD class (both ischemic risk and risk for heart failure). On May 18, 2007, the *New England Journal of Medicine* (NEJM) published on-line a separate meta-analysis of rosiglitazone trials performed by Nissen and Wolski on study level data with a reported 43% increased risk of myocardial infarction (MI) and a 64% increased risk of cardiovascular (CV) death. This publication resulted in extensive press coverage and Congressional inquiries, including several interviews with multiple FDA scientists by Congressional staff during the on-going review process. As a result of the public considerable and understandable concern, the FDA is presenting data from completed and ongoing reviews to this Joint Advisory Committee comprised of members from Endocrine and Metabolic Advisory Committee, Drug Safety and Risk Management Committee, and specialists in cardiovascular disease from the CardioRenal Drugs Advisory Committee to gain expert advice on the cardiac ischemic risk of rosiglitazone. As this meeting is being convened several months earlier than planned, time constraints preclude a thorough discussion of the risk of heart failure associated with rosiglitazone and pioglitazone. This memo and the presentations will focus only on cardiac ischemic risk, primarily focused on rosiglitazone.

Ms. Joy Mele's FDA statistical review of the meta-analysis and her presentation will precede this memo and its clinical presentation. She has identified certain baseline patient characteristics, concomitant medication use, and comparator groups that may contribute notably to the overall risk estimate in the

meta-analysis. The purpose of this memo is to present clinical data from large, prospective, controlled clinical trials that may aid in the interpretation of a finding of excess cardiac risk from the meta-analysis of 42 controlled studies.

Thiazolidinediones/PPAR-gamma agonists

Thiazolidinediones (TZDs) are selective ligands of the nuclear transcription factor peroxisome-proliferator-activator-receptor-γ (PPAR-γ). Also referred to as PPAR- γ agonists, these drugs have been developed to target the insulin resistance associated with type 2 diabetes mellitus (T2DM); however, TZDs have also been studied in other insulin-resistant states including polycystic ovarian syndrome and more recently, the treatment of pre-diabetic states. To date, the FDA has reviewed four New Drug Applications (NDAs) for different compounds with PPAR-γ activity for the treatment of adults with T2DM. Troglitazone (Rezulin®) was approved in 1997 and initially showed promise with significant reductions in hemoglobin A1c (HbA1c) and improvements in insulin sensitivity, thus allowing many patients to avoid initiation of insulin or markedly reduce their daily dosing requirements. However, shortly after its approval, severe cases of hepatotoxicity were observed and in March 2000 the drug was withdrawn from the market due to an increased risk of liver failure resulting in death or necessitating liver transplantation. In 1999, the FDA approved rosiglitazone (Avandia®) and pioglitazone (Actos®). Clinical trial experience and close post-marketing surveillance of these two compounds have shown an absence of the unacceptable risk of hepatotoxicity seen with troglitazone. On average, the expected HbA1c reductions with these agents range from 0.5 to 1.5% with effect sizes variable by patient characteristics (e.g., drug-naïve vs. prior treatment, or monotherapy vs add-on therapy).

The fourth NDA was for the non-TZD, PPAR-α/γ agonist, muraglitazar (Pargluva®), where PPAR-α agonism was intended to impart favorable clinical effects on lipid parameters. This application was discussed at a public advisory committee in September 2005 where FDA expressed concerns over an imbalance in cardiovascular events and deaths in the phase 3 trials. Despite an overall recommendation for approval by the Endocrine and Metabolic Drugs Advisory Committee, an approvable action was issued. In May 2006, Bristol-Myers Squib announced the discontinuation of this clinical development program.

Numerous Investigational New Drug Applications (INDs) have been submitted to the agency for drugs targeting PPAR-α or –γ receptors to treat T2DM and dyslipidemia. More recently, applications for pan-agonists targeting α, γ, and δ receptors have been submitted to treat the so-called metabolic syndrome, including obesity. As a class, PPAR agonists with gamma activity are associated with anemia, hemodilution, weight gain, edema, and exacerbation or development of heart failure. In addition, nonclinical studies have raised concerns regarding carcinogenic potential with evidence of multiple tumors (across multiple species and in both genders) observed with several of these compounds. Consequently, partial clinical holds are imposed on all these drugs requiring that two-year animal carcinogenicity studies be conducted and data submitted for review prior to initiation of clinical studies beyond 6 months' duration. Findings from many nonclinical studies have resulted in discontinuation of several INDs or have led to limitations in the maximal clinical dose for Phase 3 clinical trials. Reasons for cessation of clinical development for drugs in the PPAR class include findings in animals of tumors of the bladder, liver, and adipose tissue; muscle/skeletal toxicity (specific to PPAR-α activity); cardiac myopathy and necrosis, and severe edema at doses consistent with the exposure range for human clinical doses. Aside from muraglitazar, a few programs have also been discontinued after renal and cardiac safety findings appeared with more extensive clinical trial experience in Phase 3 (tesaglitazar and farglitazar).

Similarly, the marketed TZDs, rosiglitazone and pioglitazone, are associated with anemia, weight gain, edema, and risk of heart failure. Unique to pioglitazone, which appears to have some α-agonistic activity, was an association with urinary bladder tumors in its carcinogenicity studies dosed at approximately 14x

the maximum recommended clinical dose. Benign and/or malignant transitional cell neoplasms were observed in male rats at doses equivalent to maximum recommended clinical dose based on mg/m^2. Two large placebo-controlled clinical studies have also observed an imbalance in the number of bladder cancers [6 pioglitazone (0.16%), 2 placebo (0.05%)], although there are not definitive data to date to conclude that the animal findings signal a significant clinical risk. These findings are in the labeling for pioglitazone, and the potential human correlates for the animal findings are continuing to be actively addressed.

Rosiglitazone

Rosiglitazone maleate was approved in 1999 for the treatment of T2DM in adults. Initial approval was for monotherapy use and as add-on to metformin in the setting of inadequate glycemic control with the single agent. Although rosiglitazone was not a first-in-class oral anti-diabetic, the NDA was under review during the safety deliberations over Rezulin® (troglitazone), and was therefore discussed before a public advisory committee. During the advisory committee meeting, discussions on safety focused on known concerns at that time: liver toxicity, anemia/hemodilution, fluid-retention/edema, and elevations in cholesterol (C) levels. Any concerns of cardiac ischemic safety at that time were based on the increases in total-C and low density lipoprotein cholesterol (LDL-C) observed with rosiglitazone, for which most members advised inclusion in labeling, with recommendations for monitoring of patients. No increased risk for direct cardiac ischemia was identified. There were non-clinical findings of cardiac toxicity consisting of increased heart weight, pericardial effusion, atrial thrombi, and CV deaths that were interpreted as due to heart failure observed across several different species. These signals were not evident in the pre-marketing clinical database which consisted of a total of 4598 patients exposed to rosiglitazone; 2061 of these patients received drug for at least 12 months. FDA and GSK agreed on a Phase 4 study commitment to further explore durability of efficacy and several safety issues, including hepatotoxicity and edema/heart failure. GSK diligently conducted this study, called ADOPT, and fulfilled the regulatory requirement regarding the postmarketing commitment. ADOPT is discussed subsequently in this memo.

The clinical development program for rosiglitazone has been extensive with numerous studies conducted in patients with T2DM since approval. Several of these studies were included in the meta-analysis submitted by GSK and have been previously reviewed by FDA. While the meta-analysis combines the findings from 42 controlled clinical studies with exposures in 14,237 patients (8604 on RSG/RSG-containing treatment vs 5633 on non-RSG containing treatment), the majority of the studies included in the meta-analysis were of short duration (average duration of exposure ≤ 180 days). Thirty studies were 6 months in duration, 8 were less than 6 months, and 4 were at least one year in duration (there was a single 2-year study). None of the studies in the meta-analysis was specifically designed to evaluate cardiovascular benefit and all but one had no prospective blinded committee adjudication of CV events. For the combined data from these 42 studies, a retrospective adjudication for cardiovascular adverse events (heart failure or myocardial ischemia) was undertaken in a blinded review of narratives for serious adverse events (SAEs) by physicians in a GSK Working Group and a cardiologist in an External Review Group. Blinded review of individual investigator-provided verbatim terms was also performed by GSK physicians. As stated in Ms. Mele's review, a recent different analysis of these 42 controlled trials was submitted to the Agency on May 31, 2007. In this analysis, GSK applied the composite endpoints of stroke, MI, and CV death to further assess risk between rosiglitazone and the comparators in this pooled database. Although this analysis has its limitations, particularly for identifying the stroke component, it is a commonly used composite in clinical trials evaluating cardiovascular risks and benefits of interventions, including the long-term, controlled studies discussed in this memo. This composite (referred to as MACE or APTC by different reviewers) allows for a similar endpoint for comparisons to be made across clinical trials and databases.

Not included in the meta-analysis are four large, prospective, long-term, controlled studies that were either completed *after* the cut-off date for inclusion in the meta-analysis or are still ongoing. Unlike the 42 studies in the meta-analysis, these studies had a prospective collection of CV events. Most of these studies had an endpoint adjudication committee prospectively reviewing CV events in a blinded fashion. These four studies, combined, will yield data for approximately 16,000+ patients studied for approximately 3 to 5 years. These studies' combined patient-year exposure is several multiples that of the studies included in the meta-analysis. This briefing memo will describe these long-term, controlled clinical trials with respect to the following:

- status (completed vs ongoing; if completed, data available to FDA)
- study design
- study objective
- patient population
- study outcome, if available

In addition, this briefing memo will describe CV risk evaluation of the other marketed TZD, pioglitazone. Although there are no direct head-to-head CV outcomes studies comparing rosiglitazone to pioglitazone, these studies are important in the consideration of rosiglitazone's risk-benefit profile relative to other available therapies.

LONG-TERM CONTROLLED CLINICAL TRIALS WITH ROSIGLITAZONE

The following table summarizes the key features of the large controlled trials presented in this memo. Four of these employ rosiglitazone as the specific or predominant investigational TZD (ADOPT, DREAM, RECORD, and BARI-2D) and one study involves the use of pioglitazone (PROactive).

Table I: Tabular Summary of Basic Design of Large Prospective Trials of Thiazolidinediones					
	PROactive[1]	**ADOPT[2]**	**DREAM[3]**	**RECORD[4]**	**BARI 2D[5]**
Status of Trial	Complete, submitted to FDA, reviewed	Complete, submitted to FDA, review ongoing	Complete, not yet submitted to FDA	Ongoing	Ongoing
TZD Used	Pioglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone	Rosiglitazone
Sponsor of Trial	Takeda	GSK	McMaster University, Canada	GSK	NHLBI
Status of Data	Full study report received by FDA, reviewed, labeled	Full study report received by FDA, review ongoing	Published, study report not yet received by FDA	Ongoing, interim safety analysis published	Ongoing
Primary Objective	"To demonstrate that pioglitazone reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes mellitus"	Evaluate and compare effects of long-term monotherapy of T2DM with RSG, SU and MET on improvement and mnt of glycemic control in patients with recently diagnosed T2DM	To assess prospectively whether rosiglitazone can reduce the frequency of diabetes in individuals with impaired glucose tolerance, impaired fasting glucose, or both. Factorial design also examined ramipril effect.	Compare time to reach combined CV endpoint of CV death and/or CV hospitalization, between RSG-treated patients and non-RSG-treated patients, in patients with T2DM who are inadequately controlled on either MET or SU alone. First hypothesis noninferiority; then test for superiority.	Compare 5-year mortality for initial elective revascularization with aggressive medical therapy vs aggressive medical therapy alone; and to compare 5-year mortality for management of hyperglycemia with strategy of insulin-sensitizing vs insulin-providing.
Secondary Objective(s) of Particular Relevance	Characterize safety in this grp of T2DM patients	Assess long-term safety (cardiovascular, liver, hematologic, weight, lipids)	Assess effect on CV and renal outcomes	Separate comparisons for RSG vs MET and RSG vs SU for composite of CV death and/or CV hospitalization.	Examine effect of revasc + med rx vs intensive med rx alone, and examine effect of insulin-sensitizing vs insulin-providing med rx, on other CV endpoints (see below)
Number of Patients Randomized	5238	4351	5269	4447 (last randomized Apr 2003)	2368 (last randomized Mar 2005)
Duration	Mean 34.5 months	4 years originally planned; changed to 6 years due to higher-than-expected withdrawal rate and lower-than-expected monotherapy failure rate	Median 3 years	Planned median 6 years	Planned 5 years
Number of Centers (and Location[s])	321 (Europe)	473 (North America and Europe)	191 (North and South America, Europe, India, Australia)	338 (Europe and Australia)	49 (North and South America, Europe)
Randomization	1:1	1:1:1	Factorial: 1:1 RSG:pbo and 1:1 ramipril:pbo	Grp with inadequate control on SU: add RSG or MET, 1:1 Grp with inadequate control on MET: add RSG or SU, 1:1	1:1:1:1 revasc+ins-prov revasc+ins-sens ins-prov alone ins-sens alone
Stratification	None	By gender	RSG results stratified for effect of ramipril, and vice versa	By background med (SU or MET)	By revasc strategy (CABG or PCI); by center

Table I: Tabular Summary of Basic Design of Large Prospective Trials of Thiazolidinediones

	PROactive[1]	ADOPT[2]	DREAM[3]	RECORD[4]	BARI 2D[5]
Blinding	Double	Double	Double	Add-on study med is open-label; blinded adjudication of CV endpoints	Open-treatment; blinded reading of angiography
Parallel Group vs Factorial Design	Parallel	Parallel	2x2 factorial	Parallel	2x2 factorial
Patient Population	T2DM, HbA1c> ULN, history of macrovascular disease (predefined)	T2DM diagnosed ≤ 3 yrs FPG 126-240 mg/dL at scrn	Impaired glucose tolerance (FPG <126 mg/dL; 2 hr OGTT glu ≥140 and <200 mg/dL) or impaired fasting glucose (FPG ≥ 110 mg/dL and <126 mg/dL; 2 hr OGTT glu <200 mg/dL)	T2DM, inadequate control on MET or SU	T2DM with ≥50% stenosis of ≥ 2 coronary arteries; objective documentation of ischemia, or typical angina + ≥ 70% stenosis in ≥1 coronary artery
Exclusion Criteria of Particular Importance	Insulin as sole therapy for DM for ≥2 wks at any time in previous 3 months. MI, stroke, CABG or PCI in past 6 months. ACS in past 3 months. HF NYHA FC≥2. Planned CV intervention. Current TZD use.	Prior diabetes drug treatment. Unstable or severe (NYHA 3 or 4) angina. HF of any NYHA class requiring drug rx.	Prior diabetes drug treatment. CHF, history of macrovascular cardiac disease (predefined), peripheral vascular disease (predefined) or stroke	Other OHA use, dual OHA use, insulin use, prior TZD use, HF on meds	CABG or PCI in previous 12 months, HF class 3 or 4, left main coronary artery stenosis ≥50%
Study Agent Treatment(s)	Pioglitazone, force-titrated to 45 mg (added to underlying diabetes treatment[s])	RSG 4 mg up to 8 mg[6]	RSG force-titrated to 8 mg/day; ramipril, forced-titrated to 15 mg/day	Add-on RSG 4 mg up to 8 mg[7]	Medical mgmt strategy comparison: RSG or MET (titrated to max dose)[7]
Control Treatment(s)	Placebo (added to underlying diabetes treatment[s])	Metformin 500 mg up to 2000 mg Glyburide/glibenclamide 2.5 mg up to 15 mg[6]	Matching pbo RSG; matching pbo for ramipril	If on BL MET, add-on SU. If on BL SU, add-on MET.	Med mgmt strategy comparison: SU, titrated to max dose, or insulin, titrated up to 3 u/kg/day
Primary Endpoint	Time from randomization to first event in composite of: all-cause mortality; nonfatal MI (including silent); stroke; acute coronary syndrome; CABG or PCI; leg amputation above ankle; or bypass surgery or revasc in the leg	Time from randomization to monotherapy failure	Occurrence of death or diabetes (diagnostic criteria predefined)	Time to composite of CV death and/or CV hospitalization	All-cause mortality
Secondary Endpoints of Particular Relevance	Predefined: CV mortality, components of primary endpoint. Defined after trial cessation: composite of all-cause mort, nonfatal MI (excluding silent), or stroke	No predefined cardiovascular secondary endpoints	CV events composite (MI, stroke, CV death, HF, new angina, or revascularization); separate composite of MI, stroke or CV death	All cause mortality; HF; composite of all-cause mortality, MI, stroke, HF and unstable angina; time to CV death, MI, stroke and unstable angina	Composite of all-cause mortality, MI or stroke; CV mort; MI; composite of all-cause mort or MI; angina; subsequent revasc procedures

Table I: Tabular Summary of Basic Design of Large Prospective Trials of Thiazolidinediones

	PROactive[1]	ADOPT[2]	DREAM[3]	RECORD[4]	BARI 2D[5]
Did Cardiovascular Endpoints Include Heart Failure?	No	n/a (no predefined CV endpoints)	Yes	Yes	No
Non-endpoint Cardiovascular Safety Measures	Adverse CV events	Adverse CV events	Not noted in publications	Adverse CV events	Adverse CV events
Were/Are Cardiovascular Events Adjudicated?	Yes, for endpoint events	HF adjudicated post hoc; other CV events not adjudicated	Yes, for endpoint events	Yes, for endpoint events	Yes, for cause of death, and for categorization of strokes and MIs
Were/Are Cardiovascular Events Ascertained After Cessation of Study Medication?	Yes, unless pt withdrew consent	For 30 days after last dose of study med	Yes	Yes	Not noted in materials

Abbreviations: ACS = acute coronary syndrome, BL = baseline, CABG = coronary artery bypass grafting, CHF = congestive heart failure, CV = cardiovascular, FPG = fasting plasma glucose, grp = group, GSK = GlaxoSmithKline, HF = heart failure, MET = metformin, mgmt = management, MI = myocardial infarction, mnt = maintenance, mort = mortality, n/a = not applicable, NHLBI = National Heart, Lung and Blood Institute of the National Institutes of Health, NYHA FC = New York Heart Association Functional Class, OGTT = oral glucose tolerance test, pbo = placebo, PCI = percutaneous coronary intervention, prov = providing, revasc = revascularization, RSG = rosiglitazone, sens = sensitizing, rx = treatment, scrn = screening, SU = sulfonylurea, T2DM = type 2 diabetes mellitus, TZD = thiazolidinedione

1 "PROspective PioglitAzone Clinical Trial in MacroVascular Events"; source = NDA 21073, subm 026, 24 Jan 06,

2 "A Diabetes Outcome Progression Trial", source = NDA 21071, subm 026, 28 Feb 07

3 "Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication"; sources = DREAM Investigators, 2004 and 2006

4 "Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia"; source = RECORD protocol amendment 7 (27 Feb 06), and Home 2007

5 "Bypass Angioplasty Revascularization Investigation 2 Diabetes"; source = Brooks 2006 and BARI 2D manual of operations, subm 22 May 07

6 Protocol-specified up-titration based on FPG

7 Protocol-specified up-titration based on HbA1c

ADOPT (A Diabetes Outcomes Progression Trial)

This trial, performed as a Phase 4 commitment to FDA, is the only completed long-term, prospective, controlled study of rosiglitazone for which the FDA has received a complete study report and datasets. The multidisciplinary review is ongoing; this memo will present preliminary results of the clinical review of cardiovascular safety results. Because the FDA has more complete information for this trial than for other long-term clinical trials of rosiglitazone, its cardiovascular safety findings can be presented in greater detail than can the findings of other trials, which are ongoing or have not yet been submitted.

Full Title: A Randomized, Double-Blind Study to Compare the Durability of Glucose Lowering and Preservation of Pancreatic Beta-Cell Function of Rosiglitazone Monotherapy Compared to Metformin or Glyburide/Glibenclamide in Subjects with Drug-Naïve, Recently Diagnosed Type 2 Diabetes Mellitus

Status: Complete; full study report submitted to FDA; review ongoing.

DESIGN

Objectives:

- Primary: Evaluate and compare effects of long-term monotherapy of T2DM with rosiglitazone (RSG), glyburide/glibenclamide and metformin (MET) on improvement and maintenance of glycemic control in patients with recently diagnosed T2DM. This was determined by time from randomization to monotherapy failure.
- Secondary Objective Relevant to Cardiovascular Safety: Assess long-term safety in terms of incidence of alanine aminotransferase elevations, and cardiovascular and hematological safety, in addition to changes in body weight and serum lipids.

Number of Patients: 4351 randomized. Original target sample size was 3600 patients. Due to higher than anticipated early withdrawal rate and lower than anticipated monotherapy failure rate, target sample size amended to 4182 patients.

Duration: Four years originally planned; when sample size increased, follow-up period also extended to 6 years. Mean and median followup 38.9 and 47.4 months, respectively. Total patient-years = 14,103; 4954, 4244, and 4906 for the RSG, glyburide/glibenclamide and MET groups, respectively. (Hereafter, the glyburide/glibenclamide group will be abbreviated as the SU group, although glyburide/glibenclamide represent only one subclass of sulfonylureas). Less exposure for SU group than for RSG or MET groups.

Number of Centers: 473 (North America and Europe)

Randomization: 1:1:1 randomization, with stratification by gender.

Blinding:

- Double-blind.
- Investigators and patients blinded to treatment assignment (all study medications in identical capsules).
- Bottle labels did not reveal name of drug.
- Patients blinded to dose by use of placebo during protocol-defined titration period and treatment period, so that all patients titrated up to 4 capsules/day.

- External reviewers blinded during post-study review of congestive heart failure (CHF) events.

Study Agent Treatment: Rosiglitazone, initiated at 4 mg/day, with protocol-specified up-titration to 8 mg/day possible based on fasting plasma glucose.

Controls:
- Glyburide/glibenclamide, initiated at 2.5 mg/day, with protocol-specified up-titration to as high as 15 mg/day possible based on fasting plasma glucose.
- Metformin, initiated at 500 mg/day, with protocol-specified up-titration to 2000 mg/day possible based on fasting plasma glucose.

Parallel Group Design?: yes

Patient Population: Men and women, ages 30-75 years, with type 2 diabetes diagnosed ≤ 3 years. Fasting plasma glucose 126-240 mg/dL at screening.

Exclusion Criteria of Particular Importance:
Prior diabetes drug treatment. Exceptions to this exclusion:
- Insulin use during gestational diabetes
- Short-term (≤ 1 month) insulin use to maintain glycemic control for hospitalization or medical procedure/intervention
- ≤ 2 weeks of oral hypoglycemic agent ≥ 2 weeks prior to screening, or >2 weeks-1 month of oral hypoglycemic agent ≥ 2 months prior to screening
- Congestive heart failure requiring drug therapy (any New York Heart Association [NYHA] class)
- Alanine aminotransferase (ALT) >2.5x the laboratory upper limit of normal (ULN)
- Serum creatinine >1.3 mg/dL (for men) or >1.2 mg/dL (for women)

Primary Endpoint: Time to monotherapy failure

Predefined Cardiovascular Secondary Endpoints: None

Adjudication of Cardiovascular Events: None predefined; post hoc adjudication of heart failure events

Duration of Ascertainment of Cardiovascular Events After Study Medication Cessation: 30 days

General Description of Study Conduct:
After a 4-week dietary and placebo run-in period, patients were randomized to double-blind treatment with RSG, SU or MET. Up-titration occurred based on fasting plasma glucose. For the first year of study, patients had study visits every two months; thereafter, visits occurred every three months. Fasting glucose and adverse event information were obtained at each study visit, as were other laboratory, history and physical examination data (see Tables A1 and A2 below). An oral glucose tolerance test was performed every six months. Patients remained on blinded study medication until they met criteria for monotherapy failure, which were:
- fasting plasma glucose >180 mg/dL on consecutive occasions following at least 6 weeks of dosing with the maximum tolerated dose of study medication, or
- judgment by independent adjudication committee that patient had achieved monotherapy failure.

The latter criterion was added in an amendment after it was noted that there were a number of patients who did not meet the definition of monotherapy failure in the first bullet, yet were likely to have been a monotherapy failure. These included patients who had a final FPG >180 mg/dL with no follow-up FPG, patients who did not meet the timing requirement related to maximum tolerated dose (MTD), patients for whom there was uncertainty about whether MTD had been achieved, patients withdrawn due to insufficient therapeutic effect but who did not meet the protocol definition, and patients who had been placed on combination oral or insulin therapy as a protocol violation. The independent adjudication committee included three independent physicians who were blinded to treatment assignment, and was expected to make a decision about whether such patients were actually monotherapy failures. An event would be counted as a monotherapy failure if the adjudication committee concluded that:

- it was probable that the event would have met the protocol definition of monotherapy failure, had the patient been retained in the study and if all evaluations had been performed as specified precisely by the protocol, and
- the event satisfied usual good clinical practice criteria for monotherapy failure. (Source: Adjudication Committee charter, pg 7798, ADOPT study report)

Patients who remained in study and did not have monotherapy failure had a minimum of 21 study visits and a maximum of 29 study visits. Adverse event data were routinely collected until 30 days after cessation of study medication. Patients who withdrew from treatment were asked for consent to be followed in a non-treatment observational follow-up period, which lasted until 48 months after their randomization date, but adverse event data were not routinely collected during this period (ADOPT study report, Table 2, footnote 10, pg 52).

The following tables present an abbreviated version of study procedures:

Table A1: Abbreviated Table of Study Procedures, Screening Through Year 1

	Pre-screen	Run-in Period Screen			Treatment Period			
Visit Number	**0**	**1**	**2**	**3 Baseline**	**4&5**	**6**	**7&8**	**9**
Week/Month Number	**-6 wks**	**-4 wks**	**-2 wks**	**0**	**8&16 wks**	**24 wks**	**8&10 mo**	**12 mo**
History, physical exam[1] and concomitant meds check		x	x	x	x	x	x	x
FPG	x	x	x	x	x	x	x	x
HbA1c, LFTs				x	x	x	x	x
OGTT, fasting lipids				x		x		x
Routine fasting chem, heme, urine panels; serum β-HCG		x		x		x		x
ECG		x						x
Signs/ symptoms/ adverse experiences check			x	x	x	x	x	x

Source: ADOPT study report, Table 2, pg 51
Abbreviations: β-HCG = human chorionic gonadotropin beta subunit, ECG = electrocardiogram, exam = examination, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LFTs = liver function tests, meds = medications, mo = months, OGTT = oral glucose tolerance test, wks = weeks
1 Full history and physical at visit 1; full physical exam at visit 9 also; focused interim history and physical at other visits

Table A2: Abbreviated Table of Study Procedures, Month 15 Through Year 6			
	Frequency of Procedure		
	Every 3 Months	**Every 6 Months**	**Every 12 Months**
Interim history, physical exam and concomitant meds	x		
Complete physical exam			x
FPG, HbA1c	x		
LFTs, OGTT		x	
Routine fasting chem, heme, urine panels; serum β-HCG; ECG			x
Adverse experiences check	x		

Source: ADOPT study report Tables 3 and 4, beg pg 53
Abbreviations: β-HCG = human chorionic gonadotropin beta subunit, ECG = electrocardiogram, exam = examination, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LFTs = liver function tests, meds = medications, mo = months, OGTT = oral glucose tolerance test, wks = weeks

Once a patient met criteria for monotherapy failure, they remained in study and had adverse event data collected for 30 days after cessation of study medication.

RESULTS

Disposition:

The following table summarizes patient disposition.

Table A3: Patient Disposition in ADOPT				
	RSG	**SU**	**MET**	**TOTAL**
Entered placebo run-in period	n/a	n/a	n/a	6385
Randomized	1456	1441	1454	4351
Withdrawn prior to first efficacy evaluation	63	104	57	224
Non-monotherapy failure withdrawals, n (%)	621 (43)	671 (47)	602 (41)	1894 (44)
Completed and monotherapy failure, n (%)	835 (57)	770 (53)	852 (59)	2457 (56)
Study-defined intention to treat (ITT) population[1]	1393	1337	1397	4127

Source: ADOPT study report, Table 6, pg 78
1 All subjects who were randomized and had at least one on-therapy value for an efficacy parameter. ITT population used for efficacy evaluation. Population of all randomized patients who received at least one dose of study medication was used for safety evaluation

A substantial percentage of patients in each treatment group discontinued treatment for reasons other than monotherapy failure. The withdrawal rate from ADOPT, both related to the endpoint of monotherapy failure, and related to other reasons, presents challenges for the interpretation of adverse event data. Methods such as expression of adverse event rates per patient year, and time-to-event analyses, were used to assist in interpretation of adverse event data in the face of differing exposure for the treatment groups.

Exposure

Mean and median durations of exposure were approximately equal for rosiglitazone and metformin, while sulfonylurea exposure was somewhat lower. Early withdrawals (within the first month of exposure) were more common among sulfonylurea group patients; this excess was primarily due to hypoglycemia. Lower exposure for SU group patients was important in assessing event rates, as it might bias rates in favor of SU over RSG or MET.

Table A4: Duration of Exposure (All Randomized Patients)

Exposure Interval		Number of Subjects, n (%)			
Days	Months[1]	RSG N=1456	GLY/GLIB N=1441	MET N=1454	Total N=4351
≤ 28	≤1	42 (2.9)	78 (5.4)	34 (2.3)	154 (3.5)
29-90	1-3	59 (4.1)	71 (4.9)	58 (4.0)	188 (4.3)
91-180	3-6	61 (4.2)	58 (4.0)	59 (4.1)	178 (4.1)
181-270	6-9	51 (3.5)	57 (4.0)	61 (4.2)	169 (3.9)
271-360	9-12	38 (2.6)	66 (4.6)	37 (2.5)	141 (3.2)
361-540	12-18	57 (3.9)	72 (5.0)	67 (4.6)	196 (4.5)
541-720	18-24	72 (4.9)	79 (5.5)	64 (4.4)	215 (4.9)
721-1080	24-36	117 (8.0)	177 (12.3)	123 (8.5)	417 (9.6)
1081-1440	36-48	146 (10.0)	179 (12.4)	163 (11.2)	488 (11.2)
>1440	>48	813 (55.8)	604 (41.9)	788 (54.2)	2205 (50.7)
Mean (Days) ±SD		1242.7±652.5	1075.6±664.8	1232.3±646.9	1183.9±659.1
Median		1463.0	1217.0	1459.0	1443.0
Range		1-2189	1-2214	1-2203	1-2214

1. Approximation
Data Source: Table 6.7.1

Source: ADOPT study report, Table 47, pg 154

Demographic and Other Baseline Characteristics

In general, baseline and demographic characteristics were similar among treatment groups. Patients in the sulfonylurea group were slightly numerically less likely to be smokers. Patients in the metformin group were slightly numerically more likely to test positive for antibodies to glutamic acid decarboxylase. Patients in the rosiglitazone group were slightly numerically less likely to have a history of cardiovascular disease. None of these differences between groups was statistically significant. Mean waist:hip ratio was very slightly numerically lower in the sulfonylurea group (0.94 SU vs 0.95 for RSG and MET), with a p-value for the difference of 0.0974.

Table A5: Summary of Demographic and Other Baseline Characteristics, Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Characteristic	Category	RSG N=1456	SU N=1441	MET N=1454	TOTAL N=4351	p-value
Gender, % male	% male	55.7	58.0	59.4	57.5	0.1218
Age, mean (SD), years		56.3 (9.99)	56.4 (10.20)	56.9 (9.34)	56.5 (10.05)	0.2892[1]
Race, %	White	87.2	89.0	89.1	88.5	0.2326
	Black	4.2	4.2	3.7	4.0	
	Asian	2.7	2.2	2.4	2.4	
	Hispanic	5.2	4.2	3.8	4.4	
	Other	0.7	0.3	1.0	0.6	
Country, %	USA	37.8	38.4	38.0	38.1	1.0000

Table A5: Summary of Demographic and Other Baseline Characteristics, Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Characteristic	Category	RSG N=1456	SU N=1441	MET N=1454	TOTAL N=4351	p-value
	Canada	14.2	14.2	14.2	14.2	
	France	9.1	8.7	9.0	9.0	
	Germany	10.8	10.6	11.1	10.8	
	United Kingdom	7.3	7.6	7.2	7.4	
	Spain	9.1	9.3	9.2	9.2	
	Other	11.1	11.1	11.4	11.4	
BMI, kg/m^2 (SD)		32.2 (6.69)	32.2 (6.27)	32.1 (6.05)	32.2 (6.34)	0.9741[1]
Weight, kg (SD)		91.5 (19.68)	92.0 (19.99)	91.6 (18.67)	91.7 (19.45)	0.9157[1]
Ratio of waist:hip circumference, cm/cm, mean (SD)		0.95 (0.091)	0.94 (0.086)	0.95 (0.096)	0.95 (0.091)	0.0974[1]
Smoker, %		15.5	13.3	15.0	14.6	0.2167
Alcohol consumers, %		46.2	44.9	45.6	45.5	0.7816
Glutamic acid decarboxylase antibody positive, %		4.0	3.6	5.1	4.2	0.1462
Duration of diabetes, %	<1 yr	44.7	44.2	46.3	45.1	0.3639
	1 yr	34.1	33.4	31.9	33.1	
	2 yrs	18.0	18.7	17.9	18.2	
	3 yrs	3.0	3.3	3.6	3.3	
	≥ 4 yrs	0.3	0.4	0.3	0.3	
Hypertension[2] present, % of patients		72.9	72.9	72.8	72.9	0.9978
On hypertension med(s), % of patients		51.1	53.3	50.7	51.3	0.6822
Diastolic BP, mmHg, mean (SD)		79.8 (8.67)	79.3 (8.96)	79.7 (8.92)	79.6 (8.85)	0.4837[1]
Systolic BP, mmHg, mean (SD)		133.0 (15.66)	132.7 (15.40)	132.8 (15.45)	132.9 (15.50)	0.8313[1]
Dyslipidemia[3] present, % of patients		66.3	63.9	66.0	65.4	0.3500
On dyslipidemia treatment, % of patients		26.0	25.7	25.9	25.9	0.9819
Medical history of CV disease[4], % of patients		15.9	17.1	18.5	17.2	0.1692

Source: ADOPT study report, Tables 13 and 14, beg pg 93
1 Kruskall-Wallis test; other p-values by chi-squared test
2 Hypertension defined as systolic BP ≥ 130 mm HG or diastolic BP ≥ 85 mmHg, or medical history of hypertension
3 Dyslipidemia defined as HDL <40 mg/dL for men, HDL <50 mg/dL for women, or TG ≥ 150 mg/dL
4 CV medical history = presence of any of a set of defined terms for myocardial ischemia, heart failure, arrhythmia and other CV conditions; list of conditions begins pg 2458, ADOPT study report

Baseline cardiovascular medication use was similar among treatment groups. A total of 24% of patients in each treatment group were taking angiotensin converting enzyme inhibitors. Nitrate use was low at baseline, with 2%, 3% and 3% of patients taking nitrates in the RSG, SU and MET groups, respectively. Angina requiring continual nitrate treatment was an exclusion criterion.

Primary endpoint

The focus of this briefing document is the cardiovascular safety of rosiglitazone, and therefore a detailed review of the efficacy findings will not be presented.

The primary efficacy endpoint was the time from randomization to monotherapy failure.

Monotherapy failure was defined as either:

- fasting plasma glucose of >180 mg/dL on consecutive occasions following at least 6 weeks of dosing with the maximum tolerated dose of the study medication, or
- for patients who failed to meet the above criterion, judgment by the independent adjudication committee that monotherapy failure had occurred (see section entitled *General Description of Study Conduct* above).

The following table and Kaplan-Meier curves present the applicant's analyses of the primary endpoint:

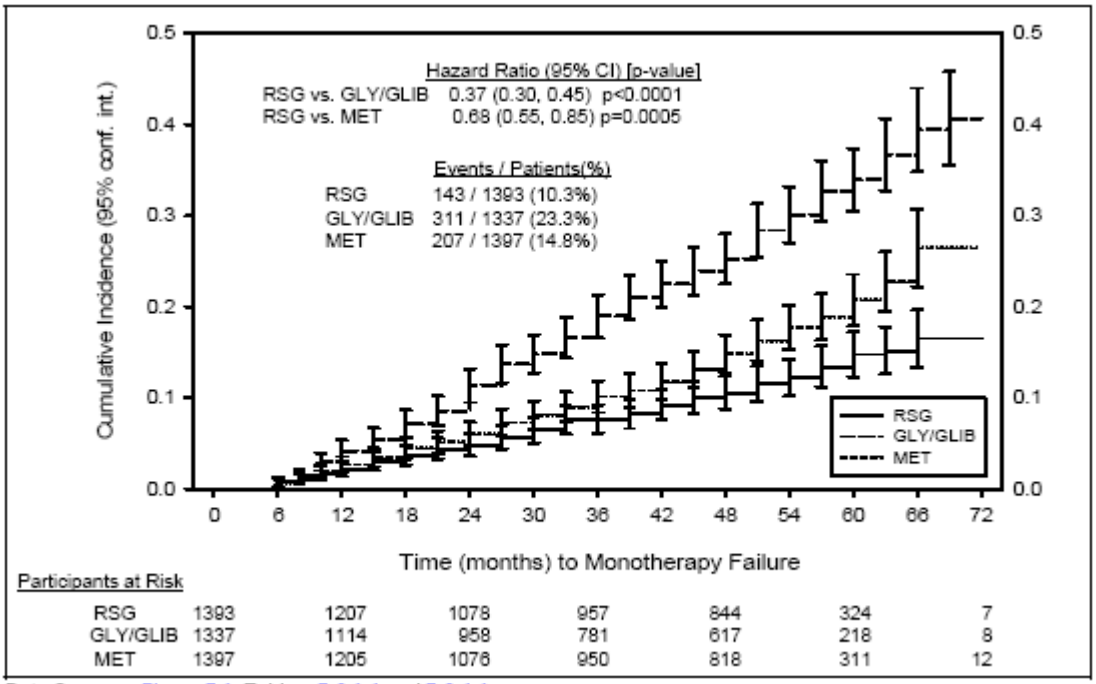
Table A6: Analysis of Time to Monotherapy Failure, Intention-to-Treat Population

	RSG N=1393	GLY/GLIB N=1337	MET N=1397
Number of subjects with event	143	311	207
Cumulative incidence (95% CI) at 5 years	0.15 (0.12, 0.17)	0.34 (0.30, 0.37)	0.21 (0.18, 0.24)
RSG vs Control			
Hazard ratio (95% CI)[1]		0.37 (0.30, 0.45)	0.68 (0.55, 0.85)
p value		<0.0001	0.0005

1. Hazard ratios reflect the ratio of the RSG hazard rate to the control treatment hazard rates. A hazard ratio less than one indicates that rate to event occurrence is slower for RSG relative to control.
Data Source: Table 7.3.1.1 and Table 7.2.1.1

Source: ADOPT study report, Table 21, pg 109

Figure A1: Cumulative Incidence of Monotherapy Failure, Intention-to-Treat Population



Source: ADOPT study report, Figure 11, pg 110

By these analyses, rosiglitazone was associated with a lower rate of monotherapy failure (by specified criteria) over time than was metformin or glyburide/glibenclamide.

Multiple secondary endpoints were also analyzed, but are not included in the focus of this briefing document.

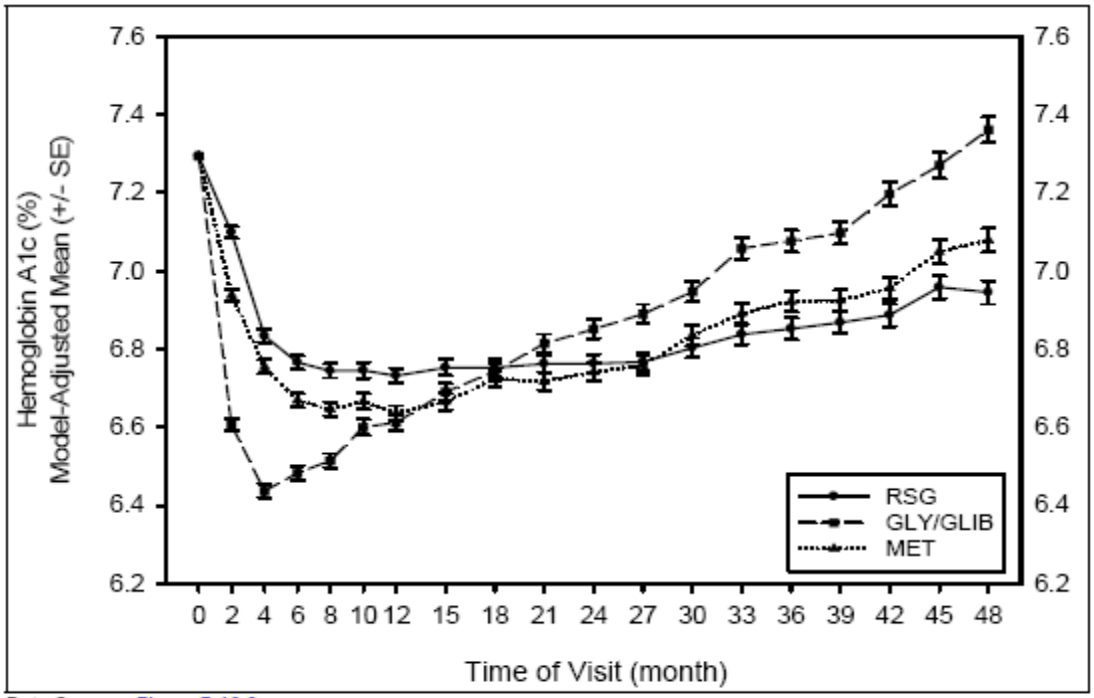
Hemoglobin A1c, Lipids and Blood Pressure at Endpoint

When examining cardiovascular safety, differences in cardiovascular risk factors between treatment groups over the course of study can complicate interpretation. In an ideal setting, values for risk factors such as blood sugar, lipids and blood pressure would be equal between treatment groups over time. In some trials (such as the ongoing BARI 2D trial), active management of cardiovascular risk factors occurs, with the goal of achieving equal control between groups; this facilitates a better estimate of cardiovascular risk or benefit. Other trials (such as PROactive) have been complicated by differences in risk factor values at endpoint, leading to discussion regarding whether any positive benefits were simply due to risk factor changes, with the possibility that, risk factors being equal, there would have been no demonstrable effect of the drug. Therefore, risk factors were also examined in the review of ADOPT.

Because RSG was associated with fewer monotherapy failures than SU or RSG, one might logically expect lower hemoglobin A1c (HbA1c) among RSG-treated patients than among patients in the MET and SU groups. Analyses of HbA1c were complicated by withdrawals due to monotherapy failure. In the first year of therapy, mean HbA1c was lower in the sulfonylurea group than in the other two groups, and HbA1c in the metformin group was somewhat lower than HbA1c in the rosiglitazone group. Over time, HbA1c in the RSG group became lower than that in either group. It seems that this would be expected, as more patients in the SU and MET groups

began to have high blood sugars that led to monotherapy withdrawal; these high blood sugars would likely have been associated with higher HbA1cs. GSK performed analyses using multiple models; results were qualitatively similar.

Figure A2: Model-Adjusted Mean HbA1c (%) Values by Visit to 48 Months, ITT Population



Data Source: Figure 7.10.2

Source: ADOPT study report, Figure 19, pg 118. Model described on pg 73; multivariate linear model incorporating on-therapy values at all time points up to 48 months. Model incorporated effects for baseline, country group, treatment, gender, time and treatment-time interaction.

Low density lipoprotein cholesterol (LDL) increased in the RSG group over the first 6 months of study, and then declined until end of study. In the SU and MET groups, LDL declined gradually throughout study. At 48 months, LDL was statistically significantly higher in the RSG group than in the other treatment groups.

Table A7: Multivariate Linear Model Analysis of Log-Transformed Low Density Lipoprotein Cholesterol (mg/dL)

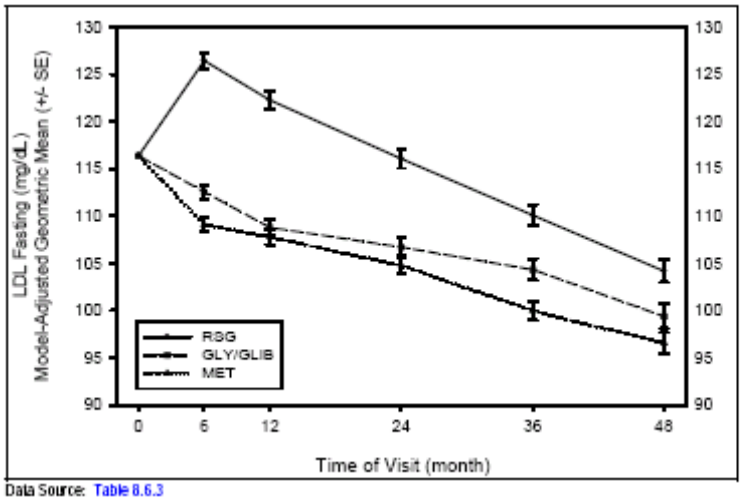
	RSG N=1456	GLY/GLIB N=1441	MET N=1454
LDL Cholesterol , n[1]	1186	1174	1215
Baseline, Geometric mean (CV[2]%[2]) mg/dL	116.9 (30.9)	116.1 (33.5)	116.3 (30.1)
Baseline, Geometric mean (CV[2]%[2]) mmol/L	3.0403 (30.9)	3.0175 (33.5)	3.0248 (30.1)
% Change from Baseline to 48 Months			
Adjusted Mean (%) (95% CI)	-10.5 (-12.5, -8.4)	-14.6 (-16.7, -12.4)	-17.0 (-18.9, -15.1)
Comparison of RSG versus Control at 48 Months			
Adjusted Geometric Mean Difference (%)		4.8	7.9
(95% CI)		(1.4, 8.4)	(4.5, 11.4)
p-value		0.0059	<0.0001

1. Number of subjects with On-Therapy data.
2. CV = coefficient of variation.
3. % change based on log-transformed data

Data Source: Table 8.11.1

Source: ADOPT study report, Table 113, pg 246

Figure A3: Model-Adjusted Geometric Mean LDL Cholesterol (mg/dL, ±SE) by Visit to 48 Months, Population of All Randomized Patients Who Received at Least One Dose of Study Medication



Data Source: Table 8.6.3

Source: ADOPT study report, Figure 73, pg 246

High-density lipoprotein (HDL) cholesterol increased over time in all three treatment groups. The increase from baseline to 48 months was greater for the RSG group than for either of the other treatment groups.

Table A8: Multivariate Linear Model Analysis of Log-Transformed High Density Lipoprotein Cholesterol (mg/dL), Population of All Randomized Patients Who Received at Least One Dose of Study Medication

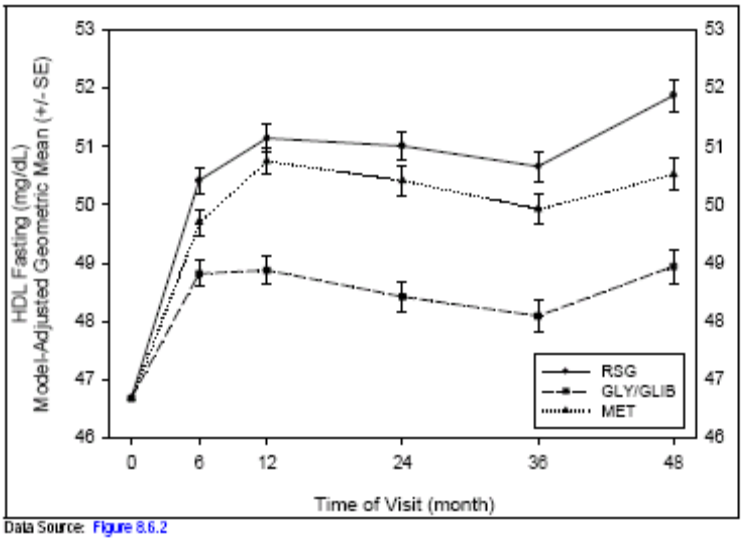
	RSG N=1456	GLY/GLIB N=1441	MET N=1454
HDL Cholesterol , n[1]	1281	1231	1296
Baseline, Geometric mean (CV[2]%[2]) mg/dL	46.4 (24.8)	46.6 (25.3)	46.6 (24.9)
Baseline, Geometric mean (CV[2]%[2]) mmol/L	1.2064 (24.8)	1.2128 (25.3)	1.2128 (24.9)
% Change from Baseline to 48 Months			
Adjusted Mean (%)	11.1	4.8	8.2
(95% CI)	(10.0, 12.3)	(3.6, 6.1)	(7.1, 9.4)
Comparison of RSG versus Control at 48 Months			
Adjusted Geometric Mean Difference (%)		6.0	2.7
(95% CI)		(4.4, 7.6)	(1.2, 4.2)
p-value		<0.0001	0.0004

1. Number of subjects with On-Therapy data.
2. CV = coefficient of variation.
3. % change based on log-transformed data

Data Source: Table 8.11.1

Source: ADOPT study report, Table 112, pg 245

Figure A4: Model-Adjusted Geometric Mean HDL (mg/dL, ±SE) by Visit to 48 Months, Population of All Randomized Patients Who Received at Least One Dose of Study Medication



Data Source: Figure 8.6.2

Source: ADOPT study report, Figure 72, pg 244

Triglyceride (TG) levels increased in the RSG group over the first 6 months of study, then declined throughout the rest of study. In the SU and MET groups, TG levels declined over the first 6 months of study, and gradually increased over the remainder of study. At 48 months, TG levels were statistically significantly lower in the RSG group than in the SU group, although the absolute difference was small and may not be clinically meaningful. There was no significant difference in TG levels at 48 months when comparing RSG to MET.

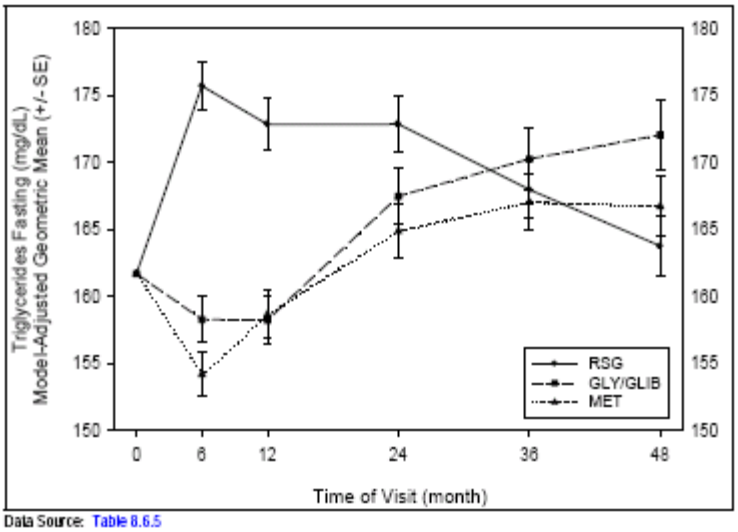
Table A9: Multivariate Linear Model Analysis of Log-Transformed Triglycerides, Population of All Randomized Patients Who Received at Least One Dose of Study Medication

	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Triglycerides; n[1]	1286	1240	1296
Baseline, Geometric mean (CV[2]%[3]) mg/dL	165.9 (59.3)	160.2 (57.8)	165.5 (60.0)
Baseline, Geometric mean (CV[2]%[3]) mmol/L	1.8741 (59.3)	1.18103 (57.8)	1.8697 (60.0)
% Change from Baseline to 48 Months			
Adjusted Mean (%) (95% CI)	1.3 (-1.4, 4.0)	6.4 (3.3, 9.6)	3.1 (0.4, 5.9)
Comparison of RSG versus Control at 48 Months			
Adjusted Geometric Mean Difference (%) (95% CI) p-value		-4.8 (-8.4, -1.0) 0.0131	-1.8 (-5.3, 1.9) 0.3433

1. Number of subjects with On-Therapy data.
2. CV = coefficient of variation.
3. % change based on log-transformed data

Source: ADOPT study report, Table 114, pg 248

Figure A5: Model-Adjusted Geometric Mean Triglycerides (mg/dL, ±SE) by Visit to 48 Months, Population of All Randomized Patients Who Received at Least One Dose of Study Medication



Data Source: Table 8.6.5

Source: ADOPT study report, Figure 74, pg 247

Mean systolic blood pressure declined slightly in the RSG group over time, while rising slightly in the MET and SU treatment groups. The difference in this change from baseline to 48 months was statistically significant for the RSG vs SU comparison (no adjustment for multiple comparisons), but not for the RSG vs MET comparison.

Table A10: Multivariate Linear Model Analysis of Change from Baseline in Systolic Blood Pressure (mmHg), Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Systolic Blood Pressure	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Number of subjects with event	1394	1331	1397
Mean±SD at Baseline	132.8±15.53	132.8±15.40	132.8±15.54
Change from Baseline to 48 Months ±SE	-0.8±0.47	1.1±0.53	0.3±0.47
95% CI	-1.8, 0.1	0.0, 2.1	-0.6, 1.2
RSG vs. Control			
Adjusted Mean Difference (95% CI)		-1.9 (-3.3, -0.6)	-1.1 (-2.4, 0.1)
p-value		0.0058	0.0831

Data Source: Table 8.6.5

Source: ADOPT study report, Table 104, pg 229

Mean diastolic blood pressure declined slightly in all 3 treatment groups over time; the decline from baseline to 48 months was statistically significantly greater in the RSG group compared to the other two treatment groups.

Table A11: Multivariate Linear Model Analysis of Change from Baseline in Diastolic Blood Pressure (mmHg), Population of All Randomized Patients Who Received at Least One Dose of Study Medication

Diastolic Blood Pressure	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Number of subjects with event	1394	1331	1397
Mean±SD at Baseline	79.7±8.60	79.3±8.94	79.8±8.95
Change from Baseline to 48 Months ±SE 95% CI	-3.1±0.29 -3.6, -2.5	-1.0±0.33 -1.7, -0.4	-1.6±0.29 -2.2, -1.1
RSG vs. Control Adjusted Mean Difference (95% CI) p-value		-2.0 (-2.9, -1.2) <0.0001	-1.4 (-2.2, -0.6) 0.0004

Data Source: Table 8.6.5

Source: ADOPT study report, Table 105, pg 229

These differences in risk factors at endpoint were generally slightly favorable for RSG, except for LDL cholesterol, which was unfavorably higher for RSG. The expected difference in CV risk associated with these changes is difficult to quantify, although there are some models which have been employed, such as a UKPDS-based model which was used for a published post hoc evaluation of the PROactive data, and which suggested that most of the numerically favorable cardiovascular risk reduction for pioglitazone could be accounted for by changes in risk factors (Holman 2006). Data for UKPDS have never been submitted to the FDA, although the FDA requested the data, and therefore the FDA cannot verify the validity of this model. The UKPDS was not conducted under a U.S. IND and was not sponsored by a pharmaceutical company, but rather by the UKPDS study group. A cardiovascular event rate model based on modification of CV risk factors has not yet been employed for the ADOPT risk factor data. Some uncertainty remains about the contribution of differential risk factor results to expected CV event risk in ADOPT.

Deaths

A total of 96 deaths were reported. Of these, 48 occurred during treatment or within 30 days of cessation of treatment. There were 21 deaths that occurred more than 30 days after cessation of treatment, but were due to an adverse event that occurred on treatment or within 30 days of cessation of treatment. There were 27 deaths that occurred more than 30 days after cessation of treatment and were due to an adverse event that also occurred more than 30 days after cessation of treatment. Adverse events were captured until 30 days after cessation of treatment, but were not routinely captured after that. Therefore, data for deaths and other adverse events occurring more than 30 days after cessation of treatment are possibly incomplete.

The following table summarizes the numbers of reported deaths in each of the treatment groups.

Table A12: Summary of Deaths Occurring On-therapy and Post-therapy, Population of All Patients Who Received at Least One Dose of Study Medication						
	RSG N=1456 PY[1]=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	# Deaths/ 100 PY	n (%)	# Deaths/ 100 PY	n (%)	# Deaths/ 100 PY
Total Deaths	34 (2.3)	0.7	31 (2.2)	0.7	31 (2.1)	0.6
Deaths occurring on treatment or within 30 days of cessation of treatment	12 (0.8)	0.2	21 (1.5)	0.5	15 (1.0)	0.3
Deaths occurring >30 days after cessation of treatment, but due to an event that had onset during treatment or within 30 days of cessation of treatment	11 (0.8)	0.2	6 (0.4)	0.1	4 (0.3)	0.1
Deaths occurring >30 days after cessation of treatment, and due to event that occurred >30 days after cessation of treatment	11 (0.8)	0.2	4 (0.3)	0.1	12 (0.8)	0.2
Source: ADOPT study report Table 1697, pg 6619 **1 Patient-years on treatment**						

The following tables list each of these deaths; the clinical reviewer examined each death narrative (unblinded) to assess for appropriateness of assignment of cause of death.

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
040-80119	RSG	64	f	181	181	181	Road traffic accident	Injuries from motor vehicle accident	Same as reported cause
189-81714	RSG	65	f	917	917	917	Myocardial infarction	Sudden death myocardial infarction	Sudden death with possible MI per later report by primary care physician; no description of event; no autopsy
306-82363	RSG	66	m	872	281	873	Prostate cancer	Prostate cancer (terminal phase)	Same
313-82618	RSG	68	m	884	882	885	Myocardial infarction	Myocardial infarction	Sudden death; probable MI (sudden collapse in street, preceded 3 days earlier by precordial pain)
315-83636	RSG	66	m	995	508	1022	Esophageal carcinoma	Hepatorenal insufficiency due to esophageal cancer	Hepatorenal failure due to esophageal cancer with hepatic metastases
324-82710	RSG	54	m	1009	1009	1009	Drowning	Drowning	Same
405-80736	RSG	72	m	81	82	82	Cardiac failure acute	Acute heart failure	"Acute heart failure" with no prior symptoms; no description of symptoms and no autopsy
537-81012	RSG	59	m	45	64	64	Ventricular fibrillation	Ventricular fibrillation	Same
792-25702	RSG	33	m	1380	1381	1382	Cerebrovascular accident	Apoplexy	Cerebrovascular accident
792-26191	RSG	53	m	61	62	62	Cardiac failure acute	Acute heart failure	Probable acute heart failure; symptoms not described
841-91751	RSG	71	m	634	568	649	Abdominal neoplasm	Neoplasia intra-abdominal	Same
844-22604	RSG	55	m	368	298	374	Colon cancer	Sigmoid colon adenocarcinoma PT3PN1 with hepatic and peritoneal metastases	Same
137-79184	SU	56	m	1038	1066	1066	Death (sic)	Unknown	Possible hypoglycemia; found on floor in asystole with BG 20
204-22661	SU	69	m	124	55	145	Metastases to abdominal cavity	Disseminated cancer (primary cancer unknown)	Metastatic cancer of unknown primary
204-83418	SU	70	m	1555	1569	1575	Cardiac arrest/ cardiac failure	Heart failure and cardiac arrest	Heart failure with subsequent in-hospital cardiac arrest

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
206-82233	SU	74	f	1861	1862	1887	Diabetic complication	Diabetic complications	In-hospital death after hypoglycemic coma, renal failure, and multiple recent partial lower extremity amputation procedures
207-82244	SU	71	m	27	43	48	Cerebral ischemia	Cerebral anoxemia due to cardiac arrest	Cardiac arrest with probable cerebral anoxia; death 7 days later
234-23558	SU	64	m	303	323	323	Arrhythmia	Myocardial ischemia and secondary arrhythmia	Arrhythmia per autopsy
234-26868	SU	69	f	116	117	117	Subarachnoid hemorrhage	Subarachnoid hemorrhage	Same
276-83292	SU	65	m	34	35	36	Myocardial infarction	Myocardial infarction but waiting for autopsy	Myocardial infarction
280-78680	SU	57	m	858	860	860	Myocardial infarction	Myocardial infarction	Myocardial infarction with asystole
283-78672	SU	72	f	901	901	904	Myocardial infarction/ pulmonary edema	Anterior myocardial infarction, cardiogenic shock, no death certificate available, death summary only	Anterior myocardial infarction
284-83321	SU	61	m	336	273	336	Epiglottic carcinoma	Hemorrhage of the pharynx	Pharyngeal hemorrhage due to epiglottic cancer
327-80905	SU	55	m	496	497	497	Completed suicide	Suicide	Same
328-80909	SU	56	m	114	114	114	Road traffic accident	Public way accident	Motor vehicle accident
338-80859	SU	70	m	941	942	942	Sudden death	Cause unknown, possible pulmonary embolism or massive myocardial infarction	Sudden death shortly after episode of chest discomfort and dyspnea
424-80648	SU	55	m	826	847	847	Respiratory failure	Respiratory insufficiency	Ventricular fibrillation with hypoxic brain damage followed by pneumonia and respiratory failure
474-91315	SU	68	f	1230	1231	1243	Pneumonia	Pneumonia	Same
705-81122	SU	74	m	1282	1287	1287	Myocardial infarction	Myocardial infarction	Same
797-25790	SU	75	f	326	326	328	Cerebrovascular accident	Apoplexia	Same

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
811-22102	SU	74	m	1295	1296	1296	Cerebrovascular accident	Probable acute stroke	Same
906-80462	SU	70	m	372	377	379	Cardiac arrest/ pulmonary edema	Pulmonary embolus	Pulmonary embolus after stroke
964-80531	SU	73	f	1192	1140	1198	Metastases to liver	Liver metastatic disease	Metastatic colon cancer
030-79292	MET	56	m	260	275	275	Pulmonary embolism	Cardiac arrest, pulmonary embolus, status post coronary artery bypass	Probable pulmonary embolus
077-79927	MET	67	m	978	952	987	Lung neoplasm malignant	Metastatic squamous cell cancer of lung	Same
183-81863	MET	69	m	553	554	577	Pancreatic mass	Pancreatic mass	Pancreatic cancer
196-82164	MET	68	m	1443	1443	1447	Cerebrovascular accident	Massive stroke	Same
232-23582	MET	56	m	433	434	434	Cardiac arrest	Cardiac arrest	Sudden out-of-hospital death
278-26729	MET	62	m	1111	575	1125	Brain neoplasm	Cancerous brain tumor	Same
324-82709	MET	69	m	770	770	770	Aortic dissection	Aortic dissection	Same
403-82416	MET	64	m	954	954	954	Crushing injury of trunk	Car accident	Same
455-82445	MET	72	f	571	571	571	Cerebral infarction	Cerebral infarction with left hemiplegia	Same
498-82456	MET	75	m	811	812	831	Cardiac failure	Sepsis	Heart failure
691-91348	MET	66	f	154	154	167	Esophageal varices hemorrhage	Esophagus varicose vein bleeding	Same
792-28149	MET	71	m	539	549	549	Circulatory collapse	Cardiovascular breakdown	Sudden in-hospital death after rib fracture complicated by pneumonia
807-81209	MET	51	m	104	104	104	Cardiac arrest	Cardiac arrest	Same
952-80532	MET	67	m	245	245	245	Myocardial ischemia	Acute myocardial ischemia	Sudden death with autopsy report of acute myocardial ischemia

Table A13: Listing of Deaths Occurring on Treatment or Within 30 Days of Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
956-90891	MET	55	m	1348	1316	1348	Abdominal sepsis	Acute respiratory distress syndrome (pulmonary edema, pneumonia, lung collapse) due to intra-abdominal sepsis	Acute respiratory distress after postoperative intra-abdominal infection

Source: ADOPT study report, Table 8.4, beg pg 4229

Based on this post hoc, unblinded review of death narratives, the clinical reviewer counted the numbers of cardiovascular deaths which occurred within 30 days of cessation of study medication, and broke down the total number by subcategories of CV death.

Table A14: Numbers of Cardiovascular Deaths Which Occurred During Treatment or Within 30 Days of Cessation of Treatment

Category	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Any cardiovascular cause	6 (0.41)	0.12	13 (0.90)	0.31	8 (0.55)	0.16
Myocardial ischemia likely (includes sudden unexplained deaths)	2 (0.14)	0.04	6 (0.42)	0.14	3 (0.21)	0.06
Cerebrovascular	1 (0.07)	0.02	4 (0.28)	0.09	2 (0.14)	0.04
Heart failure	2 (0.14)	0.04	1 (0.07)	0.02	1 (0.07)	0.02
Arrhythmia	1 (0.07)	0.02	2 (0.14)	0.05	0	n/a
Other	0	n/a	0	n/a	2 (0.14)	0.04
Non-heart-failure cardiovascular	4 (0.27)	0.08	12 (0.83)	0.28	7 (0.48)	0.14

Source: Table A13 above

From these numbers, it does not appear that RSG was associated with a higher incidence of overall CV death, or of death from a particular category of cardiovascular cause. The total number of cardiovascular deaths is small, which limits conclusions. The post hoc and unblinded nature of the clinical reviewer's assessment of cause of death is also subject to bias, although every effort at objectivity was made.

These numbers of cardiovascular deaths may vary from those identified by GSK in their post hoc analyses of MACE endpoints; in those analyses, non-CHF deaths were included, and were identified as deaths occurring due to an SAE that had a MedDRA Lower Level Term within the set of non-CHF cardiovascular events that were prespecified for the ADOPT CV event groupings (source, NDA 21071 SE8 022, 31 May 07 submission, pages 52-77).

Table A15: Listing of Deaths Occurring >30 Days After Cessation of Treatment, but Due to an Adverse Event that Had Its Onset During Treatment or Within 30 Days of Cessation of Treatment

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
234-26873	RSG	55	m	47	12	726	Sarcoma	Sarcoma with pulmonary metastases	Same
236-26763	RSG	56	m	675	675	720	Adenocarcinoma	Metastatic adenocarcinoma of unknown etiology	Same
293-83158	RSG	58	f	506	409	595	Pancreatic carcinoma	Pancreatic carcinoma	Same
316-80901	RSG	68	f	979	974	1030	Rectal cancer	Terminal evolution of rectal adenocarcinoma	Metastatic rectal adenocarcinoma
324-83746	RSG	65	f	1001	973	1203	Metastases to liver	Liver metastases	Metastatic carcinoma of unknown primary
336-82286	RSG	47	f	819	820	1067	Pancreatic carcinoma metastatic	Primary cancer of the pancreas	Metastatic pancreatic carcinoma
431-82443	RSG	68	m	704	698	745	Gastric cancer	Gastric cancer	Same
455-82501	RSG	70	m	83	33	285	Lung neoplasm malignant	Lung cancer	Same
499-22765	RSG	69	m	1392	1377	1430	Hepatic neoplasm malignant	Organ failure due to cancer progression	Hepatocellular carcinoma
816-91795	RSG	67	m	647	623	681	Lung adenocarcinoma	Lung adenocarcinoma	Same
925-82775	RSG	70	m	163	65	324	Pancreatic carcinoma	Carcinoma pancreas	Same
232-23579	SU	75	m	1440	1441	1602	Subarachnoid hemorrhage	Respiratory failure	Subarachnoid hemorrhage
306-25732	SU	73	m	211	203	269	Metastases to liver	Liver metastases	Metastatic cancer, possibly of pancreatic primary
315-82636	SU	46	m	370	252	543	Gastric cancer	Stomach adenocarcinoma	Gastric adenocarcinoma
896-22952	SU	72	m	511	533	767	Renal cell carcinoma stage unspecified	Renal cancer	Same
917-26409	SU	74	m	190	161	451	Lung neoplasm malignant	Malignant neoplasm of lung	Same
957-90922	SU	66	m	1824	1842	1916	Lung cancer metastatic	Lung cancer with brain + liver secondaries (sic)	Metastatic lung cancer
302-25723	MET	73	m	441	442	509	Small intestine carcinoma	Complication of digestive surgery (high occlusion by cancer)	Enteral hemorrhage after surgery for small intestine carcinoma

Table A15: Listing of Deaths Occurring >30 Days After Cessation of Treatment, but Due to an Adverse Event that Had Its Onset During Treatment or Within 30 Days of Cessation of Treatment

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
321-83732	MET	64	m	869	868	1088	Gastric cancer	"Epidermmoide carcinoma oesophage with ganglionnar and pulmonary development" (sic)	Gastric cancer
442-91285	MET	61	f	30	16	108	Glioblastoma multiforme	Glioblastoma multiforme right frontal	Same
829-91261	MET	74	m	469	464	507	Adenocarcinoma	Cardiorespiratory arrest due to adenocarcinoma	Metastatic adenocarcinoma of unknown primary

Source: ADOPT study report, Table 8.4, beg pg 4229

Based on this post hoc, unblinded review of death narratives, the clinical reviewer counted one cardiovascular death which occurred more than 30 days of cessation of study medication, but was due to an adverse event which had its during study treatment or <30 days after cessation of study treatment.

Table A16: Cardiovascular Death Which Occurred More than 30 Days After Cessation of Treatment, but Was Due to An Adverse Event Which Had Its Onset During Treatment or Within 30 Days of Cessation of Treatment

Category	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Any cardiovascular cause	0	n/a	1 (0.07)	0.02	0	n/a
Cerebrovascular	0	n/a	1 (0.07)	0.02	0	n/a
Non-heart-failure cardiovascular	0	n/a	1 (0.07)	0.02	0	n/a

Source: Table A15 above

The majority of all deaths which fell into this time category were due to malignancies. There was one cerebrovascular death in the SU group, but no other cardiovascular deaths.

Table A17: Listing of Deaths Occurring >30 Days after Cessation of Treatment and Due to an Adverse Event that Had Its Onset >30 Days after Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
077-79370	RSG	54	m	626	1410	1410	not assigned	Cardiac arrest	No death narrative
135-81418	RSG	45	m	372	712	712	not assigned	Cancer, type unknown	No death narrative
176-24748	RSG	66	m	1010	1088	1088	Pulmonary embolism	Pulmonary embolism	Probable pulmonary embolism
176-79764	RSG	63	m	1372	1424	1424	Road traffic accident	Motor vehicle accident	Motor vehicle accident; possible suicide
240-21895	RSG	56	m	1006	1053	1053	Cardiac disorder	Atherosclerotic coronary artery disease	"Widespread heart disease"
442-91283	RSG	68	m	1	41	41	Death (sic)	Reason unknown; no autopsy	Death of unknown cause; study medication not found
610-83483	RSG	73	f	785	1549	1549	not assigned	Died in fire	No death narrative
792-80721	RSG	60	m	435	1278	1278	Myocardial infarction	Myocardial infarction	Probable myocardial infarction
804-22579	RSG	54	m	139	1453	1453	not assigned	Respiratory failure secondary to respiratory infection related to amyotrophic lateral sclerosis	No death narrative
822-22348	RSG	66	m	22	553	1154	Lung neoplasm malignant	Lung cancer	Same
842-91764	RSG	66	m	17	871	871	not assigned	Suicide	No death narrative
034-78765	SU	59	m	968	1035	1035	not assigned	Cerebrovascular accident	No death narrative
180-81962	SU	71	m	246	1454	1454	not assigned	Cancer	No death narrative
256-91028	SU	61	m	1113	1664	1664	not assigned	Subdural haemotoly (sic)	No death narrative
902-22752	SU	49	f	43	502	502	not assigned	Cancer of pancreas with metastases	No death narrative
075-81378	MET	70	m	1	544	544	not assigned	Hepatic failure	No death narrative

Table A17: Listing of Deaths Occurring >30 Days after Cessation of Treatment and Due to an Adverse Event that Had Its Onset >30 Days after Cessation of Treatment, Population of All Patients Who Received at Least One Dose of Study Medication

ID	Tx Grp	Age (yrs)	Gender	Days on Med	Day of Onset of AE	Day of Death	SAE MedDRA Preferred Term	Reported Cause of Death	Cause of Death on Narrative Review
153-78609	MET	59	m	1457	1520	1520	Sudden cardiac death	Sudden cardiac death	Same
179-79818	MET	65	m	211	315	316	Cardiac failure	Heart failure	Same
331-25762	MET	68	m	12	702	702	not assigned	Suicide	No death narrative
331-82582	MET	65	f	998	1653	1653	not assigned	Stroke	No death narrative
403-82449	MET	69	m	502	546	546	Myocardial infarction	Heart infarction	Myocardial infarction
432-80822	MET	51	m	51	1407	1407	not assigned	Heart failure	No death narrative
702-81106	MET	74	m	1477	1768	1768	Arteriosclerosis coronary artery	Heart disease	"Heart disease" on autopsy; found dead
792-26159	MET	56	f	141	495	495	not assigned	Cardiovascular system failure	No death narrative
792-91361	MET	46	m	473	657	657	not assigned	Hyperosmeslatic (sic) coma	No death narrative
841-22181	MET	63	m	174	1123	1123	not assigned	Head pancreas adenocarcinoma	No death narrative
843-91647	MET	41	m	309	923	923	not assigned	Car accident	No death narrative

Source: ADOPT study report, Table 8.4, beg pg 4229

Based on this post hoc, unblinded review of death narratives, the clinical reviewer counted the numbers of cardiovascular deaths which occurred more than 30 days after cessation of study medication, and which were due to an event which had its onset more than 30 days after cessation of study medication. The total number of these cardiovascular deaths was then broken down by subcategories of CV death.

Table A18: Numbers of Cardiovascular Deaths Which Occurred More Than 30 Days after Cessation of Treatment, and Which Were Due to an Event Which Had Its Onset More Than 30 Days After Cessation of Treatment

Category	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Any cardiovascular cause	4 (0.27)	0.08	2 (0.14)	0.05	7 (0.48)	0.14
Myocardial ischemia likely (includes sudden unexplained deaths)	4 (0.27)	0.08	0	n/a	3 (0.21)	0.06
Cerebrovascular	0	n/a	2 (0.14)	0.05	1 (0.07)	0.02
Heart failure	0	n/a	0	n/a	3 (0.21)	0.06
Non-heart-failure cardiovascular	4 (0.27)	0.08	2 (0.14)	0.05	4 (0.28)	0.08

Source: Table A17 above

As mentioned earlier, ascertainment of deaths in this time category was likely incomplete for all treatment groups; patients were routinely followed only to 30 days after cessation of study medication, and later reporting of death was dependent upon non-protocol-specified investigator reporting. For reported deaths in this time category, there were slightly numerically more cardiovascular deaths in the MET group than in the RSG group, with the fewest CV deaths occurring in the SU group. There were no deaths categorized as due to myocardial ischemia in the SU group, while there were 4 and 3 in the RSG and MET groups respectively. The total number of cardiovascular deaths is small, which limits conclusions. The post hoc and unblinded nature of the clinical reviewer's assessment of cause of death is also subject to bias, although every effort at objectivity was made.

For some patients who died more than 30 days after cessation of treatment, from an event that also occurred more than 30 days after cessation of treatment, the clinical reviewer could not find death narratives in the study report. On 28 Jun 07, the clinical reviewer requested that GSK identify the locations of these narratives. On 2 Jul 07, GSK responded:

"Narratives were not provided for these deaths. All of these subjects died more than 30 days after that (sic) last dose of study medication and the event which led to death also occurred more than 30 days after the last dose of study medication. Post-study follow-up for serious adverse events was up to 30 days after the last dose of study medication. The information on the deaths of these subjects was collected on a designated form in the CRF 'Form D'. This form collected the certified case of death, date of death, and whether a post-mortem was performed. Therefore, very limited information is available for these subjects."

After review of all available death narratives, the clinical reviewer did not find evidence of classification of cardiovascular deaths as deaths due to noncardiovascular causes. For each treatment group, there were no narratives for a few deaths which occurred more than 30 days after cessation of treatment and which were due to an event which occurred more than 30 days after cessation of treatment. Overall, the likelihood of significant lack of ascertainment of cardiovascular death seems low. The clinical reviewer did not find evidence of an excess occurrence of cardiovascular death or total mortality among patients treated with rosiglitazone compared to patients treated with glyburide/glibenclamide or metformin.

Cardiovascular Safety

The analyses performed by GSK to assess cardiovascular adverse events are consistent with low and similar rates across treatment groups. The clinical review of cardiovascular safety to date has concentrated both on examining reported rates of events, and on assessing for possible problems with ascertainment and/or categorization of events.

All Serious Cardiovascular Events

The following table presents all serious cardiovascular events identified by the clinical reviewer, by MedDRA System Organ Class and MedDRA preferred term. All terms from the cardiac and vascular System Organ Classes are included. For other System Organ Classes, terms which may represent cardiac or vascular disease are included. The clinical reviewer included all terms which could potentially represent cardiovascular events; some terms are not specific and may represent non-cardiovascular events.

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Cardiac disorders	**Any**	81 (5.6)	1.6	52 (3.6)	1.2	85 (5.8)	2.0	218 (5.0)	1.5
	Acute coronary syndrome	0	n/a	1 (0.1)	<0.1	3 (0.2)	0.1	4 (0.1)	<0.1
	Acute myocardial infarction	3 (0.2)	0.1	3 (0.2)	0.1	3 (0.2)	0.1	9 (0.2)	0.1
	Angina pectoris	8 (0.5)	0.2	8 (0.6)	0.2	19 (1.3)	0.4	35 (0.8)	0.2
	Angina unstable	8 (0.5)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	22 (0.5)	0.2
	Aortic valve disease	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic valve stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arrhythmia	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Arteriosclerosis coronary artery	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Atrial fibrillation	6 (0.4)	0.1	4 (0.3)	0.1	11 (0.8)	0.2	21 (0.5)	0.1
	Atrial flutter	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.1)	<0.1
	Atrial tachycardia	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Atrioventricular block complete	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bradyarrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bradycardia	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Bundle branch block left	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiac arrest	0	n/a	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.1)	<0.1
	Cardiac disorder	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cardiac failure	2 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.3)	0.1	8 (0.2)	0.1
	Cardiac failure acute	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Cardiac failure congestive	4 (0.3)	0.1	1 (0.1)	<0.1	4 (0.3)	0.1	9 (0.2)	0.1
	Cardiac tamponade	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cardiomyopathy	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Congestive cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cor pulmonale	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery disease	12 (0.8)	0.2	6 (0.4)	0.1	16 (1.1)	0.3	34 (0.8)	0.2
	Coronary artery insufficiency	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Coronary artery occlusion	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery stenosis	3 (0.2)	0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	7 (0.2)	<0.1
	Intracardiac thrombus	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Ischemic cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Left ventricular failure	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Mitral valve disease	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Myocardial infarction	20 (1.4)	0.4	8 (0.6)	0.2	15 (1.0)	0.3	43 (1.0)	0.3
	Myocardial ischemia	2 (0.1)	<0.1	4 (0.3)	0.1	2 (0.1)	<0.1	8 (0.2)	0.1
	Pericardial calcification	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Pericarditis	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Right ventricular failure	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Silent myocardial infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Sinus arrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Sinus tachycardia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Supraventricular tachycardia	1 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Tachyarrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Tachycardia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular dyskinesia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular extrasystoles	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular fibrillation	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular tachycardia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
General disorders and administration site conditions	Any (CV or non-CV)	19 (1.3)	0.4	14 (1.0)	0.3	21 (1.4)	0.4	54 (1.2)	0.4
	Chest discomfort	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Chest pain	1 (0.1)	<0.1	0	n/a	3 (0.2)	0.1	4 (0.1)	<0.1
	Edema peripheral	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Generalized edema	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Local swelling	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
Hepatobiliary disorders	Any (CV or non-CV)	11 (0.8)	0.2	7 (0.5)	0.2	8 (0.6)	0.2	26 (0.6)	0.2
	Ischemic hepatitis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Injury, poisoning and procedural complications	**Any (CV or non-CV)**	41 (2.8)	0.8	39 (2.7)	0.9	40 (2.8)	0.8	120 (2.8)	0.9
	Coronary artery restenosis	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
Nervous system disorders	**Any (CV or non-CV)**	31 (2.1)	0.6	30 (2.1)	0.7	42 (2.9)	0.9	103 (2.4)	0.7
	Carotid artery occlusion	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Carotid artery stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	6 (0.1)	<0.1
	Cerebellar infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cerebral hemorrhage	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebral infarction	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebral ischemia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cerebrovascular accident	9 (0.6)	0.2	8 (0.6)	0.2	11 (0.8)	0.2	28 (0.6)	0.2
	Hemorrhagic cerebral infarction	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Intracranial aneurysm	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Subarachnoid hemorrhage	3 (0.2)	0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Syncope	2 (0.1)	<0.1	3 (0.2)	0.1	7 (0.5)	0.1	12 (0.3)	0.1
	Syncope vasovagal	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Transient ischemic attack	3 (0.2)	0.1	3 (0.2)	0.1	5 (0.3)	0.1	11 (0.3)	0.1
Respiratory, thoracic and mediastinal disorders	**Any (CV or non-CV)**	24 (1.6)	0.5	16 (1.1)	0.4	13 (0.9)	0.3	53 (1.2)	0.4
	Acute pulmonary edema	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Brain hypoxia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Dyspnea	4 (0.3)	0.1	2 (0.1)	<0.1	0	n/a	6 (0.1)	<0.1
	Pulmonary edema	0	n/a	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.1)	<0.1
	Pulmonary embolism	2 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	4 (0.1)	<0.1
Vascular disorders	**Any**	18 (1.2)	0.4	12 (0.8)	0.3	12 (0.8)	0.2	42 (1.0)	0.3
	Aneurysm ruptured	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Angiopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic aneurysm	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Aortic dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Aortic stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Arterial occlusive disease	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Arterial stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arterial thrombosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arteriosclerosis	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Arteritis	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Circulatory collapse	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1

Table A19: Serious Cardiovascular Adverse Events by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Deep vein thrombosis	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Embolism	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Extremity necrosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Femoral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Hematoma	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Hemodynamic instability	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hemorrhage	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hypertension	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Hypertensive crisis	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Hypotension	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Intermittent claudication	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ischemic limb pain	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Labile hypertension	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Peripheral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Peripheral ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Thrombosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Varicose vein	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Vascular stenosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Venous insufficiency	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Venous thrombosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Visceral arterial ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1

Source: ADOPT study report, Table 8.2.3.1, beg pg 4011

Few individual serious cardiovascular adverse event terms occurred more frequently among RSG group patients than among comparator group patients. Out of the above 104 serious adverse cardiovascular event terms that occurred in any patient, the following 4 individual terms were recorded as SAEs for ≥1% more RSG group patients than for patients in one of the comparator groups, or had a rate/100 PY that was ≥0.1 more for the RSG group than for one of the comparator groups.

Table A20: Individual Cardiovascular SAE Terms that Were Recorded for ≥ 1% More RSG Group Patients Than for Patients in One of the Comparator Groups, or Had a Rate/100 PY that was ≥ 0.1 More for the RSG Group Than for One of the Comparator Groups

MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Angina unstable	8 (0.5)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	22 (0.5)	0.2
Coronary artery disease	12 (0.8)	0.2	6 (0.4)	0.1	16 (1.1)	0.3	34 (0.8)	0.2
Myocardial infarction	20 (1.4)	0.4	8 (0.6)	0.2	15 (1.0)	0.3	43 (1.0)	0.3
Dyspnea	4 (0.3)	0.1	1 (0.1)	<0.1)	0	n/a	6 (0.1)	<0.1

Source: Table A19 above

For the above terms, none were recorded as serious adverse cardiovascular events for ≥2% more RSG group patients than for patients in one of the comparator groups. Only myocardial infarction had a rate/100 PY that was ≥0.2 more for the RSG group than for one of the comparator groups (0.4 RSG, 0.2 SU, 0.3 MET). The single event term of myocardial infarction would not include all terms which are likely to represent a serious myocardial ischemic event; for example, terms such as acute myocardial infarction and acute coronary syndrome were also used as individual terms in Table A19 above. A more complete picture of myocardial ischemic event rates may be obtained by constructing a group of events which are likely to represent myocardial ischemia. Analyses using groupings for myocardial ischemic events and other categories of cardiovascular adverse events are discussed in later sections.

The table below includes both serious and nonserious cardiovascular events from the study. All terms from the cardiac and vascular System Organ Classes are included. For other System Organ Classes, terms which may represent cardiac or vascular disease are included. The clinical reviewer included all terms which could potentially represent cardiovascular events; some terms are not specific and may represent non-cardiovascular events.

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Cardiac disorders	**Any**	191 (13.1)	3.9	157 (10.9)	3.7	220 (15.1)	4.5	568 (13.1)	4.0
	Acute coronary syndrome	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	5 (0.1)	<0.1
	Acute myocardial infarction	3 (0.2)	0.1	3 (0.2)	0.1	3 (0.2)	0.1	9 (0.2)	0.1
	Angina pectoris	59 (4.1)	1.2	42 (2.9)	1.0	62 (4.3)	1.3	163 (3.7)	1.2
	Angina unstable	8 (0.5)	0.2	7 (0.5)	0.2	8 (0.6)	0.2	23 (0.5)	0.2
	Aortic valve disease	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (<0.1)	<0.1
	Aortic valve disease mixed	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic valve incompetence	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Aortic valve sclerosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Aortic valve stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arrhythmia	2 (0.1)	<0.1	14 (1.0)	0.3	6 (0.4)	0.1	22 (0.5)	0.2
	Arrhythmia supraventricular	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arteriosclerosis coronary artery	0	n/a	3 (0.2)	0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Atrial fibrillation	26 (1.8)	0.5	17 (1.2)	0.4	26 (1.8)	0.5	69 (1.6)	0.5
	Atrial flutter	2 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.3)	0.1	8 (0.2)	0.1
	Atrial hypertrophy	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Atrial tachycardia	1 (0.1)	<0.1	3 (0.2)	0.1	0	n/a	4 (0.1)	<0.1
	Atrial thrombosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Atrioventricular block	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Atrioventricular block complete	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Atrioventricular block first degree	12 (0.8)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	26 (0.6)	0.2

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Atrioventricular block second degree	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Bradyarrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bradycardia	7 (0.5)	0.1	5 (0.3)	0.1	6 (0.4)	0.1	18 (0.4)	0.1
	Bundle branch block	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Bundle branch block bilateral	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Bundle branch block left	2 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.3)	0.1	9 (0.2)	0.1
	Bundle branch block right	2 (0.1)	<0.1	3 (0.2)	0.1	8 (0.6)	0.2	13 (0.3)	0.1
	Cardiac aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cardiac arrest	0	n/a	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.1)	<0.1
	Cardiac disorder	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Cardiac failure	6 (0.4)	0.1	3 (0.2)	0.1	5 (0.3)	0.1	14 (0.3)	0.1
	Cardiac failure acute	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Cardiac failure congestive	8 (0.5)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	18 (0.4)	0.1
	Cardiac flutter	2 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	3 (0.1)	<0.1
	Cardiac tamponade	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cardiac valve disease	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiomegaly	6 (0.4)	0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	10 (0.2)	0.1
	Cardiomyopathy	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.3)	0.1	6 (0.1)	<0.1
	Cardiovascular deconditioning	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiovascular disorder	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	6 (0.1)	<0.1
	Congestive cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Cor pulmonale	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery disease	26 (1.8)	0.5	17 (1.2)	0.4	31 (2.1)	0.6	74 (1.7)	0.5
	Coronary artery insufficiency	0	n/a	3 (0.2)	0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Coronary artery occlusion	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Coronary artery stenosis	3 (0.2)	0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	7 (0.2)	<0.1
	Cyanosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Diastolic dysfunction	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Dilatation atrial	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Dilatation ventricular	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Extrasystoles	4 (0.3)	0.1	1 (0.1)	<0.1	3 (0.2)	0.1	8 (0.2)	0.1
	Heart valve insufficiency	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hypertensive heart disease	0	n/a	2 (0.1)	<0.1	5 (0.3)	0.1	7 (0.2)	<0.1
	Intracardiac thrombus	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Ischemic cardiomyopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Left ventricular failure	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.1)	<0.1
	Mitral valve disease	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Mitral valve incompetence	6 (0.4)	0.1	2 (0.1)	<0.1	5 (0.3)	0.1	13 (0.3)	0.1
	Mitral valve prolapse	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Myocardial infarction	22 (1.5)	0.4	11 (0.8)	0.3	18 (1.2)	0.4	51 (1.2)	0.4
	Myocardial ischemia	7 (0.5)	0.1	6 (0.4)	0.1	8 (0.6)	0.2	21 (0.5)	0.1
	Palpitations	24 (1.6)	0.5	20 (1.4)	0.5	36 (2.5)	0.7	80 (1.8)	0.6
	Pericardial calcification	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Pericardial effusion	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Pericarditis	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Postinfarction angina	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Pulmonary valve incompetence	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Right ventricular failure	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Sick sinus syndrome	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Silent myocardial infarction	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Sinus arrhythmia	0	n/a	0	n/a	3 (0.2)	0.1	3 (0.1)	<0.1
	Sinus bradycardia	6 (0.4)	0.1	2 (0.1)	<0.1	6 (0.4)	0.1	14 (0.3)	0.1
	Sinus tachycardia	2 (0.1)	<0.1	0	n/a	0	n/a	2 (<0.1)	<0.1
	Supraventricular extrasystoles	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Supraventricular tachycardia	2 (0.1)	<0.1	6 (0.4)	0.1	3 (0.2)	0.1	11 (0.3)	0.1
	Tachyarrhythmia	2 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Tachycardia	8 (0.5)	0.2	10 (0.7)	0.2	7 (0.5)	0.1	25 (0.6)	0.2
	Tachycardia paroxysmal	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Tricuspid valve incompetence	3 (0.2)	0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	6 (0.1)	<0.1
	Ventricular arrhythmia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Ventricular dysfunction	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1	5 (0.1)	<0.1
	Ventricular dyskinesia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ventricular extrasystoles	6 (0.4)	0.1	5 (0.3)	0.1	3 (0.2)	0.1	14 (0.3)	<0.1
	Ventricular fibrillation	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Ventricular hypertrophy	5 (0.3)	0.1	6 (0.4)	0.1	5 (0.3)	0.1	16 (0.4)	<0.1
	Ventricular hypokinesia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Ventricular tachycardia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Eye disorders	**Any (CV or non-CV)**	250 (17.2)	5.0	207 (14.4)	4.9	222 (15.3)	4.5	679 (15.6)	4.8
	Macular ischemia	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Ocular vascular disorder	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Optic ischemic neuropathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
General disorders and administration site conditions	**Any (CV or non-CV)**	505 (34.7)	10.2	423 (29.4)	10.0	432 (29.7)	8.8	1360 (31.3)	9.6
	Chest discomfort	7 (0.5)	0.1	4 (0.3)	0.1	5 (0.3)	0.1	16 (0.4)	0.1
	Chest pain	12 (0.8)	0.2	7 (0.5)	0.2	14 (1.0)	0.3	33 (0.8)	0.2
	Edema	21 (1.4)	0.4	9 (0.6)	0.2	10 (0.7)	0.2	40 (0.9)	0.3
	Edema face	2 (0.1)	<0.1	0	n/a	4 (0.3)	0.1	6 (0.1)	<0.1
	Edema generalized	10 (0.7)	0.2	2 (0.1)	<0.1	0	n/a	12 (0.3)	0.1
	Edema gravitational	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Edema mucosal	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Edema peripheral	189 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0	407 (9.4)	2.9
	Edema pitting	4 (0.3)	0.1	5 (0.3)	0.1	0	n/a	9 (0.2)	0.1
	Local swelling	4 (0.3)	0.1	6 (0.4)	0.1	7 (0.5)	0.1	17 (0.4)	0.1
Hepatobiliary disorders	**Any (CV or non-CV)**	36 (2.5)	0.7	33 (2.3)	0.8	42 (2.9)	0.9	111 (2.6)	0.8
	Ischemic hepatitis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
Injury, poisoning and procedural complications	**Any (CV or non-CV)**	462 (31.7)	9.3	384 (26.6)	9.0	453 (31.2)	9.2	1299 (29.9)	9.2
	Cardiac procedure complication	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Coronary artery restenosis	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Stent occlusion	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
Investigations	**Any (CV or non-CV)**	321 (22.0)	6.5	254 (17.6)	6.0	267 (18.4)	5.4	842 (19.4)	6.0
	Abdominal bruit	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Blood pressure decreased	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Blood pressure diastolic decreased	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Blood pressure increased	12 (0.8)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	22 (0.5)	0.2
	Blood pressure systolic increased	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Cardiac murmur	15 (1.0)	0.3	9 (0.6)	0.2	14 (1.0)	0.3	38 (0.9)	0.3
	Cardiac murmur functional	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Carotid bruit	5 (0.3)	0.1	3 (0.2)	0.1	6 (0.4)	0.1	14 (0.3)	0.1
	Catheterization cardiac abnormal	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	ECG signs of myocardial ischemia	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	ECG signs of ventricular hypertrophy	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Ejection fraction abnormal	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Ejection fraction decreased	1 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Electrocardiogram PQ interval prolonged	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram PR shortened	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram Q wave abnormal	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram Q waves	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram QRS complex abnormal	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram QT prolonged	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram ST segment abnormal	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Electrocardiogram ST segment depression	0	n/a	1 (0.1)	<0.1	3 (0.2)	0.1	4 (0.1)	<0.1
	Electrocardiogram ST-T change	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram ST-T abnormal	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Electrocardiogram T wave abnormal	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Electrocardiogram T wave amplitude decreased	2 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Electrocardiogram T wave inversion	0	n/a	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.1)	<0.1
	Electrocardiogram abnormal	1 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.2)	0.1	6 (0.1)	<0.1
	Electrocardiogram change	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Electrocardiogram repolarization abnormality	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Femoral bruit	0	n/a	2 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Gallop rhythm present	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Heart rate decreased	2 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	3 (0.1)	<0.1
	Heart rate increased	7 (0.5)	0.1	3 (0.2)	0.1	4 (0.3)	0.1	14 (0.3)	0.1
	Heart rate irregular	3 (0.2)	0.1	9 (0.6)	0.2	5 (0.3)	0.1	17 (0.4)	0.1
	Pulse absent	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Pulse pressure decreased	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
Nervous system disorders	**Any (CV or non-CV)**	548 (37.6)	11.1	513 (35.6)	12.1	554 (38.1)	11.3	1615 (37.1)	11.5
	Aphasia	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1

Table A21: Cardiovascular Adverse Events (Serious or Nonserious) by MedDRA System Organ Class and MedDRA Preferred Term, Population of All Randomized Patients

MedDRA System Organ Class	MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Carotid artery atheroma	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Carotid artery disease	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Carotid artery occlusion	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Carotid artery stenosis	3 (0.2)	0.1	7 (0.5)	0.2	6 (0.4)	0.1	16 (0.4)	0.1
	Cerebellar infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cerebral arteriosclerosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Cerebral hemorrhage	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebral infarction	0	n/a	0	n/a	3 (0.2)	0.1	3 (0.1)	<0.1
	Cerebral ischemia	0	n/a	4 (0.3)	0.1	2 (0.1)	<0.1	6 (0.1)	<0.1
	Cerebrovascular accident	12 (0.8)	0.2	9 (0.6)	0.2	12 (0.8)	0.2	33 (0.8)	0.2
	Cerebrovascular disorder	0	n/a	0	n/a	2 (0.1)	<0.1	2 (<0.1)	<0.1
	Cerebrovascular insufficiency	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Hemorrhagic cerebral infarction	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Intracranial aneurysm	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Lacunar infarction	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Subarachnoid hemorrhage	3 (0.2)	0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Syncope	18 (1.2)	0.4	9 (0.6)	0.2	13 (0.9)	0.3	40 (0.9)	0.3
	Syncope vasovagal	6 (0.4)	0.1	4 (0.3)	0.1	6 (0.4)	0.1	16 (0.4)	0.1
	Transient ischemic attack	7 (0.5)	0.1	6 (0.4)	0.1	11 (0.8)	0.2	24 (0.6)	0.2
Respiratory, thoracic and mediastinal disorders	**Any (CV or non-CV)**	421 (28.9)	8.5	368 (25.5)	8.7	310 (21.3)	6.3	910 (20.9)	6.5
	Acute pulmonary edema	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Brain hypoxia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Dyspnea	72 (4.9)	1.5	45 (3.1)	1.1	42 (2.9)	0.9	159 (3.7)	1.1
	Dyspnea at rest	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Dyspnea exacerbated	4 (0.3)	0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	7 (0.2)	<0.1
	Dyspnea exertional	27 (1.9)	0.5	19 (1.3)	0.4	16 (1.1)	0.3	62 (1.4)	0.4
	Nocturnal dyspnea	0	n/a	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Pulmonary edema	3 (0.2)	0.1	3 (0.2)	0.1	2 (0.1)	<0.1	8 (0.2)	0.1
	Pulmonary embolism	3 (0.2)	0.1	3 (0.2)	0.1	0	n/a	6 (0.1)	<0.1
	Pulmonary hypertension	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
Vascular disorders	**Any**	328 (22.5)	6.6	327 (22.7)	7.7	391 (26.9)	8.0	1046 (24.0)	7.4
	Aneurysm ruptured	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Angiodysplasia	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Angiopathy	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1

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		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Aortic aneurysm	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.4)	0.1	9 (0.2)	0.1
	Aortic arteriosclerosis	1 (0.1)	<0.1	0	n/a	2 (0.1)	<0.1	3 (0.1)	<0.1
	Aortic dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Aortic stenosis	6 (0.4)	0.1	2 (0.1)	<0.1	3 (0.2)	0.1	11 (0.3)	0.1
	Arterial occlusive disease	2 (0.1)	<0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	5 (0.1)	<0.1
	Arterial rupture	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Arterial stenosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arterial thrombosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Arteriosclerosis	2 (0.1)	<0.1	2 (0.1)	<0.1	3 (0.2)	0.1	7 (0.2)	<0.1
	Arteritis	3 (0.2)	0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Artery dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Blood pressure fluctuation	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Circulatory collapse	1 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Deep vein thrombosis	3 (0.2)	0.1	2 (0.1)	<0.1	0	n/a	5 (0.1)	<0.1
	Diabetic microangiopathy	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Embolism	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Essential hypertension	1 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	4 (0.1)	<0.1
	Extremity necrosis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Femoral arterial stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Femoral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Flushing	4 (0.3)	0.1	8 (0.6)	0.2	2 (0.1)	<0.1	14 (0.3)	0.1
	Hematoma	11 (0.8)	0.2	2 (0.1)	<0.1	14 (1.0)	0.3	27 (0.6)	0.2
	Hemodynamic instability	1 (0.1)	<0.1	0	n/a	0	n/a	1 (0.1)	<0.1
	Hemorrhage	3 (0.2)	0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	5 (0.1)	<0.1
	Hot flush	19 (1.3)	0.4	13 (0.9)	0.3	28 (1.9)	0.6	60 (1.4)	0.4
	Hypertension	216 (14.8)	4.4	253 (17.6)	6.0	297 (20.4)	6.1	766 (17.6)	5.4
	Hypertensive crisis	3 (0.2)	0.1	2 (0.1)	<0.1	4 (0.3)	0.1	9 (0.2)	0.1
	Hypotension	13 (0.9)	0.3	12 (0.2)	0.3	12 (0.8)	0.2	28 (0.6)	0.2
	Iliac artery stenosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Intermittent claudication	6 (0.4)	0.1	6 (0.4)	0.1	4 (0.3)	0.1	16 (0.4)	0.1
	Ischemic limb pain	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Labile blood pressure	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Labile hypertension	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.4)	0.1	9 (0.2)	0.1
	Lymphedema	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Orthostatic hypertension	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Orthostatic hypotension	2 (0.1)	<0.1	5 (0.3)	0.1	5 (0.3)	0.1	12 (0.3)	0.1
	Pallor	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Peripheral arterial occlusive disease	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1

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		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
	Peripheral artery aneurysm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Peripheral artery dissection	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Peripheral ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Peripheral vascular disorder	2 (0.1)	<0.1	5 (0.3)	0.1	3 (0.2)	0.1	10 (0.2)	0.1
	Periphlebitis	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Phlebitis	9 (0.6)	0.2	7 (0.5)	0.2	6 (0.4)	0.1	22 (0.5)	0.2
	Phlebitis superficial	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Phlebolith	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Poor peripheral circulation	3 (0.2)	<0.1	2 (0.1)	<0.1	1 (0.1)	<0.1	6 (0.1)	<0.1
	Raynaud's phenomenon	2 (0.1)	<0.1	1 (0.1)	<0.1	5 (0.3)	0.1	8 (0.2)	0.1
	Systolic hypertension	1 (0.1)	<0.1	1 (0.1)	<0.1	0	n/a	2 (<0.1)	<0.1
	Temporal arteritis	1 (0.1)	<0.1	0	n/a	1 (0.1)	<0.1	2 (<0.1)	<0.1
	Thrombophlebitis	3 (0.2)	0.1	1 (0.1)	<0.1	2 (0.1)	<0.1	6 (0.1)	<0.1
	Thrombophlebitis superficial	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1
	Thrombosis	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Varicose ulceration	0	n/a	3 (0.2)	0.1	2 (0.1)	<0.1	5 (0.1)	<0.1
	Varicose vein	15 (1.0)	0.3	8 (0.6)	0.2	13 (0.9)	0.3	36 (0.8)	0.3
	Vascular calcification	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Vascular rupture	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Vascular shunt	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vascular stenosis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vasculitis	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vasodilation	1 (0.1)	<0.1	0	n/a	0	n/a	1 (<0.1)	<0.1
	Vasospasm	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Vein disorder	0	n/a	0	n/a	1 (0.1)	<0.1	1 (<0.1)	<0.1
	Venous insufficiency	15 (1.0)	0.3	12 (0.8)	0.3	12 (0.8)	0.2	39 (0.9)	0.3
	Venous occlusion	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1
	Venous stasis	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1	4 (0.1)	<0.1
	Venous thrombosis	1 (0.1)	<0.1	2 (0.1)	<0.1	0	n/a	3 (0.1)	<0.1
	Visceral arterial ischemia	0	n/a	1 (0.1)	<0.1	0	n/a	1 (<0.1)	<0.1

Source: ADOPT study report, Table 8.2.1, beg pg 3564

Out of some 240 cardiovascular adverse event Preferred Terms in the above table, few occurred with greater frequency among RSG group patients than among patients in the comparator groups. The following terms were recorded as adverse cardiovascular events for ≥1% more RSG group patients than for patients in one of the comparator groups, or had a rate/100 PY that was ≥0.1 more for the RSG group than for one of the comparator groups.

Table A22: Individual Cardiovascular AE Terms (Combined Serious and Nonserious) that Were Recorded for ≥ 1% More RSG Group Patients Than for Patients in One of the Comparator Groups, or Had a Rate/100 PY that was ≥ 0.1 More for the RSG Group Than for One of the Comparator Groups

MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Angina pectoris	59 (4.1)	1.2	42 (2.9)	1.0	62 (4.3)	1.3	163 (3.7)	1.2
Atrial fibrillation	26 (1.8)	0.5	17 (1.2)	0.4	26 (1.8)	0.5	69 (1.6)	0.5
Atrioventricular block first degree	12 (0.8)	0.2	7 (0.5)	0.2	7 (0.5)	0.1	26 (0.6)	0.2
Cardiac failure congestive	8 (0.5)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	18 (0.4)	0.1
Coronary artery disease	26 (1.8)	0.5	17 (1.2)	0.4	31 (2.1)	0.6	74 (1.7)	0.5
Myocardial infarction	22 (1.5)	0.4	11 (0.8)	0.3	18 (1.2)	0.4	51 (1.2)	0.4
Tachycardia	8 (0.5)	0.2	10 (0.7)	0.2	7 (0.5)	0.1	25 (0.6)	0.2
Edema	21 (1.4)	0.4	9 (0.6)	0.2	10 (0.7)	0.2	40 (0.9)	0.3
Edema generalized	10 (0.7)	0.2	2 (0.1)	<0.1	0	n/a	12 (0.3)	0.1
Edema peripheral	189 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0	407 (9.4)	2.9
Edema pitting	4 (0.3)	0.1	5 (0.3)	0.1	0	n/a	9 (0.2)	0.1
Blood pressure increased	12 (0.8)	0.2	3 (0.2)	0.1	7 (0.5)	0.1	22 (0.5)	0.2
Cardiac murmur	15 (1.0)	0.3	9 (0.6)	0.2	14 (1.0)	0.3	38 (0.9)	0.3
Syncope	18 (1.2)	0.4	9 (0.6)	0.2	13 (0.9)	0.3	40 (0.9)	0.3
Dyspnea	72 (4.9)	1.5	45 (3.1)	1.1	42 (2.9)	0.9	159 (3.7)	1.1
Dyspnea exertional	27 (1.9)	0.5	19 (1.3)	0.4	16 (1.1)	0.3	62 (1.4)	0.4
Angiopathy	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1
Deep vein thrombosis	3 (0.2)	0.1	2 (0.1)	<0.1	0	n/a	5 (0.1)	<0.1
Hematoma	11 (0.8)	0.2	2 (0.1)	<0.1	14 (1.0)	0.3	27 (0.6)	0.2
Hypotension	13 (0.9)	0.3	12 (0.2)	0.3	12 (0.8)	0.2	28 (0.6)	0.2
Phlebitis	9 (0.6)	0.2	7 (0.5)	0.2	6 (0.4)	0.1	22 (0.5)	0.2
Thrombophlebitis superficial	3 (0.2)	0.1	0	n/a	0	n/a	3 (0.1)	<0.1
Varicose vein	15 (1.0)	0.3	8 (0.6)	0.2	13 (0.9)	0.3	36 (0.8)	0.3
Venous insufficiency	15 (1.0)	0.3	12 (0.8)	0.3	12 (0.8)	0.2	39 (0.9)	0.3

Source: Table A21 above

The following terms were recorded as adverse cardiovascular events for ≥2% more RSG group patients than for patients in one of the comparator groups, or had a rate/100 PY that was ≥0.2 more for the RSG group than for one of the comparator groups.

Table A23: Individual Cardiovascular AE Terms (Combined Serious and Nonserious) that Were Recorded for ≥ 2% More RSG Group Patients Than for Patients in One of the Comparator Groups, or Had a Rate/100 PY that was ≥ 0.2 More for the RSG Group Than for One of the Comparator Groups

MedDRA Preferred Term	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Angina pectoris	59 (4.1)	1.2	42 (2.9)	1.0	62 (4.3)	1.3	163 (3.7)	1.2
Edema	21 (1.4)	0.4	9 (0.6)	0.2	10 (0.7)	0.2	40 (0.9)	0.3
Edema generalized	10 (0.7)	0.2	2 (0.1)	<0.1	0	n/a	12 (0.3)	0.1
Edema peripheral	189 (13.0)	3.8	118 (8.2)	2.8	100 (6.9)	2.0	407 (9.4)	2.9
Syncope	18 (1.2)	0.4	9 (0.6)	0.2	13 (0.9)	0.3	40 (0.9)	0.3
Dyspnea	72 (4.9)	1.5	45 (3.1)	1.1	42 (2.9)	0.9	159 (3.7)	1.1
Dyspnea exertional	27 (1.9)	0.5	19 (1.3)	0.4	16 (1.1)	0.3	62 (1.4)	0.4
Source: Table A22 above								

Angina pectoris occurred numerically somewhat more frequently among RSG-treated patients than among SU-treated patients. Edema-related events occurred more frequently among RSG-treated patients than among patients in either of the other treatment groups.

At the time this briefing document is being prepared, the clinical reviewer is examining all narratives of adverse events that were included in the ADOPT study report; these narratives cover some 1700 pages. This review is intended to confirm appropriate assignment of event terms, appropriate characterization of adverse event outcomes, and inclusion of secondary but also serious adverse events which may have occurred in a given patient. To date, no misclassification or omissions have been identified.

Cardiovascular Event Grouping Analyses by GSK

The applicant designated groupings of cardiovascular adverse events of special interest. These four groupings include myocardial ischemia; arrhythmia and conduction disorders; HF and pulmonary edema; and "other". The MedDRA lower level terms which were included in each of these groupings, and which had at least one patient reporting an event, are included in Appendix 12. Lower level MedDRA terms that GSK selected for the AEs of special interest that were not experienced by at least one patient were not included in the ADOPT study report. The clinical reviewer examined (blinded to treatment assignment) all terms which were assigned to each of the CV event groupings, to assess for appropriateness of categorization and ascertainment. In general, assignment of terms to each group appeared appropriate. However, there were some terms which were included in the "other CV events" category which could reasonably have been assigned to one of the other categories. Most terms in the "other CV events" category were related to valvular disease, pericardial disease and nonspecific ECG findings. The following table lists the terms from the "other CV events" category which the clinical reviewer identified as terms which could reasonably have been assigned to one of the other CV event groupings.

Table A24: MedDRA Lower Level Terms Which Were Assigned to Applicant's Grouping of "Other Cardiovascular Events" Which Might Reasonably Have Been Assigned to Another CV Event Grouping

Lower Level Term Assigned to "Other CV Events" Grouping	CV Event Grouping to Which Term Might Reasonably Have Been Assigned	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		TOTAL N=4351 PY=14103.1	
		n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Cardiomegaly	HF/ pulm edema	4 (0.28)	0.08	1 (0.07)	0.02	1 (0.07)	0.02	6 (0.14)	0.04
Cardiomyopathy	HF/ pulm edema	1 (0.07)	0.02	1 (0.07)	0.02	4 (0.28)	0.08	6 (0.14)	0.04
Dilatation ventricular	HF/ pulm edema	1 (0.07)	0.02	0	n/a	0	n/a	1 (0.02)	0.01
Dilated cardiomyopathy	HF/ pulm edema	1 (0.07)	0.02	0	n/a	0	n/a	1 (0.02)	0.01
Electrocardiogram Q wave abnormal	Myocardial ischemia	0	n/a	0	n/a	1 (0.07)	0.02	1 (0.02)	0.01
Heart enlarged	HF/ pulm edema	2 (0.14)	0.04	1 (0.07)	0.02)	1 (0.07)	0.02	4 (0.09)	0.03
Left ventricular dilatation	HF/ pulm edema	1 (0.07)	0.02	0	n/a	0	n/a	1 (0.02)	0.01

Source: ADOPT study report Table 8.2.4.3, beg pg 4177

Some of the above terms are somewhat nonspecific, which may account for their assignment to the "other" category. These terms were discussed with Dr. Ellis Unger, FDA cardiologist and Acting Deputy Director of the Office of Surveillance and Epidemiology; he stated that he would not have assigned these terms to the heart failure or myocardial ischemia groupings of CV AEs due to the nonspecificity of the terms. Most of the terms in question are potentially related to heart failure. Even if the HF terms were added to the HF group, their proportions are such that they would not change the overall conclusion regarding relative risk of heart failure (see Table A29 and Figures A12-13 below).

The clinical reviewer is also examining all MedDRA Lower Level Terms which were actually used for events that occurred in ADOPT, to verify that the sets of terms identified by GSK for inclusion in event groupings were fully inclusive. This process is complicated by the fact that Lower Level Terms were included in the groupings, while MedDRA Preferred Terms were used for summary reporting. Cross-checking of thousands of text terms using datasets, and the MedDRA terms dictionary, is required. To date, very few terms have been noted which might reasonably have been added, but a complete cross-check is needed to fully evaluate for ascertainment issues related to selection of terms for CV event groupings.

The following table by GSK summarizes the numbers of events which occurred in each of their specified cardiovascular event groupings.

Table A25: Summary of Numbers of Events Within GSK's Groupings of Cardiovascular Adverse Events: All On-Therapy CV AEs, All On-Therapy CV SAEs, and All CV AEs that Led to Withdrawal (Population of All Patients who Received at Least One Dose of Study Medication)

Preferred Term / Sub-categories	Number of Subjects, n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with On-Therapy AEs	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 (4.7)	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 (5.8)	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 On-therapy SAEs	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
Subjects with On-therapy AEs leading to Withdrawal	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	-

a. Note: Sorted by frequency of adverse events in RSG group.
Data Source: Table 8.2.4.3, Table 8.2.3.3, Table 8.5.1, and *Ad hoc* Table 1707

Source: ADOPT study report, Table 63, pg 174

The percentage of patients with any on-therapy CV event within one of GSK's groupings was numerically highest for the metformin group, followed by the rosiglitazone group and then the sulfonylurea group. Because of lower exposure for sulfonylurea patients, consideration of duration of exposure and therefore the rate of events (e.g. per hundred patient-years) is important. When this is considered, the rate for metformin group patients is numerically somewhat higher than the rate for the other comparators, with an approximately equal rate for the rosiglitazone and sulfonylurea groups. For myocardial ischemia events, the percentage of patients who experienced an event was approximately equal for the rosiglitazone and metformin groups, and somewhat numerically lower for the sulfonylurea group; however, rates/PY were similar for the three groups. Angina events appear to have contributed to the numerical difference in the percentage of patients experiencing a myocardial ischemic event. The percentages of patients with a reported myocardial infarction were 1.9, 1.6 and 1.3% for the rosiglitazone, metformin and sulfonylurea groups, respectively. The myocardial infarction rates/100 PY for these groups were similar at 0.6, 0.5 and 0.4, respectively. For arrhythmia and conduction system events, rates/100 PY were similar for each of the treatment groups. Heart failure and pulmonary edema events occurred at similar rates among

rosiglitazone and metformin group patients, with a slightly numerically lower rate among SU group patients.

For serious on-therapy CV events, the percentage of patients who experienced an event was similar for the rosiglitazone and metformin groups, and slightly numerically lower for the sulfonylurea group. As with overall CV AEs, the percentage of patients for whom a myocardial ischemic event was reported was numerically slightly lower for SU group patients than for RSG or MET group patients, but rates/ 100 PY were similar. The percentages of patients who had a reported SAE of MI were 1.6, 1.4 and 1.0 for the rosiglitazone, metformin and sulfonylurea groups, respectively; rates/ 100 PY for these groups were 0.5, 0.4 and 0.3 respectively. Rates/ 100 PY of serious arrhythmia or conduction system events were similar among treatment groups. The number of reported events of serious heart failure or pulmonary edema was low; a numerically smaller percentage of patients in the SU group had a reported event than did patients in the RSG or MET groups. Rates/ 100 PY of serious heart failure or pulmonary edema were similar among treatment groups.

A slightly higher percentage of patients in the RSG group withdrew from study due to an on-therapy CV AE than did patients in the MET or SU groups. Withdrawal due to heart failure or pulmonary edema contributed to this difference, with 0.7% of RSG group patients withdrawing compared to 0.3% of patients in each of the other groups. A total of 0.5% of RSG group patients withdrew due to MI, while 0.4% of patients in each of the other groups did so.

The effect of the study withdrawal rate on interpretation of adverse event data presents a challenge. Time-to-event analyses take into account censoring of data by subject withdrawal over time. The following tables and Kaplan-Meier curves present time-to-event data for overall CV events and for the CV event groupings.

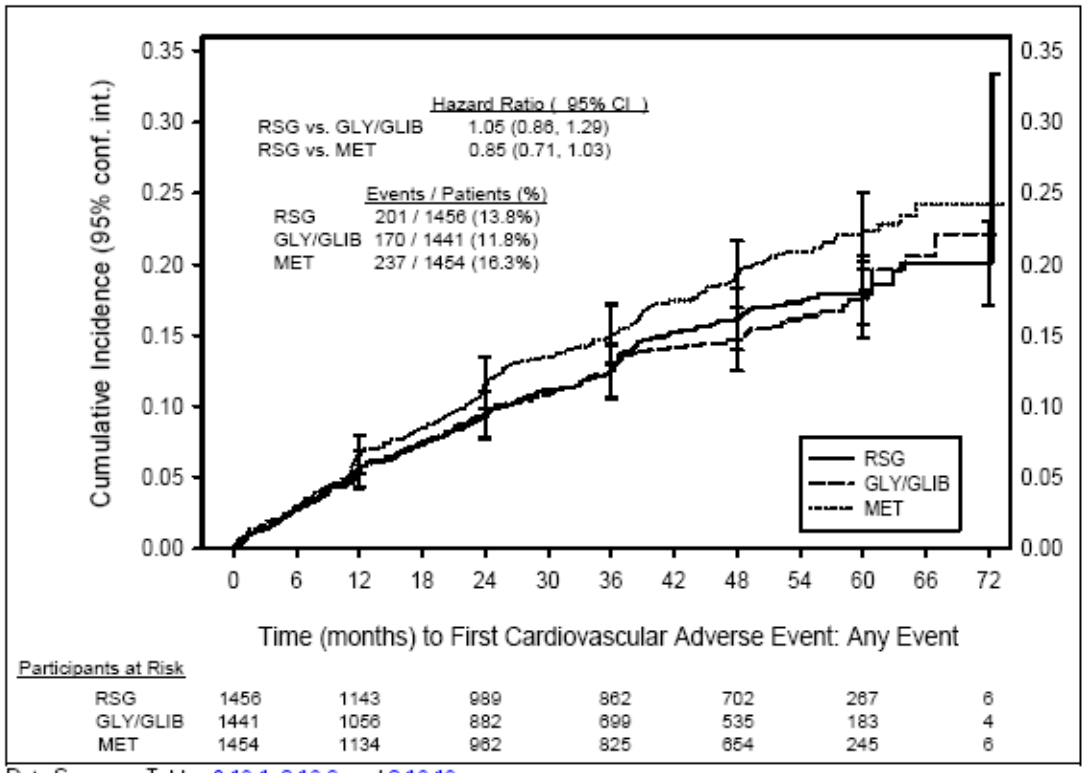
Table A26: Analyses by GSK of Time-to-First Cardiovascular AE and Time-to-First Cardiovascular SAE, Population of All Patients who Received at Least One Dose of Study Medication

All cardiovascular AEs	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Total subjects with events during study, n	201	170	237
60-month Cumulative Incidence (95% CI)	0.18 (0.16, 0.21)	0.18 (0.15, 0.20)	0.22 (0.20, 0.25)
RSG vs. Control			
Hazard ratio (95% CI)		1.051 (0.857, 1.289)	0.851 (0.705, 1.028)
p-value		0.6338	0.0935
Serious Adverse Events			
Total subjects with events during study, n	82	54	86
60-month Cumulative Incidence (95% CI)	0.08 (0.06, 0.10)	0.06 (0.04, 0.07)	0.08 (0.06, 0.10)
RSG vs. Control			
Hazard ratio (95% CI)		1.378 (0.977, 1.944)	0.990 (0.731, 1.340)
p-value		0.0679	0.9485

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 65, pg 175

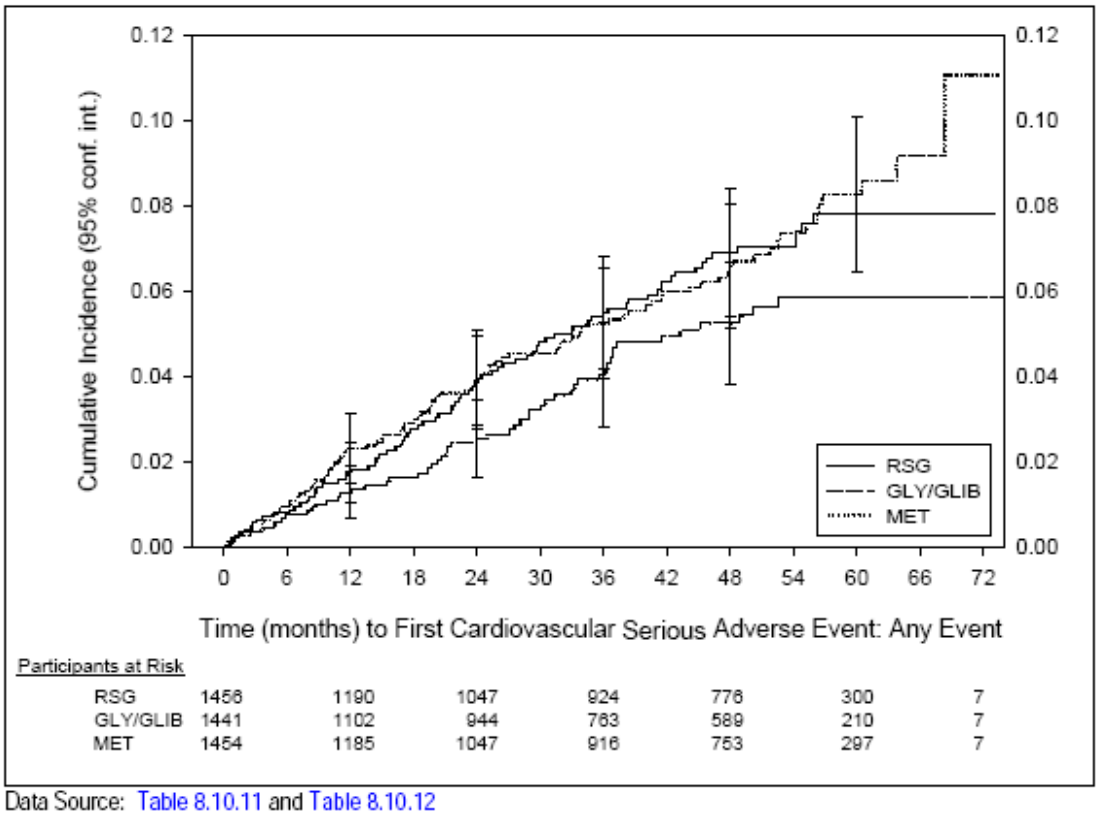
Figure A6: Cumulative Incidence of First Cardiovascular AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Sources: Tables 8.10.1, 8.10.9, and 8.10.10.

Source: ADOPT study report, Figure 44, pg 176

Figure A7: Cumulative Incidence of First Cardiovascular Serious AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 45, pg 177

When considering time-to-event analyses for all CV AEs, or all CV SAEs, 95% confidence intervals for the hazard ratios include 1, and p-values exceed 0.05, for all comparisons of RSG to SU or to MET. If one uses a threshold of a p-value of 0.1, CV events of any severity occurred somewhat less frequently with RSG than with MET, and serious CV SAEs occurred somewhat more frequently with RSG than with SU.

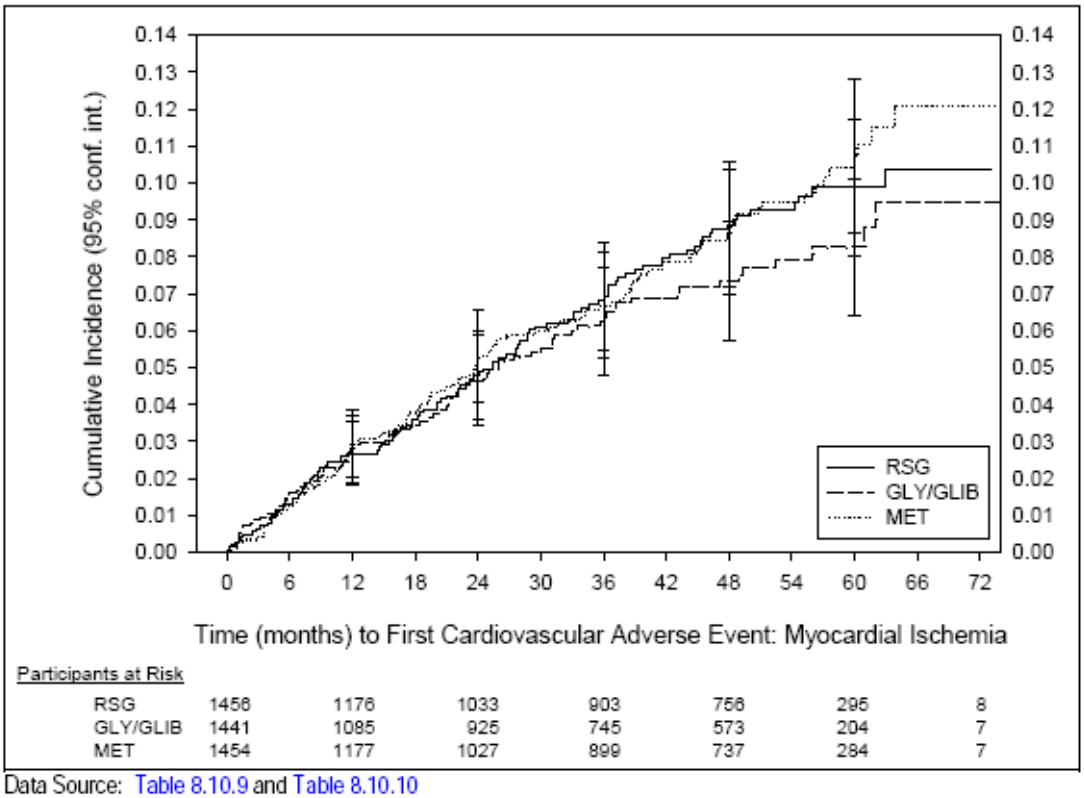
Table A27: Analyses by GSK of Time-to-First Myocardial Ischemia AE and Time-to-First Myocardial Ischemia SAE, Population of All Patients who Received at Least One Dose of Study Medication

Myocardial Ischemia	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Total subjects with event during study, n	106	82	111
60-month Cumulative Incidence (95% CI)	0.10 (0.08, 0.12)	0.08 (0.06, 0.10)	0.11 (0.09, 0.13)
RSG vs. Control			
Hazard ratio (95% CI)		1.178 (0.882, 1.572)	0.993 (0.760, 1.296)
p-value		0.2667	0.9559
Serious Adverse Events			
Total subjects with event during study, n	55	43	60
60-month Cumulative Incidence (95% CI)	0.05 (0.04, 0.07)	0.05 (0.03, 0.06)	0.06 (0.04, 0.07)
RSG vs. Control			
Hazard ratio (95% CI)		1.161 (0.778, 1.731)	0.955 (0.662, 1.377)
p-value		0.4646	0.8042

Data Sources: Table 8.10.1, Table 8.10.9 ,Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 67, pg 178

Figure A8: Cumulative Incidence of First Myocardial Ischemia AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



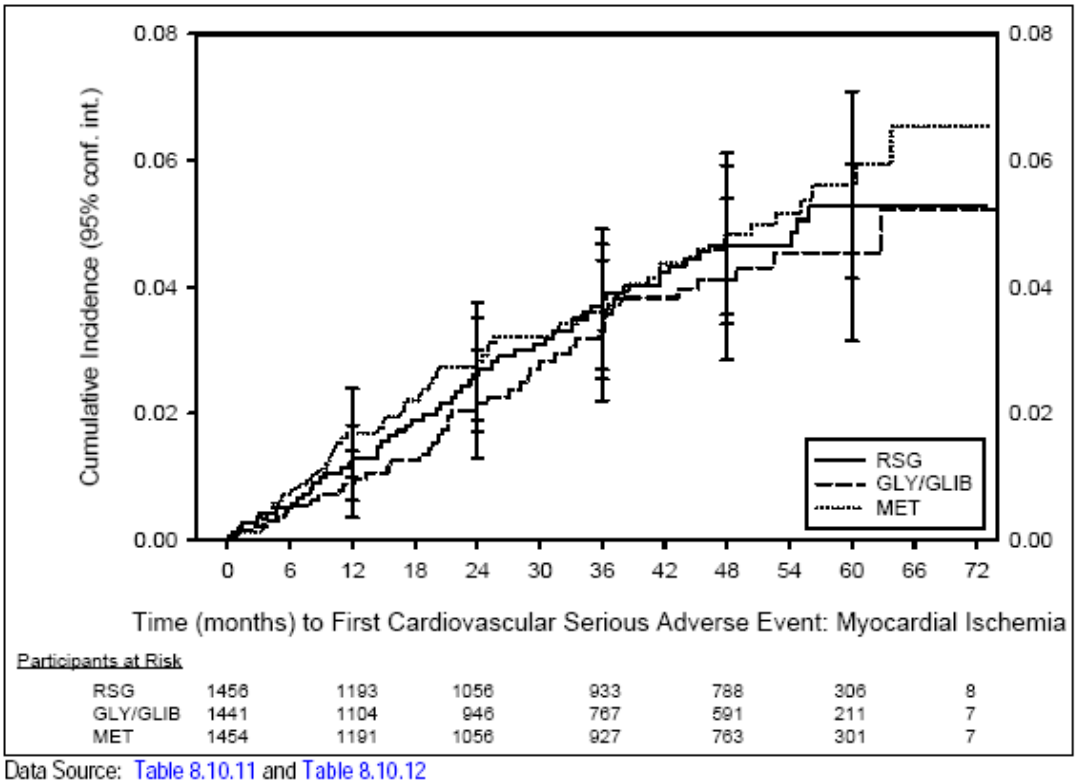
Participants at Risk

RSG	1456	1176	1033	903	756	295	8
GLY/GLIB	1441	1085	925	745	573	204	7
MET	1454	1177	1027	899	737	284	7

Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 46, pg 179

Figure A9: Cumulative Incidence of First Myocardial Ischemia Serious AE, Population of All Patients who Received at Least One Dose of Study Medication



Participants at Risk

RSG	1456	1193	1056	933	788	306	8
GLY/GLIB	1441	1104	946	767	591	211	7
MET	1454	1191	1056	927	763	301	7

Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 47, pg 180

When considering time-to-event analyses for myocardial ischemia AEs, or myocardial ischemia SAEs, 95% confidence intervals for the hazard ratios include 1, and all p-values exceed 0.2, for all comparisons of RSG to SU or to MET.

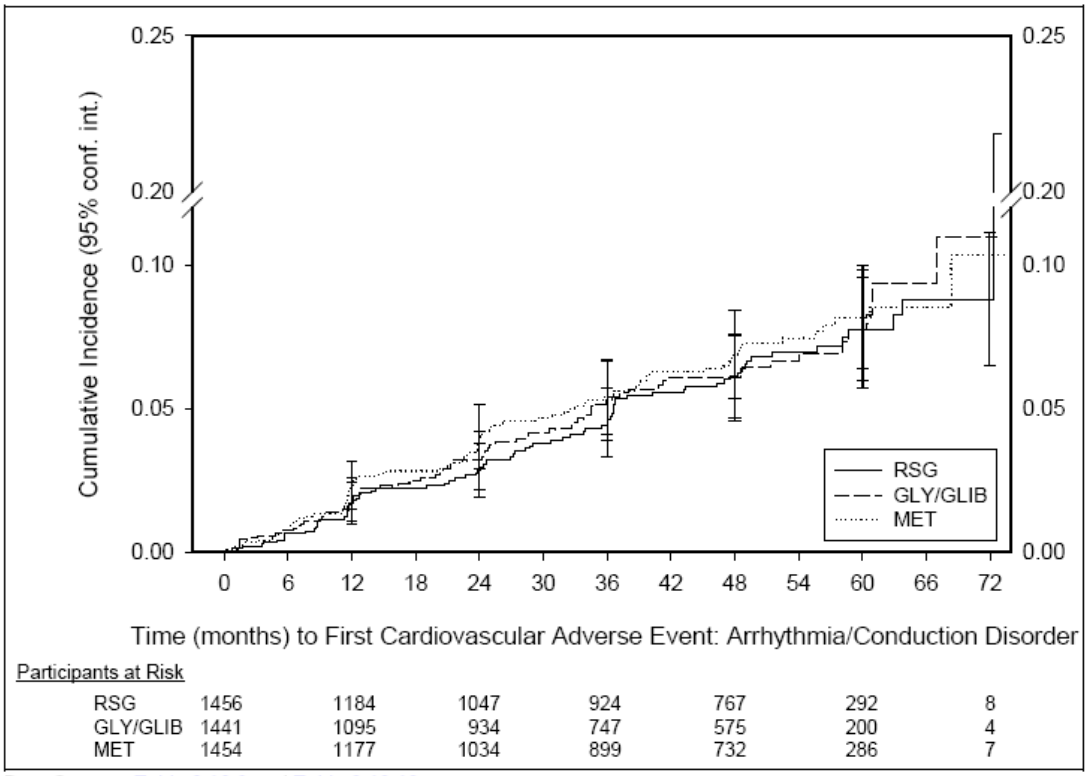
Table A28 Analyses by GSK of Time-to-First Arrhythmia or Conduction Disorder AE and Time-to-First Arrhythmia or Conduction Disorder SAE, Population of All Patients who Received at Least One Dose of Study Medication

Arrhythmia and Conduction Disorders	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Total subjects with event during study, n	79	71	85
60-month Cumulative Incidence (95% CI)	0.08 (0.06, 0.10)	0.08 (0.06, 0.10)	0.08 (0.06, 0.10)
RSG vs. Control			
Hazard ratio (95% CI)		0.963 (0.699, 1.328)	0.928 (0.683, 1.260)
p-value		0.8204	0.6306
Serious Adverse Events			
Total subjects with event during study, n	14	9	19
60-month Cumulative Incidence (95% CI)	0.01 (0.01, 0.02)	0.01 (0.00, 0.02)	0.02 (0.01, 0.03)
RSG vs. Control			
Hazard ratio (95% CI)		1.381 (0.597, 3.195)	0.740 (0.371, 1.477)
p-value		0.4510	0.3932

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report Table 69, pg 181

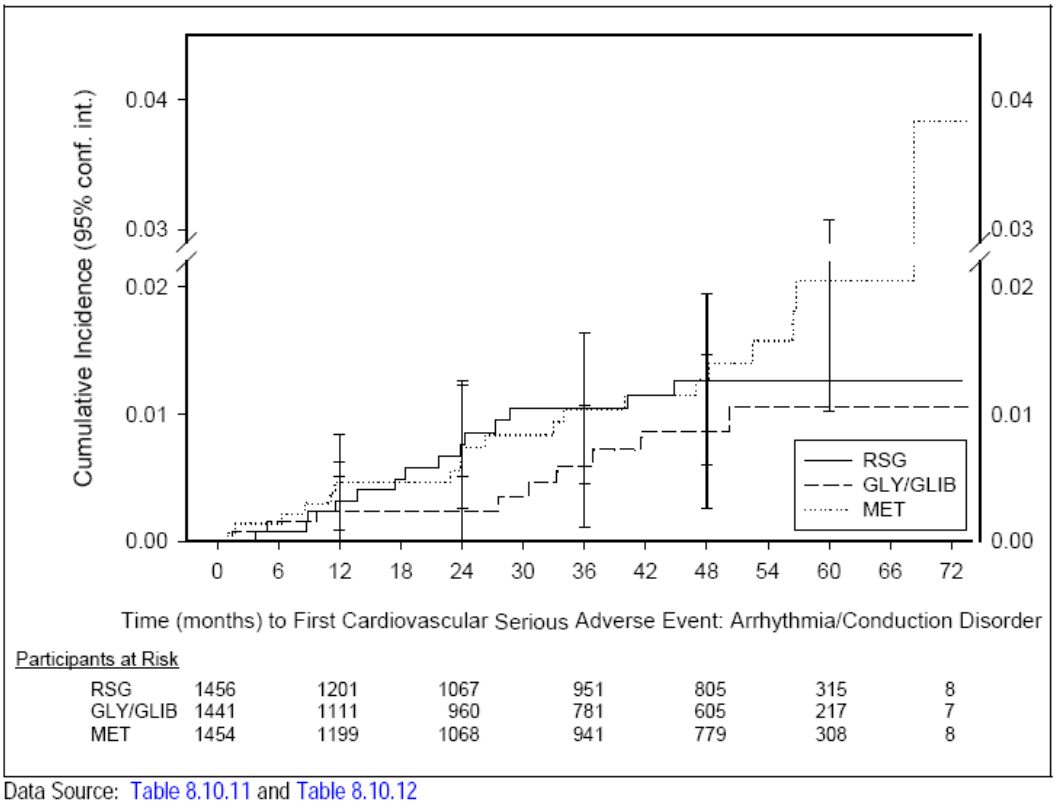
Figure A10: Cumulative Incidence of First Arrhythmia or Conduction Disorder AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 48, pg 182

Figure A11: Cumulative Incidence of First Serious Arrhythmia or Conduction Disorder Serious AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 49, pg 183

When considering time-to-event analyses for arrhythmia or conduction disorder AEs, or arrhythmia or conduction disorder SAEs, 95% confidence intervals for the hazard ratios include 1, and all p-values exceed 0.3, for all comparisons of RSG to SU or to MET.

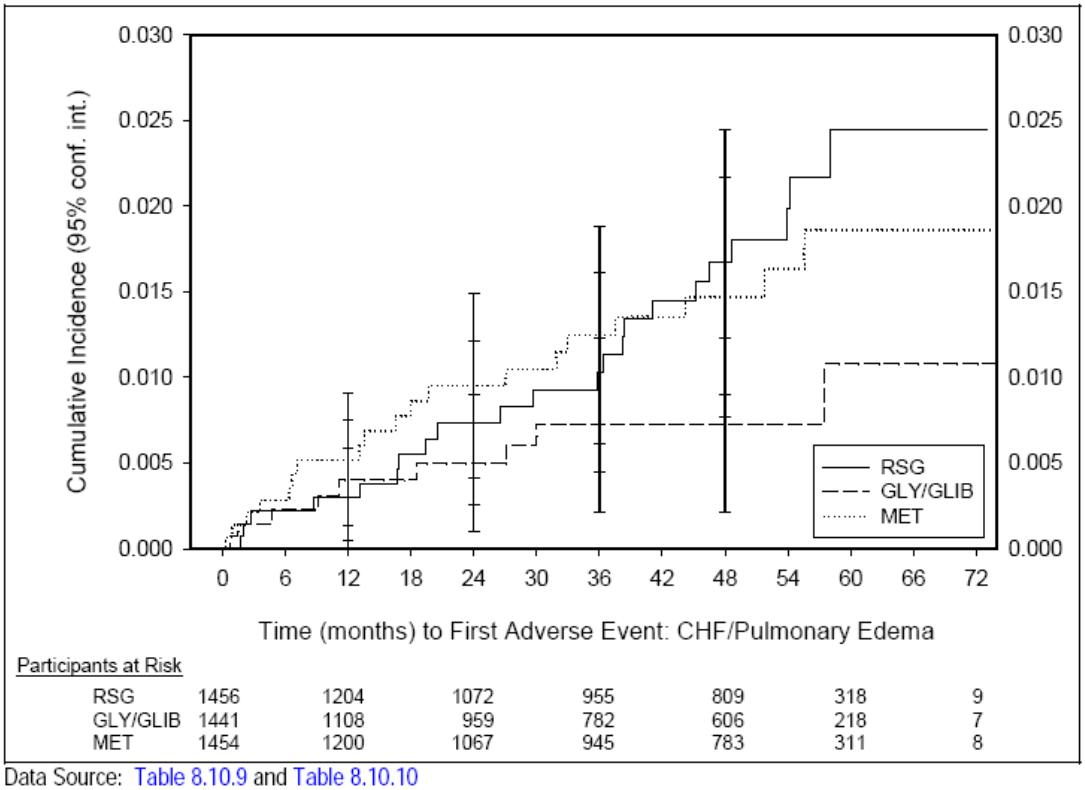
Table A29: Analyses by GSK of Time-to-First Heart Failure or Pulmonary Edema AE and Time-to-First Heart Failure or Pulmonary Edema SAE, Population of All Patients who Received at Least One Dose of Study Medication

CHF/Pulmonary Edema Events	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Number of subjects with events	22	9	19
60-month Cumulative Incidence (95% CI)	0.02 (0.01, 0.04)	0.01 (0.00, 0.02)	0.02 (0.01, 0.03)
RSG vs. Control			
Hazard ratio (95% CI)		2.202 (1.012, 4.789)	1.222 (0.661, 2.259)
p-value		0.0465	0.5231
Serious Adverse Events			
Number of subjects with events, n	12	3	12
60-month Cumulative Incidence (95% CI)	0.01 (0.01, 0.02)	0.00 (0.00, 0.01)	0.01 (0.01, 0.02)
RSG vs. Control			
Hazard ratio (95% CI)		3.618 (1.019, 12.840)	1.068 (0.479, 2.379)
p-value		0.0466	0.8727

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 71, pg 184

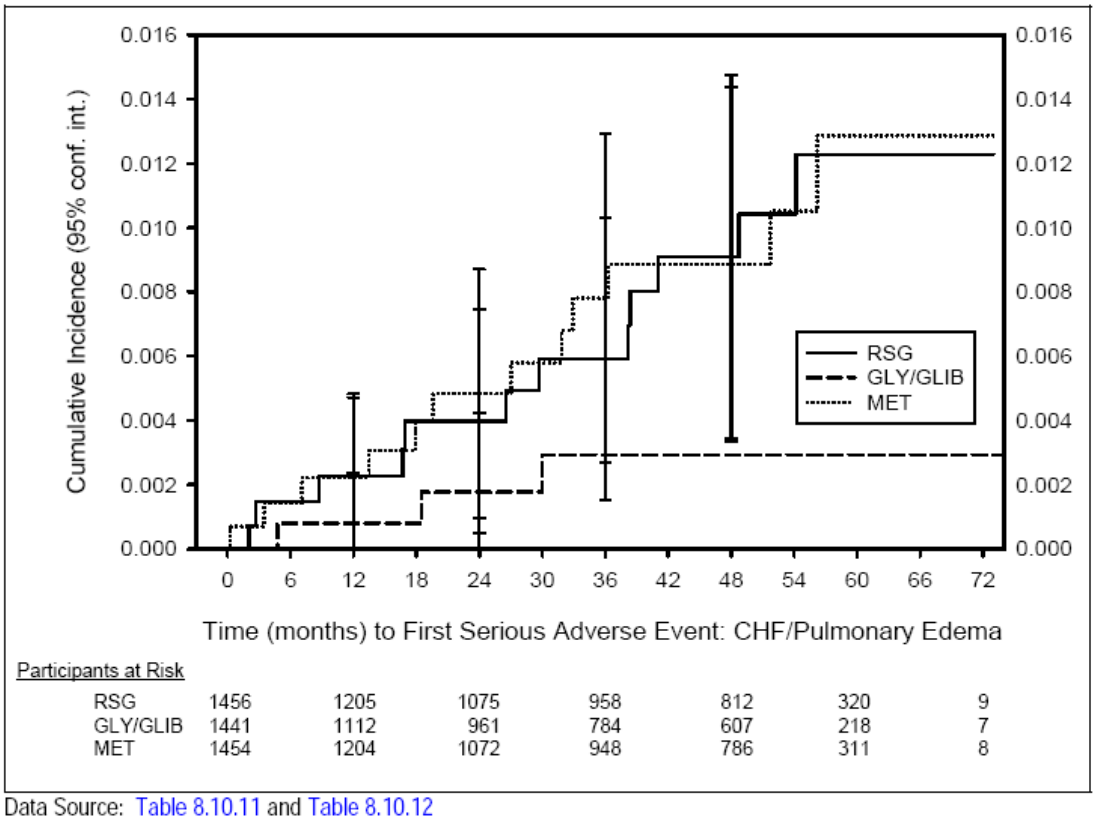
Figure A12: Cumulative Incidence of First Heart Failure or Pulmonary Edema AE (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 50, pg 185

Figure A13: Cumulative Incidence of First Serious Heart Failure or Pulmonary Edema AE, Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 51, pg 186

When considering time-to-event analyses for heart failure or pulmonary edema AEs, or for heart failure or pulmonary edema SAEs, the rate of heart failure for the RSG group exceeded that of the SU group, for both overall HF/pulm edema AEs (HR 2.2, 95% CI 1.01, 4.79) and serious HF/pulm edema AEs (HR 3.6, 95% CI 1.02, 12.84). For the comparison of RSG to MET, 95% CIs included 1, and p-values for both overall and serious AEs exceeded 0.5.

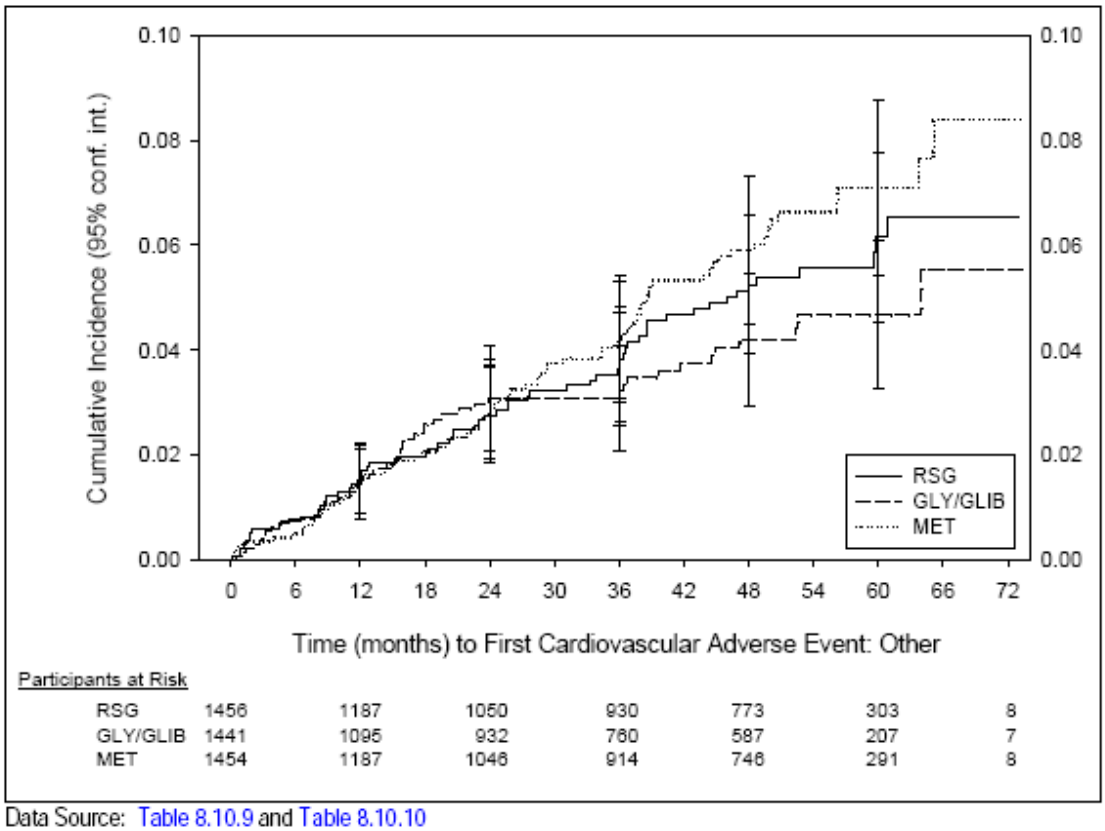
Table A30: Analyses by GSK of Time-to-First Cardiovascular Event Categorized as "Other" and First Serious Cardiovascular Event Categorized as "Other", Population of All Patients Who Received at Least One Dose of Study Medication

Cardiovascular Events Categorized as "Other"	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Adverse Events			
Subjects with events during study, n	63	46	73
60-month Cumulative Incidence (95% CI)	0.06 (0.05, 0.08)	0.05 (0.03, 0.06)	0.07 (0.05, 0.09)
RSG vs. Control			
Hazard ratio (95% CI)		1.195 (0.816, 1.748)	0.859 (0.613, 1.203)
p-value		0.3597	0.3762
Serious Adverse Events			
Subjects with events during study, n	7	4	1
60-month Cumulative Incidence (95% CI)	0.01 (0, 0.01)	0.01 (0, 0.01)	0 (0, 0.01)
RSG vs. Control			
Hazard ratio (95% CI)		1.561 (0.455, 5.353)	7.410 (0.911, 60.278)
p-value		0.4791	0.0611

Data Sources: Table 8.10.1, Table 8.10.9, Table 8.10.3, and Table 8.10.11

Source: ADOPT study report, Table 76, pg 192

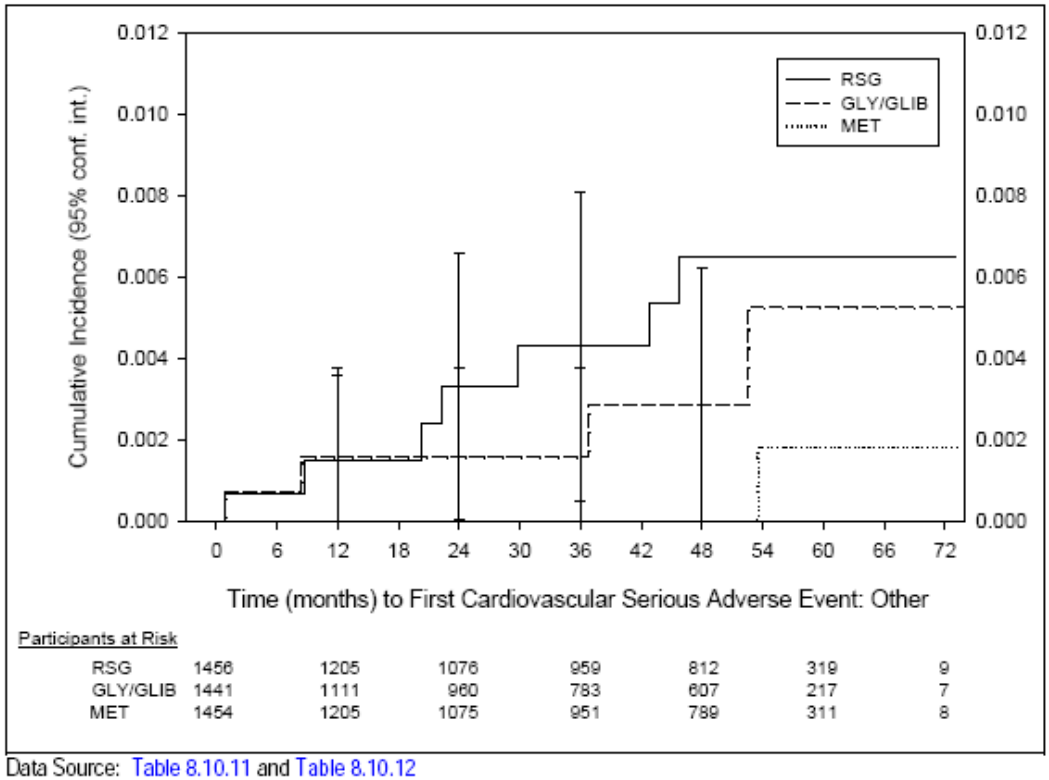
Figure A14: Cumulative Incidence of First Cardiovascular AE Classified as "Other" (Serious or Nonserious), Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.9 and Table 8.10.10

Source: ADOPT study report, Figure 53, pg 193

Figure A15: Cumulative Incidence of First Serious Cardiovascular AE Classified as "Other", Population of All Patients who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 54, pg 194

When considering time-to-event analyses for all CV AEs and SAEs classified as "other", 95% confidence intervals for the hazard ratios include 1, and p-values exceed 0.05, for all comparisons of RSG to SU or to MET. The rate of serious AEs within this category was low; there were 7, 4 and 1 events, respectively, in the RSG, SU and MET groups. For the comparison of RSG to MET, the HR was 7.4, with a very wide confidence interval of 0.91 to 60.28 due to the low event rate, and a p-value of 0.06.

Time-to-Event Analyses of Serious Cardiovascular Endpoints by FDA Statistical Reviewer

Ms. Joy Mele performed time-to-event analyses for multiple cardiovascular endpoints. Time-to-event analyses are useful when withdrawal rates differ between treatment groups. In these analyses, patients who discontinue for any reason are censored and dropped from the group at risk at that point in time; therefore 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. This is particularly important for this trial, in which dropout rates differ between treatment groups.

Please refer to Ms. Mele's briefing document for further explanation of her methods. Her proportional hazards model differed slightly from that of GSK. In addition to terms for treatment and number of major cardiovascular risk factors, she also included gender as a stratifier since randomization had been stratified on gender. The following table presents the results of Ms. Mele's analyses.

Table A31: Proportional Hazards Model Analysis Results for Ischemic et al Cardiovascular Endpoints		
	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=0.08	0.8 (0.4, 1.8), p=0.7
MI	1.6 (0.8, 3.1), p=0.17	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 0.08. 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 0.17.

Ms. Mele also performed subgroup analyses by baseline nitrate and angiotensin converting enzyme inhibitor use; no interaction was noted. However, baseline nitrate use was very infrequent.

Assessment of Cardiovascular Event Coding and Additional Endpoints by FDA Cardiology

Dr. Ellis Unger, an FDA cardiologist and Acting Deputy Director of the Office of Surveillance and Epidemiology, conducted an independent and blinded review of the adverse experiences dataset for ADOPT. The objectives of his review were to examine the appropriateness of coding of cardiovascular adverse event terms, to assign events to a set of endpoints representing clinically meaningful categories of cardiovascular adverse events, and to assess for signals of excess risk within these categories. He analyzed the adverse experiences dataset (ae.xpt) for the ADOPT study. The data set contained 49,695 records. After removal of 2,473 records classified as pre-treatment, he analyzed 47,222 records. All records describing adverse experiences relevant to cardiovascular safety were re-coded. The classification was based on: MedDRA higher level term text, MedDRA lower level dictionary term text, AE enhanced text, MedDRA dictionary synonym, and verbatim term. Each subject was characterized as having experienced or not experienced a given event. Various subgroup explorations were conducted. Dr. Unger's categories include all events, regardless of time relationship to treatment cessation, i.e. events that occurred more than 30 days after cessation of medication are also included. The following table presents the number and percentage of patients in each treatment group who experienced an event within each of the categories defined by Dr. Unger.

Table A32: Number and Percentage of Patients With Events Within Cardiovascular Event Groupings Defined by FDA Cardiology

	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)
CHF or pulmonary edema	20 (1.4)	8 (0.6)	17 (1.2)
CHF	17 (1.2)	8 (0.6)	15 (1)
Pulmonary edema	4 (0.3)	2 (0.1)	2 (0.1)
EF decreased, LV dysfunction	3 (0.2)	3 (0.2)	5 (0.3)
Edema, fluid retention	220 (15.1)	138 (9.6)	119 (8.2)
Death	10 (0.7)	5 (0.3)	5 (0.3)
Cardiac arrest; asystole, SCD	1 (0.1)	5 (0.3)	5 (0.3)
Acute MI	29 (2)	18 (1.2)	23 (1.6)
CAD, CHD	104 (7.1)	79 (5.5)	110 (7.6)
CAD, worse; progressive	8 (0.5)	8 (0.6)	11 (0.8)
Myocardial ischemia	4 (0.3)	3 (0.2)	5 (0.3)
Angina	66 (4.5)	45 (3.1)	68 (4.7)
Non-specific ST-T wave changes	3 (0.2)	4 (0.3)	5 (0.3)
ECG C/W ischemia	2 (0.1)	2 (0.1)	3 (0.2)
Unstable angina, ACS, R/O MI	10 (0.7)	9 (0.6)	12 (0.8)
Chest pain, non-cardiac	92 (6.3)	86 (6)	99 (6.8)
PTCA or CABG	5 (0.3)	5 (0.3)	8 (0.6)
PTCA/ PCI	3 (0.2)	2 (0.1)	5 (0.3)
CABG	2 (0.1)	3 (0.2)	3 (0.2)
Vascular disease, PVD	57 (3.9)	59 (4.1)	66 (4.5)
PVD	20 (1.4)	17 (1.2)	10 (0.7)
Aortic stenosis, sclerosis	8 (0.5)	3 (0.2)	5 (0.3)
Hypertension, BP increased	227 (15.6)	260 (18)	310 (21.3)
Hypertensive crisis	3 (0.2)	2 (0.1)	4 (0.3)
Embolism	4 (0.3)	3 (0.2)	2 (0.1)
Pulmonary embolus	4 (0.3)	3 (0.2)	1 (0.1)
DVT	3 (0.2)	3 (0.2)	0 (0)
Thrombophlebitis, phlebitis	21 (1.4)	16 (1.1)	9 (0.6)
Arrhythmia	66 (4.5)	66 (4.6)	65 (4.5)
Tachycardia	19 (1.3)	20 (1.4)	11 (0.8)
Bradycardia	13 (0.9)	8 (0.6)	13 (0.9)
Supra-ventricular	39 (2.7)	36 (2.5)	45 (3.1)
Atrial fibrillation/flutter	27 (1.9)	19 (1.3)	30 (2.1)
Ventricular arrhythmia	8 (0.5)	5 (0.3)	6 (0.4)
VT	0 (0)	0 (0)	1 (0.1)
VF	2 (0.1)	0 (0)	1 (0.1)
PVCs	6 (0.4)	5 (0.3)	4 (0.3)
Conduction disturbance	18 (1.2)	13 (0.9)	23 (1.6)
QRS prolonged, BBB	5 (0.3)	5 (0.3)	14 (1)
AV block	13 (0.9)	8 (0.6)	9 (0.6)
Pre-syncope or syncope	32 (2.2)	24 (1.7)	23 (1.6)
Pre-syncope	10 (0.7)	8 (0.6)	3 (0.2)
Syncope	23 (1.6)	16 (1.1)	21 (1.4)
CVA, TIA, SAH	18 (1.2)	14 (1)	21 (1.4)
SAH	3 (0.2)	2 (0.1)	1 (0.1)

Table A32: Number and Percentage of Patients With Events Within Cardiovascular Event Groupings Defined by FDA Cardiology			
	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)
CVA	13 (0.9)	12 (0.8)	20 (1.4)
TIA	9 (0.6)	7 (0.5)	11 (0.8)
ICH (not SAH)	4 (0.3)	3 (0.2)	3 (0.2)
Cerebral ischemia (non-stroke)	2 (0.1)	6 (0.4)	4 (0.3)

Source: Dr. Ellis Unger, email 5 Jul 07
Abbreviations: ACS = acute coronary syndrome, AV = atrioventricular, BBB = bundle branch block, BP = blood pressure, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CHD = coronary heart disease, CVA = cerebrovascular accident, DVT = deep venous thrombosis, ECG = electrocardiogram, EF = ejection fraction, ICH = intracranial hemorrhage, LV = left ventricular, PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, R/O = rule out, SAH = subarachnoid hemorrhage, SCD = sudden cardiac death, TIA = transient ischemic attack, VF = ventricular fibrillation, VT = ventricular tachycardia

The above data are presented as the number of patients who experienced an event within each of the event groupings. The following table, prepared by the clinical reviewer, presents the rate/ 100 PY for events which occurred at a higher frequency in the RSG group than in one of the other treatment groups. This takes into account the lower duration of exposure for patients randomized to SU.

Table A33: Rate/100 PY for Events Within Cardiovascular Event Groupings Defined by FDA Cardiology			
	RSG N=1456 PY=4953.8 Rate/100 PY	SU N=1441 PY=4243.6 Rate/ 100 PY	MET N=1454 PY=4905.6 Rate/ 100 PY
CHF or pulmonary edema	0.40	0.19	0.35
CHF	0.34	0.19	0.31
Pulmonary edema	0.08	0.05	0.04
EF decreased, LV dysfunction	0.06	0.07	0.10
Edema, fluid retention	4.44	3.25	2.43
Death	0.20	0.12	0.10
Cardiac arrest; asystole, SCD	0.02	0.12	0.10
Acute MI	0.59	0.42	0.47
CAD, CHD	2.10	1.86	2.24
CAD, worse; progressive	0.16	0.19	0.22
Myocardial ischemia	0.08	0.07	0.10
Angina	1.33	1.06	1.39
Non-specific ST-T wave □s	0.06	0.09	0.10
ECG C/W ischemia	0.04	0.05	0.06
Unstable angina, ACS, R/O MI	0.20	0.21	0.24
Chest pain, non-cardiac	1.86	2.03	2.02
PTCA or CABG	0.10	0.12	0.16
PTCA/ PCI	0.06	0.05	0.10
CABG	0.04	0.07	0.06
Vascular disease, PVD	1.15	1.39	1.35
PVD	0.40	0.40	0.20
Aortic stenosis, sclerosis	0.16	0.07	0.10

Table A33: Rate/100 PY for Events Within Cardiovascular Event Groupings Defined by FDA Cardiology			
	RSG N=1456 PY=4953.8 Rate/100 PY	**SU N=1441 PY=4243.6 Rate/ 100 PY**	**MET N=1454 PY=4905.6 Rate/ 100 PY**
Hypertension, BP increased	4.58	6.13	6.32
Hypertensive crisis	0.06	0.05	0.08
Embolism	0.08	0.07	0.04
Pulmonary embolus	0.08	0.07	0.02
DVT	0.06	0.07	n/a
Thrombophlebitis, phlebitis	0.42	0.38	0.18
Arrhythmia	1.33	1.56	1.33
Tachycardia	0.38	0.47	0.22
Bradycardia	0.26	0.19	0.27
Supra-ventricular	0.79	0.85	0.92
Atrial fibrillation/flutter	0.54	0.45	0.61
Ventricular arrhythmia	0.16	0.12	0.12
VT	n/a	n/a	0.02
VF	0.04	n/a	0.02
PVCs	0.12	0.12	0.08
Conduction disturbance	0.36	0.31	0.47
QRS prolonged, BBB	0.10	0.12	0.29
AV block	0.26	0.19	0.18
Pre-syncope or syncope	0.65	0.57	0.47
Pre-syncope	0.20	0.19	0.06
Syncope	0.46	0.38	0.43
CVA, TIA, SAH	0.36	0.33	0.43
SAH	0.06	0.05	0.02
CVA	0.26	0.28	0.41
TIA	0.18	0.16	0.22
ICH (not SAH)	0.08	0.07	0.06
Cerebral ischemia (non-stroke)	0.04	0.14	0.08

Source: calculated from Table A32 above
Abbreviations: ACS = acute coronary syndrome, AV = atrioventricular, BBB = bundle branch block, BP = blood pressure, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CHD = coronary heart disease, CVA = cerebrovascular accident, DVT = deep venous thrombosis, ECG = electrocardiogram, EF = ejection fraction, ICH = intracranial hemorrhage, LV = left ventricular, PCI = percutaneous coronary intervention, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, R/O = rule out, SAH = subarachnoid hemorrhage, SCD = sudden cardiac death, TIA = transient ischemic attack, VF = ventricular fibrillation, VT = ventricular tachycardia

From Dr. Unger's cardiovascular event groupings, the following event categories occurred at a frequency ≥1% higher among RSG-treated patients than among SU- or MET- treated patients, or occurred at a rate/100 PY that was ≥0.2 higher for the RSG group than for the SU or MET groups.

Table A34: Cardiovascular Event Groupings From FDA Cardiology Categories that Occurred in ≥1% More Patients in RSG Group than in a Comparator Group; or Events That Occurred at a Rate/ 100 PY that was ≥0.2 Higher for RSG Than for a Comparator

	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
Event Category	**n (%)**	**Rate/ 100 PY**	**n (%)**	**Rate/ 100 PY**	**n (%)**	**Rate/ 100 PY**
Edema, fluid retention	220 (15.1)	4.44	138 (9.6)	3.25	119 (8.2)	2.43
CAD, CHD	104 (7.1)	2.10	79 (5.5)	1.86	110 (7.6)	2.24
Angina	66 (4.5)	1.33	45 (3.1)	1.06	68 (4.7)	1.39
CHF or pulmonary edema events combined	20 (1.4)	0.40	8 (0.6)	0.19	17 (1.2)	0.35
CHF events only	17 (1.2)	0.34	8 (0.6)	0.19	15 (1.0)	0.31
Thrombophlebitis/ phlebitis	21 (1.4)	0.42	16 (1.1)	0.38	9 (0.6)	0.18

Source: Tables A32 and A33 above

Edema and heart failure events occurred more commonly among RSG group patients than among patients in the SU or MET groups. Events within the category "CAD, CHD" occurred with similar frequency in the RSG and MET groups, and at a somewhat lower frequency in the SU group. Per Dr. Unger, this category included all events wherein the occurrence of the event very strongly implies the presence of coronary artery disease. For the category of angina, the frequency pattern of RSG≈MET>SU was also noted.

Overall, Dr. Unger did not note a significant signal for cardiovascular risk within the categories he constructed. He noted that the rate of myocardial infarction appeared low overall, and was not much higher than the rate of stroke. He noted that the rate of MI is often significantly higher than the rate of stroke in large cardiovascular trials, and expressed concern about underascertainment of MI. The clinical reviewer searched for expected rates of strokes and MIs in an early diabetes population, and did not find a population that was entirely analogous to the ADOPT population. In CARDS (Collaborative Atorvastatin Diabetes Study, Colhoun 2004), patients with diabetes and no prior history of cardiovascular disease were included. However, this population was likely at greater cardiovascular risk than the ADOPT population, because all CARDS patients had at least one cardiovascular risk factor in addition to diabetes. In the placebo group in CARDS, 61/1410 patients had a myocardial infarction, and 35 had a stroke. In Dr. Unger's event categorization there were 70 myocardial infarctions among 4351 patients, and 45 strokes. The ratio of stroke to myocardial infarction for both CARDS and ADOPT was 0.6. The rates of MI and stroke in ADOPT were lower than those in the somewhat higher risk population of CARDS, but proportionately so. Myocardial infarctions in ADOPT were not adjudicated, and therefore were not "down-coded" in an adjudication process, which could have resulted in lower numbers. Dr. Unger's coding of events, which included review of verbatim terms, did not identify a concern with inappropriate assignment of event terms. It is unclear whether the rate of MI is lower than expected for this particular diabetic population. This question of underascertainment of MI remains unresolved.

Peripheral Vascular Events

Peripheral vascular events were analyzed separately by GSK, as illustrated in the following table. The clinical reviewer might not have included aortic stenosis or aortic sclerosis as peripheral vascular events. Nevertheless, the incidence of other identified events was low and did not differ between treatment groups.

Table A35: Summary of Peripheral Vascular Events by GSK, Events that Occurred in At Least 2 Patients in Any Treatment Group, Population of All Patients who Received at Least One Dose of Study Medication

	Number of Subjects with AEs of peripheral vascular disease, n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
Preferred Term	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with On-therapy AEs	36 (2.5)	0.7	31 (2.2)	0.7	27 (1.9)	0.6
Aortic stenosis	6 (0.4)	0.1	2 (0.1)	<0.1	3 (0.2)	0.1
Carotid bruit	4 (0.3)	0.1	3 (0.2)	0.1	4 (0.3)	0.1
Intermittent claudication	4 (0.3)	0.1	2 (0.1)	<0.1	0	0
Carotid artery stenosis	3 (0.2)	0.1	7 (0.5)	0.2	6 (0.4)	0.1
Arterial murmur	2 (0.1)	<0.1	0	0	0	0
Claudication	2 (0.1)	<0.1	4 (0.3)	0.1	3 (0.2)	0.1
Femoral artery stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	0	0
Peripheral vascular disease	2 (0.1)	<0.1	5 (0.3)	0.1	3 (0.2)	0.1
Poor peripheral circulation	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.01
Aortic sclerosis	1 (0.1)	<0.1	0	0	2 (0.1)	<0.1
Carotid murmur	1 (0.1)	<0.1	0	0	2 (0.1)	<0.1
Femoral bruit	0	0	2 (0.1)	<0.1	0	0
Subjects with On-therapy SAEs	7 (0.5)	0.1	4 (0.3)	0.1	6 (0.4)	0.1
Aortic stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	1 (0.1)	<0.1
Carotid artery stenosis	2 (0.1)	<0.1	1 (0.1)	<0.1	3 (0.2)	0.1
Claudication	1 (0.1)	<0.1	0	0	0	0
Arterial occlusion	1 (0.1)	<0.1	1 (0.1)	<0.1	0	0
Vascular stenosis	1 (0.1)	<0.1	0	0	0	0
Arterial occlusive disease	0	0	0	0	1 (0.1)	<0.1
Arterial stenosis	0	0	1 (0.1)	<0.1	0	0
Arterial thrombosis	0	0	1 (0.1)	<0.1	0	0
Ischemic limb pain	0	0	1 (0.1)	<0.1	0	0
Peripheral ischemia	0	0	1 (0.1)	<0.1	0	0
Visceral arterial ischemia	0	0	1 (0.1)	<0.1	0	0
Subjects with On-therapy AEs leading to Withdrawal	0	-	1 (0.1)	-	1 (0.1)	-
Aortic stenosis	0	-	0	-	1 (0.1)	-
Ischemic limb pain	0	-	1 (0.1)	-	0	-

a. Note: Sorted by frequency of adverse events in RSG group.
Data Sources: Table 8.2.4.3, Table 8.2.3.3, Table 8.5.1, and *Ad hoc* Table 1707

Source: ADOPT study report, Table 82, pg 200

Reasons for Withdrawal from Study

A significant percentage of patients withdrew from study for reasons other than monotherapy failure. This, along with the monotherapy failure withdrawals, presents challenges to the evaluation of adverse events. The following table categorizes reasons for withdrawal from the study.

Table A36: Summary of Reasons for Withdrawal by Category of Reason, Population of All Patients Who Received at Least One Dose of Study Medication

	Number of Subjects, n (%)			
On-Therapy (All Randomized Population)	RSG N = 1456	GLY/GLIB N = 1441	MET N = 1454	Total N = 4351
Monotherapy failure not requiring adjudication	102 (7)	243 (16.9)	146 (10.0)	491 (11.3)
Monotherapy failure requiring adjudication	41 (2.8)	68 (4.7)	61 (4.2)	170 (3.9)
Completed without monotherapy failure	692 (47.5)	459 (31.9)	645 (44.4)	1796 (41.3)
Total Withdrawn excluding monotherapy failure	621 (42.7)	671 (46.6)	602 (41.4)	1894 (43.5)
Adverse Event	169 (11.6)	215 (14.9)	178 (12.2)	562 (12.9)
Insufficient therapeutic effect	36 (2.5)	64 (4.4)	53 (3.6)	153 (3.5)
Protocol deviations (including non-compliance)	64 (4.4)	61 (4.2)	51 (3.5)	176 (4.0)
Lost to follow-up	73 (5.0)	79 (5.5)	82 (5.6)	234 (5.4)
Other	279 (19.2)	252 (17.5)	238 (16.4)	769 (17.7)
Withdrew consent	111 (7.6)	110 (7.6)	107 (7.4)	328 (7.5)
Administrative reasons[1]	105 (7.2)	68 (4.7)	68 (4.7)	241 (5.5)
Other	63 (4.3)	74 (5.1)	63 (4.3)	200 (4.6)
On-Therapy prior to first efficacy evaluation				
Withdrawn excluding monotherapy failure	63 (4.3)	104 (7.2)	57 (3.9)	224 (5.1)
Adverse Event	19 (1.3)	54 (3.7)	23 (1.6)	96 (2.2)
Protocol deviations (including non-compliance)	15 (1.0)	17 (1.2)	9 (0.6)	41 (0.9)
Lost to follow-up	9 (0.6)	10 (0.7)	7 (0.5)	26 (0.6)
Other (including withdrawn consent)	20 (1.4)	23 (1.6)	18 (1.2)	61 (1.4)
On-Therapy after first efficacy evaluation (ITT Population)	RSG N = 1393	GLY/GLIB N = 1337	MET N = 1397	Total N = 4127
Monotherapy failure	143 (10.3)	311 (23.3)	207 (14.8)	661 (16.0)
Completed without monotherapy failure	692 (49.7)	459 (34.3)	645 (46.2)	1796 (43.5)
Withdrawn excluding monotherapy failure	558 (40.1)	567 (42.4)	545 (39.0)	1670 (40.5)
Adverse Event	150 (10.8)	161 (12.0)	155 (11.1)	466 (11.3)
Insufficient therapeutic effect	36 (2.6)	64 (4.8)	53 (3.8)	153 (3.7)
Protocol deviations (including non-compliance)	49 (3.5)	44 (3.3)	42 (3.0)	135 (3.3)
Lost to follow-up	64 (4.6)	69 (5.2)	75 (5.4)	208 (5.0)
Other reason (including withdrawn consent)	259 (18.6)	229 (17.1)	220 (15.7)	708 (17.2)

1. Subject did not remain in study until 15MAR2006; not able or unwilling to enter extension, and site closure.

Data Source: Table 6.3.1

Source: ADOPT study report, Table 8, pg 80

Withdrawals due to adverse events were more common among SU group patients than among RSG or MET group patients.

The most common category of reason for non-monotherapy-failure withdrawal was listed as "other". In studies in which a substantial percentage of patients are listed as withdrawing due to "other" reasons, the clinical reviewer routinely examines the verbatim reasons given for withdrawal in order to determine if some withdrawals that were due to adverse events were misclassified as due to "other" reasons. On 18 Jun 07, GSK submitted a full listing of these reasons. The clinical reviewer examined each patient's reason for withdrawal, for all 769 withdrawals due to "other" reasons, and did not find substantial evidence that withdrawals due to adverse events were classified as due to "other" reasons. There was no significant evidence that withdrawals due to cardiovascular events were classified as due to "other" reasons. Most reasons given were typical of administrative withdrawals, e.g. patients moving and sites closing. For ADOPT, many patients chose not to re-consent to participation when the decision was made to amend the protocol and continue the study for longer than the patients had originally consented to participate, and several Institutional Review Boards refused to approve the extension of the study. The following table lists those few reasons listed as "other" that could possibly have been due to an adverse event based on the verbatim reason for withdrawal.

Table A37: Reasons for Withdrawal Listed as "Other" That Could Possibly Have Been Classified as Due to an Adverse Event, Population of All Randomized Patients

Verbatim Reason for Withdrawal	RSG N=1456 n (%)	SU N=1441 n (%)	MET N=1454 n (%)	TOTAL N=4351 n (%)
"Withdrew consent" multiple stress (situational) and fears about study medication (sic)	1 (0.4)			1 (0.1)
Patient self-withdrew consent was unhappy with treatment and due to anxiety (sic)	1 (0.4)			1 (0.1)
Alcohol abuse			1 (0.4)	1 (0.1)
Cardiac valve operation in near future	1 (0.4)			1 (0.1)
Creatinine >1.4 mg/dL not an AE, investigator decision (sic)			1 (0.4)	1 (0.1)
Decision of investigator due to liver enzymes elevated		1 (0.4)		1 (0.1)
Heart insufficiency – no AE as discussed with SB Harlow by Oliver Kaikante (sic)		1 (0.4)		1 (0.1)
Hypoglycemia in the post (sic) with study medications		1 (0.4)		1 (0.1)
Hypoglycemias (sic) episodes		1 (0.4)		1 (0.1)
Intolerability to study drug (sic)		1 (0.4)		1 (0.1)
Investigator's discretion but pt unwilling to increase to DL 4 due to intolerable gastrointestinal side effects at DL3	1 (0.4)			1 (0.1)
Patient experienced some symptoms which are related to the medication but which could have resulted from gastroenteritis (patient chose to leave trial)			1 (0.4)	1 (0.1)
Patient stressed by other factors and aggravated by insomnia which he feels is related to study meds? (sic)		1 (0.4)		1 (0.1)
Possible liver toricities (sic) due to methotrexate			1 (0.4)	1 (0.1)
Principal investigator felt best to withdraw pt. due to decline in health status	1 (0.4)			1 (0.1)
Pt felt diabetic neuropathy worsened on study medication	1 (0.4)			1 (0.1)
The patient is sure of the treatment is responsible for GGT increase (sic)		1 (0.4)		1 (0.1)
The patient was withdrawn from study medication due to the complexity of associated pathologies and multiple treatment (sic) the patient has recently received (investigator's decision)			1 (0.4)	1 (0.1)
Tolerance problems		1 (0.4)		1 (0.1)
Unable to tolerate study drug		1 (0.4)		1 (0.1)

Source: NDA 21071 SE8 026 submission 18 Jun 07, Ad-hoc Table 1995, pages 1-14

Overall, these reasons do not indicate a significant problem with misclassification of reasons for withdrawal. These few reasons, even if added to adverse event data, would not change the distribution of adverse event withdrawals among the treatment groups.

The following table presents cardiovascular adverse events which led to withdrawal from study. The clinical reviewer included all terms which could potentially represent cardiovascular events; some terms are not specific and may represent non-cardiovascular events.

Table A38: Cardiovascular Adverse Events Which Led to Withdrawal from Study				
MedDRA System Organ Class	**MedDRA Preferred Term**	**RSG N=1456 n (%)**	**SU N=1441 n (%)**	**MET N=1454 n (%)**
Cardiac disorders	**Any**	24 (1.6)	12 (0.8)	18 (1.2)
	Acute coronary syndrome	0	1 (0.1)	1 (0.1)
	Acute myocardial infarction	1 (0.1)	2 (0.1)	0
	Angina pectoris	2 (0.1)	2 (0.1)	1 (0.1)
	Angina unstable	1 (0.1)	0	1 (0.1)
	Arrhythmia	0	1 (0.1)	0
	Atrial fibrillation	0	2 (0.1)	1 (0.1)
	Atrial flutter	0	1 (0.1)	0
	Bradycardia	0	1 (0.1)	0
	Cardiac arrest	0	0	2 (0.1)
	Cardiac failure	4 (0.3)	1 (0.1)	2 (0.1)
	Cardiac failure acute	2 (0.1)	0	0
	Cardiac failure congestive	1 (0.1)	3 (0.2)	2 (0.1)
	Cor pulmonale	1 (0.1)	0	0
	Coronary artery disease	1 (0.1)	1 (0.1)	3 (0.2)
	Ischemic cardiomyopathy	1 (0.1)	0	0
	Left ventricular failure	0	0	1 (0.1)
	Mitral valve disease	1 (0.1)	0	0
	Myocardial infarction	7 (0.5)	3 (0.2)	4 (0.3)
	Myocardial ischemia	0	0	1 (0.1)
	Palpitations	1 (0.1)	0	0
	Pericardial calcification	1 (0.1)	0	0
	Right ventricular failure	1 (0.1)	0	0
	Ventricular dyskinesia	1 (0.1)	0	0
	Ventricular tachycardia	0	0	1 (0.1)
General disorders and administration site conditions	**Any (CV or non-CV)**	25 (1.7)	17 (1.2)	10 (0.7)
	Chest pain	1 (0.1)	0	0
	Edema	1 (0.1)	0	0
	Edema face	1 (0.1)	0	0
	Edema generalized	3 (0.2)	0	0
	Edema peripheral	12 (0.8)	5 (0.3)	4 (0.3)
	Edema pitting	1 (0.1)	0	0
	Sudden death	0	1 (0.1)	0
Investigations	**Any (CV or non-CV)**	33 (2.3)	24 (1.7)	25 (1.7)
	Electrocardiogram PQ interval prolonged	1 (0.1)	0	0
Metabolism and nutrition disorders	**Any (CV or non-CV)**	14 (1.0)	101[1] (7.0)	25 (1.7)
	Fluid retention	1 (0.1)	0	1 (0.1)
Nervous system disorders	**Any (CV or non-CV)**	15 (1.0)	17 (1.2)	9 (0.6)
	Cerebral infarction	0	0	1 (0.1)
	Cerebrovascular accident	5 (0.3)	4 (0.3)	3 (0.2)
	Hemiparesis	0	0	1 (0.1)
	Subarachnoid hemorrhage	0	1 (0.1)	1 (0.1)
	Syncope	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	**Any (CV or non-CV)**	8 (0.5)	9 (0.6)	0
	Acute pulmonary edema	1 (0.1)	0	0

Table A38: Cardiovascular Adverse Events Which Led to Withdrawal from Study				
MedDRA System Organ Class	**MedDRA Preferred Term**	**RSG N=1456 n (%)**	**SU N=1441 n (%)**	**MET N=1454 n (%)**
	Dyspnea	3 (0.2)	1 (0.1)	0
	Dyspnea exertional	0	2 (0.1)	0
	Pulmonary edema	0	1 (0.1)	0
Vascular disorders	**Any**	2 (0.1)	3 (0.2)	2 (0.1)
	Aortic dissection	0	0	1 (0.1)
	Aortic stenosis	0	0	1 (0.1)
	Hypertension	1 (0.1)	1 (0.1)	0
	Hypotension	0	1 (0.1)	0
	Ischemic limb pain	0	1 (0.1)	0
	Varicose vein	1 (0.1)	0	0
Source: ADOPT study report, Table 8.5, beg pg 4238 **1 For SU, 70 withdrawals due to hypoglycemia and 24 withdrawals due to hyperglycemia**				

For the terms acute myocardial infarction or myocardial infarction, there were 8, 5 and 4 withdrawals for the RSG, SU and MET groups respectively. Withdrawals due to heart failure or edema were more common among RSG-treated patients than among patients in the SU or MET groups.

Other Notable Safety Findings

As might be expected with an insulin secretagogue, sulfonylurea treatment was associated with a substantially higher incidence of hypoglycemic events, and withdrawals due to hypoglycemia, as illustrated in the following table.

Table A39: Summary of Hypoglycemic Events, Population of All Patients Who Received at Least One Dose of Study Medication

Preferred Term / Lower Level Term	Number of subjects with hypoglycemic events, n (%)					
	RSG N=1456 PY=4953.8		GLY/GLIB N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with On-therapy AEs	142 (9.8)	2.9	557 (38.7)	13.1	168 (11.6)	3.4
Hypoglycemia	128 (8.8)	2.6	510 (35.4)	12.0	148 (10.2)	3.0
Hypoglycemic episode	13 (0.9)	0.3	76 (5.3)	1.8	22 (1.5)	0.4
Blood sugar decreased	3 (0.2)	0.1	3 (0.2)	0.1	0	0
Hypoglycemic reaction	2 (0.1)	<0.1	3 (0.2)	0.1	2 (0.1)	<0.1
Hypoglycemia aggravated	1 (0.1)	<0.1	0	0	1 (0.1)	<0.1
Plasma glucose decreased	1 (0.1)	<0.1	0	0	0	0
Blood glucose decreased	0	0	4 (0.3)	0.1	0	0
Fasting blood glucose decreased	0	0	2 (0.1)	0.1	0	0
Glucose decreased	0	0	2 (0.1)	0.1	0	0
Hypoglycemia night	0	0	3 (0.2)	0.1	0	0
Subjects with On-therapy SAEs[1]	1 (0.1)	<0.1	8 (0.6)	0.2	1 (0.1)	<0.1
Subjects with On-therapy AEs leading to Withdrawal	0	-	70 (4.9)	-	5 (0.3)	-
Hypoglycemia	0	-	66 (4.6)		5 (0.3)	-
Hypoglycemic episode	0	-	4 (0.3)	-	0	-

1. All SAEs were coded to the lower level term of hypoglycemia.
a. Note: Sorted by frequency of adverse events in RSG group.
Data Sources: Table 8.2.4.3, Table 8.2.3.3, Table 8.5.1, and *Ad hoc* Table 1707

Source: ADOPT study report, Table 85, pg 202

The incidence and time course of occurrence of hypoglycemic events was similar for RSG and MET, as illustrated in the following time-to-event analysis and Kaplan-Meier curves.

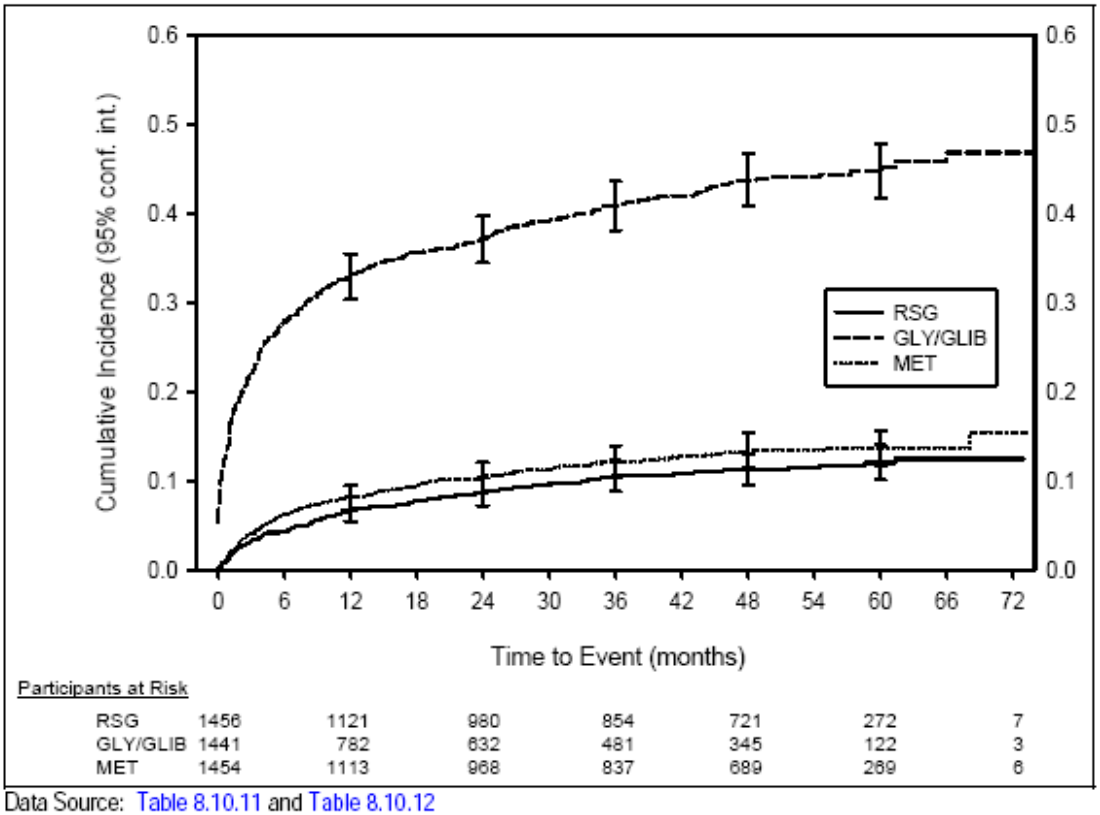
Table A40: Analysis of Time-to-First Hypoglycemic Adverse Event, Population of All Patients Who Received at Least One Dose of Study Medication

Hypoglycemia	RSG N=1456	GLY/GLIB N=1441	MET N=1454
Subjects with event during study, n	142	557	168
60-month Cumulative Incidence (95% CI)	0.12 (0.10, 0.14)	0.45 (0.42, 0.48)	0.14 (0.12, 0.16)
RSG vs. Control			
Hazard ratio (95% CI)	-	0.195 (0.162, 0.234)	0.838 (0.670, 1.047)
p-value	-	<0.0001	0.1204

Data Sources: Table 8.10.15 and Table 8.10.17

Source: ADOPT study report, Table 86, pg 203

Figure A16: Cumulative Incidence of First Hypoglycemic Adverse Event, Population of All Patients Who Received at Least One Dose of Study Medication



Data Source: Table 8.10.11 and Table 8.10.12

Source: ADOPT study report, Figure 55, pg 203

Bladder Neoplasms

The other approved thiazolidinedione, pioglitazone, is associated with bladder tumors in animals and humans. In ADOPT, for which rosiglitazone was the TZD under study, the incidence of bladder neoplasms was low and did not differ between treatment groups.

Table A41: Incidence of Bladder Neoplasms, Population of All Patients Who Received at Least One Dose of Study Medication

Event	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Bladder cancer	2 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1
Bladder neoplasm	1 (0.1)	<0.1	2 (0.1)	<0.1	2 (0.1)	<0.1
Bladder papilloma	0	n/a	0	n/a	1 (0.1)	<0.1

Source: ADOPT study report, Table 8.2.3.1, beg pg 4037

Data from both ADOPT (rosiglitazone) and PROactive (pioglitazone) were consistent with an increased incidence of fracture among women. These tended to be extremity fractures, rather than vertebral or hip fractures. Both sponsors have agreed to place information in their product labels regarding this safety finding, and both have widely sent Dear Healthcare Provider letters informing physicians of this concern.

"MACE" (Major Adverse Cardiovascular Events) Composite Endpoint Post Hoc Analyses

As the results of the FDA meta-analysis of diabetes trials began to support an increased short-term risk of myocardial ischemic events with rosiglitazone, the FDA began to explore methods of further assessing this signal. The usual practice after a meta-analysis of small trials suggests a safety concern is to search for larger, longer term trials that one can use to see if the finding is consistent. A significant issue in this process is the desire to examine similar endpoints across data sources, so that one can "compare apples to apples", if possible. This can be a very difficult process, because adverse event data across different trials may be collected and adjudicated in different ways. 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. After discussions with the FDA regarding the desirability of utilizing a common endpoint across data sources, GSK performed analyses utilizing a composite of cardiovascular death, serious adverse events of myocardial infarction, and serious adverse events of stroke. Events for this endpoint were ascertained by use of the same unadjudicated SAE terms that had been used by GSK for their CV AE groupings analyses. For cardiovascular deaths, non-CHF deaths were included, and were identified as deaths occurring due to an SAE that had a MedDRA Lower Level Term within the set of non-CHF cardiovascular events that were prespecified for the ADOPT CV event groupings (source, NDA 21071 SE8 022, 31 May 07 submission, pages 52-77).

The following table summarizes GSK's analyses of CV safety in ADOPT using this endpoint.

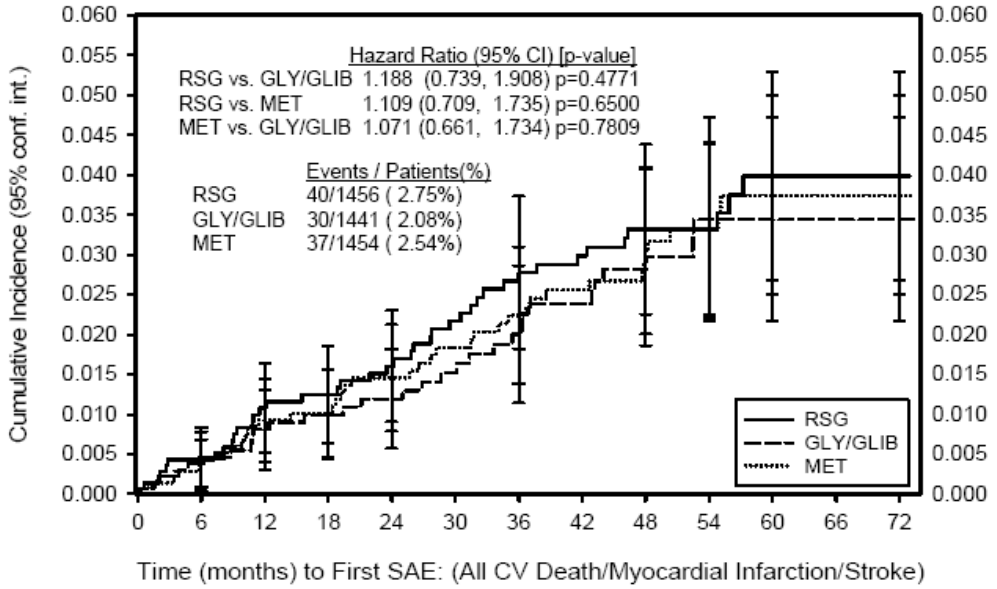
Table A42: Analysis of "MACE" Composite and Components in ADOPT ("MACE" = Endpoint of Cardiovascular Mortality, Serious Adverse Events of Myocardial Infarction [Fatal or Nonfatal] and Serious Adverse Events of Stroke [Fatal or Nonfatal])

Endpoint	RSG N=1456 PY=4953.8		SU N=1441 PY=4243.6		MET N=1454 PY=4905.6		Comparison	HR (95% CI)	p-value
	# events (%)	Rate/ 100 PY	# events (%)	Rate/ 100 PY	# events (%)	Rate/ 100 PY			
MACE	40 (2.75)	0.81	30 (2.08)	0.71	37 (2.54)	0.75	RSG vs MET	1.109 (0.709, 1.735)	0.6500
							RSG vs SU	1.188 (0.739, 1.908)	0.4771
							MET vs SU	1.071 (0.661, 1.734)	0.7809
CV Mortality	5 (0.34)	0.10	8 (0.56)	0.19	4 (0.28)	0.08	RSG vs MET	1.304 (0.350, 4.859)	0.6929
							RSG vs SU	0.582 (0.190, 1.783)	0.3429
							MET vs SU	0.446 (0.134, 1.484)	0.1881
Myocardial Infarction SAE	24 (1.65)	0.48	14 (0.97)	0.33	20 (1.38)	0.41	RSG vs MET	1.227 (0.677, 2.221)	0.5004
							RSG vs SU	1.518 (0.785, 2.938)	0.2149
							MET vs SU	1.238 (0.625, 2.453)	0.5407
Stroke SAE	13 (0.89)	0.26	12 (0.83)	0.28	17 (1.17)	0.35	RSG vs MET	0.773 (0.376, 1.593)	0.4860
							RSG vs SU	0.944 (0.430, 2.071)	0.8849
							MET vs SU	1.220 (0.582, 2.557)	0.5986

Source: NDA 21071 SE8 022 submission from 31 May 07, analyses Table 4, pg 9

The following Kaplan-Meier curves illustrate the cumulative incidence of events from this composite endpoint in ADOPT.

Figure A17: Cumulative Incidence of Composite of Cardiovascular Mortality, Serious Myocardial Infarction, and Serious Stroke



Participants at Risk

RSG	1456	1197	1067	945	799	310	8
GLY/GLIB	1441	1108	956	779	600	214	7
MET	1454	1199	1069	941	779	306	8

Source: NDA 21071 subm dated 31 May 07, Figure 3, pg 10

For this combined endpoint, with the ascertainment methods used by GSK, there was little difference between treatment groups for the composite. This endpoint, and all other cardiovascular endpoints which have been used for ADOPT and for the pooled diabetes studies meta-analyses, are post hoc and subject to weaknesses related to retrospective analyses. As discussed earlier, detailed review of ascertainment is continuing.

Limitations of Study With Respect to Interpretation of Cardiovascular Safety Data

All clinical trials have limitations, which must be considered during review. The following are some of the limitations of ADOPT with respect to interpretation of cardiovascular safety data.

- This was an efficacy and general safety trial, and was not specifically designed as a cardiovascular safety trial; there were no predefined cardiovascular endpoints.
- There was a high withdrawal rate, both for failure of monotherapy and for non-monotherapy-failure reasons.
- As a result of greater withdrawal rates for sulfonylurea group patients, there was greater exposure for rosiglitazone and metformin than for sulfonylurea, confounding the interpretation of events per arm. Time-to-event analyses, and consideration of rates by patient-year, can somewhat address this issue, but questions of the effect of the high withdrawal rate remain.
- An active comparator design was used; if comparator agents themselves have an adverse effect on cardiovascular safety, this may obscure cardiovascular effects of rosiglitazone.
- Adverse events were only routinely ascertained out to 30 days after cessation of study medication. This is common in clinical trials, but because patients were expected to withdraw from this study due to monotherapy failure, it would have been desirable to continue to follow patients for a longer period after study medication cessation.

- Lipids and blood pressure were not intensively managed in order to equalize these risk factors, and differences were present at endpoint for these cardiovascular risk factors, as well as for HbA1c. Differences in these values at endpoint create difficulty in true comparison of cardiovascular risk, which is often highly dependent on traditional risk factors. The contribution of these traditional risk factors may outweigh any independent contribution of the drug in question.
- Patients had early diabetes at entry, and were perhaps at lower risk for cardiovascular events than an average type 2 diabetic population. This might impact generalizability of any conclusions to a broader use population.
- Predefined adjudication of cardiovascular events did not occur; use of investigator terms and/or Preferred Terms may not correlate perfectly with adjudicated terms.
- Lower Level MedDRA terms were used to construct groupings of cardiovascular event terms; use of these terms rather than Preferred Terms complicates verification of inclusiveness.
- The post hoc cardiovascular endpoints for ADOPT were not identical to the endpoints used in the retrospective meta-analysis of pooled diabetes studies. While some relatively well-accepted composite cardiovascular endpoints exist that may allow one to look at similar endpoints for these and other sources of cardiovascular safety data for rosiglitazone, one must recognize that differences between trials may result in differences in the exact events included in these composites. A single, or even several, composite endpoints, used across data sources, may not fully characterize cardiovascular safety.
- Small numbers of cardiovascular events increase uncertainty of estimates; many estimates are therefore unstable, and only a few added events in one group or another could significantly change the estimates.

Strengths of ADOPT

- The duration of ADOPT was much longer than the mean duration of trials in the pooled diabetes studies included in the meta-analysis.
- ADOPT had a large number of patients.
- Because ADOPT was a single study, issues of between-study heterogeneity, which are important in meta-analyses, were not relevant.
- Because ADOPT was a single study, randomization could be maintained for adverse event analyses.
- Baseline risk factors and other characteristics were generally well-matched between treatment groups.
- While a comparison to placebo is useful in characterization of absolute event rates, real-world management of diabetes does not usually involve choosing between one drug or no drug at all. The choice is usually between one drug and another drug of a different class. In ADOPT, active comparison of rosiglitazone to sulfonylurea or metformin was more relevant to the types of treatment decisions often faced by physicians who treat diabetes.

Summary of Cardiovascular Safety Findings from Ongoing Clinical Review of ADOPT

As of the writing of this briefing document, the findings of the cardiovascular safety review of ADOPT include:

- A large percentage of patients withdrew from study, both due to reaching the primary endpoint of monotherapy failure, and due to non-monotherapy failure reasons. The withdrawal rate was higher in the SU group, and the exposure was lower in this group. The issues of high withdrawal and differential exposure necessitate caution in interpretation of CV safety data.
- Glycemic control, blood pressure values, and lipid values were statistically significantly different between treatment groups at 48 months. Ideally, one would wish for cardiovascular risk factors

to be similar at endpoint, so that one could assess the independent CV effect of a drug, with all other significant risk factors being roughly equal.

- Total mortality across the entire course of study was similar between treatment groups. When considering deaths that occurred during the adverse event ascertainment period of the study (out to 30 days after cessation of treatment), total mortality occurred at rates/ 100 PY of 0.2, 0.5, and 0.1 for the RSG, SU, and MET groups, respectively. In a time-to-event analysis by FDA Biometrics, the odds ratio for total mortality for RSG vs SU was 0.5 (95% CI 0.3, 1.1; p-value 0.08).
- The incidence of cardiovascular death was low, and was not significantly different between treatment groups.
- Total MedDRA Cardiovascular System Organ Class events occurred with similar frequency among patients in the RSG and MET treatment groups, and with somewhat lower frequency among patients in the SU group.
- Total MedDRA Vascular System Organ Class events occurred with similar frequency in patients in each of the treatment groups.
- Out of some 240 cardiovascular adverse event MedDRA Preferred Terms which occurred in any patient in ADOPT, few individual cardiovascular adverse event terms were reported with greater frequency among RSG group patients than among patients in the SU and MET groups. The individual serious adverse event term "myocardial infarction" (not including other myocardial ischemic event terms such as "acute myocardial infarction") occurred at rates/100 PY of 0.4, 0.2 and 0.3 for RSG, SU and MET group patients, respectively. When considering all adverse event terms (serious and nonserious), adverse event terms of edema and dyspnea were reported more frequently among RSG group patients than among MET or SU group patients. The single term "syncope" was reported at rates/100 PY of 0.4, 0.2 and 0.3 for RSG, SU and MET group patients, respectively.
- Consideration of individual event terms does not allow for full characterization of events within categories of cardiovascular events. In event grouping analyses performed by GSK, rates of total myocardial ischemic events and total arrhythmia events did not differ significantly between treatment groups. Heart failure and pulmonary edema events occurred with similar frequency in the RSG and MET groups, but occurred at a lower frequency in the SU group. There was also a group of "other" cardiovascular adverse events, for which there was no significant difference between treatment groups. Examination of GSK's assignment of event terms to groupings did not reveal significant inappropriate assignment of terms to the "other CV events" category. Examination of the inclusiveness of the event groupings is ongoing as a search for lack of ascertainment; this process will require reconciliation of assignment of thousands of events. Thus far, this search has not revealed evidence of omission of important cardiovascular events from groupings.
- FDA Biometrics also performed time-to-event analyses for multiple endpoints involving adverse cardiovascular events. These included all-cause mortality, cardiovascular mortality, stroke, all cardiac ischemic events and all serious cardiac ischemic events. A composite of CV death, MI and stroke was also analyzed. A statistically significant difference between RSG and comparator was not established for any of these endpoints. For all-cause mortality, the odds ratio for RSG vs SU was 0.5 (95% CI 0.3, 1.1), favoring RSG, with a p-value of 0.08. For myocardial infarction, the odds ratio for RSG vs SU was 1.6 (95% CI 0.8, 3.1), with a p-value of 0.17. For comparisons of RSG to MET, no p-values approached statistical significance.
- An independent and blinded review of all adverse event terms (>49,000 records) in the ADOPT adverse event database was conducted by Dr. Ellis Unger, an FDA cardiologist and Acting Deputy Director of the Office of Surveillance and Epidemiology. His objective was to assess the appropriateness of coding of cardiovascular adverse events, to assign events to a set of endpoints representing clinically meaningful categories of cardiovascular events, and to assess for signals of excess risk within these categories. His review did not reveal evidence of significant miscoding

of CV events, and did not reveal a significant signal of excess risk within his endpoint categories. He did note a relatively low incidence of myocardial infarction overall, and raised a concern about possible underascertainment.

- Withdrawals from study due to adverse events of heart failure or edema were more common among RSG group patients than among comparator group patients. For the terms "acute myocardial infarction" and "myocardial infarction" there were a total of 8, 5 and 4 withdrawals for the RSG, SU and MET groups, respectively. Withdrawals from study due to any adverse event were more common among SU group patients than among the other treatment group patients; this excess was largely due to hypoglycemia.
- Limitations of ADOPT with regard to assessment of cardiovascular safety are discussed above.
- Overall, ADOPT does not appear to present a significant signal of excess myocardial ischemic event risk, of excess total mortality, or of excess cardiovascular mortality, for RSG vs SU or MET. Conversely, ADOPT's results also cannot provide complete reassurance of a lack of excess cardiovascular risk; it is difficult for any clinical trial to "clear" a drug of a signal of increased risk.

DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)
Status: This study was not conducted or analyzed by GSK. Results were analyzed by the Population Health Research Institute at McMaster University. The completed trial results for rosiglitazone (separately from the ramipril findings) were published in *Lancet* September 2006 by the independent DREAM investigators. The FDA does not have access to the full clinical datasets for this trial.

Study Design and Study Objectives: This was a multi-center, multi-national, double-blind, randomized, placebo-controlled clinical trial of patients with impaired fasting glucose or impaired glucose tolerance. 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. Death was included to account for the association between diabetes and mortality and to avoid the problem of competing risk (i.e., diabetes may develop at a different rate in individuals who die than in individuals who do not).

Incident diabetes was ascertained based on any of the following:

- locally measured fasting plasma glucose of 7.0 mmol/L (126 mg/dL) or greater or 2 hr plasma glucose concentration of 11.1 mmol/L (200 mg/dL) or greater during a 75 g OGTT that was confirmed by another test on a different day
- a single test consistent with diabetes without reason for exclusion of diagnosis based on blinded adjudicator assessment
- physician diagnosed diabetes outside of the study that was supported by the prescription of an antidiabetic agent and either a FPG > 7.0 mmol/L or any glucose level > 11.1 mmol/L

Secondary outcomes included: regression to normal fasting and 2hr post-prandial glucose concentrations; a composite of CV events (MI, stroke, CV death, revascularization procedures, heart failure, new angina with objective evidence of ischemia, or ventricular arrhythmia requiring resuscitation); individual components of the CV composite; renal events and a composite cardiorenal outcome; and glucose concentrations. Clinical outcomes were adjudicated by a committee blinded to study treatment assignment.

The predicted incidence of the primary outcome in this population was 4.5% or greater per year. A sample size of at least 5000 patients was estimated to provide 90% power to detect a minimum 22% risk reduction attributable to either ramipril or rosiglitazone.

Patient Population
DREAM enrolled patients at risk for developing diabetes based on fasting and challenged glucose levels. Since this trial is evaluating the effect of a therapy on preventing diabetes, it is reasonable to assume that the study population is at lower risk for a cardiovascular event than other studies enrolling patients with established diabetes mellitus. And by definition, this population is also referred to as treatment-naïve. Limiting enrollment to a low risk CV population is further achieved by specific exclusion criteria (e.g., CV disease including EF < 40% or CHF or prior MI or stroke, renal or hepatic disease). Current use of an ACE-inhibitor was also an exclusion criterion.

A total of 24,872 individuals were screened and 5269 were randomized to the following treatment groups: 1321 placebo; 1325 rosiglitazone monotherapy; 1313 ramipril monotherapy; 1310 rosiglitazone + ramipril. In the *Lancet* publication, the treatment groups were collapsed into two comparison groups: rosiglitazone-containing treatment groups versus the ramipril monotherapy/placebo groups. The latter group was referred to as the placebo group. The following table summarizes certain baseline characteristics and demographics of the study population as presented in the *Lancet* publication.

Table D1: Selected Baseline Characteristics and Demographics of DREAM Study Participants		
	Rosiglitazone N=2635	**Placebo N=2634**
Mean age (yrs)	54.6	54.8
Women	58.3%	60.1%
Medical history		
History of HTN	44.0%	43.0%
Current or former tobacco use	43.9%	45.3%
> 3 ETOH drinks/wk	21.1%	19.1%
Baseline Meds		
ASA/antiplatelets	14.4%	14.3%
Thiazide diuretics	9.3%	10.1%
Other diuretics or aldosterone antagonists	6.0%	5.5%
Angiotensin receptor blocker	5.8%	5.1%
Beta-blocker	17.8%	16.8%
Calcium channel blocker	12.5%	13.3%
Statin/fibrate	14.8%	14.8%
Mean BMI (kg/m2)	30.8	31.0

The DREAM population is obviously different from the patients contributing data to the meta-analysis which combined studies in patients with *established* T2DM. With respect to baseline CV risk, patients who are naïve to drug therapy in the meta-analysis are likely to be a more comparable patient population to DREAM than the previously-treated patients.

Study Outcome

The median follow-up was 3.0 years. The following table is from the *Lancet* September 2006 publication which summarizes the primary and secondary outcomes.

Table D2: Primary and Secondary Outcomes in DREAM

	Rosiglitazone group (n=2635)	Placebo group (n=2634)	HR (95% CI)	p
Composite primary outcome*	306 (11·6%)	686 (26·0%)	0·40 (0·35–0·46)	<0·0001
Diabetes	280 (10·6%)	658 (25·0%)	0·38 (0·33–0·44)	<0·0001
Diagnosed by FPG/OGTT	231 (8·8%)	555 (21·1%)	0·38 (0·33–0·44)	<0·0001
Physician diagnosed	49 (1·9%)	103 (3·9%)	0·47 (0·33–0·66)	<0·0001
Death	30 (1·1%)	33 (1·3%)	0·91 (0·55–1·49)	0·7
Regression (FPG <6·1 mmol/L)†	1330 (50·5%)	798 (30·3%)	1·71 (1·57–1·87)	<0·0001
Regression (FPG <5·6 mmol/L)†	1016 (38·6%)	540 (20·5%)	1·83 (1·65–2·04)	<0·0001
Cardiovascular events composite*	75 (2·9%)	55 (2·1%)	1·37 (0·97–1·94)	0·08
Myocardial infarction	15 (0·6%)	9 (0·3%)	1·66 (0·73–3·80)	0·2
Stroke	7 (0·3%)	5 (0·2%)	1·39 (0·44–4·40)	0·6
Cardiovascular death	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·7
Confirmed heart failure‡	14 (0·5%)	2 (0·1%)	7·03 (1·60–30·9)	0·01
New angina	24 (0·9%)	20 (0·8%)	1·20 (0·66–2·17)	0·5
Revascularisation	35 (1·3%)	27 (1·0%)	1·29 (0·78–2·14)	0·3
Myocardial infarction, stroke, or cardiovascular death	32 (1·2%)	23 (0·9%)	1·39 (0·81–2·37)	0·2

Data are number (%). *Rows are not mutually exclusive for components of the composite—if a participant had more than one component of the composite then they are counted in the relevant row. †Regression implies achieving a normal fasting glucose concentration (as defined in both rows) and 2-h plasma glucose level. ‡Defined as acute treatment with at least two of the following criteria: typical signs and symptoms, typical radiological evidence, use of diuretics, vasodilators, or inotropes. FPG=fasting plasma glucose. OGTT=oral glucose tolerance test.

Table 2: Primary and other outcomes

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).

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 TZDs. In 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 GSK meta-analysis.

However, as noted earlier, the results summarized in the September 2006 publication combined the factorial groups into rosiglitazone- versus non-rosiglitazone-containing treatment groups. The results of ramipril were published separately in the *New England Journal of Medicine* in October 2006.[1] A letter to the *Lancet* by Lubson and Poole-Wilson questioned the choice of presenting these data in aggregated groupings, rather than by individual treatment cells.[2] The following table summarizes the CV outcomes by factorial group, as provided by the DREAM investigators to the FDA.

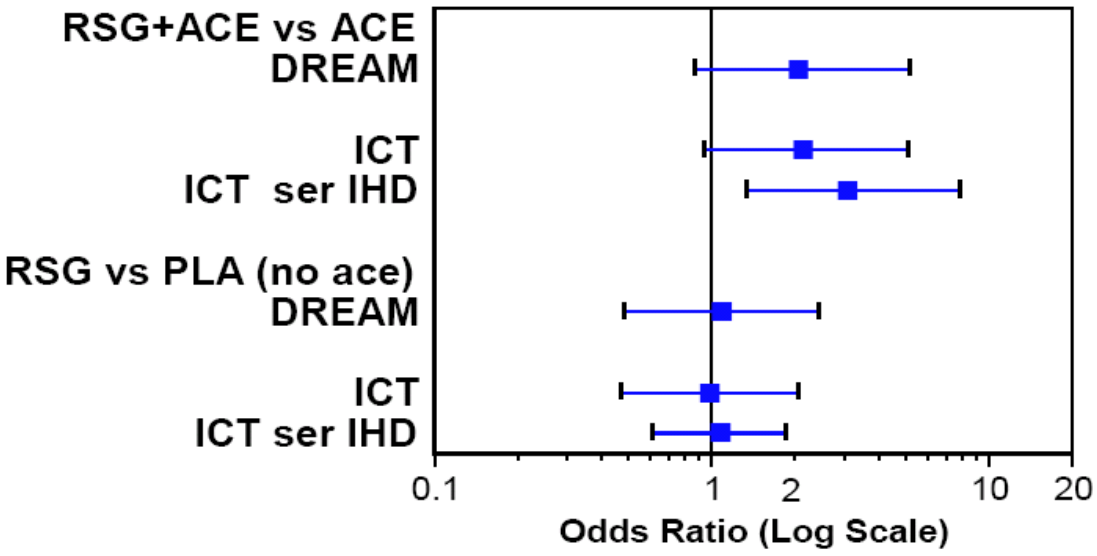
[1] The Dream Trial Investigators. Effect of Ramipril on the incidence of diabetes. *N Engl J Med* 2006; 355:1551-1562.
[2] Lubson J and Poole-Wilson PA. Letter to editor. *Lancet* 2006; 368:2050.

Table D3: CV Outcomes in DREAM Presented by Factorial Groups								
	Ramipril+Rosiglitazone N=1310		**Ramipril Only N=1313**		**Rosiglitazone Only N=1325**		**Placebo N=1321**	
	N	%	N	%	N	%	N	%
CV Composite	45	3.4	24	1.8	32	2.4	32	2.4
MI	11	0.8	3	0.2	5	0.4	6	0.5
Stroke	2	0.2	2	0.2	5	0.4	3	0.2
All Death	15	1.1	16	1.2	15	1.1	17	1.3
CV Death	7	0.5	5	0.4	5	0.4	5	0.4
Revasc	18	1.4	10	0.8	19	1.4	19	1.4
New Angina	15	1.1	9	0.7	9	0.7	11	0.8
CHF	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 in the author's reply 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, 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



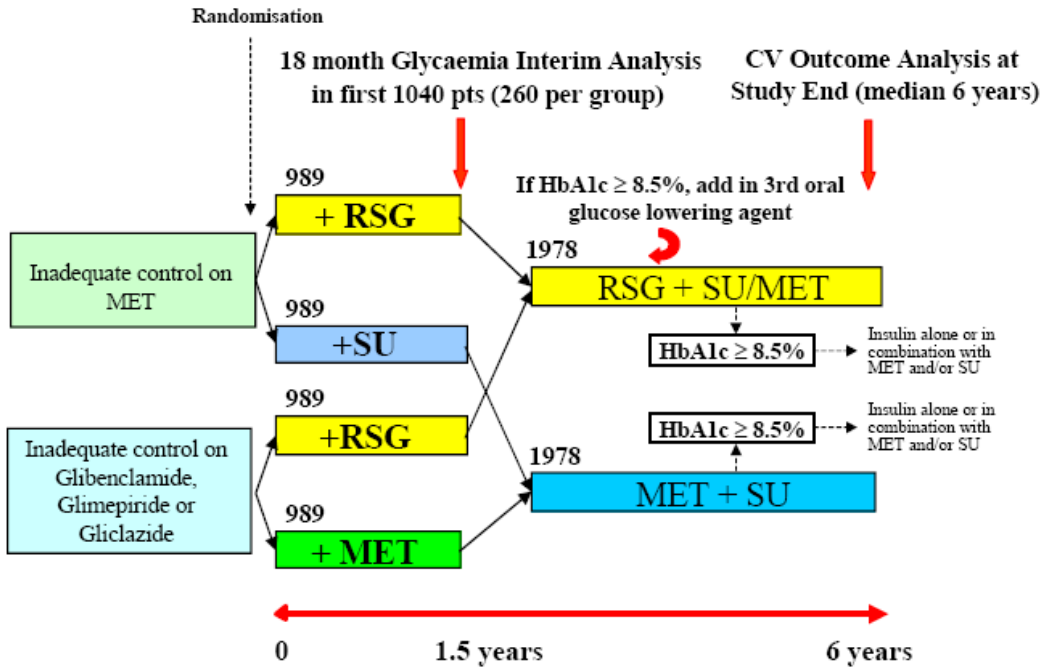
RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes)

Status: This study was initiated as a post-marketing commitment for marketing authorization by the European Medicines Agency (EMEA) in July 2000. This study was not conducted under the U.S. IND. Separate clinical/statistical reviews for RECORD by Drs. Hylton Joffe and John Lawrence are included in this briefing document. The study was initiated in April 2001, is ongoing with final results projected to be available in May 2009. However, recent publication on the increased risk of CV events and Congressional inquiries prompted release of interim study results in May 2007. The FDA has received only these interim results. No clinical datasets are available to the FDA.

Study Design:

This is a 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. Rosiglitazone was initiated at 4 mg/day. The following diagram depicts the study design.

Figure 1 Study Design



Glycemic control was targeted at HbA1c < 7.0% throughout the study with a planned interim analysis at 18 months in a subset of patients to assess glycemic control. If HbA1c is >7.0% at any point after 8 weeks of treatment, the investigator has the option to increase the dose of the *add-on* medication, but NOT the background medication. If HbA1c is ≥ 8.5% despite treatment at maximum permitted or tolerated dose of add-on medication for at least 8 weeks, a second confirmatory test is performed at least 4 weeks after the first test showing ≥ 8.5%. If this second test confirms the inadequate glycemic control

then additional therapy is initiated as depicted in the following algorithm obtained from the applicant's study protocol.

Figure 2 Treatment Algorithm for Add On Study Medication

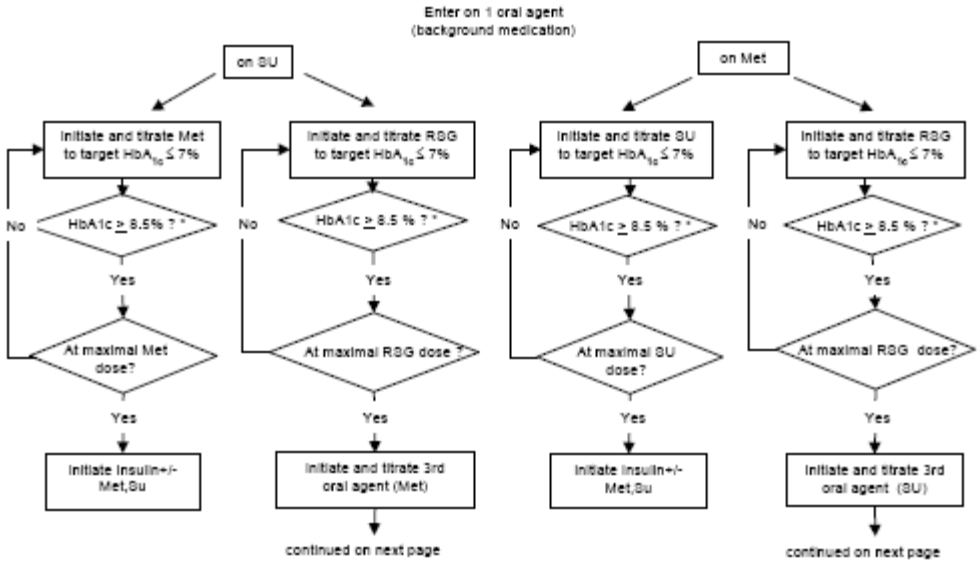
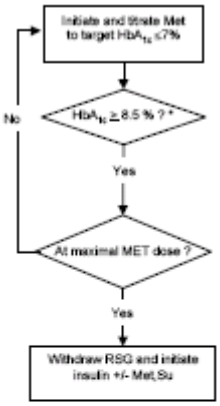
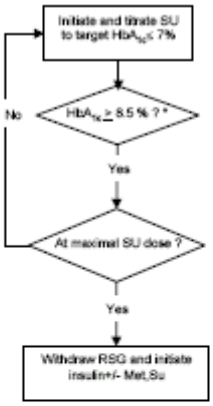


Figure 2 Treatment Algorithm for Add On Study Medication – continued





Study target : HbA1c ≤ 7%
*** Please note:**
- **Treatment with 3rd oral agent or insulin (+/- oral agent) should be initiated only after two consecutive values HbA1c ≥ 8.5% and at least 8 weeks of treatment with maximum dose of add-on study medication.**
- **Initiations and dose adjustments of add-on study medication and insulin should be implemented according to clinical practice and tablet strength(s) available**

Background Medication - patients must be taking the following doses upon entry into the study**
- **Metformin: 1.7g/day**
- **Glibenclamide: 15mg/day (10.5mg micronized form)**
- **Gliclazide: 240mg/day (90mg modified release formulation)**
- **Glimepiride: 4mg/day**

****Patient's taking lower doses (see protocol for list of minimum's) can also be eligible but they must have proven intolerance in source docs. Patients taking high doses will also be eligible.**
NOTE: dose of background medication should remain unchanged throughout the study unless the patient experiences recurrent side effects. Additionally in specified circumstances, patients will be allowed to change background SU type and formulation and increase the dose of background SU or MET whilst in the RT phase of the study (see section 3.1.2.3 for details).

The dose of add-on medication (sulphonylurea or metformin) may be increased but should NOT exceed the allowable maximum dose as specified by local guidelines and labelling requirements – see section 3.1.2.3 for details).

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, if not impossible.

Study Objective:

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

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.

Patient Population

This trial enrolled patients with established type 2 diabetes whose baseline HbA1c was between 7.0 and 9.0%, inclusive, and had been on a single oral glucose-lowering drug for at least 6 months prior to screening. Use of insulin or a combination of 2 or more oral agents 6 months prior to screening was an exclusion criterion. Patients were also excluded if they had been hospitalized for a major CV event in the last 3 months or had been diagnosed with heart failure. A total of 4458 patients (2228 previously on metformin and 2230 previously on SU) underwent randomization. Eleven did not receive study medication resulting in 2220 patients randomized and treated with rosiglitazone + metformin or SU versus 2227 randomized and treated with metformin + SU. The following table summarizes some baseline characteristics and demographics of the RECORD study population.

Table R1. Baseline Characteristics and Demographics of RECORD Study Cohort (from *N Engl J Med* e-publication on June 5, 2007).

Table 1. Baseline Characteristics of the Patients.*

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)
Previous medication — no. (%)		
Metformin only	1117 (50.3)	1105 (49.6)
Sulfonylurea only	1103 (49.7)	1122 (50.4)
Age — yr	58.4±8.3	58.5±8.3
Male sex — no. (%)	1142 (51.4)	1152 (51.7)
White race — no. (%)†	2200 (99.1)	2199 (98.7)
Time since diagnosis — yr	7.0±5.0	7.1±4.9
Body-mass index	31.6±4.7	31.5±4.9
Glycated hemoglobin — %	7.9±0.7	7.9±0.7
Fasting plasma glucose — mg/dl	177±43	177±40
Hypertension — no. (%)‡	1754 (79.0)	1774 (79.7)
Ischemic heart disease — no. (%)		
Any disease	359 (16.2)	374 (16.8)
Stable angina	222 (10.0)	228 (10.2)
Myocardial infarction	102 (4.6)	114 (5.1)
Unstable angina	20 (0.9)	30 (1.3)
Cerebrovascular disease — no. (%)		
Any disease	100 (4.5)	97 (4.4)
Stroke	54 (2.4)	54 (2.4)
Transient ischemic attack	50 (2.3)	47 (2.1)
Peripheral arterial disease — no. (%)	124 (5.6)	131 (5.9)
Congestive heart failure — no. (%)	12 (0.5)	6 (0.3)
Lipid disorder — no. (%)§	2123 (95.6)	2100 (94.3)
Smoking history — no. (%)		
Current smoker	363 (16.4)	343 (15.4)
Former smoker	565 (25.5)	539 (24.2)

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was determined by the investigators.
‡ Hypertension was defined as a systolic blood pressure of more than 130 mm Hg or a diastolic blood pressure of more than 80 mm Hg.
§ A lipid disorder was defined by investigator-reported diagnosis or as a low-density lipoprotein cholesterol level of 100 mg per deciliter or more, a triglyceride level of 200 mg per deciliter or more, or a high-density lipoprotein cholesterol level of less than 40 mg per deciliter for men or less than 50 mg per deciliter for women.

Data on Baseline concomitant medications are not available to the FDA. As per Ms. Mele's review, an analysis of CV events by baseline nitrate and ACE-inhibitor use is of interest.

Ms. Mele identified two meta-groups in her analysis that had the highest OR for total ischemic events: rosiglitazone + metformin and rosiglitazone + insulin use. The use of rosiglitazone and insulin is not a pre-defined treatment group in any of the long-term studies. RECORD and perhaps BARI-2D (discussed

below) have rosiglitazone + metformin groups. In Appendix 4 (page 43) of Ms. Mele's review, a comparison of the RSG+MET meta-group to the above table shows similar baseline characteristics in these two databases. The increased ischemic risk of RSG+MET in the meta-analysis is based on a comparison to placebo+MET whereas RECORD compares RSG+MET to MET+SU. This latter comparison has more practical application in the clinical setting as patients not achieving adequate control on a single anti-diabetic regimen will require addition of other drugs. RECORD may inform prescribers which second agent should be added to failed metformin monotherapy.

Study Outcome
The study is ongoing; however, an interim analysis was performed with events collected from time of randomization until March 30, 2007. Loss to follow-up was higher and event rate was lower than predicted, raising concerns that the study will not retain enough power to meet its stated objective.

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 R2: 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/MI[1]	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. 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.

BARI-2D (The Bypass Angioplasty Revascularization Investigation 2 Diabetes)
Status: This study is sponsored by the National Institutes of Health (NIH), National Heart Lung and Blood Institute (NHLBI) and is currently ongoing. It is not conducted under the IND for Avandia® and the FDA does not have any clinical datasets for review. Dr. David Gordon from the NHLBI has been invited to present the study design and objectives for purposes of providing the committee members of knowledge on future cardiovascular data that may potentially address rosiglitazone CV safety concerns.

Study Design and Study Objectives: This is a 2x2 factorial design trial comparing revascularization combined with aggressive medical management of T2DM versus aggressive medical management alone in patients with documented stable CAD. In addition, the factorial design seeks to compare 2 glycemic treatment strategies: insulin-sensitizing versus insulin-providing therapies. The following two hypotheses are tested in this trial:

1. Coronary revascularization hypothesis: a strategy of initial elective revascularization of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared to a strategy of aggressive medical therapy alone.

2. Method of glycemic control hypothesis: with a target of HbA1c < 7.0%, a strategy of hyperglycemia management directed at insulin sensitization results in lower 5-year mortality compared to a strategy of insulin provision.

Insulin sensitizing drugs included metformin and TZDs. As per correspondence between Dr. Nesto (one of the PIs) and the applicant, the agency was informed that approximately 90% of the TZD used is rosiglitazone. Insulin providing drugs include SU, glinides, and insulin. A detailed glycemic control strategy is established for each treatment group to ensure uniform levels of HbA1c. In addition, other risk factors for CHD such as hypertension, dyslipidemia, tobacco use, and obesity are intensively monitored and managed by separate committees to ensure uniformity of results and in compliance with current treatment guidelines.

A total of 2800 patients was targeted to be randomized to initial elective revascularization with aggressive medical therapy or aggressive medical therapy alone with equal probability, and simultaneously being assigned at random to an insulin-providing or insulin-sensitizing glycemic control regimen as summarized from the Manual of Operations for this trial.

Number of Patients Per Treatment Assignment		Revascularization Strategy	
		Revascularization	Medical
Glycemic Control Strategy	Insulin Providing (IP)	700	700
	Insulin Sensitizing (IS)	700	700

The primary endpoint is all-cause mortality.
The principal secondary endpoint is the composite of death, MI, or stroke.
Other secondary endpoints are discussed in the publications provided under Appendix 7.

At the time of the publication of the trial design in *American Journal of Cardiology* June 2006, 2368 patients had been enrolled at 49 clinical centers.

Patient Population
Unlike other studies described in this memo thus far, this trial specifically targets patients with established heart disease. The inclusion and exclusion criteria are summarized below:

Inclusion Criteria for BARI 2D
1. Diagnosis of Type 2 diabetes mellitus. 2. Coronary arteriogram showing one or more vessels amenable to revascularization (≥50% stenosis). 3. Objective documentation of ischemia **OR** subjectively documented typical angina with ≥70% stenosis in at least one artery. 4. Suitability for coronary revascularization by at least one of the available methods (does not require the ability to achieve complete revascularization). 5. Ability to perform all tasks related to glycemic control and risk factor management. 6. Age 25 or older. 7. Informed written consent.

Exclusion Criteria for BARI 2D
1. Definite need for invasive intervention as determined by the attending cardiologist. 2. Prior bypass surgery (CABG) or prior catheter-based intervention within the past 12 months. 3. Planned intervention for disease in bypass graft(s) if the patient is randomized to a strategy of initial revascularization. 4. Class III or IV CHF. 5. Creatinine > 2.0 mg/dl. 6. HbA1c > 13%. 7. Need for major vascular surgery concomitant with revascularization (*e.g.,* carotid endarterectomy). 8. Left main stenosis ≥ 50%. 9. Non-cardiac illness expected to limit survival. 10. Hepatic disease (ALT> 2 times the ULN). 11. Fasting triglycerides > 1000 mg/dl in the presence of moderate glycemic control (HbA1c <9.0%). 12. Current alcohol abuse. 13. Chronic steroid use judged to interfere with the control of diabetes, exceeding 10 mg. of Prednisone per day or the equivalent. 14. Pregnancy, known, suspected, or planned in next 5 years. 15. Geographically inaccessible or unable to return for follow-up. 16. Enrolled in a competing randomized trial or clinical study. 17. Unable to understand or cooperate with protocol requirements.

With respect to the meta-analysis, the BARI-2D population may be most similar to Studies 211 and 352 summarized in Appendix 4 of Ms. Mele's review. These were the only studies in the meta-analysis which specifically enrolled patients with a history of heart disease (Study 352) or Class I or II heart failure (Study 211).

Study Outcomes: No interim data have been provided to the FDA. The Agency was informed that the DSMB was previously aware of the GSK meta-analysis results. Shortly after the publication of Dr. Nissen's meta-analysis, the DSMB re-convened an unplanned meeting and after a review of the available data, a decision was again made to continue with the trial without modification.

PIOGLITAZONE

PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events)
PROactive is the only completed prospective CV outcomes trial with a TZD. This was a European trial involving 321 study centers, and 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%. Ages ranged from 35-75 years. All patients had a history of macrovascular disease, which was predefined. Notable exclusion criteria include heart failure at entry (NYHA FC 2 or higher), recent insulin monotherapy, or the current use of any TZD. The mean duration of treatment was 34.5 months.

The following tables summarizes certain relevant Baseline characteristics of the PROactive cohort.

Table P1: Mean Baseline Characteristics in PROactive

Characteristic	Pioglitazone N=2605 Mean (SD)	Placebo N=2633 Mean (SD)	Overall N=5238 Mean (SD)
Age (yrs)	61.9 (7.6)	61.6 (7.8)	61.8 (7.7)
Duration of diabetes (yrs)	9.4 (6.9)	9.6 (7.1)	9.5 (7.0)
Weight (kg)	87.6 (15.5)	88.5 (15.6)	88.0 (15.6)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Body mass index (BMI) (kg/m^2)	30.7 (4.7)	31.0 (4.8)	30.9 (4.8)
Waist circumference[1] (cm)	104.9 (11.7)	105.5 (12.1)	105.2 (11.9)
Systolic blood pressure (mm Hg)	143.5 (17.7)	143.3 (17.8)	143.4 (17.8)
Diastolic blood pressure (mm Hg)	82.8 (9.9)	83.2 (9.4)	83.0 (9.7)

Source: Applicant's Table 10.c, pg 68, Part A, study report
1 Waist circumference measured at the midpoint between the lower rib margin and the iliac crest

Table P2: Summary of Macrovascular Disease Entry Criteria in PROactive

Characteristic	Pioglitazone N=2605 n (%)	Placebo N=2633 n (%)	Overall N=5238 n (%)
MI at least 6 months before entry into study	1230 (47.2)	1215 (46.1)	2445 (46.7)
Stroke at least 6 months before entry into study	486 (18.7)	498 (18.9)	984 (18.8)
PCI or CABG at least 6 months before entry into study	804 (30.9)	807 (30.6)	1611 (30.8)
ACS at least 3 months before entry into study	355 (13.6)	360 (13.7)	715 (13.7)
Objective evidence of coronary artery disease	1246 (47.8)	1274 (48.4)	2520 (48.1)
Symptomatic peripheral arterial obstructive disease	504 (19.3)	539 (20.5)	1043 (19.9)
≥ 2 criteria	1223 (46.9)	1278 (48.5)	2501 (47.7)

Source: Applicant's Table 10.d, pg 69, Part A, study report

Table P3: Baseline Mean and Median HbA1c, Lipid and Creatinine Values in PROactive				
Parameter	**Pioglitazone N = 2605**		**Placebo N = 2633**	
	Mean (SD)	**Median (IQR[1])**	**Mean (SD)**	**Median (IQR)**
HbA1c (%)	8.1 (1.4)	7.8 (7.0-8.9)	8.1 (1.4)	7.9 (7.1-8.9)
LDL (mg/dL)	114.5 (36.0)	111.8 (88.9-135.3)	114.5 (36.9)	110.6 (88.9-135.3)
HDL (mg/dL)	44.9 (12.3)	42.5 (34.8-50.3)	44.9 (11.8)	42.9 (34.8-50.3)
TG (mg/dL)	197.5 (163.6)	160.3 (115.1-230.3)	199.3 (158.0)	162.1 (115.1-230.3)
Cr (mg/dL)	0.9 (0.2)	0.9 (0.8-1.0)	0.9 (0.3)	0.9 (0.8-1.1)
1 Interquartile range				
Source: Applicant's Table 10.e., pg 70, Part A, study report				

Table P4: Baseline Antidiabetes Therapy in PROactive		
Therapy	**Pioglitazone N = 2605 n (%)**	**Placebo N = 2633 n (%)**
Metformin only	253 (9.7)	261 (9.9)
Sulfonylureas only	508 (19.5)	493 (18.7)
Metformin + sulfonylureas only	654 (25.1)	660 (25.1)
Insulin only	5 (0.2)	8 (0.3)
Insulin + metformin	456 (17.5)	475 (18.0)
Insulin + sulfonylureas	209 (8.0)	219 (8.3)
Insulin + metformin + sulfonylureas	105 (4.0)	107 (4.1)
Other	306 (11.7)	305 (11.6)
Diet only	109 (4.2)	105 (4.0)
Source: Applicant's Table 10.f., pg 71, Part A, study report		

Table P5 Baseline Cardiovascular Medications in PROactive		
Medications	**Pioglitazone N = 2605 n (%)**	**Placebo N = 2633 n (%)**
Antiplatelet medications	2221 (85.3)	2175 (82.6)
Angiotensin converting enzyme (ACE) inhibitors	1630 (62.6)	1658 (63.0)
Beta blockers	1423 (54.6)	1434 (54.5)
Statins	1108 (42.5)	1137 (43.2)
Nitrates	1018 (39.1)	1137 (39.7)
Calcium channel blockers	892 (34.2)	964 (36.6)
Thiazide diuretics	401 (15.4)	430 (16.3)
Loop diuretics	372 (14.3)	378 (14.4)
Fibrates	264 (10.1)	294 (11.2)
Angiotensin II receptor antagonists	170 (6.5)	184 (7.0)
Alpha blockers	155 (6.0)	154 (5.8)
Potassium sparing diuretics	159 (6.1)	178 (6.8)
Cardiac glycosides	129 (5.0)	127 (4.8)
Source: Applicant's Table 10.g, pg 71, Part A, study report		

Study treatments were added to the patients' entry diabetes medications. Patients were randomized to the addition of pioglitazone or a matching placebo. Pioglitazone was initiated at 15 mg/day and was force-titrated to 45 mg/day over a period of two months. Titration was permitted for underlying medications for diabetes, hypertension and lipids; International Diabetes Federation goals were to be used to guide titration. Despite these recommendations, there were imbalances between the two treatment groups for

control of certain risk factors for CVD, generally favoring the pioglitazone treatment group. Consequently, it is difficult to determine if any favorable CV observations are due to a positive effect of pioglitazone or these imbalances in CV risk factors. Recall that one of the BARI-2D objectives is to achieve uniform control of multiple CV risks to avoid imbalance that complicate the interpretation of final study results.

The following table summarizes HbA1c change in PROactive over the study duration. Other imbalances between pioglitazone and placebo groups, respectively, include a 12.1% versus 8.4% increase in HDL-C and a 4.0 mmHg versus 2.6 mmHg reduction in systolic BP at final visit.

Table P6: Mean Change from Baseline in HbA1c (%) in PROactive

	Pioglitazone		Placebo	
Visit	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	2568	8.1 (1.4)	2597	8.1 (1.4)
6 months	2414	-0.8 (1.2)	2405	-0.1 (1.2)
12 months	2368	-0.9 (1.2)	2386	-0.3 (1.2)
24 months	2256	-0.8 (1.3)	2236	-0.2 (1.3)
Final visit	2249	-0.9 (1.3)	2258	-0.4 (1.4)

Source: Applicant's Table 11.r., pg 93, Part A, study report

The primary efficacy endpoint, measured at end-of-study, was a composite of:

- All-cause mortality
- Nonfatal myocardial infarction (including silent MI)
- Stroke
- Acute coronary syndrome
- Cardiac intervention (coronary artery bypass grafting or percutaneous coronary intervention)
- Major leg amputation (above ankle)
- Bypass surgery or revascularization in the leg

Neither the primary endpoint, nor any of the other efficacy endpoints, included heart failure.

The difference between pioglitazone and placebo for the primary endpoint was not statistically significant. Patients in the pioglitazone group experienced 514 first events (19.7% of patients), compared to 572 first events in the placebo group (21.7% of patients), for a hazard ratio of 0.90 (95% confidence interval [CI] 0.80, 1.02; p 0.0954). This was measured at end-of-study for each patient, with a mean follow-up of 34.5 months. There was no significant interaction by baseline diabetes therapy or ACE-inhibitor use. On June 19, 2007, a request was made to Takeda to analyze the primary endpoint and its components by baseline nitrate use. The response to this request is pending.

The statistical plan left no alpha for consideration of secondary endpoints in the event of a failed primary. Therefore, all secondary endpoints would be considered exploratory. Predefined secondary endpoints included cardiovascular mortality, and the individual components of the primary endpoint. There was no significant difference between pioglitazone and placebo for any of these individual endpoints; point estimates for most hazard ratios were <1, favoring pioglitazone, but all 95% confidence intervals (CIs) included one.

Table P7: Results for Predefined Secondary Endpoints for PROactive (Measured at End-of-Study, Mean Follow-up 34.5 Months)

Endpoint	Pio N=2605 n (%)	Pbo N=2633 n (%)	HR (95% CI)	p-value
Cardiovascular mortality	127 (4.9)	136 (5.2)	0.94 (0.74, 1.20)	0.6163
All-cause mortality	177 (6.8)	186 (7.1)	0.96 (0.78, 1.18)	0.6784
Nonfatal myocardial infarction	119 (4.6)	144 (5.5)	0.83 (0.65, 1.06)	0.1312
Stroke	86 (3.3)	107 (4.1)	0.81 (0.61, 1.07)	0.1398
Acute coronary syndrome	56 (2.1)	72 (2.7)	0.78 (0.55, 1.11)	0.1680
Major leg amputation	26 (1.0)	26 (1.0)	1.01 (0.58, 1.73)	0.9822
Coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention)	169 (6.5)	193 (7.3)	0.88 (0.72, 1.08)	0.2335
Leg revascularization	80 (3.1)	65 (2.5)	1.25 (0.90, 1.73)	0.1884

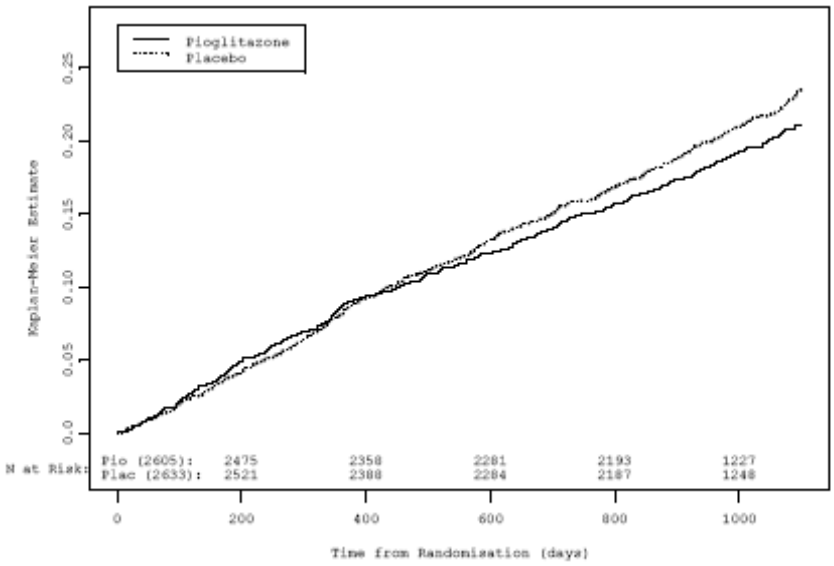
Source: Takeda's Tables 11.a., 11.g., and 11.h.; pgs 74, 80 and 81; part A, PROactive study report

PROactive ended on 31 Jan 05. On 12 May 05, Takeda submitted a new statistical plan with a new endpoint, which they designated their "main secondary endpoint". Takeda stated that unblinding occurred on 23 May 05. Because of the chronology of the addition of this endpoint, and because it was added in a trial with a failed primary endpoint, this endpoint appeared to be more consistent with an exploratory post hoc analysis rather than a prospectively defined endpoint. For this endpoint, which included all-cause mortality, nonfatal myocardial infarction (excluding silent myocardial infarction), and stroke, measured at end of follow-up, Takeda reported a statistically significant difference between pioglitazone and placebo, favoring pioglitazone. In the pioglitazone group, a total of 301 first events occurred (11.6% of patients), while there were 358 first events in the placebo group (13.6% of patients). This was associated with a hazard ratio of 0.84 (95% CI 0.72, 0.98; p 0.0277, without adjustment for multiple comparisons). Because of the potential bias associated with selection of individual components in a post hoc fashion, this endpoint raises concerns for the selection of a "best case scenario" endpoint.

The long-term nature of PROactive was important; if it had been a study of 6 months or less (as were 38/42 studies in the rosiglitazone retrospective pooled studies analyses), point estimates would have favored placebo rather than pioglitazone for the primary endpoint and most of its individual components (including myocardial infarction), as illustrated in the following table and Kaplan-Meier plots.

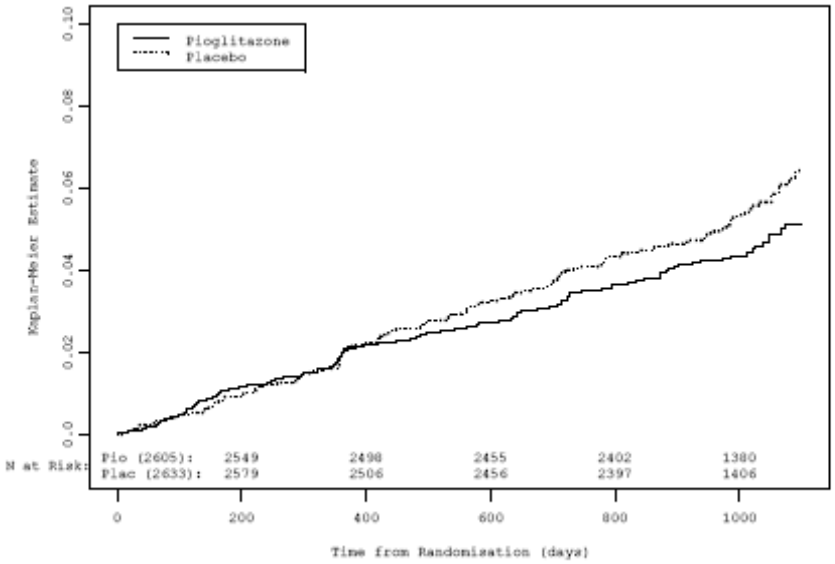
Table P8: Results for Predefined Secondary Endpoints for PROactive (Measured at 6 Months)			
Endpoint	**Pio N=2605 n (%)**	**Pbo N=2633 n (%)**	**HR[1]**
Cardiovascular mortality	20 (0.8)	27 (1.0)	0.8
All-cause mortality	25 (1.0)	30 (1.1)	0.9
Nonfatal myocardial infarction	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	1.3
Acute coronary syndrome	14 (0.5)	8 (0.3)	1.7
Major leg amputation	4 (0.2)	2 (0.1)	2.0
Coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention)	33 (1.3)	32 (1.2)	1.1
Leg revascularization	18 (0.7)	9 (0.3)	2.3
Source: Tables 1-12, Table 2.1, Table 2.2, provided by Takeda by email 13 May 07 **1 Pio rate/ pbo rate; confidence intervals for the 6-month hazard ratios not provided**			

Figure P1: Kaplan-Meier Plot of Time to Primary Composite Endpoint, PROactive Trial of Pioglitazone



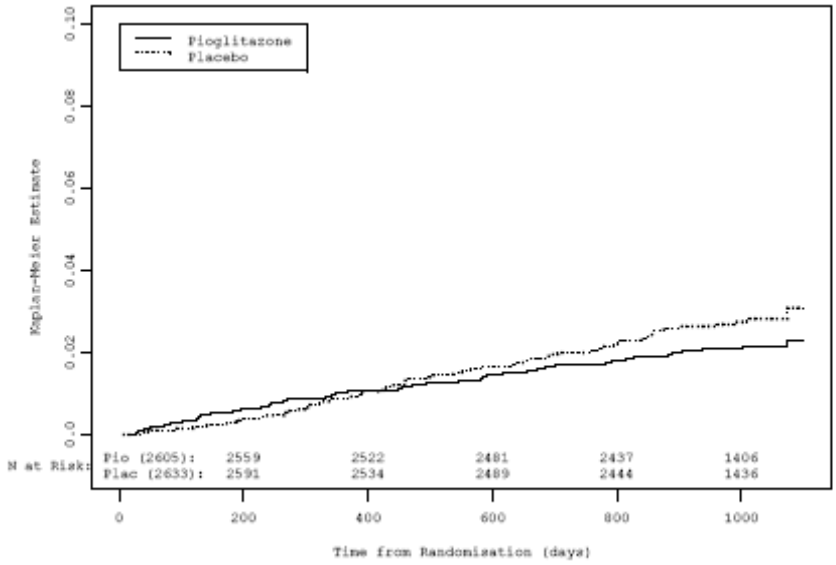
Source: Figure 15.2.1, pg 388, PROactive study report, NDA 21073 supplement 026

Figure P2: Kaplan-Meier Plot of Time to Nonfatal Myocardial Infarction, PROactive Trial of Pioglitazone



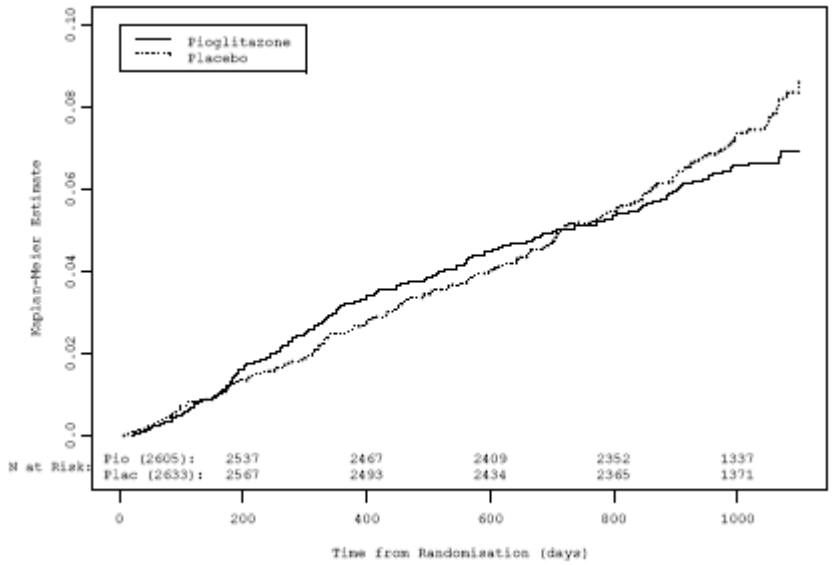
Source: Figure 15.2.4.2, pg 394, PROactive study report, NDA 21073 supplement 026

Figure P3: Kaplan-Meier Plot of Time to Acute Coronary Syndrome, PROactive Trial of Pioglitazone



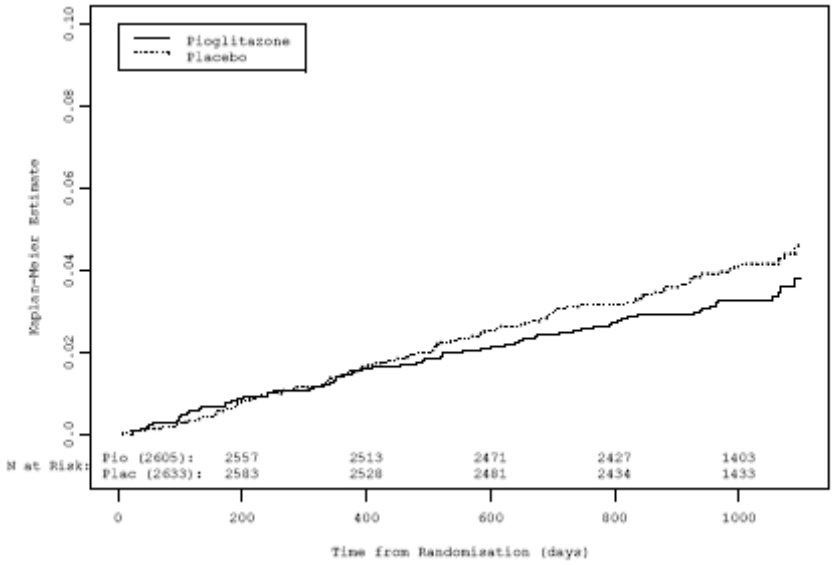
Source: Figure 15.2.4.3, pg 395, PROactive study report, NDA 21073 supplement 026

Figure P4: Kaplan-Meier Plot of Time to Cardiac Intervention (Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention), PROactive Trial of Pioglitazone



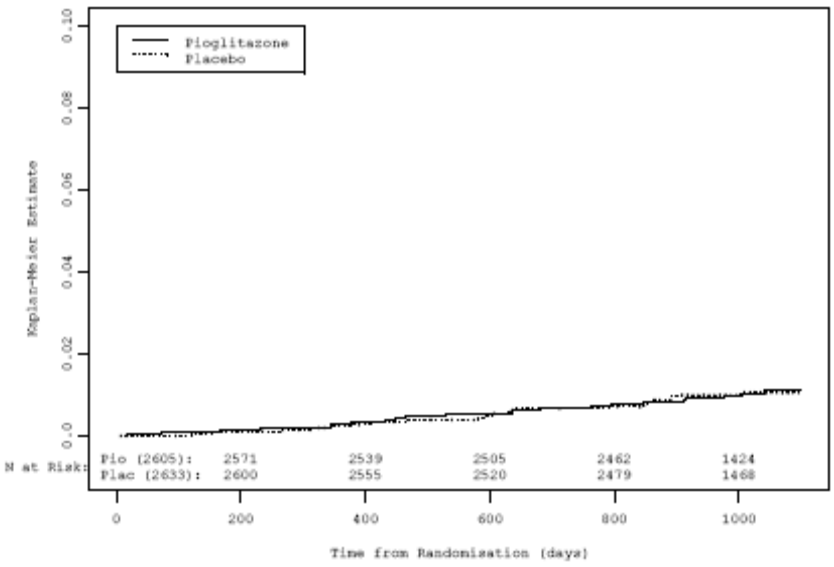
Source: Figure 15.2.4.4, pg 396, PROactive study report, NDA 21073 supplement 026

Figure P5: Kaplan-Meier Plot of Time to Stroke, PROactive Trial of Pioglitazone



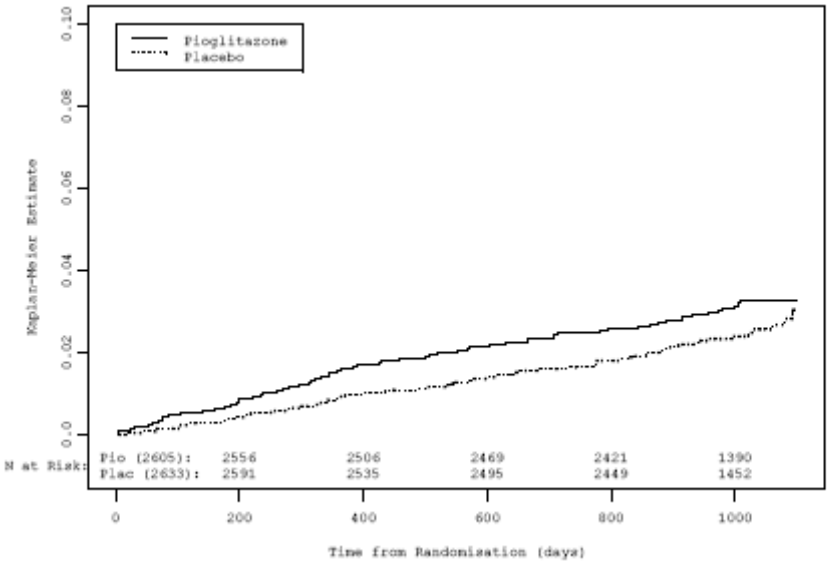
Source: Figure 15.2.4.5, pg 397, PROactive study report, NDA 21073 supplement 026

Figure P6: Kaplan-Meier Plot of Time to Major Leg Amputation, PROactive Trial of Pioglitazone



Source: Figure 15.2.4.6, pg 398, PROactive study report, NDA 21073 supplement 026

Figure P7: Kaplan-Meier Plot of Time to Bypass Surgery or Revascularization in the Leg, PROactive Trial of Pioglitazone



Source: Figure 15.2.4.7, pg 399, PROactive study report, NDA 21073 supplement 026

Had PROactive been a six-month study, one might have been concerned about a possible increased macrovascular risk with pioglitazone. In the longer term, pioglitazone had a neutral effect on macrovascular outcomes, which were associated with favorable hazard ratios. Separation of curves on Kaplan-Meier plots did not become favorable for pioglitazone until after 400 days of study for the primary endpoint, and for secondary endpoints of myocardial infarction, acute coronary syndrome and stroke. There are limits to the interpretation of these six-month data, including confounding introduced by the censoring of data from patients who died, and relatively low event rates at that 6-month point. Nevertheless, presentation of these 6-month data illustrate that clinically meaningful analyses of

cardiovascular outcomes typically require long-term follow-up and accumulation of a minimum number of events.

There are no clear data demonstrating the long-term reduction of risk of macrovascular events for any diabetes drug. In the Diabetes Control and Complications Trial (DCCT 1998, 1993), aggressive control of HbA1c in type 1 diabetic patients with intensive insulin therapy was associated with a reduced risk of microvascular events, such as diabetic retinopathy. In the DCCT, there was an initial worsening of retinopathy, followed by long-term reduction in progression, for intensive-control group patients compared to "conventional-control" group patients. This microvascular benefit of HbA1c-lowering took time to declare itself.

As mentioned earlier, Takeda did not include heart failure in any of the PROactive endpoints. The incidence of serious heart failure among patients in the pioglitazone group was 5.7%, compared to 4.1% in the placebo group. If one were to add these events to any of the efficacy composites, the difference between pioglitazone and placebo for overall cardiovascular risk would be negligible.

While the Division of Metabolism and Endocrinology Products (DMEP) did not consider the efficacy findings of the trial significant enough to permit Takeda to promote pioglitazone as having a cardiovascular benefit, DMEP did feel that the neutrality of the trial for long-term risk of macrovascular events other than heart failure was important safety information. Therefore, although Takeda requested the addition of efficacy information, including their post hoc secondary endpoint, to the Clinical Studies section of the Actos® label, DMEP did not concur. However, in order to convey what DMEP felt was a significant safety finding, a table of the results for the components of the primary composite endpoint was included in the Adverse Reactions section. The heart failure findings in PROactive were important, and were included in the Warnings section.

Study H6E-US-GLAI Study of Lipid Effects of Pioglitazone vs Rosiglitazone
This was a 6-month, double-blind trial involving 369 patients randomized to pioglitazone 30 mg daily for 12 weeks followed by 45 mg daily for 12 weeks, and 366 patients randomized to rosiglitazone 4 mg once daily for 12 weeks followed by 4 mg twice daily for 12 weeks. The primary endpoint was change in triglyceride level. This study was submitted as a supplement to the NDA for pioglitazone requesting comparative lipid-efficacy claims in January 2005. The application was not approved as the clinical relevance of greater TG-lowering associated with pioglitazone over rosiglitazone was not known. The following table summarizes the lipid changes at Week 24 for the two treatment groups.

	Actos	Avandia
TG (% change from baseline)	-12	15
HDL-C (% change)	15	8
LDL-C (% change)	16	23
Total-C (% change)	6	16

The difference in lipid effects between these two drugs was already known as these two agents were approved in 1999 and their applications were discussed within days of each other at a public advisory committee with the unfavorable lipid effects of rosiglitazone also included in its approved labeling.

This study was not designed as a cardiac safety study and cardiac serious adverse events were not adjudicated. There was one death in the pioglitazone group (MVA) and two in the rosiglitazone group (brain tumor and found deceased in hotel room). There were two cardiac serious adverse events in the pioglitazone group (0.3%) and 6 (1.6%) in the rosiglitazone group. Pioglitazone group cardiac SAEs

included one event each of myocardial infarction and triple-vessel CABG. Rosiglitazone group cardiac SAEs included one event each of myocardial infarction, triple-vessel CABG, unstable angina, coronary artery occlusion, coronary artery atherosclerosis and "chest pain cardiac".

Meta-analysis of Pioglitazone Controlled Clinical Trials
On April 23, 2007, the agency requested that Takeda perform a similar meta-analysis to that performed for rosiglitazone. Studies to consider included double-blind, randomized, placebo/comparator controlled trials of at least 12 weeks' duration. The company was asked to submit a statistical plan for a formal meta-analysis of MI and CHF.

On June 1, 2007, the agency received a tabular summary of pioglitazone clinical safety and efficacy studies. Review of the pioglitazone studies which meet the criteria for inclusion in a meta-analysis revealed notable differences between the rosiglitazone and pioglitazone clinical trials.

- 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 while in the pioglitazone database the number is only **6%**
- In the rosiglitazone database, about **26%** of the patients were naïve to therapy while in the pioglitazone database the number is about **48%**

As noted in Ms. Mele's review of the rosiglitazone meta-analysis, overall comparisons of rosiglitazone to placebo showed an increased risk (OR ~ 1.5) while comparisons head-to-head against metformin or SU did not demonstrate an increased risk (OR ~ 0.8). A greater risk was also observed in previously-treated patients versus patients naïve to therapy. These differences raise concern on the comparability of meta-analyses of the two TZDs.

At the time of preparation of this document, the statistical plan has not been received by the Agency. Given the time constraints and reviewer resources, it is unlikely a meaningful meta-analysis of pioglitazone controlled studies will be performed by the July 30th advisory committee meeting date.

Analysis of a Common Cardiovascular Endpoint Composite Across Data Sources

The data sources which have been discussed in this briefing document are heterogeneous, and a variety of endpoints have 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 are predefined and adjudicated composite and individual endpoints, but the exact composites differ from study to study. Biometricians and clinicians, both within and outside of the FDA, have suggested that use of a common composite endpoint could allow for a better perspective on the risk information provided by these data sources. There are many endpoints which could be 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 utilizing 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 included in the composite is difficult to confirm and compare; and the heterogeneity of the study populations limits comparability. However, there may be some value in assessing whether the estimates for cardiovascular risk generally trend in the same direction across data sources.

The following table presents this "MACE" composite for the major data sources presented in this document. The table is followed by a description of some of the limitations of these analyses. They should not be interpreted as a "final answer" about the cardiovascular risk associated with rosiglitazone.

Table M1: 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 Clinical Trials of Thiazolidinediones

			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), 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

Table M1: 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 Clinical Trials of Thiazolidinediones

			HR or OR (95% CI), p-value			
Data Source	**Comparison**	**Analysis Model**	**CV Mort + MI + Stroke ("MACE")**	**CV Mort**	**MI**	**Stroke**
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

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.
GSK analyses used proportional hazards model including covariate for baseline risk and term for treatment. Included CV mortality, MI SAEs and stroke SAEs. NDA 21071 sub 31 May 07, pg 5
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.
2 GSK analyses source NDA 21071 EDR 31 May 07, proportional hazards model with terms for treatment and number of major CV risk factors
FDA analyses by J Mele, DFS 3 Jul 07; proportional hazards model with terms for treatment and number of major CV risk factors, and with gender as stratifier
3 DREAM investigators model (DREAM Investigators, 2006), analyses with Cox proportional hazards model with ramipril interaction term
FDA analyses by J Lawrence, in FDA statistical review authored by J Mele, NDA 21071, DFS 3 Jul 07. Conditional MLE of odds ratio, Fisher exact test p-value
4 From published RECORD interim analysis (Home 2007). MI = acute myocardial infarction. Cox proportional hazards regression stratified by background medication.
5 From PROactive study report, NDA 21073 suppl 026, Tables 11.l (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.

There are several limitations to viewing this endpoint across data sources; some of these include:

- Between data sources, the patient populations are heterogeneous in terms of cardiovascular risk factors, duration of diabetes, and other important characteristics.
- Within the pooled studies, heterogeneity exists, and therefore pooling for an overall estimate may not be appropriate. Please refer to Ms. Mele's statistical briefing packet for estimates for the individual meta-groups, which she carefully selected as more appropriate pools for comparisons.
- Methods of ascertainment differed between data sources. There are likely differences in the precise sets of cardiovascular adverse event terms that were included within each of the components. For the pooled studies, events were migrated from WHO terms to MedDRA terms.
- Not all events were adjudicated. In ADOPT, none were adjudicated. In DREAM and PROactive, essentially all were. Results in RECORD are presented by adjudication status. In the pooled studies database, CV death and MI were adjudicated, but stroke was not. 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 are much longer.
- Analysis models differed somewhat.

These limitations are not unique to this particular endpoint, however; virtually any endpoint one chose would have similar concerns regarding interpretability of cardiovascular event data across data sources. It is important to bear in mind that the meta-analysis itself, which has raised this concern of cardiovascular risk, is 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 are not possible. Some observations include:

- For the composite of CV death, stroke and MI, for the two sources of cardiovascular outcome data (RECORD for RSG and PROactive for PIO), hazard ratios are <1, and confidence intervals overlap. 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 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 are <1, and confidence intervals overlap. 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 HRs <1, and multiple HRs >1.

A noteworthy observation is that the incidence of all-cause mortality (which requires no adjudication) is similar between rosiglitazone and comparators in all long-term controlled trials for which such data are available.

Table M2: Incidence of All-Cause Mortality in Long-term Controlled Trials		
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)

SUMMARY

An increased risk of cardiac ischemia was identified in a pooled analysis of 42 controlled clinical studies of rosiglitazone in patients with T2DM. The majority of the studies were of short duration with average treatment exposure of approximately 180 days (6 mos) and no systematic or rigorous follow-up of patients for CV events. Of the 14,237 patients, only 1243 (8.7%) were studied for at least one year; 716 (5%) received rosiglitazone alone or in combination with some other anti-diabetic therapy for at least one year. The studies considered in this pooled analysis also involved diverse treatment regimens including monotherapy, combination therapy, placebo vs active comparator, add-on vs initial therapy, etc. Different diabetic treatment regimens utilized often reflect patient populations with different baseline risk factors for cardiovascular events. Perhaps reflecting this heterogeneity in the pooled clinical trial database, are the following observations made in Ms. Mele's review:

- rosiglitazone was associated with a greater risk of ischemia in previously-treated patients than in treatment-naïve patients
- the risk of cardiac ischemia was increased in placebo-controlled studies with an OR of 1.6 (p=0.02) whereas active-controlled studies had an OR of 0.8 (p=0.8)
- combined use of rosiglitazone and metformin is associated with a higher risk of ischemia than metformin alone; however, these findings are not consistent across the 10 studies contributing to this subgroup and there was marked heterogeneity across these studies
- a consistent increase in risk of cardiac ischemia was observed in all studies in which rosiglitazone was added on to insulin; exclusion of these five studies from the meta-analysis resulted in no significant increase in ischemic risk
- evaluation of time-to-event for studies from the meta-analysis that are > 1 yr in duration shows no difference in risk in the composite endpoint of stroke/MI/CV death and serious ischemic events.

Since the current opinion of increased cardiac ischemic risk associated with rosiglitazone is not based on findings from a single trial but from a pooling of multiple, heterogeneous trials, one might also want to compare the findings from the meta-analysis with the results of the long-term controlled studies. Indeed, many of the observations made on the meta-analysis may be better addressed with these long-term controlled studies. In particular, risk in treatment-naïve patients can be addressed by DREAM and ADOPT, which specifically studied such patients. Results from ADOPT and RECORD may clarify the observation in the meta-analysis of lower risk in active control trials, as these two studies compared rosiglitazone to other anti-diabetic agents. RECORD and perhaps BARI-2D may provide information on the risk of combining rosiglitazone and metformin. As these two studies enrolled a patient population with greater baseline risk for CVD, the use of nitrates and ACE-inhibitors may be in a sufficient number of patients to further evaluate any interaction with rosiglitazone and the risk of cardiac ischemia. Finally, the observation that longer term studies in the meta-analysis had similar risks between rosiglitazone and comparators highlights the importance of looking to these long-term controlled studies to confirm this finding.

The risk of ischemia associated with rosiglitazone and insulin co-administration is not likely to be addressed with these long-term studies. This observation will need further discussion by the committee members as the following questions are considered at the close of GSK and FDA presentations.

QUESTIONS TO COMMITTEE MEMBERS

1. Please comment on the strengths/limitations of the meta-analysis of the 42 controlled clinical studies submitted by GSK to the Agency on defining cardiac ischemic risk for Avandia. Comment on the following areas is of particular relevance:

- types of studies selected (e.g., comparison groups)
- patient populations
- treatment duration of studies
- endpoints (total ischemic events, composite of stroke/MI/CV death) and their ascertainment

2. Please comment on the completed and on-going long-term clinical studies for Avandia with respect to whether cardiac ischemic risk identified in the meta-analysis can be addressed by:

- DREAM
- ADOPT
- RECORD
- BARI-2D

3. Do the available data support a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes mellitus (VOTE requested)?

- If yes, is there evidence that this risk is greater than other available therapies for the treatment of type 2 diabetes mellitus?

4. Does the overall risk-benefit profile of Avandia support its continued marketing in the US (VOTE requested)?

- If yes, please comment on what FDA should do to maximize the risk-benefit considerations (e.g., limit to certain patients, incorporate a boxed warning….)

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TAB 4

CLINICAL REVIEW
The RECORD Trial: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

Clinical Reviewer: Hylton V. Joffe, M.D., M.M.Sc.
Review Division: Division of Metabolism and Endocrinology Products
Drug Name: Avandia (rosiglitazone)
Sponsor: GlaxoSmithKline
NDA: 21-071
Date Review Completed: July 5, 2007

1. RATIONALE

In 2000, the Committee for Proprietary Medicinal Products (CPMP) granted marketing authorization for rosiglitazone with a regulatory commitment that the Sponsor conduct a large, long-term clinical trial evaluating the effects of rosiglitazone on cardiovascular (CV) risk. The impetus for this study was based on the potentially adverse effects of rosiglitazone on weight gain and lipids.

The RECORD study was designed to meet the above regulatory commitment, and was endorsed by the CPMP in December 2000.

Below, I quote verbatim the rationale for the study that was included with the original RECORD protocol:

> *"In patients with type 2 diabetes mellitus, rosiglitazone (RSG) reduces insulin resistance, hyperglycaemia and hyperinsulinaemia, all of which have been associated with an increased risk of cardiovascular disease. It also increases body weight (albeit without altering known weight-associated cardiovascular risk factors), has a multifactorial effect on lipids (some effects putatively beneficial, some putatively adverse), and leads to a modest increase in plasma volume.*
>
> *The effects of the most widely used oral combination therapy (Su[lphonylurea] plus metformin) on cardiovascular outcome have never been formally characterised.*
>
> *For diabetic patients inadequately controlled on a single oral agent, there is a need formally to evaluate long term cardiovascular outcome, both for those who receive the most widely used oral combination therapy (sulfonylurea (Su) plus metformin (Met)), and for those who are given rosiglitazone in addition to their first-line therapy (metformin or Su).*
>
> *Furthermore, there is a need to compare the ability of RSG combination therapy to improve hyperglycaemia (and other metabolic defects associated with type 2 diabetes) with that of Su plus metformin within a formal clinical trial.*
>
> *This clinical trial is designed to address these two needs."*

2. THE RECORD PROTOCOL

Reviewer's comments: This review only includes information from the RECORD study that is pertinent to assessing CV risk with rosiglitazone. Endpoints and assessments that are unrelated to CV risk are intentionally not included in this review.

2.1. Primary Objective: To compare the time to reach the combined endpoint of CV death or CV hospitalization between rosiglitazone-treated patients and patients not treated with rosiglitazone.

All serious adverse events are undergoing blinded screening by the trial's contract organization to identify potential CV endpoints. Below are the pre-specified definitions of CV death and CV hospitalization. These events are being blindly adjudicated by the Clinical Endpoint Committee, which is comprised of one diabetologist, five cardiologists, and other appropriate experts, as required.

CV death: Death is classified as "cardiovascular" if an unequivocal non-cardiovascular cause cannot be established. CV death includes death from:

- Definite heart failure (see definition below)
- Myocardial infarction (death must occur within 30 days)
- Sudden death (see Appendix 4.1 for a detailed definition)
- Acute vascular events (aortic dissection, aortic aneurysm, pulmonary embolism, stroke, or other vascular cause)

Deaths which are due to unknown causes will be classified as "unknown deaths" but will be counted as CV deaths for the analysis of the primary endpoint.

CV hospitalization: Hospitalization involving a change in date (no date change required for unplanned ambulatory percutaneous CV interventions) for

- Acute myocardial infarction (defined using the 2000 European Society of Cardiology/American College of Cardiology Consensus Statement – see Appendix 4.1 for a detailed definition)
- Definite heart failure (change in dose or intravenous medication or introduction of a new class of medication specific for the treatment of heart failure in the context of objective evidence of cardiac dysfunction)
- Stroke (see Appendix 4.1 for a detailed definition)
- Unstable angina pectoris (cardiac ischemic symptoms requiring treatment but not qualifying as acute myocardial infarction by cardiac biochemical markers)
- Transient ischemic attack (sudden onset, focal neurological deficit with complete recovery within 24 hours)
- Invasive cardiovascular procedure for an acute condition or patient deterioration (coronary, carotid, or peripheral arteries)
- Extremity amputation due to macrovascular peripheral vascular disease related to diabetes (not amputations due to clear trauma)

- Other CV or undefined CV reason

The CEC will exclude routine or planned hospitalizations that are not associated with a worsening of the patient's diseases.

Reviewer's comments: A more ideal primary endpoint would limit CV death and CV hospitalization to events related only to atherosclerosis and heart failure, and not include events like pulmonary embolism (not likely to be related to the assigned treatments).

RECORD was powered based on the above composite endpoint. Important caveats of this approach include:

- **A difference between treatment groups in the composite endpoint may primarily be driven by one or more of the individual components that comprise the endpoint**
- **There will be smaller numbers of events and lower power for detecting differences between treatment groups with regard to individual components of the composite endpoint (e.g., acute myocardial infarction)**

2.2. Secondary Objectives include:

-Rosiglitazone add-on to metformin vs. sulfonylurea add-on to metformin
-Rosiglitazone add-on to sulfonylurea vs. metformin add-on to sulfonylurea

- Time to reach the endpoint of CV death or CV hospitalization

-Rosiglitazone add-on to metformin vs. sulfonylurea add-on to metformin
-Rosiglitazone add-on to sulfonylurea vs. metformin add-on to sulfonylurea
-Rosiglitazone-treated patients vs. non-rosiglitazone-treated patients

- Time to all-cause mortality
- Time to first occurrence of definite heart failure
- Time to first occurrence of all-cause mortality, acute myocardial infarction, stroke, definite heart failure, and unstable angina
- Time to first occurrence of CV death, acute myocardial infarction, stroke, and unstable angina
- Combined CV death or CV hospitalization plus diabetes-related microvascular events
- Total number of events in the CV death or CV hospitalization endpoint
- Changes in glycemia (e.g., HbA1c, fasting plasma glucose) and related metabolic parameters (e.g., lipids) at Month 18 (interim analysis in a subset of patients), Year 3, and study end
- Time to failure of glycemic control and initiation of insulin

2.3. Hypothesis: The rosiglitazone group is non-inferior to the non-rosiglitazone group when comparing the hazard of the primary endpoint (CV death or CV hospitalization). If non-inferiority is established, the Sponsor will perform a test for superiority.

2.4. Study Design: Multicenter (~370 centers in Europe, Australia, and New Zealand), randomized, open-label, parallel group study in ~3,956 patients. After a four-week run-in period, patients will be followed for a median of six years.

The Sponsor justifies an open-label design because of the need to otherwise

- Provide dummy versions of the five add-on treatments (rosiglitazone, metformin, and the three acceptable sulfonylureas) at different doses
- Persuade participants who may be using a variety of other therapies to take both active and dummy treatments for a long period of time

In addition, the Sponsor states that patients will be unblinded when insulin is started because the time of introduction of insulin therapy differs in the rosiglitazone and non-rosiglitazone arms (see below).

The Sponsor states that bias is unlikely because

- CV death and CV hospitalization will be adjudicated blindly
- Objective biochemical measurements will be performed in a central laboratory

Reviewer's comments: Bias can still be introduced into the study if knowledge of treatment assignment affects behaviors of the participants or study personnel (e.g., rates of loss-to-followup, management of other CV risk factors such as blood pressure or lipids).

During the run-in period, patients continue taking their background oral anti-diabetic medication (metformin or sulfonylurea) and undergo reinforcement of diet and exercise. Randomization has been stratified according to background anti-diabetic medication.

- Patients inadequately controlled on metformin (n=1,978) are randomized to receive add-on rosiglitazone 4 mg/day (n=989) or add-on sulfonylurea (glibenclamide, gliclazide, or glimepiride) (n=989)

- Patients inadequately controlled on a sulfonylurea (n=1,978) are randomized to receive add-on rosiglitazone 4 mg/day (n=989) or add-on metformin (n=989)

The metformin and sulfonylurea add-on therapy is initiated in line with local clinical practice and the available tablet/capsule strengths.

Based on this design, there are four treatment groups:

Rosiglitazone add-on to metformin
Sulfonylurea add-on to metformin
Rosiglitazone add-on to sulfonylurea
Metformin add-on to sulfonylurea

Reviewer's comments: For some analyses, the Sponsor will combine the rosiglitazone add-on to metformin group with the rosiglitazone add-on to sulfonylurea group (this new combined group = rosiglitazone-treated patients).

Similarly, the Sponsor will combine the sulfonylurea add-on to metformin group with the metformin add-on to sulfonylurea group (this new combined group = non-rosiglitazone-treated patients). For the primary endpoint, the Sponsor will compare the rosiglitazone-treated group with the non-rosiglitazone-treated group.

Each patient will undergo 21-27 scheduled visits, which corresponds to 5-7 years of treatment (the number of scheduled visits depends on the timing of enrollment needed to achieve a median follow-up of six years). Clinic visits occur at Screening (Week -4), Baseline (Day 0), every two months during Year 1, every three months during Year 2, and every four months thereafter.

The Sponsor is performing tablet counting at each visit to assess compliance.

The protocol permits switching the background metformin from one brand to another and switching between different formulations of sulfonylureas because of intolerance, economic reasons, or medication availability. Choosing equivalent doses of the new sulfonylurea is left to the discretion of the investigator and local guidelines.

The protocol also permits increases (to improve glycemic control) or decreases (because of adverse effects) in background sulfonylurea or background metformin doses (see below).

2.5. Glycemic control:

Patients in both treatment groups are being treated to a target hemoglobin A1c (HbA1c) ≤7.0% to eliminate the possibility of confounding due to between-group differences in glycemic control.

If the HbA1c is >7.0% after at least eight weeks of treatment, the investigator can increase the dose of the add-on medication to 4 mg bid for rosiglitazone and up to the maximal allowed doses for add-on metformin and sulfonylurea. The Sponsor permits adjustment of the background or add-on anti-diabetic medication if there are unacceptable side effects (e.g., hypoglycemia or gastrointestinal effects), and permits interruption of the add-on therapy if there is an excessive reduction in HbA1c. Patients who have interruption of add-on therapy because of an excessive reduction in HbA1c will remain in the Randomized Treatment Phase, and will restart the same randomized treatment, if required.

Patients with HbA1c ≥8.5% after at least eight weeks at the maximum permitted or tolerated dose of add-on study medication will have a repeat HbA1c measurement at least four weeks later. Patients will start additional anti-diabetic medications if this second test confirms HbA1c ≥8.5% (or if the elevation of the first HbA1c requires immediate treatment, based on the investigator's judgment).

- Patients not receiving rosiglitazone who are on maximal doses of metformin + sulfonylurea will be switched to insulin (with or without sulfonylurea or metformin

according to local clinical practice) and will enter the Post-Randomized Treatment Phase of the trial where they will continue to be assessed for CV outcomes (see below).

- Rosiglitazone-treated patients will start a third oral agent (sulfonylurea or metformin). Patients with HbA1c ≥8.5% after at least eight weeks at maximal permitted or tolerated doses of triple oral therapy will have a repeat HbA1c measurement at least four weeks later. Rosiglitazone will be discontinued and patients will be switched to insulin (with or without sulfonylurea or metformin according to local clinical practice) and proceed into the Post-Randomized Treatment Phase of the trial (where they will continue to be assessed for CV outcome – see below) if this second test confirms HbA1c ≥8.5% (or if the elevation of the first HbA1c requires immediate treatment, based on the investigator's judgment).

<u>Reviewer's comments</u>: One limitation of RECORD is that rosiglitazone is discontinued when patients in the rosiglitazone group require insulin. Many of these patients will be followed for CV endpoints in the Post-Randomized Treatment Phase (see below). Premature discontinuation of rosiglitazone due to the need for insulin (i.e., discontinuation of rosiglitazone prior to study end or prior to the development of a CV endpoint) is not expected to reflect the full effects of rosiglitazone on CV outcomes. Although the Sponsor is performing sensitivity analyses of the primary CV endpoint using the Per Protocol population (patients still on randomized study medication at the time of the primary CV event or at the end of the study), the study's primary conclusion will be based on the All Randomized and Treated Patients population (randomized patients who have received ≥1 dose of add-on study medication).

The interim results (mean followup of 3.75 years) from RECORD show that 6% of patients in the rosiglitazone group and 11% of patients in the metformin + sulfonylurea group have been switched to insulin.

The protocol does not specify the rationale for discontinuing rosiglitazone upon initiation of insulin, but the most likely explanation is that combination rosiglitazone and insulin therapy is contraindicated in the European Union.

Exposures to rosiglitazone may be longer than exposures to the comparator drugs (metformin and sulfonylurea), because rosiglitazone-treated patients can be treated with three oral anti-diabetic agents before switching to insulin whereas the non-rosiglitazone treated patients initiate insulin upon failing dual combination therapy.

- For patients reaching the upper permitted level of glycemia but who wish to remain in the Randomized Treatment Phase, the protocol permits increases up to the allowable maximum dose (based on local guidelines and labeling

requirements) of background or add-on sulfonylurea or metformin or switching between brands of metformin or formulations/type of sulfonylurea.

Reviewer's comments: This amendment was added because some patients strongly expressed reluctance to initiate insulin therapy.

The protocol does not discuss how study personnel should manage other CV risk factors during the course of the study (e.g., blood pressure, lipids, and the use of aspirin). Because this is an open-label trial, differential management of these CV risk factors in the rosiglitazone and non-rosiglitazone treated patients could bias results.

2.6. Post-Randomized Treatment Phase

Patients enter the Post-Randomized Treatment Phase (also known as the "CV Outcomes Assessment" Phase) if they:

- Withdraw from the Randomized Treatment Phase of the study (will be followed for at least five years from the time of randomization) OR
- Have insufficient glycemic control on oral agents (will be followed until study end) OR
- Are treated for >4 weeks with any protocol-prohibited anti-diabetic agents (e.g., pioglitazone)

During this phase, patients:

- Undergo assessment for CV outcomes, liver function, and glycemia (where possible)
- Have no restrictions on medical care or anti-diabetic therapy except for treatment with PPARγ-agonists
- Have regular telephone visits (questioned about hospitalization and CV events) and yearly visits (physical exam, vital signs, weight, smoking history, HbA1c, liver tests, and electrocardiograms)

Reviewer's comments: Any differences in medical care (e.g., management of blood pressure, lipids) between the treatment groups during this phase of the study may affect interpretability of the results.

The interim results show that 12% of rosiglitazone-treated patients and 19% of non-rosiglitazone treated patients have thus far withdrawn from receiving study drugs but are still in follow-up. As mentioned above, premature withdrawal of study drug (i.e., discontinuation of study drug prior to study end or prior to the development of a CV endpoint) is not expected to reflect the full effects of that study drug on CV outcomes.

Serious adverse events and medication changes will be recorded for patients who are followed for CV death and CV hospitalization, but not for patients who are only followed

for survival status and date/reason of death. For non-serious adverse events, only microvascular, diabetes-related adverse events will be collected.

Reviewer's comments: The Sponsor is limiting adverse event collection during this phase to events that may constitute study endpoints. Other non-serious adverse events are not being collected because patients will no longer be receiving add-on study medications during this phase.

2.7. Study Population:

2.7.1. Inclusion Criteria Include:

1. Type 2 diabetes (1999 WHO criteria) with HbA1c >7.0% to ≤9.0%
2. Men and women 40-75 years old with body mass index >25.0 kg/m^2
3. Oral glucose lowering agent for ≥6 months prior to screening with no change in dose for ≥2 months prior to screening
4. Inadequate control on metformin ≥1,700 mg/day (or ≥1,000 mg/day with proven intolerance to higher doses) OR inadequate control on one of the following sulfonylureas:
   Glibenclamide ≥15 mg/day (≥10.5 mg micronized formulation)
   Gliclazide ≥240 mg/day (≥90 mg modified-release formulation)
   Glimepiride ≥4 mg/day
   (Patients taking at least one-half of these sulfonylurea doses for at least two months can be enrolled if there is proven intolerance to higher doses)

2.7.2. Exclusion Criteria Include:

1. >1 oral anti-diabetic agent at any time within the prior six months
2. Prior insulin use (transient use OK to stabilize newly-diagnosed patients, for acute infections/hospitalizations, and in the setting of pregnancy)
3. Prior thiazolidinedione use
4. Hospitalization for a major CV event within the prior three months or scheduled major CV intervention (e.g., cardiac surgery)
5. Presence of gangrene
6. Treated or untreated heart failure
7. Blood pressure >180/105 mmHg on optimal anti-hypertensive therapy
8. Fasting triglycerides >1,062 mg/dL
9. Serum creatinine >1.47 mg/dL
10. Liver tests >2.5x upper limit of normal
11. Hemoglobin <11.0 g/dL (men) or <10.0 g/dL (women)

Reviewer's comments: Based on these criteria, the Sponsor is not targeting enrollment towards patients at high risk for CV events. The study would be better powered if the Sponsor focused enrollment on patients at higher risk for CV events (e.g., patients with additional CV risk factors or patients with a prior history of a CV event).

2.8. Assessments include:

1. Vital signs and body weight at all visits (heart rate and blood pressure measured only once per visit)
2. Yearly assessment of smoking history
3. Fasting blood samples, including
    - Fasting plasma glucose and HbA1c at all visits
    - Standard hematology and biochemistry at screening, baseline, every six months for the first year, then yearly thereafter
    - Liver tests at screening, baseline, every two months for the first year, Month 18, then every four months starting at Year 2
    - Cholesterol panel at screening, baseline, every six months for the first two years, then yearly thereafter
4. Albumin/creatinine at baseline and every six months for the first two years then yearly thereafter
5. Yearly electrocardiograms
6. 24-hour ambulatory blood pressure monitoring at baseline, Months 6, 12

Reviewer's comments: Blood pressure is an important CV risk factor. Only a single measurement of blood pressure is obtained at each visit. Because there is inherent variability in blood pressure measurements, a more ideal approach would have been to measure blood pressures at least twice at each visit and use the mean results for statistical analyses.

Safety Assessments include:

1. External Data Safety Monitoring Board, which meets twice annually to review unblinded safety data
2. Withdrawal of patients with two consecutive elevations in ALT >3x above the upper limit of normal
3. Withdrawal of metformin for patients with two consecutive serum creatinine concentrations >1.47 mg/dL

2.9. Statistical Plan:

Please see Dr. John Lawrence's statistical review for details.

2.9.1. Patient populations:

All Randomized and Treated Patients population: Randomized patients who have received ≥1 dose of add-on study medication. This population will be used for the primary endpoint.

Per Protocol population: Patients still on randomized study medication at the time of the primary CV event or at the end of the study. This population will also be used for the primary endpoint, but the Sponsor will base the study conclusion on the All Randomized Patients Population if there are conflicting results.

Intent-to-Treat population (ITT): All randomized and treated patients with a valid baseline and post-baseline measurement for the parameter of interest.

2.9.2. Statistical Hypotheses:

2.9.2.1. Primary comparison of interest:

CV outcomes: The rosiglitazone group (rosiglitazone add-on to metformin combined with rosiglitazone add-on to sulfonylurea) will be concluded to be non-inferior to the non-rosiglitazone group (metformin add-on to sulfonylurea combined with sulfonylurea add-on to metformin) if the upper bound of the one-sided 95% confidence interval for the hazard ratio of the combined primary endpoint in the rosiglitazone group relative to the non-rosiglitazone group falls below 1.20. The Sponsor will claim superiority of rosiglitazone if the upper bound of this confidence interval is <1.0. The statistical model will include stratum (background therapy with metformin vs. sulfonylurea) as a covariate.

Reviewer's comments: The goal of a non-inferiority study is to show that a treatment is not worse than an active control by more than a certain amount (non-inferiority margin). The CPMP agreed with the Sponsor's plan to use a non-inferiority margin of 20%, but the Sponsor's rationale for this choice of margin is not specified in the protocol. In addition, the CV effects of combination metformin + sulfonylurea have not been definitively established or quantified in well-designed studies. Does metformin + sulfonylurea combination therapy have beneficial, neutral, or detrimental effects on CV outcomes and (if beneficial or detrimental) what is the magnitude of these effects? Are the CV effects in the metformin + sulfonylurea treatment arm in RECORD spuriously low or high? Knowing the CV effects of metformin + sulfonylurea combination therapy from well-designed studies would provide answers to these questions and provide crucial information for interpreting RECORD's results and the appropriateness of the non-inferiority margin.

2.9.2.2. Other Statistical Tests: Secondary CV endpoints will be compared by testing the null hypothesis of no treatment effect with a two-sided test and a significance level of 0.05.

2.9.3. Power Calculations:

Primary CV Outcome: The study will have ~99% power for the primary non-inferiority analysis based on the proposed sample sizes, a combined CV endpoint of 11% per year in the control group (3% CV deaths and 8% CV hospitalizations), 2% per year loss-to-followup, a one-sided alpha 0.025, and a true hazard ratio between treatment groups of 1.0. The 11% annualized event rate was derived from the diabetes subgroups in the CARE (*Circulation*. 1998; 98: 2513-9) and MICRO-HOPE (*Lancet*. 2000; 355: 253-59) studies.

<u>Reviewer's comments</u>: Dr. Lawrence reports that the power of the study is more closely related to the number of events rather than to the number of patients. He constructed Table 1, which shows RECORD's power for different assumed rates of annual events (keeping the other assumptions described above constant).

Table 1. Power Based on Various Annual Event Rates			
Annual event rate	**Expected number of events**	**Power to exclude hazard ratio of 1.20**	**Power to exclude hazard ratio of 1.40**
2%	430	47%	93%
3%	620	62%	99%
4%	810	74%	>99%
5%	990	82%	>99%
6%	1160	87%	>99%
7%	1320	91%	>99%
8%	1470	94%	>99%
9%	1620	96%	>99%
10%	1750	97%	>99%
11%	1880	98%	>99%
From Dr. Lawrence's statistical review			

The recently published interim analyses (see Section 3) show that the overall annual event rate for the combined primary endpoint is much lower than predicted (3.1% for adjudicated + pending events instead of an anticipated 11% annual event rate) and the loss-to-followup rate is higher than predicted (2.6-2.7% per year instead of 2% per year). Dr. Lawrence has calculated the conditional power for claiming non-inferiority at study completion based on the findings from the interim analysis (Table 2). The conditional power calculations have been performed for the primary combined endpoint and for one of the secondary endpoints (composite of CV death, myocardial infarction, and stroke).

Table 2. Conditional Power Calculations Based on the Interim Data (from Dr. Lawrence's statistical review)			
True Hazard Ratio[1]	**Conditional Power to Exclude the Following Hazard ratios**		
	1.20	**1.30**	**1.40**
Primary endpoint			
1.00	46%	94%	>99%
1.08[2]	22%	80%	99%
Composite endpoint of CV death, myocardial infarction, and stroke			
1.00	43%	82%	97%
0.97[2]	50%	87%	98%
1 Hazard ratio for data following the interim analysis 2 Assumes hazard ratio for data after the interim analysis is equal to the observed hazard ratio at interim analysis			

In the protocol, the Sponsor reports >80% power for the secondary outcomes.

2.10. Patient Retention:

In the protocol, the Sponsor reports that a large number of patients have completely withdrawn from the study without providing follow-up data. To address this issue, the Sponsor amended the protocol in February 2006 to stress the importance of patient retention, and created a substudy to track former RECORD patients, in countries where this is permitted.

Reviewer's comments: As acknowledged by the Sponsor, loss-to-followup of a substantial number of patients may jeopardize the results of the study, because we will be unable to assess whether the CV outcomes of interest subsequently occurred (or would have occurred if treatment was continued) in the patients lost-to-followup.

To encourage retention, the current version of the protocol:

1. Permits modification of the frequency and schedule of assessments in the Post-Randomized Treatment Phase
2. Requests that investigators seek permission to contact a nominated person (e.g. relative, healthcare professional, neighbor) to obtain follow-up information for patients refusing to enter the Post-Randomized Treatment Phase. At the end of the study, investigators will review public records (e.g. National Death Registry) for patients who have completely withdrawn from the study (if possible) to ascertain survival status.

Reviewer's comments: Information obtained from public records or via a nominated person will not be as reliable as adjudicated information obtained in the setting of the clinical trial.

2.11. Tracking Substudy for Former RECORD Patients:

The Sponsor is attempting to obtain written informed consent for this substudy from patients who have withdrawn from RECORD (but not those that have withdrawn consent), in countries where this is permitted. Patients who refuse to participate will be asked whether the investigator can contact a nominated person yearly for survival status and date and cause of death. If no consent is given for either of the above, investigators will review public records at the end of the study to ascertain survival status (if possible).

Patients enrolled in the substudy will have no restrictions on medical care or glucose-lowering therapy except that treatment with a PPARγ agonist should be avoided, if possible. Patients who agree to provide CV outcomes data will have annual clinic visits and regular telephone visits. This schedule is identical to the schedule for the Post-Randomized Treatment Phase, and can also be modified to encourage patient retention

in the substudy. Patients who agree to provide CV outcomes data in this tracking study will be followed for CV death and CV hospitalization (same definitions as used for RECORD), serious adverse events, and non-serious microvascular-diabetes-related adverse events. The Sponsor will attempt to obtain endpoint data from the period since the last contact in RECORD through to enrollment into the tracking sub-study.

3. RECORD – INTERIM RESULTS (*N Engl J Med*. 2007; 357: 28-38)

Table 3 summarizes the baseline characteristics of patients enrolled in RECORD, as reported in the interim analysis. For comparison purposes, Table 3 also includes the baseline characteristics of patients enrolled in pioglitazone's PROactive study (*Lancet*. 2005; 366: 1279-89). To be eligible for PROactive, patients were required to have evidence of extensive macrovascular disease prior to enrollment. Therefore, as expected, PROactive enrolled a higher proportion of men and former smokers and enrolled slightly older patients with a higher baseline prevalence of coronary artery disease, stroke, and peripheral artery disease.

Table 3. Baseline Characteristics in RECORD and PROactive

	RECORD		PROactive	
Variable	**Rosiglitazone (N = 2220)**	**Control (N = 2227)**	**Pioglitazone (N=2605)**	**Placebo (N=2633)**
Previous medication, n (%)				
Metformin only	1117 (50)	1105 (50)	253 (10)	261 (10)
Sulfonylurea only	1103 (50)	1122 (50)	508 (20)	493 (19)
Age, yr	58.4±8.3	58.5±8.3	61.9±7.6	61.6±7.8
Male sex, n (%)	1142 (51)	1152 (52)	1735 (67)	1728 (66)
White race, n (%)	2200 (99)	2199 (99)	2564 (98)	2600 (99)
Time since diagnosis, yr	7±5	7±5	8 (4-13)*	8 (4-14)*
Body-mass index, kg/m^2	31.6±4.7	31.5±4.9	30.7±4.7	31.0±4.8
Glycated hemoglobin, %	7.9±0.7	7.9±0.7	7.8 (7.0-8.9)*	7.9 (7.1-8.9)*
Fasting plasma glucose, mg/dL	177±43	177±40	Not specified	Not specified
Hypertension, n (%)†	1754 (79)	1774 (80)	1947 (75)	2005 (76)
Ischemic heart disease, n (%)				
Any disease	359 (16)	374 (17)	1246 (48)	1274 (48)
Stable angina	222 (10)	228 (10)	Not specified	Not specified
Myocardial infarction	102 (5)	114 (5)	1230 (47)	1215 (46)
Unstable angina	20 (1)	30 (1)	Not specified	Not specified
Cerebrovascular disease, n (%)				
Any disease	100 (5)	97 (4)	Not specified	Not specified
Stroke	54 (2)	54 (2)	486 (19)	498 (19)
Transient ischemic attack	50 (2)	47 (2)	Not specified	Not specified
Peripheral arterial disease, n (%)	124 (6)	131 (6)	504 (19)	539 (20)
Congestive heart failure, n (%)	12 (0.5)	6 (0.3)	Not specified	Not specified
Lipid disorder, n (%)	2123 (96)	2100 (94)	Not specified	Not specified
Smoking history, n (%)				
Current smoker	363 (16)	343 (15)	340 (13)	381 (14)
Former smoker	565 (26)	539 (24)	1199 (46)	1159 (44)

Plus–minus values are means ± SD
*Median with interquartile range
†>130/80 mmHg for RECORD; criteria not specified for PROactive

Table 6 in Appendix 4.2 summarizes the baseline characteristics of patients in each of the meta-groups used by Ms. Joy Mele in her statistical review of the rosiglitazone meta-analysis.

Table 4 summarizes patient disposition from the interim analysis of the RECORD study. I have integrated this information into my review of the RECORD protocol, where applicable.

Table 4. Patient disposition: Interim results of RECORD	
Rosiglitazone-treated patients	2,220
Add-on to metformin	1,117 (50%)
Add-on to sulfonylurea	1,103 (50%)
Switched to insulin	140 (6%)
Withdrew study drugs but still in follow-up	263 (12%)
Still receiving assigned treatment at the latest visit	1,626 (73%)
Loss-to-followup	218 (9.8%) or ~2.6% per year
Non-rosiglitazone-treated patients	2,227
Sulfonylurea add-on to metformin	1,105 (50%)
Metformin add-on to sulfonylurea	1,122 (50%)
Switched to insulin	244 (11%)
Withdrew study drugs but still in follow-up	412 (19%)
Still receiving assigned treatment at the latest visit	1,476 (66%)
Loss-to-followup	223 (10.0%) or ~2.7% per year
Causes of dropout that led to loss-to-followup *	
Adverse event	37 (0.8%)
Loss to followup	87 (2.0%)
Consent withdrawn	244 (5.5%)
Site closure	15 (0.3%)
Other	51 (1.1%)
Unknown	7 (0.2%)
Based on data available as of March 30, 2007 Mean duration of follow-up is 3.75 years *Results only available for the overall study	

Table 5 summarizes the CV results from the interim analysis of RECORD. In the interim analysis, there were 419 adjudicated primary endpoints. There are an additional 91 patients (50 in the rosiglitazone group and 41 in the metformin + sulfonylurea group) with potential primary events that were pending adjudication as of the cutoff date of March 30, 2007.

For adjudicated primary endpoints (217 in the rosiglitazone group and 202 in the control group), the hazard ratio was 1.08 (95% confidence interval 0.89-1.31). When events pending adjudication are included, the hazard ratio for the primary endpoint is 1.11

(95% confidence interval 0.93-1.32). Therefore, the data for the primary endpoint are compatible with as much as a 7-11% improvement or as much as a 31-32% worsening in cardiovascular risk with rosiglitazone compared to metformin + sulfonylurea.

The rosiglitazone group had a statistically significant higher risk of heart failure compared to the control group. There were no statistically significant differences between the rosiglitazone group and the control group for the other secondary endpoints listed in Table 5; however, there is low power to detect significant differences in these endpoints.

Time-to-event curves for the primary endpoint and select secondary endpoints are shown in the *N Engl J Med* paper, which is included in the Advisory Committee background package.

Table 5. Interim Results from RECORD

Variable	Rosiglitazone Group	Control Group	Hazard Ratio (95% CI)	p value
Adjudicated events				
Primary endpoint	217	202	1.08 (0.89-1.31)	0.43
Cardiovascular (CV) death	29	35	0.83 (0.51-1.36)	0.46
Death from any cause	74	80	0.93 (0.67-1.27)	0.63
Myocardial infarction (MI)	43	37	1.16 (0.75-1.81)	0.50
Heart failure	38	17	2.24 (1.27-3.97)	0.006
Death from CV, MI, stroke	93	96	0.97 (0.73-1.29)	0.83
Events adjudicated and pending adjudication				
Primary endpoint	267	243	1.11 (0.93-1.32)	0.26
CV death	37	46	0.80 (0.52-1.24)	0.32
MI	49	40	1.23 (0.81-1.86)	0.34
Heart failure	47	22	2.15 (1.30-3.57)	0.003
Death from CV, MI, stroke	109	114	0.96 (0.74-1.24)	0.74

CI = confidence interval
Each patient was counted only once for each category

4. APPENDIX

4.1. Pre-Specified Definitions of Sudden Death, Myocardial Infarction, and Stroke:

Sudden death

- Death within one hour after onset of new symptoms OR
- Witnessed death without new symptoms during the 72 hours preceding death OR
- Cardiac arrest followed by death within 30 days even if temporarily recovered OR
- Unwitnessed death in the absence of new symptoms

Acute myocardial infarction: Adjudicated according to the definition from a consensus document issued by the Joint European Society of Cardiology/American College of Cardiology (EHJ 2000 vol. 21; 1502-1513)

Hospitalization with either typical symptoms of cardiac ischemia or new pathological electrocardiographic findings (as defined in EHJ 2000 article)

PLUS

Elevation of troponin I or troponin T above the upper limit of normal (ULN) OR creatine kinase (CK)-MB isoenzyme ≥ 2x ULN OR CK >2x ULN

Stroke: Confirmed by a neurologist, CT, or MR whenever possible

- Rapid onset of focal (or global, if related to subarachnoid hemorrhage or deep coma) disturbance of cerebral function lasting >24 hours (unless interrupted by thrombolysis, surgery or death), with no apparent cause other than a vascular origin
- Secondary stroke events (e.g., resulting from polycythemia vera, brain tumors, trauma) will be excluded

Definite focal signs:

- Unilateral or bilateral motor impairment (including dyscoordination)
- Unilateral or bilateral sensory impairment
- Aphasias/dysphasias (non-fluent speech)
- Hemianopia (half-sided impairment of visual fields)
- Diplopia
- Forced gaze (conjugate deviation)
- Dysphagia of acute onset
- Apraxia of acute onset
- Ataxia of acute onset
- Perception deficit of acute onset

The following symptoms are listed in the protocol as not being acceptable as sole evidence of focal dysfunction:

- Dizziness, vertigo
- Localized headache
- Blurred vision of both eyes
- Dysarthria (slurred speech)
- Impaired cognitive function (including confusion)
- Impaired consciousness
- Seizures

4.2. Baseline Characteristics of Patients in the Meta-Groups Used in Joy Mele's Meta-Analysis:

Table 6. Baseline Characteristics for the Meta-Groups Used in Joy Mele's Meta-Analysis									
Variable	**RSG alone (n=4236)**	**RSG + background medications**			**RSG + sulfonylurea**		**RSG + metformin (n=3469)**	**RSG + insulin (n=1530)**	**RSG + metformin + sulfonylurea (n=837)**
		211 (n=224)	**334 (n=194)**	**352 (n=61)**	**All but 135 (n=4018)**	**135 (n=227)**			
Age (yr)	58 (10)	64 (9)	67 (7)	64 (7)	58 (10)	68 (6)	57 (10)	58 (9)	56 (9)
Men, %	63%	81%	56%	74%	57%	73%	57%	53%	60%
Body mass index (kg/m^2)	30 (5)	29 (4)	29 (5)	30 (4)	30 (5)	31 (5)	32 (6)	32 (5)	33 (6)
Diabetes duration (yr)	5 (6)	6 (6)	4 (4)	8 (7)	7 (6)	7 (6)	6 (5)	13 (8)	8 (6)
Heart failure (%)	1%	100%	2%	0%	1%	5%	2%	3%	1%
Coronary heart disease (%)	11%	67%	15%	100%	13%	29%	11%	19%	16%
HbA1c (%)	8.5 (1)	8 (1)	7 (1)	7 (1)	9 (1)	8 (1)	8 (1)	9 (1)	9 (1)
HDL-C (mg/dL)	45 (11)	42 (11)	47 (12)	43(11)	46 (12)	44(11)	47 (12)	48 (13)	50 13)
LDL-C (mg/dL)	131 (36)	113 (32)	120 (32)	97 (25)	125 (34)	113 (30)	117 (33)	122 (34)	112 (33)
Diastolic blood pressure (mmHg)	81 (9)	78 (8)	82 (8)	85 (8)	81 (9)	78 (9)	80 (8)	79 (9)	80 (8)

RSG = rosiglitazone
Numbers with parentheses are means and standard deviations
Table adapted from Joy Mele's statistical review of the rosiglitazone meta-analysis – please see Ms. Mele's review for further details.

STATISTICAL REVIEW AND EVALUATION

NDA #:	21-071 SE8-022
Applicant:	GlaxoSmithKline
Name of Drug:	Avandia® (rosiglitazone)
Indication:	Treatment of type 2 diabetes
Document reviewed:	RECORD interim analysis data published in NEJM
Date of submission:	June 5, 2007
Statistical Reviewer:	John Lawrence, Ph.D.
Statistical Team Leader:	J. Todd Sahlroot, Ph.D.
Medical Reviewer:	Hylton Joffe, M.D. (HFD-510)

This is a statistical review consisting of conditional power calculations based on interim data for the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes; also known by the Study Identifier: BRL-049653/231). The study is a long term, open label, randomized non-inferiority study in patients with type 2 diabetes, comparing the combination of rosiglitazone (RSG) and either metformin (MET) or sulphonylurea (SU) with metformin plus sulphonylurea on cardiovascular endpoints and glycaemia. The primary endpoint is the first occurrence of CV death or CV hospitalization. The protocol-specified null hypothesis is $H_0 : \lambda \geq 1.2$ where λ is the hazard ratio and 1.2 is the non-inferiority margin.

4447 patients with type 2 diabetes treated with MET or SU have enrolled in the study. As of the interim analysis, the mean duration of follow-up is 3.75 years with a total duration of follow-up of 16,675 patient years. There have been a total of 419 adjudicated primary endpoints and the article states that the investigators expect to observe 750 primary endpoints by the end of the study based on an expected annual event rate of 3.1% per year, far below the 11% rate assumed in the protocol. Therefore, I will

assume that the fraction of the total information observed at this interim analysis is t_1 = 419/750 = 55.9% in the conditional power calculations below. The purpose of the calculations to calculate the (conditional) power of the study to reject the null hypothesis assuming a "true" hazard rate for data after the interim analysis, conditional on the observed hazard ratio from the interim analysis. The calculations are performed for the primary endpoint and a second endpoint which is a composite of CV death, MI and stroke.

1. For the primary endpoint, the observed log-hazard ratio is log(1.08) ≈ 0.077 with a standard error of 0.098. If the true hazard ratio is λ, the final test statistic for testing the null hypothesis $H_0 : \lambda \geq \lambda_0$ conditional on the observed data will have a normal distribution with mean $\sqrt{t_1}\,\dfrac{0.077-\log(\lambda_0)}{0.098}+\sqrt{1-t_1}\,\dfrac{\log(\lambda)-\log(\lambda_0)}{0.098\sqrt{\dfrac{t_1}{1-t_1}}}$

   $=\dfrac{0.077t_1+\{1-t_1\}\log(\lambda)-\log(\lambda_0)}{0.098\sqrt{t_1}}$ and variance $1-t_1=0.441$. The conditional power is $\Phi\left(\dfrac{-1.96-\dfrac{0.077t_1+\{1-t_1\}\log(\lambda)-\log(\lambda_0)}{0.098\sqrt{t_1}}}{\sqrt{1-t_1}}\right)$. For example,

   a) If the true hazard ratio is 1 and the null hypothesis is $H_0 : \lambda \geq 1.2$ where 1.2 is the protocol-specified non-inferiority margin, then the conditional power is

$$\Phi\left(\frac{-1.96-\frac{0.077t_1-\log(1.2)}{0.098\sqrt{t_1}}}{\sqrt{1-t_1}}\right)\approx 46\%.$$

b) If the true hazard ratio is 1 and the null hypothesis is $H_0:\lambda\geq 1.4$, then the

conditional power is $\Phi\left(\frac{-1.96-\frac{0.077t_1-\log(1.4)}{0.098\sqrt{t_1}}}{\sqrt{1-t_1}}\right)\approx 99\%.$

c) If the true hazard ratio is 1.08 and the null hypothesis is $H_0:\lambda\geq 1.2$, then the

conditional power is $\Phi\left(\frac{-1.96-\frac{0.077t_1+\{1-t_1\}\log(1.08)-\log(1.2)}{0.098\sqrt{t_1}}}{\sqrt{1-t_1}}\right)\approx 22\%.$

d) If the true hazard ratio is 1.08 and the null hypothesis is $H_0:\lambda\geq 1.4$, then the

conditional power is $\Phi\left(\frac{-1.96-\frac{0.077t_1+\{1-t_1\}\log(1.08)-\log(1.4)}{0.098\sqrt{t_1}}}{\sqrt{1-t_1}}\right)\approx 99\%.$

2. For the endpoint of death from cardiovascular causes, myocardial infarction, and stroke, the observed log-hazard ratio is log(0.97) ≈ – 0.03 with a standard error of 0.145. If the true hazard ratio is λ, the final test statistic for testing the null hypothesis $H_0:\lambda\geq\lambda_0$ conditional on the observed data will have a normal distribution with mean $\sqrt{t_1}\frac{-0.03-\log(\lambda_0)}{0.145}+\sqrt{1-t_1}\frac{\log(\lambda)-\log(\lambda_0)}{0.145\sqrt{\frac{t_1}{1-t_1}}}$

$= \dfrac{-0.03t_1 + \{1-t_1\}\log(\lambda) - \log(\lambda_0)}{0.145\sqrt{t_1}}$ and variance $1-t_1 = 0.441$. The conditional power is $\Phi\left(\dfrac{-1.96 - \dfrac{-0.03t_1 + \{1-t_1\}\log(\lambda) - \log(\lambda_0)}{0.145\sqrt{t_1}}}{\sqrt{1-t_1}} \right)$. For example,

a) If the true hazard ratio is 1 and the null hypothesis is $H_0 : \lambda \geq 1.2$, then the conditional power is $\Phi\left(\dfrac{-1.96 - \dfrac{-0.03t_1 - \log(1.2)}{0.145\sqrt{t_1}}}{\sqrt{1-t_1}} \right) \approx 43\%.$

b) If the true hazard ratio is 1 and the null hypothesis is $H_0 : \lambda \geq 1.4$, then the conditional power is $\Phi\left(\dfrac{-1.96 - \dfrac{-0.03t_1 - \log(1.4)}{0.145\sqrt{t_1}}}{\sqrt{1-t_1}} \right) \approx 97\%.$

c) If the true hazard ratio is 0.97 and the null hypothesis is $H_0 : \lambda \geq 1.2$, then the conditional power is $\Phi\left(\dfrac{-1.96 - \dfrac{\log(0.97) - \log(1.2)}{0.145\sqrt{t_1}}}{\sqrt{1-t_1}} \right) \approx 50\%.$

d) If the true hazard ratio is 0.97 and the null hypothesis is $H_0 : \lambda \geq 1.4$, then the conditional power is $\Phi\left(\dfrac{-1.96 - \dfrac{\log(0.97) - \log(1.4)}{0.145\sqrt{t_1}}}{\sqrt{1-t_1}} \right) \approx 98\%.$

These results and additional results for the intermediate null hypothesis $H_0 : \lambda \geq 1.3$ are summarized in Table 1 below. The results are clearly sensitive to the range of hazard ratios that were investigated.

Table 1. RECORD conditional power calculations

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

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:	July 6, 2007
To:	Mary Parks, MD Director Division of Metabolic and Endocrine Products
From:	Gerald Dal Pan, MD, MHS Director Office of Surveillance and Epidemiology
Subject:	Supervisory Memo for Review of RECORD Study
Drug Name(s):	Rosiglitazone (Avandia)
Application Type/Number:	NDA 21-071
Submission Number:	SE8-022
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2006-331

1 INTRODUCTION

This memorandum documents my comments on Dr. David Graham's review of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) protocol and his review of the interim analysis of that study.

2 MATERIAL REVIEWED

I have reviewed the following documents:

GlaxoSmithKline Submissions:

The RECORD study protocol.

Interim analysis of RECORD

FDA Reviews:

Graham, DJ. Review of protocol for RECORD. July 5, 2007

Graham, DJ. Review of interim analysis for RECORD. July 6, 2007

Lawrence J. Statistical review and evaluation of RECORD protocol and interim analysis. July 3, 2007

3 DISCUSSION

Two basic questions that are fundamental to an understanding of cardiovascular risk associated with rosiglitazone are: 1) Is rosiglitazone associated with a risk of myocardial ischemia and myocardial infarction? and 2) Is the risk of myocardial ischemia and myocardial infarction

associated with rosiglitazone different from that associated with other oral antidiabetic agents, such as metformin, a sulfonylurea (SU), or pioglitazone?

The RECORD study was designed because of "a need formally to evaluate long term cardiovascular outcomes, both for those who receive the most widely used oral combination therapy (SU plus metformin), and for those who will be given rosiglitazone in addition to their first-line therapy (SU or metformin)"[1] and also to address "a need to compare the ability of rosiglitazone combination therapy to improve hyperglycaemia (and other metabolic defects associated with type 2 diabetes) with that of SU plus metformin within a formal clinical trial."[2] The study was not designed to examine specifically the outcomes of myocardial ischemia and myocardial infarction. (Dr. Graham's review and this memorandum address only the cardiovascular aim of the study, and do not comment on the glucose-lowering aim.)

I concur with Dr. Graham that there are a number of design and methodological considerations that make interpretation of the results of the RECORD study difficult and potentially unreliable. The principal limitations of RECORD include:

1) The ***open-label design***, which can lead to bias in outcome ascertainment.

2) The ***treatment groups*** studied, which do not allow for a direct measure of rosiglitazone's cardiovascular adverse effects, though this design could allow for comparisons between rosiglitazone and other oral antidiabetic agents. However, because of other design limitations, it is unlikely that the RECORD study will provide high quality comparative data on cardiovascular risk among the oral antidiabetic agents studied in this protocol.

3) The ***composite cardiovascular outcome***, which does not focus on the specific events of current interest, myocardial ischemia and myocardial infarction, but rather collects a broad range of cardiovascular endpoints. It should be noted that when RECORD was designed, these two endpoints were not identified in the RECORD protocol as specific items of concern. The broad range of cardiovascular events included in the primary composite cardiovascular outcome may obscure important differences in myocardial ischemia and myocardial infarction among the oral agents studied.

4) The ***non-inferiority study design***, which, if not carefully executed, can lead to an erroneous conclusion that two or more treatments are similar to each other (ie, non-inferior), when they actually are not. In this regard, it is important to note that the RECORD protocol does not appear to justify the selection of a 20% increase in relative risk (ie, an upper limit of the 95% confidence interval of the hazard ratio equal to 1.2) as the magnitude of excess cardiovascular risk that is to be excluded.

5) The ***statistical power*** of the study is based on the composite cardiovascular endpoint and an assumption of an event rate of 11% per year in the control group. Data from the interim analysis, however, indicate that the actual event rate is much lower than the assumed event rate. The lower observed event rate leads to a substantial reduction in the power of the study to exclude a relative hazard of 1.2 for the primary composite outcome.[3] In addition, because the composite outcome

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[1] GlaxoSmithKline. RECORD Study Protocol – Amendment 7 (document date 27 February 2006). Section 1.2.6, page 26.

[2] *Ibid.*

[3] Dr. Graham and Dr. Lawrence have each provided power calculations in their reviews. While the actual estimates of statistical power are different in the two reviews, presumably because of variations in methodology and assumptions, they both conclude that, based on the observed event rates in the interim analysis, RECORD does not have sufficient statistical power to meet its primary objective.

endpoint includes events that are not of primary interest for the issue at hand, there is insufficient power to exclude a relative hazard of 1.2 for myocardial ischemia and myocardial infarction.

The above features of the RECORD study represent, in my view, the major substantial limitations in this study. Dr. Graham and Dr. Lawrence have each identified additional limitations that must also be considered.

4 CONCLUSIONS AND RECOMMENDATIONS

There are a number of design and methodological considerations that will make interpretation of the results of the RECORD study difficult and potentially unreliable. By its design, RECORD will not be able to determine if treatment with rosiglitazone has a risk of myocardial ischemia and myocardial infarction relative to treatment without rosiglitazone. Furthermore, for reasons stated above, RECORD will be poorly able to ascertain differences in the risk of myocardial ischemia and myocardial infarction with rosiglitazone relative to that with metformin and sulfonylureas. In addition, there is poor statistical power for analyses of the events of interest.

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/s/

Gerald DalPan
7/9/2007 01:52:49 PM
MEDICAL OFFICER

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:	July 6, 2007
To:	Mary Parks, MD Director, Division of Metabolic and Endocrine Drug Products
Thru:	Gerald Dal Pan, MD, MHS Director, Office of Epidemiology and Surveillance
From:	David J. Graham, MD, MPH Associate Director for Science and Medicine Office of Epidemiology and Surveillance
Subject:	Review of protocol for RECORD
Drug Name(s):	AVANDIA® (rosiglitazone maleate)
Application Type/Number:	21-071
Submission Number:	SE8-022
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2006-331

CONTENTS

EXECUTIVE SUMMARY

RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes) is a noninferiority design, open-label, parallel group clinical trial comparing patients who have failed monotherapy with either metformin (Met) or sulfonylurea (SU) and who are then randomized to add-on rosiglitazone or add-on Met or SU. Patients will be followed for a median of 6 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. The noninferiority margin was 20%. The study included patients with treated type 2 diabetes mellitus (T2DM) with glycosylated hemoglobin A1c (HgbA1c) greater than 7.0% and less than or equal to 9.0%. The study was powered under the assumption of a combined outcome rate (CVD+CVH) of 11 per 100 per year. The study was designed to compare RSG (+Met or +SU) *vs*. non-RSG (Met+SU). Secondary analyses will compare RSG+Met *vs*. SU+Met or RSG+SU *vs*. Met+SU.

The design of RECORD cannot address the question of RSG's specific cardiovascular risk because it does not include a placebo group. If no difference is found between RSG and non-RSG therapies, or between RSG and Met or RSG and SU, the question of RSG's cardiovascular risk will still remain because RECORD cannot distinguish between an increased cardiovascular risk with all three drugs, and no increase in cardiovascular risk with any of the drugs.

The use of the noninferiority design, by its nature, is especially sensitive to actions that serve to misclassify or obscure differences between study groups.[12-16] In the setting of a safety outcome, this liability is magnified because sponsors and investigators alike generally are not focused on showing that their drug has a safety problem. The noninferiority margin for RECORD is unacceptably large, as demonstrated by the clinical value attached to similar levels of risk reduction from statin or aspirin use for prevention of AMI. A 20% relative increase in AMI or CVD+AMI risk associated with RSG use would translate into thousands of excess cardiovascular injuries and deaths.

The open-label nature of the study substantially increases the likelihood of bias in how outcomes are identified, labeled, classified, and reported. Coupled with the noninferiority design, these two factors seriously undermine the credibility and validity of the study.

The use of the composite outcome, CVD+CVH, is overly broad and non-specific, thereby masking the types of cardiovascular outcomes of greatest concern (sudden death + fatal+nonfatal AMI). This renders the primary outcome for RECORD unreliable for purposes of establishing the presence or absence of cardiovascular risk with RSG or non-RSG therapies.

Finally, the statistical power of RECORD is extremely low creating a situation that strongly biases this study against any possibility of uncovering a cardiovascular risk in the event such a risk is present.

RECORD does not now, nor will it at completion, provide meaningful evidence to demonstrate with any degree of certainty that RSG does not increase the risk of AMI, AMI+sudden death, or the APTC outcome. The biased design of RECORD renders it useless as an objective measure of RSG's cardiovascular safety. Its results cannot be trusted because they are too subject to bias. The design and statistical power limitations of RECORD are such that it is probably unethical to continue the study because it cannot produce scientifically reliable or valid results.

The preliminary and final results of RECORD should not be considered reliable or valid and should not be used by FDA in any consideration of risk or benefit associated with RSG use.

BACKGROUND/HISTORY

At the direction of the European Medicines Evaluation Agency's Committee for Proprietary Medicinal Products, the manufacturer designed and initiated a postmarketing randomized clinical trial to evaluate the use of rosiglitazone for the occurrence of increased cardiovascular toxicity. The original protocol was completed in February 2001 and was amended seven times, with the current version dated 27 February 2006. The study name is RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes).

1 REVIEW METHODS AND MATERIALS

Study overview

Study design. RECORD is a noninferiority design, open-label, randomized, parallel group clinical trial comparing patients who failed monotherapy with either metformin (Met) or sulfonylurea (SU). For patients failing on Met, randomization to receive either add-on rosiglitazone (RSG) or add-on SU was performed at a 1:1 ratio. For patients failing on SU, randomization to receive either add-on RSG or add-on Met was performed at a 1:1 ratio. The primary comparison groups will be RSG (Met+RSG and SU+RSG) *vs*. non-RSG (Met+SU and SU+Met). Patients will be followed for a median of 6 years.

Study population. The study included patients with treated type 2 diabetes mellitus (T2DM) with glycosylated hemoglobin A1c (HgbA1c) greater than 7.0% and less than or equal to 9.0%, with inadequate control on either Met or SU monotherapy. Patients had to have at least 6 months of oral hypoglycemic therapy with at least 2 months on a stable dose of Met or SU to be included in the study. Patients were excluded from study participation if they used 2 or more oral agents during the previous 6 months, had ever used insulin, had ever used a thiazolidinedione, had uncontrolled hypertension, actively treated CHF, or a cardiovascular hospitalization within the previous 3 months. Target goal for diabetes control was an HgbA1c less than 7.0%.

Study outcomes and statistical considerations. The primary cardiovascular outcome was defined as time to occurrence of cardiovascular death (CVD) and/or cardiovascular hospitalization (CVH) and 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. The noninferiority margin was 20%. For RSG to be considered not inferior to non-RSG, the upper bound of the 95% confidence interval for the hazard ratio of CVD/CVH comparing RSG *vs*. non-RSG must be less than 1.20. Secondary cardiovascular outcomes included time to: all-cause mortality; first occurrence of congestive heart failure (CHF); CVD+acute myocardial infarction (AMI)+stroke (CVA)+CHF+transient ischemic attack (TIA)+unstable angina (UA); CVD+AMI+CVA+TIA+UA.

The study was powered using the following assumptions: combined outcome rate (CVD+CVH) of 11 per 100 per year (CVD: 3 per 100 per year; CVH: 8 per 100 per year); lost to follow-up: 2% per year; alpha=0.025 (one-sided); true hazard ratio=1.0.

Definition of cardiovascular outcomes. Cardiovascular death included any death that could not be clearly ascribed to a non-cardiovascular cause. This included death from unknown cause; sudden death; death following CHF or AMI; or death from "acute vascular events" (aortic dissection, aortic aneurysm, pulmonary embolism, CVA, or "any other vascular cause").

Cardiovascular hospitalization included an overnight stay in hospital for AMI, CHF, CVA, TIA, UA, invasive cardiovascular procedure (bypass grafting, angioplasty, stenting), or extremity amputation.

2 RESULTS OF REVIEW

Exposure groups. The study was designed to compare RSG (+Met or +SU) *vs*. non-RSG (Met+SU). Secondary analyses will compare RSG+Met *vs*. SU+Met or RSG+SU *vs*. Met+SU. The main problem with these active comparator analyses is that they do not directly address the question of additional risk conferred by RSG itself because there is no comparison of add-on RSG *vs*. add-on placebo (PBO). From the planned analyses, a comparison of RSG *vs*. Met and RSG *vs*. SU will be obtainable, but this will not inform the question of whether RSG increases the risk of AMI or CVD, a risk that is suggested by FDA's meta-analysis of RSG clinical trials data and by the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial.[1] Most of the trials contributing to the FDA meta-analysis were PBO-controlled, either as RSG monotherapy *vs*. PBO or as RSG add-on *vs*. PBO add-on. This analysis design permitted the separate and specific effect of RSG on ischemic cardiovascular risk to be described. Similarly, DREAM involved comparison of RSG *vs*. PBO in pre-diabetic patients. The design of RECORD cannot address the question of RSG's specific risk because it does not include a PBO group. If no difference is found between RSG and non-RSG therapies, or between RSG and Met or RSG and SU, the question of RSG's cardiovascular risk will still remain because RECORD cannot distinguish between an increased cardiovascular risk with RSG, Met, and SU, and no increase in cardiovascular risk with any of the three drugs. Additionally, low study power and the noninferiority design (see below) substantially undermine the ability of this study to detect clinically important differences between RSG and either Met or SU.

Composite outcome. RECORD was designed to evaluate the composite outcome of CVD+CVH. 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, namely, AMI+AMI-related or sudden death. The definition of CVD used in this study included some events that are not typically thought of as being related to ischemic cardiovascular disease (pulmonary embolism; aortic dissection; ruptured aortic aneurysm; death due to "other vascular causes"). More problematic is the issue of how deaths from "unknown cause" are handled. Per protocol, deaths of unknown cause will be counted as cardiovascular deaths. If follow-up efforts are suboptimal, a large number of deaths will 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). A narrower definition that focused on the types of ischemic cardiovascular events identified in FDA's meta-analysis would be more appropriate and meaningful. This modified definition of cardiovascular death would include sudden death + fatal AMI and possibly + fatal CVA.

Use of CVH as a component of the primary outcome is very broad and includes events that are not typical of studies evaluating ischemic cardiovascular risk. Typical outcome studies focus on AMI or AMI+CVA. Events such as TIA, UA, CHF, and limb amputation are not typically included, and invasive cardiovascular procedures are sometimes included and sometimes excluded in cardiovascular outcome studies. Of note, reported diagnoses such as TIA, UA, and CHF have low clinical accuracy meaning that misclassification error will be high, serving to reduce or mask differences between groups.

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 have the effect of masking the association of greatest concern, basically by increasing background "noise." This is particularly important because the leading cause of death among patients with diabetes is ischemic cardiac disease,[2] and any increase in this risk conferred by a medication used to treat T2DM would have a substantial population impact.

From the interim safety analysis provided to the data safety monitoring board of RECORD and submitted to FDA (a portion of which was recently published),[3] there were 38 primary outcome CVD events and 383 primary outcome CVH events in the RSG and non-RSG groups combined. Among CVD events, 7 (18.4%) were due to AMI and 18 (47.4%) were due to AMI or sudden death. The majority of deaths were from less specific or non-cardiac causes. Among CVH events, 70 (18.2%) were due to AMI and 130 (33.9%) were due to AMI or CVA. Nearly two-thirds of CVH events were for conditions not typically classified as ischemic cardiovascular disease.

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.[4,5] Failure to implement double-blinding of treatment allocation is a well-recognized source of bias leading to results favorable to a company's interests.[6,7] A recently published review of statin comparative trials examined the contribution of various factors to bias favoring the sponsoring pharmaceutical company.[8] 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).[8]

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.[9] 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.[9] 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.[9] The end result is a marked increase in the likelihood that noninferiority will be concluded when clinically meaningful differences exist between treatments.

Noninferiority design. While RECORD was designed as a noninferiority 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.[10]

There are a number of issues specific to the use of a noninferiority 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.[11] In a noninferiority trial, these incentives don't exist because the goal of the study is to show that there is "no difference" between treatments.[11] In other words, a noninferiority 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 will be less than optimal study implementation will be high. Similarly, the protocol did not discuss issues related to quality assurance or quality control, issues of heightened importance in a study using a noninferiority design.

Another concern is that the noninferiority 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.[12,13] That means there is very limited experience using this design for the specific purpose of establishing a safety claim. Given the variety of difficulties documented with use of the noninferiority design for efficacy studies, whereby noninferiority is frequently falsely claimed,[12-15] caution and close scrutiny of the application of this method to safety is necessary because the consequence of a false claim of noninferiority is that a drug will be considered equally safe to other drugs when it is actually more dangerous.

A critical element for using the noninferiority 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 noninferiority. 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.[12-16] It is also important that a justification be given for selection of the noninferiority margin chosen.[12-16] The protocol for RECORD stated that a 20% margin was chosen. No justification for selecting a 20% margin was given in the protocol.

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.[12,13] 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 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 noninferiority compared to another treatment.[13,16] 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.

Statistical power. 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 1).

Table 1. Cardiovascular event rates from various diabetes outcome studies.

			Rates per 100 person-years				
Study	N	PYRs	AMI	CVD	AMI+CVD	APTC	CVD+CVH
Pre-diabetes							
DREAM[1]	2634	7902	0.11	0.13	0.24	0.29	
Early diabetes							
ADOPT[18]	2895	10571	0.11		0.39	0.73	
Established diabetes							
ARIC[19]	1558	14019		0.96	1.23		
UKPDS[20]	1138	11188	0.95	1.09	2.04	2.40	
Diabetes with documented vascular disease							
HOPE[21]	1769	7961	2.88	2.16		4.41	
PROactive[11]	2633	7570		2.46	3.70	5.11	
RECORD							
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.[1] The placebo group in this randomized trial experienced rates per 100 person-years of AMI, CVD, AMI+CVD, and the Antiplatelet Trialists' Collaboration (APTC)[17] outcome (CVD+nonfatal AMI + nonfatal CVA) of 0.11, 0.13, 0.24 and 0.29 respectively.[1] In A Diabetes Outcome Progression Trial (ADOPT), patients newly diagnosed with diabetes were randomized to receive Met, SU or RSG.[18] 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,[19] 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.[20] 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.

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.[11] 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.

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.[21] 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+nofatal 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.[19]

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.

In the protocol, the sponsor stated that with 3956 subjects, it would have 99.2% power to exclude a hazard ratio of 1.2 for the composite outcome of CVD+CVH. Using a software program from the UK's Medical Research Council Clinical Trials Unit written for the statistical software package, Stata, the sponsor's power calculations were reproduced fairly closely using its study specifications (outcome rate in controls 11% per year; lost to follow-up 2% per year; 1-sided alpha=0.025; true hazard ratio=1.0). Using this program and the sponsor's assumptions, the calculated power was 98.5% (table 2).

Table 2. Power calculation for RECORD based on sponsor's original study specifications.

Type of trial	Noninferiority - time-to-event outcome
Statistical test assumed	Unweighted logrank test (local)
Number of groups	2
Allocation ratio	Equal group sizes
Total number of periods	6
Length of each period	One year
Survival probs per period (group 1)	0.890 0.793 0.707 0.630 0.561 0.500
Survival probs per period (group 2)	0.869 0.757 0.659 0.574 0.500 0.435
Number of recruitment periods	0
Number of follow-up periods	6
Method of accrual	Uniform
Hazard ratios as entered (groups 1,2)	1, 1.2
Alpha	0.050 (two-sided)
Power (designed)	0.985
Total sample size (calculated)	3957
Expected total number of events	2004

To achieve this level of statistical power, 2004 events of CVD+CVH would be required. With 419 adjudicated CVD+CVH events, the study currently has about 17% power to exclude a hazard ratio of 1.2 for its primary composite outcome (analysis not shown). Based on the event rate for CVD+CVH observed from the interim analysis of RECORD, 13525 patients would be required to achieve 98.5% power, 3-times greater than the 4447 actually enrolled (table 3).

Table 3. Estimated sample size required to exclude a hazard ratio of 1.2 for the composite outcome of cardiovascular death plus cardiovascular hospitalization, given the event rates observed from the interim safety analysis for RECORD.

Type of trial	Noninferiority - time-to-event outcome
Statistical test assumed	Unweighted logrank test (local)
Number of groups	2
Allocation ratio	Equal group sizes
Total number of periods	6
Length of each period	One year
Survival probs per period (group 1)	0.974 0.949 0.925 0.902 0.878 0.856
Survival probs per period (group 2)	0.969 0.940 0.911 0.883 0.856 0.830
Number of recruitment periods	0
Number of follow-up periods	6
Method of accrual	Uniform
Hazard ratios as entered (groups 1,2)	1, 1.2
Alpha	0.050 (two-sided)
Power (designed)	0.985
Total sample size (calculated)	13525
Expected total number of events	2009

Using more realistic expected rates for AMI, AMI+CVD, and the APTC outcome in a general population of patients with diabetes, the statistical power of RECORD to exclude a hazard ratio of 1.2 is well-below 5% for each of these outcomes (table 4).

Table 4. Estimated power of RECORD to exclude a hazard ratio of 1.2 for the outcomes of acute myocardial infarction, acute myocardial infarction plus cardiovascular death, or the Antiplatelet Trialists' Collaboration outcome (cardiovascular death plus nonfatal myocardial infarction or stroke).

	Expected rate per 100 person-years	Number of events from RECORD	Power to exclude hazard ratio of 1.2
AMI	1.0	77	< 5%
AMI+CVD	2.0	108	< 5%
APTC outcome	2.5	168	< 5%

4 SUMMARY AND RECOMMENDATIONS

The design of RECORD does not permit the direct comparison of rosiglitazone against its nonuse for the occurrence of AMI or AMI+sudden death. One of the strengths of the FDA's meta-analysis of company clinical trials is that most of it was based on randomization to RSG or placebo add-on, within the context of other existing therapy, which was identical within each meta-group stratum that contributed to the analysis. Similarly, DREAM also employed randomization to either RSG or placebo.[1] In PROactive, patients under treatment for T2DM were randomized to add-on pioglitazone or add-on placebo.[11] Such a design permits the direct determination of the added effect of a specific thiazolidinedione to cardiovascular risk. RECORD (and also ADOPT)[18] relied on active comparators so that any difference or absence of difference in risk between groups tells us nothing about the intrinsic risk of RSG compared with its nonuse.

Multiple specific design elements of RECORD are problematic, and will work together to bias the outcome in a direction that will likely falsely show no difference between treatment groups. These include its noninferiority design, the lack of blinding to treatment, a broad primary outcome that does not focus on the safety question of greatest importance (AMI+sudden death or AMI+CVD), and extremely low statistical power.

The use of the noninferiority design, by its nature, is especially sensitive to actions that serve to misclassify or obscure differences between study groups.[12-16] In the setting of a safety outcome, this liability is magnified because sponsors and investigators alike generally are not focused on showing that their drug has a safety problem. Also, RECORD's 20% noninferiority margin is unacceptably high as demonstrated by the clinical value attached to similar levels of risk reduction from statin or aspirin use for prevention of AMI.

The open-label nature of the study substantially increases the likelihood of bias in how outcomes will be identified, labeled, classified, and reported. Coupled with the noninferiority design, these two factors undermine the credibility and validity of the study.

The use of the composite outcome, CVD+CVH, is overly broad and non-specific, thereby masking the types of cardiovascular outcomes of greatest concern (sudden death + fatal+nonfatal AMI). This renders the primary outcome for RECORD unreliable for purposes of establishing the presence or absence of cardiovascular risk with RSG or non-RSG therapies. Reliance on an overly broad outcome definition increases the degree of misclassification within the study because it mixes less common outcomes that are of greatest concern to this Office with more common and far less serious outcomes, many of which are not suspected of being associated with RSG use.

Finally, the statistical power of RECORD is extremely low, creating a situation that strongly biases this study against any possibility of uncovering a cardiovascular risk in the event such a risk is present. An inconclusive finding resulting from low statistical power is not synonymous with demonstration of noninferiority, and in fact, can occur in the setting of substantially increased risk.[10]

Based on the above, RECORD does not now, nor will it at completion, provide meaningful evidence to demonstrate with any degree of certainty that RSG does not increase the risk of AMI, AMI+sudden death, or the APTC outcome. The biased design of RECORD renders it useless as an objective measure of RSG's cardiovascular safety. Its results cannot be trusted because they are too subject to bias. The design and statistical power limitations of RECORD are such that it is probably unethical to continue the study because it cannot produce scientifically reliable or valid results.

The preliminary and final results of RECORD should not be considered reliable or valid and should not be used by FDA in any consideration of risk or benefit associated with RSG use.

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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:	July 6, 2007
To:	Mary Parks, MD Director, Division of Metabolic and Endocrine Drug Products
Thru:	Gerald Dal Pan, MD, MHS Director, Office of Epidemiology and Surveillance
From:	David J. Graham, MD, MPH Associate Director for Science and Medicine Office of Epidemiology and Surveillance
Subject:	Review of interim safety analysis for RECORD
Drug Name(s):	AVANDIA® (rosiglitazone maleate)
Application Type/Number:	21-071
Submission Number:	SE8-022
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2006-331

CONTENTS

EXECUTIVE SUMMARY

RECORD is an open-label, randomized, noninferiority trial comparing RSG to non-RSG treatment for the occurrence of cardiovascular death (CVD) + cardiovascular hospitalization (CVH) as well as for individual components of this composite outcome. A review from the Office of Surveillance and Epidemiology (OSE) described and critiqued the study design of RECORD and found that it will not provide reliable or valid results.

Results from an interim analysis of RECORD were summarized and the statistical power of this study to exclude a hazard ratio of 1.2 was calculated for specific cardiovascular outcomes. Analyses were also performed to determine the statistical power of RECORD to exclude a hazard ratio of 1.4 (a 40% increase in risk; the level of ischemic cardiovascular risk identified by FDA in its meta-analysis of RSG clinical trials). Based on the number of outcome events collected in the RECORD study after nearly 16,000 person-years of follow-up, the number of outcome events at study completion (23,000 person-years of follow-up) was estimated. Statistical power to exclude hazard ratios of 1.2 and 1.4 were calculated based on the number of events expected at study completion.

The statistical power of RECORD to exclude a hazard ratio of 1.2 was extremely low for the outcome of CVD+CVH (17%). Statistical power was virtually nonexistent for all other outcomes. Even with a more extreme hazard ratio of 1.4, statistical power remained very low for all outcomes except CVD+CVH when comparing RSG *vs*. non-RSG. At study's end, the statistical power of RECORD to exclude a hazard ratio of 1.2 will still be low or nonexistent for all potential outcomes of interest, suggesting statistical futility.

RECORD is severely underpowered, and given the design weaknesses identified in an OSE review of the protocol for this study, its actual statistical power is even lower than that calculated here. In a noninferiority trial for a safety outcome, the end-result of such low power is that noninferiority may be concluded or else assumed when noninferiority does not hold and has not been demonstrated. For example, it may be erroneously concluded that noninferiority exists if the point estimate for risk is below the noninferiority margin, even if the upper limit of the 95% confidence interval exceeds that margin. Contrary to an FDA Alert issued on May 21, 2007, the results of this interim analysis of RECORD do not provide "contradictory evidence" in support of RSG's cardiovascular safety. Rather, the results of this interim analysis suffer from a profound lack of statistical power, made worse by multiple deficiencies in design that guarantee an optimistically biased underestimation of RSG's coronary heart disease risks. RECORD is incapable of credibly or reliably excluding clinically meaningful increases in cardiovascular risk associated with RSG use, and should play no role in FDA's benefit-risk determinations for this drug.

1 BACKGROUND/HISTORY

In May 2007, a meta-analysis of clinical trials examining rosiglitazone (RSG) use and acute myocardial infarction (AMI) and cardiovascular death (CVD) was published.[1] Following this, GlaxoSmithKline shared results of an interim safety analysis from its postmarketing randomized clinical trial of rosiglitazone (RSG) called RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes). Portions of this interim analysis were subsequently published.[2] On May 21, the Food and Drug Administration (FDA) issued an FDA Alert in which it stated that "Safety data from a pooled analysis of controlled clinical trials have shown a significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia. However, other published and unpublished data from long-term clinical trials of Avandia provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking Avandia".[3] Some of the unpublished data referred to by FDA as providing "contradictory evidence" was the interim analysis of RECORD. A review from the Office of Surveillance and Epidemiology (OSE) described and critiqued the study design of RECORD and found that this study will not provide reliable or valid results,[4] and hence does not provide evidence to "contradict" the initial report of increased AMI risk with RSG.[1] More accurately, it provides no evidence to contradict the cardiovascular risk of RSG because of its biased design and low statistical power. The present review addresses the results from the interim analysis of RECORD in light of the issues identified in that other OSE review.[4]

RECORD is an open-label, randomized, noninferiority trial comparing RSG to non-RSG treatment for the occurrence of cardiovascular death (CVD) + cardiovascular hospitalization (CVH) as well as for individual components of this composite outcome. Non-RSG treatment consisted of metformin (Met) and sulfonylurea (SU) in combination. A noninferiority margin of 20% (hazard ratio = 1.2) was established by the sponsor without an explanation medically justifying this margin. In noninferiority trials, the margin must be smaller than or equal to the smallest difference that would be considered clinically meaningless.[5-11] A 20% margin for AMI or AMI+CVD is not clinically meaningless. Patients with diabetes are at increased risk of AMI, and this increase in risk is comparable to the increased risk of recurrent AMI faced by patients without diabetes who have had a first AMI.[12] Further, both aspirin[13,14] and statin[15,16] use are associated with reductions in AMI risk of 20%-25% and this reduction in risk is considered to be "clinically important." Hence, a noninferiority margin allowing a 20% increase in cardiovascular risk is excessive; such an increase in risk would translate into thousands of excess fatal and nonfatal AMIs.

2 REVIEW METHODS AND MATERIALS

As this was an interim analysis, the large volume of data and analyses that are typically included in a full study report are not available for review.

Results from the interim analysis were summarized and the statistical power of RECORD to exclude a hazard ratio of 1.2 was calculated for specific cardiovascular outcomes. Analyses were also performed to determine the statistical power of RECORD to exclude a hazard ratio of 1.4 (the level of ischemic cardiovascular risk identified by FDA in its meta-analysis of RSG clinical trials).

Based on the number of outcome events collected in the RECORD study after nearly 16,000 person-years of follow-up, the number of outcome events was estimated at study completion (23,000 person-years of follow-up). Statistical power to exclude hazard ratios of 1.2 and 1.4 were calculated based on the number of events expected at study completion.

3 RESULTS OF REVIEW

3.1.1 Analyses of Study Results

Of note, 38% of deaths in RECORD were classified as "unknown due to insufficient data" (17/38) leading to their being analyzed as CVDs. As noted in the OSE review of the protocol for RECORD,[4] poor follow-up for cause of death was a problem to be expected because the noninferiority design provides no incentive to distinguish cardiac from non-cardiac deaths.[4]

The hazard ratios reported by the sponsor for a variety of cardiovascular outcomes comparing RSG *vs*. non-RSG treatment groups, and add-on RSG *vs*. add-on Met or add-on RSG *vs*. add-on SU are shown in Table 1. The 20% noninferiority margin was exceeded for all outcomes meaning that the interim results from RECORD do not support a claim of noninferiority compared to non-RSG treatment. Of note, the point estimate for AMI risk was 1.16 and the upper bound of the 95% confidence interval for AMI was 1.81 for RSG *vs*. non-RSG and 2.73 for RSG *vs*. Met, signifying potentially very high excess risk.

Table1. Hazard ratios (95% confidence intervals) for various outcomes from the interim safety analysis of the RECORD study.[†]

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	1.08 (0.89-1.31)	0.99 (0.75-1.31)	1.16 (0.90-1.51)
AMI	1.16 (0.75-1.81)	1.44 (0.76-2.73)	0.95 (0.52-1.76)
CVD	0.83 (0.51-1.36)	0.89 (0.44-1.77)	0.78 (0.39-1.56)
APTC	0.97(0.73-1.29)	0.98 (0.65-1.47)	0.96 (0.64-1.43)
CVA	0.76 (0.47-1.23)	0.58 (0.27-1.21)	0.95 (0.50-1.80)
CHF	2.24 (1.27-3.97)	2.87 (1.21-6.78)	1.80 (0.83-3.91)
All cause mortality	0.93 (0.67-1.27)	1.00 (0.63-1.60)	0.86 (0.56-1.33)

[†] CVD (cardiovascular death), CVH (cardiovascular hospitalization), AMI (acute myocardial infarction), CVA (cerebrovascular accident, stroke), APTC (Anti-Platelet Trialists' Collaboration outcome: CVD + nonfatal AMI + nonfatal CVA), CHF (congestive heart failure)

Source: GlaxoSmithKline submission of interim safety analyses for RECORD

The hazard ratios shown in Table 1 were based on the number of events shown for each outcome category presented in Table 2. The total number of AMIs and CVDs were low, and were even lower when stratified by RSG *vs*. Met and RSG *vs*. SU.

Table 2. Number of adjudicated events for various outcomes from the interim safety analysis of the RECORD study.

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	419	193	226
AMI	80	39	41
CVD	64	32	32
APTC	189	93	96
CVA	67	30	37
CHF	55	27	28
All cause mortality	154	72	82

Source: GlaxoSmithKline submission of interim safety analyses for RECORD

The statistical power of RECORD to exclude a hazard ratio of 1.2 was extremely low for the outcome of CVD+CVH (17%). Statistical power was virtually nonexistent for all other outcomes (Table 3).

Table 3. Statistical power of the RECORD study to exclude a hazard ratio of 1.2 for various outcomes based on data from the interim safety analysis.

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	0.17	< 0.01	< 0.01
AMI	< 0.01	< 0.01	< 0.01
CVD	< 0.01	< 0.01	< 0.01
APTC	< 0.01	< 0.01	< 0.01
CVA	< 0.01	< 0.01	< 0.01
CHF	< 0.01	< 0.01	< 0.01
All cause mortality	< 0.01	< 0.01	< 0.01

Source: Sample size program for noninferiority trials: Medical Research Council Clinical Trials Unit, London, UK; assumptions: loss to follow-up=2% per year, expected event rate=11% per year (per RECORD protocol), 4 years of follow-up; Stata v. 9.

Even with a more extreme hazard ratio of 1.4 (40% increase in risk, comparable to that found by FDA in its meta-analysis of RSG clinical trials), statistical power remained very low for all outcomes except CVD+CVH when comparing RSG *vs*. non-RSG (Table 4).

Table 4. Statistical power of the RECORD study to exclude a hazard ratio of 1.4 for various outcomes based on data from the interim safety analysis.

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	0.92	0.50	0.61
AMI	< 0.01	< 0.01	< 0.01
CVD	< 0.01	< 0.01	< 0.01
APTC	0.48	< 0.01	< 0.01
CVA	< 0.01	< 0.01	< 0.01
CHF	< 0.01	< 0.01	< 0.01
All cause mortality	0.33	< 0.01	< 0.01

Source: Sample size program for noninferiority trials: Medical Research Council Clinical Trials Unit, London, UK; assumptions: loss to follow-up=2% per year, expected event rate=11% per year (per RECORD protocol), 4 years of follow-up; Stata v. 9.

Based on the progress reported thus far in RECORD, estimates of the total number of outcome events to be expected at study conclusion are shown in Table 5.

Table 5. Estimated number of various outcome events expected at the conclusion of the RECORD study, given currently observed event rates.

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	602	277	325
AMI	115	56	59
CVD	92	46	46
APTC	272	134	138
CVA	96	43	53
CHF	79	39	40
All cause mortality	222	104	118

Source: The number of events shown in Table 2 accrued over 16,000 patient-years of study time. The estimated number of events expected at study conclusion (~23,000 patient-years) were obtained by multiplying each number from Table 2 by (23,000/16,000) [e.g., x/419=23,000/16,000; 603=419*(23,000/16,000)]

At study's end, the statistical power of RECORD to exclude a hazard ratio of 1.2 will still be low or nonexistent for all potential outcomes of interest (Table 6), suggesting statistical futility.

Table 6. Estimated statistical power of the RECORD study to exclude a hazard ratio of 1.2 for various outcomes at study conclusion, given currently observed event rates.

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	0.45	< 0.01	0.01
AMI	< 0.01	< 0.01	< 0.01
CVD	< 0.01	< 0.01	< 0.01
APTC	< 0.01	< 0.01	< 0.01
CVA	< 0.01	< 0.01	< 0.01
CHF	< 0.01	< 0.01	< 0.01
All cause mortality	< 0.01	< 0.01	< 0.01

Source: Sample size program for noninferiority trials: Medical Research Council Clinical Trials Unit, London, UK; assumptions: loss to follow-up=2% per year, expected event rate=11% per year (per RECORD protocol), 6 years of follow-up; Stata v. 9.

Using a more extreme hazard ratio of 1.4, RECORD will have adequate power for the composite outcome of CVD+CVH but power will be suboptimal to nonexistent for all other outcomes (Table 7).

Table 7. Estimated statistical power of the RECORD study to exclude a hazard ratio of 1.4 for various outcomes at study conclusion, given currently observed event rates.

	RSG vs. Non-RSG	RSG(+SU) vs. Met(+SU)	RSG(+Met) vs. SU(+Met)
CVD+CVH	> 0.95	0.74	0.83
AMI	0.11	< 0.01	< 0.01
CVD	< 0.01	< 0.01	< 0.01
APTC	0.73	0.22	0.25
CVA	0.01	< 0.01	< 0.01
CHF	< 0.01	< 0.01	< 0.01
All cause mortality	0.60	0.05	0.13

Source: Sample size program for noninferiority trials: Medical Research Council Clinical Trials Unit, London, UK; assumptions: loss to follow-up=2% per year, expected event rate=11% per year (per RECORD protocol), 4 years of follow-up; Stata v. 9.

3.1.2 OSE Comments on Study Results

The findings of this review document that at the time of the interim safety analysis, RECORD had extremely low statistical power. In a superiority trial, statistical power represents the probability of correctly identifying a difference between treatments given that a difference truly exists.[17] Superiority trials are typically designed with 90% power. However, with noninferiority trials, the goal is not to show that two treatments are different from one another as is the case with a superiority trial, but to show that two treatments are not different with respect to a particular effect, almost always an efficacy claim.[5-11] In this setting, the importance of the type II error (the probability of concluding that two treatments do not differ when in reality they do differ) and study power (1-type II error) are paramount. One could reasonably argue that in a noninferiority setting, especially when dealing with a major safety outcome, study power should be greater than 97.5% to minimize the likelihood of falsely concluding there is no difference in risk when there really is a difference.

The above analysis was predicated entirely on the number of observed events in the interim analysis and those projected at study conclusion as the determinants of calculated study power. However, the calculated power and the actual statistical power of a study are not necessarily the same. Implicit in the concept of calculated study power is the assumption that the clinical trial or other study in question has been performed perfectly. The true statistical power of a study (as opposed to the calculated power) can be reduced by many factors related to trial implementation and execution such as misclassification of outcomes, reliance on composite outcomes that include components unrelated to the treatments under study or components having low clinical accuracy, selection of an inappropriately high noninferiority margin, drop-outs or subjects lost to follow-up, or reliance on an intention-to-treat (ITT) analysis without also performing an on-treatment or per-

protocol analysis, to name a few.[7,10,18] Each of these factors can increase the likelihood of concluding that two treatments do not differ when in reality, they do differ, but their effect on study power will not be reflected in the value calculated based on study size.

As described in OSE's review of the protocol for RECORD,[4] RECORD has many of these other factors present in its design that will substantially reduce its true statistical power below that calculated and described in this review. These include 1) its open-label rather than double-blind design, thereby increasing the likelihood of bias in case identification, classification, and reporting, as well as the potential for "cointervention" whereby investigators treat one group more aggressively than the other group for other conditions that are related to the outcome of interest;[5] 2) use of a composite outcome (CVD+CVH) that is overly broad and not focused on the outcomes of greatest safety concern to the Office of Surveillance and Epidemiology (AMI and AMI+sudden death); 3) setting an inappropriately large noninferiority margin; 4) a high level of deaths due to "unknown" cause (such deaths are classified by default as CVD even if they are not due to a cardiovascular cause); and 5) reliance on an ITT analysis without also performing an as-treated analysis (the ITT approach tends to increase the likelihood of falsely claiming noninferiority).[7,10,18]

4 SUMMARY AND RECOMMENDATIONS

RECORD is severely underpowered, and given the design weaknesses identified in an OSE review of the protocol for this study,[4] its actual statistical power is even lower than that calculated here. In a noninferiority trial for a safety outcome, the end-result of such low power is that noninferiority will be concluded or else assumed when noninferiority does not hold and has not been demonstrated. Contrary to an FDA Alert issued on May 21, 2007,[3] the results of an interim analysis of RECORD do not provide "contradictory evidence" in support of RSG's cardiovascular safety. Rather, the results of this interim analysis suffer from a profound lack of statistical power, made worse by multiple deficiencies in design that guarantee an optimistically biased underestimation of RSG's coronary heart disease risks. RECORD is incapable of credibly or reliably excluding clinically meaningful increases in cardiovascular risk associated with RSG use, and should play no role in FDA's benefit-risk determinations for this drug.

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TAB 5

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:	July 6, 2007
To:	Advisors and Consultants Staff
Thru:	Mark Avigan, M.D., C.M., Director Division of Drug Risk Evaluation (DDRE) Office of Surveillance and Epidemiology (OSE)
From:	Kate Gelperin, M.D., M.P.H. Lanh Green, Pharm.D, M.P.H. Division of Drug Risk Evaluation (DDRE) Office of Surveillance and Epidemiology (OSE)
Subject:	Additional cardiovascular safety data and analyses received after completion of DDRE consult (dated February 6, 2007)
Drug Name(s):	AVANDIA® (rosiglitazone maleate)
Application Type/Number:	NDA 21-071
Submission Number:	Supplement 022
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2006-331

1 INTRODUCTION

The attached Division of Drug Risk Evaluation (DDRE) review (dated February 7, 2007) has been provided for general background information. The conclusions and recommendations are based on data and analyses available to the reviewers at that point in time. Additional data and analyses will be presented at the EMDAC/DSaRM Advisory Committee meeting on July 30.

GSK submissions considered in the attached DDRE review include the following:

- October 13, 2005: Analysis plan and summary of preliminary results from GSK's analysis of cardiovascular events from completed double-blind controlled trials in patients with type 2 diabetes (T2DM).
- March 27, 2006: (a) SAS datasets for the analysis of cardiovascular events in Clinical Data Interchange Standards Consortium (CDISC) standard format; (b) the results of a full logistic and an exact logistic regression analysis in tabular format, which included correction of an error in the model parameterization.
- May 9, 2006: Summary of further results from statistical analyses using an expanded clinical trials dataset.
- August 4, 2006 Supplement: Prior Approval, Labeling: (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; (d) response to FDA safety data request regarding cardiovascular serious adverse events (SAEs) in rosiglitazone (RSG)-treated subjects in the pooled safety analysis.

- October 24, 2006: GSK Response to comments/questions from FDA review of observational study ("Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents").
- November 2, 2006: GSK Response to FDA Request: Study report and protocol for observational study "Balanced Cohort Study of TZDs and other Anti-diabetic Therapies and Coronary Heart Disease Outcomes", (Ingenix 2004).
- November 8, 2006: GSK Response to FDA request: clarification and comparator group information regarding cardiovascular SAEs with line listings and clinical summaries.

2 MATERIAL RECEIVED AFTER FEBRUARY 7, 2007

Since completion of the attached DDRE review, the following additional data and analyses relevant to cardiovascular safety with rosiglitazone have been received from GSK:

- February 28, 2007: Supplemental New Drug Application (sNDA) to support the use of AVANDIA as monotherapy in patients with type 2 diabetes mellitus, including Clinical Study Report for the ADOPT study (**A D**iabetes **O**utcome **P**rogression **T**rial).
- May 21, 2007: Amendment to S-022: Proposal for a Risk Management Plan to address the potential for myocardial ischemic events in patients treated with rosiglitazone.
- May 22, 2007: Response to FDA request / comment regarding source documents for cardiovascular safety data for other antidiabetic drugs included in GSK presentation at meeting with FDA on May 16, 2007.
- May 31, 2007: Amendment to S-022: New data, analyses, and datasets for the Integrated Clinical Trial (ICT) database, the ADOPT study, and the **D**iabetes **Re**duction **A**ssessment with ramipril and rosiglitazone **M**edication (DREAM) study requested by the FDA.
- June 14, 2007: Response to FDA request for additional information regarding twelve AVANDIA studies included in NEJM article[1] and narrative summaries of cardiovascular deaths in studies BRL 049653/330, BRL 049653/331, and AVA 100193.
- June 15, 2007: Amendment to S-022: Study report entitled, "An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients." nested case-control study using Integrated Healthcare Information Services (IHCIS) database.
- June 18, 2007: Amendment to S-022: Response to FDA request for additional information regarding patients withdrawing from ADOPT for reasons identified as "other", and information regarding the monitoring of study conduct for ADOPT.

[1] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007 Jun 14; 356(24):2457-71. *Erratum* in: Jul 5; 357(1):100.

- June 19, 2007: Submission of additional information on the **A**ction to **C**ontrol **C**ardiovascular **R**isk in **D**iabetes (ACCORD) and **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation Type **2 D**iabetes (BARI 2D) Clinical Trials regarding NHLBI statement on the use of rosiglitazone in clinical trials.
- June 21, 2007: Amendment to S-022: Response to FDA request for baseline datasets for the DREAM trial.

3 DISCUSSION

FDA reviews of ADOPT, DREAM and the **R**osiglitazone **E**valuated for **C**ardiac **O**utcomes and **R**egulation of glycaemia in **D**iabetes (RECORD) interim analysis are provided in separate documents.

The primary focus of the attached DDRE review is a comprehensive analysis conducted by GSK of adverse events pertaining to congestive heart failure (CHF) and separately for events of myocardial ischemia from 42 double-blind randomized clinical trials with rosiglitazone which met pre-specified criteria for inclusion in the analysis. The Sponsor's stated objective was to characterize the degree of association (if any) between rosiglitazone and events of CHF and separately for events of myocardial ischemia across the rosiglitazone clinical trials program using statistical methodology which took into account some of the subject characteristics and pre-existing conditions that can impact overall risk for cardiac adverse events. Determination of events (CHF or myocardial ischemia) was based on a retrospective blinded review of narratives for serious adverse events (SAEs) by physician members of a GSK Working Group as well as a cardiologist who was a member of an External Review Group, and blinded review of the individual investigator-provided verbatim terms for non-serious events.

The Integrated Clinical Trial (ICT) dataset described in new analyses submitted by GSK on May 31, 2007 comprises the same 42 trials previously analyzed by GSK in 2006; however, adverse events of interest were identified based on new searches of the clinical safety database and without a formal adjudication process. A new composite endpoint was identified in an effort to ascertain the incidence of a "hard endpoint" of MACE (**M**ajor **A**dverse **C**ardiovascular **E**vents), consisting of cardiovascular death, myocardial infarction serious adverse events (SAEs) or stroke SAEs, considered to represent serious and irreversible events.

DDRE has identified data limitations which can impact the reliability of the new results, especially relevant to the newly defined composite outcome (MACE) which includes stroke. We wish to acknowledge that GSK safety analysts have responded promptly to numerous requests from FDA for additional safety data and analyses; however, we feel it is important to point out the following concerns with the new analysis of the rosiglitazone integrated clinical trials.

Unlike the initial analysis completed by GSK in 2006, the new analysis does not include an adjudication process with blinded expert review of serious adverse events. In addition, the new searches of the clinical trial database were preceded by a data migration step from the original clinical safety adverse event dictionary (WHO) to MedDRA. Information about quality control or quality assurance in this data migration step has not been reviewed by FDA.

Searches for adverse events of interest were conducted based on lists of MedDRA Lower Level Terms (LLTs), which represent the most granular level of MedDRA dictionary coding. Conducting broad safety adverse event searches at the LLT level can promote incomplete ascertainment of events of interest due to excessive specificity of dictionary terms.

Lower level MedDRA terms were selected by GSK for analysis of adverse events (AEs) of special interest, including cardiovascular and cerebrovascular AEs, as identified in the ADOPT clinical study report; however, information was not provided regarding the rationale or basis for inclusion of individual specific lower level terms in each of the targeted searches.

In light of these limitations, DDRE considers the new analysis of the 42 integrated clinical trials (ICT), which includes the MACE composite endpoint and stroke serious adverse events, to be less informative and less reliable than the original analysis conducted by GSK of these same trials which included event adjudication by an expert and blinded panel.

4 CONCLUSION

Current available information points to an increased risk of cardiovascular adverse effects, including heart failure, myocardial ischemia, and cardiovascular death in diabetic patients treated with rosiglitazone. A critical question to be resolved in determining appropriate regulatory action is whether the anticipated therapeutic benefit of rosiglitazone outweighs the demonstrated cardiovascular risks.

Committee members participating in the joint EMDAC/DSaRM Advisory Committee meeting on July 30 will be asked for their recommendations.

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

/s/

Kate Gelperin
7/6/2007 02:23:38 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
7/6/2007 04:38:05 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 6, 2007

TO: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Kate Gelperin, M.D., M.P.H., Medical Epidemiologist
Lanh Green, Pharm.D., M.P.H., Safety Evaluator Team Leader
Division of Drug Risk Evaluation (DDRE)
Office of Surveillance and Epidemiology (OSE)

THROUGH: Mark Avigan, M.D., C.M., Director
Rosemary Johann-Liang, M.D., Deputy Director
Division of Drug Risk Evaluation (DDRE)
Office of Surveillance and Epidemiology (OSE)

SUBJECT: Thiazolidinediones and Cardiovascular Adverse Effects:

- Review and Analysis of Pooled Data from Randomized Controlled Trials with Rosiglitazone: Cardiovascular Event Modeling Project
- Review and Analysis of Observational Cohort Study: Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents
- Review of TZD Preclinical Cardiovascular Safety Data
- Brief Review of Published Literature
- Selected AERS Cardiovascular Adverse Events
- Oral Antidiabetic Drug Utilization Trends
- Labeling Considerations

DRUGS: Rosiglitazone (AVANDIA®, GlaxoSmithKline, IND 43,468, NDA 21-071)
Pioglitazone (ACTOS®, Takeda, NDA 21-073)

RCM#: **2006-331**

This document contains proprietary drug use data obtained by FDA under contract. The drug use information cannot be released to the public/ non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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1 Executive Summary

The Division of Drug Risk Evaluation (DDRE) has been asked to assist the Division of Metabolism and Endocrinology Products (DMEP) in reviewing cardiovascular safety data for thiazolidinediones (TZDs), and in particular, to review a pooled data analysis of cardiovascular adverse events from randomized controlled trials with rosiglitazone, and an observational cohort study for coronary heart disease outcomes with rosiglitazone, which have been completed and submitted to the Agency by GlaxoSmithKline (GSK).

Although the focus of this review is primarily on data pertaining to RSG, consideration was also given to whether specific cardiovascular risks should be regarded as TZD class effects based on currently available clinical information.

Summary of DDRE Labeling Recommendations

Thiazolidinedione Class – Congestive Heart Failure

DDRE recommends a BOXED WARNING for both rosiglitazone and pioglitazone including a clear statement of the:

- Increased risk of new or worsening congestive heart failure associated with the TZD class,
- Importance of careful monitoring for rapid or excessive weight gain, and
- Recommendation that prescribers stop the drug if this occurs.

Rosiglitazone – Myocardial Ischemia

DDRE recommends that the following information be included in a BOXED WARNING for rosiglitazone:

- In a retrospective analysis of data from pooled controlled clinical studies, an increased risk of myocardial ischemia was observed in patients treated with rosiglitazone (hazard ratio 1.31; 95% confidence interval 1.01, 1.70). Higher levels of risk were noted in patients with pre-existing serious heart disease, including heart failure, as well as in patients receiving insulin therapy.
- Rosiglitazone is not recommended in patients receiving insulin. Patients receiving concomitant therapy with insulin and rosiglitazone in randomized controlled trials experienced roughly twice as many cardiovascular adverse events as patients receiving insulin monotherapy.
- Rosiglitazone is not recommended in patients with heart failure, or serious heart disease, including symptomatic coronary artery disease.

Rosiglitazone Pooled Data from Randomized Controlled Trials

GlaxoSmithKline (GSK) conducted a comprehensive review of adverse events pertaining to congestive heart failure (CHF) and separately for events of myocardial ischemia from rosiglitazone (RSG) clinical trials completed on or before August 2005. The final analysis, submitted August 4, 2006, includes data from a total of 14,237 subjects from 42 controlled double-blind studies.

The Sponsor's stated objective was to characterize the degree of association (if any) between RSG and events of CHF and separately for events of myocardial ischemia across the RSG clinical trials program using statistical methodology which took into account some of the important subject characteristics and pre-existing conditions that can impact overall risk for cardiac adverse events. The analysis of the original dataset found that the incidence of CHF across the various treatment regimens evaluated ranged up to 1.27% for serious adverse events, and to 2.42% for total (serious + non-serious) events. Incidence of fatal CHF was 0.06% (4 cases) for RSG-treated patients and zero (no cases) for patients in comparator groups.

Results from the updated integrated dataset were generally similar to those observed in the original dataset. Overall, a total of 71/8604 (0.83%) RSG-treated subjects, and 33/5633 (0.59%) subjects in comparator groups were identified with CHF-related adverse events (serious + non-serious) in the updated integrated dataset. Of these, 30 (0.35%) RSG-treated subjects and 19 (0.34%) subjects in comparator groups experienced CHF-related events which were classified as serious. Overall, the odds ratio point estimates for CHF adverse events in the original and updated integrated datasets were elevated for subjects using RSG in combination with sulfonylurea (SU) drugs, and for subjects receiving RSG in combination with insulin.

GSK's analysis showed that the odds ratio point estimates for events relating to myocardial ischemia were generally greater than one for all treatment combinations, although all but one of the seven treatment regimens had broad 95% CIs whose lower bounds were less than one. The exception occurred in the updated integrated dataset where the odds ratio point estimate in the metformin+RSG vs. metformin monotherapy treatment regimen was 2.72 (95% CI 1.17-7.03). RSG in combination with insulin was associated with an elevated incidence of myocardial ischemia events, with an odds ratio point estimate greater than two.

The SAS datasets and programs utilized in the pooled analysis were submitted to FDA by the Sponsor, and an independent analysis was conducted by the DMEP Biostatistics reviewer. In the FDA's analysis, an increased overall risk of cardiovascular adverse events was consistently noted for patients treated with rosiglitazone. Only the between-group comparison of SAEs classified as CHF failed to achieve statistical significance, although the odds ratio point estimate was greater than one. This may be due to the fact that subjects with SAEs with characteristics of CHF as well as myocardial ischemia could only be counted in one category. In the Sponsor's analysis, cases which included SAEs of both myocardial ischemia and congestive heart failure were, in each case, adjudicated as myocardial ischemia, and counted as such in the analysis. This convention likely resulted in under-ascertainment of SAEs classified as heart failure.

FDA Analysis
Overall Between-group Comparisons of Cardiovascular
Adverse Events (Serious + Non-serious) and Serious Adverse Events (SAEs only)

	RSG Groups (n=8604)	**Comparators** (n=5633)	**OR** (95% CI)	**p-value**
Adverse Events				
Myocardial Ischemia	1.99% (171)	1.5% (85)	1.4 (1.1, 1.8)	0.012*
CHF	0.83% (71)	0.6% (33)	1.6 (1.0, 2.4)	0.036*
Either	2.67% (230)	2.04% (115)	1.4 (1.1, 1.8)	0.003*
Serious AEs				
Myocardial Ischemia	1.0% (86)	0.7% (40)	1.5 (1.0, 2.2)	0.035*
CHF	0.35% (30)	0.34% (19)	1.1 (0.6, 2.0)	0.64
Either	1.34% (115)	1.05% (59)	1.4 (1.0, 1.9)	0.047*

* Statistically significant $p<0.05$

GSK's analysis is based on the assumption that serious cardiovascular adverse events of interest can be reliably adjudicated and classified *post hoc* as representing ***either*** cardiac ischemia ***or*** heart failure. A concern exists that this method likely results in misclassification. The rationale for this concern is that information about the serious adverse events included in this pooled analysis was derived from standard case report form pages which did not include targeted or specific data fields designed to facilitate adjudication of diagnostic criteria for confirmed disease conditions. Ischemic cardiomyopathy is an important cause of heart failure, and its occult presence cannot be ruled out on the basis of the often incomplete information that is usually found in routine safety data collection. There is also a concern that

cases identified as cardiac ischemia-related diagnoses on routine case report form pages may have occasionally failed to capture full information about relevant complications, such as heart failure.

Despite these limitations, a statistically significant and clinically important increased risk of adverse cardiovascular effects was identified in rosiglitazone-treated patients, both for total cardiovascular adverse events (OR 1.4, p=0.003) and for serious cardiovascular adverse events (OR 1.4, p=0.047).

GSK conducted additional exploratory analyses to assess whether any subgroups of patients at particular risk for myocardial ischemic events could be identified. A recursive partitioning methodology was conducted using the original dataset. The results of the first stage of the analysis indicated that the best predictor of treatment emergent events of myocardial ischemia, regardless of treatment group assignment, was the presence of pre-existing coronary heart disease (CHD). Within subjects who had pre-existing CHD, the next best predictor of ischemic events was whether a subject was taking concomitant nitrates at screening.

The second stage of the exploratory analysis used a Cox proportional hazards regression to compare the risk of ischemic events for RSG vs. comparator groups. The Sponsor found that, for subjects in the higher risk subgroup only (i.e., pre-existing CHD taking nitrates at screening), RSG-treated subjects had a higher risk of ischemic events relative to those in comparator groups, with an odds ratio point estimate of 2.45 (95% CI 1.34 – 4.49). When subjects with a history of coronary heart disease were separated into those with and without concomitant nitrates, the nitrate using group was more likely to have a history of CHF at study entry, and was also more likely to be taking loop diuretics, beta blockers, calcium channel blockers and antiplatelet agents. Other evaluation of on-therapy predictors for myocardial ischemic events included AEs of edema, laboratory values for hematocrit, weight, and blood pressure. There were small differences in the mean changes from baseline in both weight and hematocrit between subjects who developed myocardial ischemic events and those who did not, suggesting that small differences in the degree of fluid retention could potentially be contributing to the development of myocardial ischemic events in subjects with severe coronary heart disease (CHD).

Observational Cohort Study - Rosiglitazone

An observational balanced cohort study, Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents (HM2006/00497/00), was also submitted by the Sponsor. Study results found that the incidence of the composite endpoint of myocardial infarction and/or coronary revascularization was 1.75 events per 100 person years for regimens containing rosiglitazone and 1.76 events per 100 person years for other anti-diabetic agents (Hazard ratio 0.93; 95% confidence interval 0.80, 1.10).

However, FDA safety reviewers identified several limitations of the observational study and considered that it was inadequate to address the cardiovascular safety issues raised by the pooled randomized controlled trial data.

The outcome analysis was limited to myocardial infarction and coronary revascularization. Numerous other cardiac related events were excluded from this definition of outcome. Examples include sudden cardiac deaths due to myocardial ischemia, congestive heart failure, unstable angina or other forms of angina. In the pooled analysis of controlled clinical trials, the endpoint was defined as the overall incidence of "CHF or myocardial ischemia". Events of myocardial ischemia in RSG-treated subjects identified in the pooled analysis included at least eleven cases consistent with sudden cardiac death. However, in the observational cohort study, the endpoint was defined as the composite endpoint of MI and/or CR, and did not include sudden deaths. Since the majority of fatal cardiovascular adverse events in both treatment groups were consistent with sudden cardiac death, the omission of such cases from the observational study endpoints is an important limitation.

Preclinical Cardiovascular Safety Issues

PPAR gamma-mediated fluid accumulation with weight gain, edema, cardiac hypertrophy and resultant heart failure were identified as potential safety issues in preclinical studies with rosiglitazone and pioglitazone prior to their approval in 1999.

Consensus Statement from the American Diabetes Association and the European Association for the Study of Diabetes

In August 2006, a consensus statement on the management of hyperglycemia in type 2 diabetes mellitus (T2DM) was published by the American Diabetes Association and the European Association for the Study of Diabetes.[1] The new guidelines recommend that "metformin therapy should be initiated concurrent with lifestyle intervention at diagnosis", as first line therapy, barring specific contraindications. The rationale provided for metformin as the drug of choice is "its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost." The guidelines state that "metformin treatment should be titrated to its maximally effective dose over 1-2 months, as tolerated."

There is no clear consensus regarding the second medication to be added if lifestyle intervention and maximal tolerated dose of metformin fail to "achieve or sustain glycemic goals", except that, for patients with symptomatic hyperglycemia or A1C >8.5%, consideration should be given to "the more effective glycemia-lowering agent, insulin".

With regard to thiazolidinediones (TZDs), the authors point out that the most common adverse effects are weight gain and fluid retention, with an increase in both adiposity and fluid retention, which usually manifests as peripheral edema, though new or worsened heart failure can occur. The authors comment that pioglitazone has a "more beneficial effect than rosiglitazone" on atherogenic lipid profiles.

PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive Study)

Increased risk of heart failure was identified as a safety issue in a recently published large randomized controlled trial of pioglitazone vs. placebo in 5238 patients with type 2 diabetes[2]. The study included patients 35 to 79 years of age with HgbA1c levels greater than 6.5% despite treatment with diet alone or with oral glucose-lowering agents with or without insulin.

Patients had to have evidence of extensive macrovascular disease to qualify for enrollment in the study; however, patients with NYHA class II heart failure or above were excluded from study participation. A statistically significant excess risk of heart failure was observed in the pioglitazone treatment group, with 11% of subjects randomized to pioglitazone experiencing heart failure, compared to 8% of subjects in the placebo group ($p<0.0001$).

Despite this concern, pioglitazone reduced the composite endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke in these high risk diabetic patients, many of whom were taking concomitant insulin, by about 16%.[3]

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[2] 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.

[3] Yki-Jarvinen H. The PROactive study: some answers, many questions. *Lancet* 2005; 366:1241-1242.

Conclusions / Recommendations:

Congestive Heart Failure

Consistent evidence shows that both rosiglitazone and pioglitazone can cause weight gain, fluid retention, and lead to new or worsening heart failure in some patients. This is not a rare occurrence. Based on review of AERS cases, as well as published case reports, it appears that not all prescribers understand the importance of stopping TZD therapy when fluid retention, excessive weight gain, or heart failure occurs. Serious and fatal cases of heart failure associated with TZD treatment have been reported during marketed experience with these drugs. Although currently approved labeling for both AVANDIA and ACTOS include WARNINGS under a bolded heading "Cardiac Failure and Other Cardiac Effects", DDRE recommends that information about adverse cardiac effects be given additional prominence by adding a BOXED WARNING describing the risk of heart failure. The rationale for this emphasis is that adverse cardiovascular effects with thiazolidinediones may be avoided or mitigated with proper patient selection and adequate monitoring of patients for weight gain and fluid retention.

Myocardial Ischemia

In GSK's retrospective analysis of data from pooled clinical trials with rosiglitazone, the overall incidence of myocardial ischemia was higher for patients receiving rosiglitazone (1.99%) versus comparators (1.51%; hazard ratio 1.31; 95% confidence interval 1.01-1.70). Also, in the same analysis, patients receiving concurrent therapy with rosiglitazone and insulin were shown to be at increased risk of adverse cardiovascular effects. Myocardial ischemia-related adverse events occurred more often in patients receiving rosiglitazone and concomitant insulin (2.77%) compared with insulin monotherapy (1.36%) in clinical trials (OR 2.02; 95% confidence interval 0.90, 4.94). Similarly, heart failure occurred more often in patients receiving rosiglitazone and concomitant insulin (2.42%) compared with insulin monotherapy (1.06%) in the pooled analysis (OR 2.50; 95% confidence interval 1.06, 5.89). These data, consistent with a doubling of risk of cardiovascular adverse effects in rosiglitazone-treated patients receiving insulin in clinical trials, support the conclusion that treatment with rosiglitazone should be avoided in patients receiving insulin.

Exploratory analyses conducted by the Sponsor on the original dataset identified a subgroup of RSG-treated patients (those with pre-existing CHD taking concomitant nitrates at screening) who demonstrated a significantly elevated risk of ischemic events relative to similar patients in the comparator groups (OR 2.45, 95% CI 1.34 – 4.49). This finding supports the conclusion that rosiglitazone therapy should be avoided in patients with serious heart disease.

Information about increased risks of myocardial ischemia with rosiglitazone warrants prominent placement in the labeling to ensure proper patient selection and appropriate monitoring for risk factors such as rapid or excessive weight gain.

Current approved labeling for rosiglitazone does not include information about myocardial ischemia risk. GSK's proposed labeling which states that risk of myocardial ischemia with rosiglitazone is not clear based on results of an observational study is not acceptable. The results of the observational study conducted by the Sponsor do not resolve the concerns about potential serious cardiovascular risks with rosiglitazone, and do not warrant inclusion in the product label.

Rosiglitazone in Combinations with Sulfonylureas and/or Metformin

GSK proposes to add the following to the AVANDIA Adverse Reactions section: "Similarly, an increased incidence of heart failure has also been observed when AVANDIA was added to a sulfonylurea or to a

sulfonylurea plus metformin. There were too few events to confirm a dose relationship; however, the incidence of heart failure appeared higher with AVANDIA 8 mg daily."

Five of the seven strata in GSK's pooled analysis comprise various combinations of rosiglitazone, sulfonylureas, and metformin. An FDA biostatistical analysis of these data is currently in progress. It would be helpful to have results of between group comparisons of total cardiovascular adverse events (heart failure + myocardial ischemia), as well as further understanding of biostatistical effects of creating multiple strata containing various combinations of these three drugs on the results of the pooled analysis. A better understanding of the relative contribution of sulfonylurea drugs on adverse cardiovascular effects in the pooled data is needed. DDRE recommends further consideration of this issue after completion of the FDA Biostatistical review.

Cardiovascular Risk versus Benefit

Antidiabetic treatment with rosiglitazone in patients with pre-existing serious coronary heart disease or heart failure, as well as in patients requiring concomitant therapy with insulin, is associated with increased cardiovascular risk, including heart failure or myocardial ischemia, which is not off-set by the magnitude of the demonstrated benefit. GSK's proposal to describe the results of the pooled data analysis in the ADVERSE REACTIONS section of the label does not provide sufficient emphasis considering the impact of identified cardiovascular risks on the benefit / risk balance of rosiglitazone. Prevention of macrovascular complications of diabetes is a desired benefit of antidiabetic therapy, and the demonstration of a failure to achieve this goal denotes a serious limitation of anticipated therapeutic benefit. Information about adverse cardiovascular effects of rosiglitazone, including heart failure and myocardial ischemia, should be prominently communicated in a BOXED WARNING.

In contrast, treatment with pioglitazone, although clearly associated with increased risk of heart failure, has not been shown to result in increased risk of myocardial ischemia, even in patients receiving concomitant insulin therapy. A pooled analysis of cardiovascular safety data from randomized controlled trials with pioglitazone has been submitted by Takeda and is currently under review by DMEP. Information about risk of heart failure with pioglitazone should be prominently communicated in a BOXED WARNING in order to assure proper patient selection and monitoring.

2 Introduction

2.1 Thiazolidinediones and Cardiovascular Adverse Effects

The Division of Drug Risk Evaluation (DDRE) has been asked to assist the Division of Metabolism and Endocrinology Products (DMEP) in reviewing cardiovascular safety data for thiazolidinediones (TZDs), and in particular, to review a pooled data analysis of cardiovascular adverse events from randomized controlled trials with rosiglitazone, and an observational cohort study for coronary heart disease outcomes with rosiglitazone, which have been completed and submitted to the Agency by GlaxoSmithKline (GSK). DMEP clinical and biostatistics reviewers are concurrently conducting separate reviews of these same GSK submissions.

2.2 Product Information

2.2.1 Thiazolidinediones

AVANDIA (rosiglitazone maleate; GlaxoSmithKline) and ACTOS (pioglitazone hydrochloride; Takeda) are oral antidiabetic agents that act primarily by decreasing insulin resistance.[4] [5] Both rosiglitazone and pioglitazone were approved by FDA in 1999, and are the only currently approved TZDs. 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 receptor γ (PPAR-gamma), which are present in high concentrations in adipocytes.[6]

The peroxisome proliferator-activated receptors (PPARs) regulate gene expression in response to ligand binding. PPAR γ is expressed most abundantly in adipose tissue but is also found in pancreatic beta cells, vascular endothelium, and macrophages. PPAR α is expressed primarily in the liver, heart and muscle, as well as in the vascular wall. PPAR α agonists (such as gemfibrozil) prevent or retard atherosclerosis.[7] Pioglitazone seems to act like a partial PPAR α agonist *in vitro*, whereas rosiglitazone seems to be a pure PPAR γ agonist. [8]

2.2.2 AVANDIA (rosiglitazone) - Recent Labeling Changes – Patients with Heart Failure

In April 2006, a new WARNING was added to the AVANDIA USPI section titled "Cardiac Failure and Other Cardiac Effects" which describes cardiovascular adverse effects observed in patients with CHF (NYHA Class 1 and 2) treated with AVANDIA (rosiglitazone) or placebo during a 52-week echocardiographic study. The new labeling states that "although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with AVANDIA treatment compared to placebo." Emergent cardiovascular events which occurred more often in the active treatment group include cardiovascular deaths (5% vs. 4%), CHF worsening (6% vs. 4%), new or worsening edema (25% vs. 9%), new or worsening dyspnea (26% vs. 17%), increases in CHF medication (33% vs. 18%), cardiovascular hospitalization (19% vs. 13%), myocardial infarction (5% vs. 2%), and angina (5% vs. 3%). The WARNING states that "AVANDIA is not recommended in patients with NYHA Class 3 and 4 cardiac status".

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[4] USPI for AVANDIA available at http://www.fda.gov/cder/foi/label/2006/021071s019s021lbl.pdf (accessed January 5, 2007).
[5] USPI for ACTOS available at http://www.fda.gov/cder/foi/label/2006/021073s027lbl.pdf (accessed January 5, 2007).
[6] Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med*. 351:1106-1118, 2004.
[7] *Ibid*, page 1106.
[8] *Ibid*, page 1110.

In addition, the following statement was added to the DOSAGE AND ADMINISTRATION section of the AVANDIA USPI: "All patients should start AVANDIA at the lowest recommended dose. Further increases in the dose of AVANDIA should be accompanied by careful monitoring for adverse events related to fluid retention. (See WARNINGS, Cardiac Failure and Other Cardiac Events.)"

2.2.3 TZD Class - Recent Labeling Changes – Macular Edema

In June 2006, a new PRECAUTION was added to the AVANDIA USPI regarding postmarketing reports of macular edema. Similarly, in August 2006, a new PRECAUTION was added to the ACTOS USPI which states that "macular edema has been reported very rarely in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione...It is unknown whether or not there is a causal relationship between pioglitazone and macular edema."

2.3 Sources of Clinical Data Included in this Review

GSK submissions considered in this review include the following:

- October 13, 2005: Analysis plan and summary of preliminary results from GSK's analysis of cardiovascular events from completed double-blind controlled trials in patients with type 2 diabetes (T2DM).
- March 27, 2006: (a) SAS datasets for the analysis of cardiovascular events in Clinical Data Interchange Standards Consortium (CDISC) standard format; (b) the results of a full logistic and an exact logistic regression analysis in tabular format, which included correction of an error in the model parameterization.
- May 9, 2006: Summary of further results from statistical analyses using an expanded clinical trials dataset.
- August 4, 2006 Supplement: Prior Approval, Labeling: (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; (d) response to FDA safety data request regarding cardiovascular serious adverse events (SAEs) in rosiglitazone (RSG)-treated subjects in the pooled safety analysis.
- October 2, 2006: GSK Response to comments/questions from FDA review of observational study ("Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents").
- November 2, 2006: GSK Response to FDA Request: Study report and protocol for observational study "Balanced Cohort Study of TZDs and other Anti-diabetic Therapies and Coronary Heart Disease Outcomes", (Ingenix 2004).
- November 8, 2006: GSK Response to FDA request: clarification and comparator group information regarding cardiovascular SAEs with line listings and clinical summaries.

2.4 Clinical Studies Included in the AVANDIA Cardiovascular Event Modeling Project

The AVANDIA Cardiovascular Event Modeling Project final report includes data from 14,237 subjects who were randomized to treatment with either rosiglitazone or a comparator in 42 controlled double-blind studies ("updated integrated dataset"). Descriptive listings of these studies are presented in Appendix 1.

2.5 Other Sources of Information Included in this Review

In addition, this review includes:

- An overview of preclinical cardiac safety data and Pharmacology / Toxicology reviews completed by FDA for rosiglitazone and pioglitazone.
- An overview of selected postmarketing cardiovascular adverse events in the Adverse Event Reporting System (AERS) database with oral antidiabetic drugs.
- A summary of oral antidiabetic drug utilization trends (Verispan data).
- A brief review of published literature pertaining to cardiovascular safety issues with thiazolidinediones.

Although the focus of this review is primarily on data pertaining to rosiglitazone, consideration will also be given to whether specific cardiovascular risks should be regarded as TZD class effects based on currently available information.

3 Background

3.1 Previous DDRE Reviews

A previous review of AERS cardiovascular safety data was included in a DDRE consult primarily focused on fluid retention and macular edema.[9] DDRE had recommended a BOXED WARNING for the TZD class with the rationale that "the toxicity from the fluid retention clinical spectrum which can result in fatal outcome (i.e., congestive heart failure) should be highlighted." However, a decision was made at that time to continue the review of cardiovascular safety data from randomized controlled trials, along with other relevant data, in order to consider more extensively the balance of benefit and risk, and make a decision about whether cardiovascular risks merit special emphasis in a BOXED WARNING for one or both TZDs, as well as whether certain subgroups of patients may demonstrate increased risk of drug-related adverse cardiovascular effects.

3.2 Preclinical Pharmacology / Toxicology

PPAR gamma-mediated fluid accumulation with weight gain, edema, cardiac hypertrophy and resultant heart failure were identified as potential safety issues in preclinical studies with rosiglitazone and pioglitazone prior to their approval in 1999. An overview of these data is presented in this section.

3.3 Rosiglitazone (AVANDIA)

The NDA review and evaluation of pharmacology and toxicology data for Rosiglitazone Maleate Tablets (BRL49653C) was completed by Dr Herman Rhee. [10]

Pertinent toxicology studies described in the review included:

1. A 13-week dietary range-finding study in mice
2. One-year study of dietary rosiglitazone in mice
3. A 26-week oral repeat dose study in rats followed by a 12-week off-dose period
4. A 26-week oral repeat dose study in dogs followed by a 12-week off-dose period

[9] Green L. DDRE Review of Macular Edema with Rosiglitazone and Pioglitazone. PID Number D050735. February 22, 2006.

[10] Rhee HM. Review and Evaluation of Pharmacology and Toxicology Data. IND#43,468. Rosiglitazone Maleate Tablets, Avandia (BRL49653C). April 26, 1999.

5. One-year oral toxicity study in dogs
6. Effects of 28-day oral administration of rosiglitazone on cardiac function and morphology in dogs
7. A 2-year dietary carcinogenicity study in mice
8. A 2-year carcinogenicity study in rats after oral (gavage) administration.

In the rosiglitazone NDA review, the pharmacology reviewer stated that "in the toxicological studies in different animals, the high doses usually produced cardiac weight increases, fluid accumulation in the chest cavity, reductions in hematocrit and atrial thrombosis in mice."[11] Information about exposure ratios (AUC) of the animals to human for studied doses at which cardiac hypertrophy, hydrothorax, and/or anemia occurred is provided in the following table reproduced from the pharmacology NDA review (Table 15).[12]

Table 15. Comparison of Histopathological Effects of Rosiglitazone in Mice, Rats, and Dogs

Spec-ies	Sex	Lesion	LED (mg/kg/day)	AUC at LED(µg.h/ml)	Exposure* Ratio(animal:man)
Mou-se	F	Cardiac Hypertrophy	10	53.5	17.8
	F	Erythrocyte Parameters	20	112.0	37.3
Rat	M	Cardiac Hypertropy	5	62.5	20.8
	M	Erythrocyte Parameters	1	16.2	5.4
Dog	M/F	Cardiac Hypertrophy	2	3.6	1.2
	M/F	Erythrocyte Parameters	2	3.6	1.2

LED stands for Lowest Effective Dose and * calculated based on human AUC 3 µg.h/ml following clinical dose at 8 mg/day.

Pharmacology Reviewer's Table 15 from rosiglitazone NDA review

As shown in the table, cardiac hypertrophy and changes in erythrocyte parameters consistent with increased plasma volume were observed in dogs at exposure levels similar to those in humans taking 8 mg of rosiglitazone daily.

In the 26-week oral repeat dose study in dogs, there were progressive reductions in hemoglobin, packed cell volume and red cell counts from week 3 to 5 of the study. Plasma volume increased in 5/6 males and 5/6 females, which was generally progressive. Heart weights were significantly increased. Changes in the heart consisting of fluid in the pericardial sac were noted in 3/8 dogs in the high dose group. Treatment related changes in the heart were noted, which include left ventricular myocardial hypertrophy.[13] A special toxicity study was performed in female beagle dogs to evaluate cardiac function and morphology at Day 1, 7, 14 and 28, as well as a terminal invasive evaluation to monitor ventricular function and contractile reserve. Statistically significant increases in left ventricular posterior wall thickness during diastole and left ventricular cardiac output, along with a significant decrease in R-R interval, were observed in rosiglitazone-treated dogs compared to control at Day 28.[14]

[11] *Ibid*, page 3.
[12] *Ibid*. page 22.
[13] *Ibid*. page 17.
[14] *Ibid*. page 23.

The 2-year carcinogenicity study in rats showed an increased incidence of "fatal cardiopathy (hypertrophy, cardiomyopathy and hydrothorax)" in males treated with the high dose, and an "increase in the incidence of and severity of atrial myocyte hypertrophy, with cardiomegaly and atrial thrombi at the high dose." [15] The pharmacology reviewer noted that "in this study designed to assess the carcinogenicity of rosiglitazone in the rat, the high dose (2 mg/kg/day) was associated with significantly higher (58% in control vs. 78%) mortality in males…The estimation of clinical exposure ratio (AUC ratio) in males and females was 12 and 19, respectively, which indicates the high dose might be near the MTD since the metabolic profile of this drug appears to be similar in rats and human." [16] The reviewer concluded that the "incidence and severity of atrial myofiber hypertrophy with cardiomegaly [coupled] with left atrial thrombi might suggest the long term toxic potential of this drug in the cardiopulmonary system. The severe cardiopulmonary action of this drug appears to be related to the drug exposure duration rather than the dose...This suggests that a chronic exposure of human or animal subjects to the drug could lead to potential cardiac and/or pulmonary complications such as cardiomyopathy, hypertrophy and hydrothorax."[17]

The pharmacology reviewer concluded that "the fundamental problems caused by exceptionally wide dosing interval were multiple...At the high dose, rosiglitazone produced various toxicities such as left atrial thrombosis, hydrothorax, cardiohypertrophy and elevations of hepatic enzymes in the high dose group. In this reviewer's opinion, it is not possible to anticipate potential human toxicities, based on limited data derived from one high dose in almost all investigations." He went on to state that "the various toxicities that were manifest by the top dose of rosiglitazone appear as long term clinical concern since the AUC ratio could not be calculated or [was] too low to draw any toxicologically viable conclusions. Taking all these together, the reviewer has insufficient evidence to predict long-term effects of rosiglitazone in human, based on existing animal toxicological data." [18] The final recommendation states "Pharmacology recommends not to approve rosiglitazone (NDA 21071) for the proposed indication for long-term human use. However, the reviewer is willing to reconsider the status if the recommended studies were conducted properly."[19]

3.4 Pioglitazone (ACTOS)

The NDA review and evaluation of pharmacology and toxicology data for Pioglitazone Hydrochloride (AD-4833) was completed by Dr Herman Rhee. [20]

Pertinent toxicology studies described in the review included:

1. Acute oral toxicity in mice
2. Acute intraperitoneal toxicity in rats
3. Acute oral escalating dose toxicity study in monkeys
4. A 13-week oral toxicity study in mice
5. A 13.week oral toxicity study in rats
6. A 26-week oral toxicity study in rats
7. One-year oral toxicity study in rats
8. A 4-week oral toxicity study in dogs
9. A 12-week oral toxicity study in dogs

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[15] *Ibid*. page 40.
[16] *Ibid*. page 40.
[17] *Ibid*. page 41.
[18] *Ibid*. pages 42 and 43.
[19] *Ibid*. page 44.
[20] Rhee HM. Review and Evaluation of Pharmacology and Toxicology Data. IND#33,729. Pioglitazone Hydrochloride, Actos (AD-4833). June 21, 1999.

10. A 26-week oral toxicity study in dogs
11. A 52-week oral toxicity study in dogs
12. A 52-week oral toxicity study in monkeys
13. A 104-week oral carcinogenicity study in mice
14. A 104-week oral (gavage) carcinogenicity study in rats.

Pioglitazone was evaluated for cardiovascular and hemodynamic effects in the anesthetized dog.[21] Cardiac hypertrophy attributed to increased plasma volume was noted which was not completely reversed by furosemide. The pharmacology reviewer notes that "in the same study, five day treatment with pioglitazone activated Na^+-K^+-ATPase in the proximal tubules and decreased Na^+ excretion in the urine, suggesting that the drug enhances the reabsorption of sodium and water."[22]

The one-year oral toxicity study in rats showed "drug-related early death due to apparent heart dysfunction in the 63 and 160 mg/kg/day males (8 and 18 deaths, respectively) and in the 160 mg/kg/day females (10 deaths)." [23] In this one-year rat study, "males were more sensitive to cardiac dysfunction [than females], and cardiomyopathy was present at doses as low as 16 mg/kg/day in males and 64 mg/kg/day in females. The cardiac enlargement was correlated with histologic multifocal or diffuse myocardial hypertrophy...At one year, all external dimensions of the heart had increased by approximately the same amount indicating that the increased weight was directly reflected in an externally measured increase in size...Changes indicating cardiac dysfunction included thoracic cavity fluid, bilateral atrial hypertrophy and increased lung weight...Because evidence of toxicity occurred at all doses and the drug-related changes were not entirely reversible following a four-month recovery phase, a NOAEL was not determined."[24]

The 52-week oral toxicity study in beagle dogs showed "a trend towards increased heart weights in the mid- and high-dose males and high-dose females at the one-year necropsy, a trend that was still evident in the high-dose males at the end of the four-month reversibility phase. Electrocardiograms and gross and microscopic tissue evaluations failed to demonstrate any significant myocardial changes." [25]

The 52-week oral toxicity study in monkeys showed no toxic effects in doses as high as 32 mg/kg/day, a dose that represents approximately 20 times the recommended human exposure. The pharmacology reviewer stated that "Cynomolgus monkeys appear to be resistant species to toxicity induced by thiazolidinediones such as troglitazone or rosiglitazone."[26]

The 104-week oral carcinogenicity studies in mice showed significant increases in the mean absolute heart weights and relative (to body weight) heart weights in the 30 and 100 mg/kg/day males and females, which was considered to be drug-related. The reviewer noted that "microscopically, the increased weight was correlated with multifocal inflammatory cell infiltration, multifocal myocardial fibrosis and perivascular inflammatory cell infiltration around the coronary arteries." [27]

The pharmacology reviewer concluded that pioglitazone "increased cardiac weight in drug-treatment duration as well as dose dependently. Experimental evidence indicates that its effect on cardiac weight might not be due to its direct actions on cardiovascular system, but as an adaptive response to its effects on hemodynamic and water distribution." The reviewer stated that pioglitazone "has a very low margin of

[21] *Ibid*. page 7.
[22] *Ibid*. page 8.
[23] *Ibid*. page 17.
[24] *Ibid*. page 18.
[25] *Ibid*. page 23.
[26] *Ibid*. page 24.
[27] *Ibid*. page 37.

safety as the ratio of animal to clinical AUC values at the threshold doses for cardiac changes (please see the table below) is usually around 10." [28]

Species	Dose(mg/kg/day)	AUC(μg.hr.ml)	AUC Ratio*
Mouse	30(C)	119.3	11.9
Rat	4(Male)	70.4	7.0
Dog	3(Male)	9.4	0.9
Monkey	8.9(C)	74.7	7.4

*Indicates animal to human AUC ratio. Clinical AUC=10 μg.hr.ml after 30 mg dose; C and M stand for combined sexes and males, respectively.

Pharmacology Reviewer's summary table from pioglitazone NDA review

The final recommendation states "Pharmacology recommends to approve pioglitazone (NDA 21073) for the proposed indication." [29]

3.5 Summary of Preclinical Cardiac Safety

An overview of preclinical and clinical cardiac safety considerations with PPAR agonists was recently presented by Dr Jeri El-Hage, formerly Pharmacology/Toxicology Team Leader in the Division of Metabolism and Endocrinology Products.[30] A few key points from that presentation which are relevant to this review are summarized below:

- Fluid accumulation and resultant adverse cardiac effects are observed preclinically and clinically with virtually all compounds with PPAR gamma activity.
- PPAR gamma-mediated fluid accumulation, edema, weight gain with consequent increased frequency of CHF is the major dose-limiting adverse event.
- PPAR gamma-mediated fluid accumulation and edema may be due to a pharmacologic effect on the kidney.
- Dogs are more sensitive to PPAR toxic effects than other species, thus not helpful for establishing safety margins for clinical doses.
- Doses which increase heart weights ≥25% in rodents at 3 months result in premature cardiac mortality in 2-year carcinogenicity studies.
- Rats are more sensitive to developing failure secondary to fluid accumulation and cardiac hypertrophy than mice.
- Fluid accumulation, weight gain, cardiac hypertrophy are observed with short latency (within 1 to 3 months).
- Drug-induced heart failure and death are observed with chronic treatment (> 6 months); led to recommendation for one-year non-rodent toxicity study in attempt to define NOAEL exposures for chronic clinical dosing.
- Cardiac toxicity is progressive (i.e., seen at lower doses / AUC exposures with longer treatment duration).

[28] *Ibid*. page 44.
[29] *Ibid*. page 45.
[30] El-Hage, J. Peroxisome Proliferator-Activated Receptor (PPAR) Agonists: Preclinical and Clinical Cardiac safety Considerations. Presented at the 42nd Annual Meeting of the Drug Information Association. Philadelphia, PA. June 18-22, 2006.

- Doses without cardiac safety signals after chronic treatment are usually 5 to 10-fold lower than doses considered safe after 12 – 16 weeks of treatment.
- Phase 3 clinical safety data with PPAR agonists suggest that humans with type 2 diabetes are more sensitive to the chronic cardiotoxic effects of PPAR agonists than the young healthy animals used in preclinical toxicology studies (i.e., drug exposures at NOAELs in rodents and monkeys overestimate safety margins).
- There is no evidence of direct cardiotoxicity with the currently approved PPAR gamma agonists; however, there is preclinical evidence for direct cardiotoxicity with dual and alpha agonists.

4 AVANDIA® Cardiovascular Event Modeling Project

GlaxoSmithKline (GSK) conducted a comprehensive review of adverse events pertaining to congestive heart failure (CHF) and separately for events of myocardial ischemia from rosiglitazone (RSG) clinical trials. The Sponsor's stated objective was to characterize the degree of association (if any) between RSG and events of CHF and separately for events of myocardial ischemia across the RSG clinical trials program using statistical methodology which took into account some of the important subject characteristics and pre-existing conditions that can impact overall risk for cardiac adverse events.

4.1 Methods

The Sponsor's initial statistical analysis was conducted on the cohort of type 2 diabetes mellitus (T2DM) subjects enrolled in the GSK-sponsored double-blind, controlled studies that utilized total daily doses of 4 milligrams (mg) or 8 mg of RSG and had statistical analysis completed on or before September 30, 2004 (subsequently known as the 'original' dataset).

The AVANDIA Cardiovascular Event Modeling Project "original dataset" includes data from 11,586 subjects from 37 controlled double-blind studies of rosiglitazone in patients with type 2 diabetes mellitus (T2DM). The Sponsor's final study report included data from five additional studies, yielding a total of 14,237 subjects from 42 controlled double-blind studies, and referred to in this review as the "updated integrated dataset". Tabular summaries describing the studies included in this review are reproduced from the Sponsor's submission and can be found in Appendix 1.

Most of the clinical studies included in the analysis were approximately six months in duration, although four of the studies (020, 135, 211 and 334) were longer. Overall, roughly 5% of subjects in the dataset had >365 days exposure to study drug. Mean duration of exposure to study medication was generally around 180 days, although exposures were longer for the RSG monotherapy vs. SU/MET monotherapy strata, with mean exposures of 241/231 days, respectively. Sponsor's Table 17 is reproduced below, and shows the mean duration of study drug exposure by treatment strata (original dataset).

Table 17 Mean Duration of Exposure to Study Medication (Original Dataset)

Treatment Comparison (days, mean ± SD)	Treatment Group	
	RSG	CONTROL
RSG Mono vs. Placebo	129.0 ± 69.1	106.8 ± 71.9
RSG Mono vs. SU/MET Mono	240.8 ± 133.0	230.7 ± 122.9
MET+RSG vs. MET Mono	155.3 ± 51.1	150.4 ± 59.2
MET+RSG vs. MET+SU	189.4 ± 59.7	198.0 ± 65.3
SU+RSG vs. SU Mono	193.3 ± 132.1	185.2 ± 130.5
SU+MET+RSG vs. SU+MET	172.9 ± 54.2	174.0 ± 59.2
INS+RSG vs. INS Mono	157.7 ± 50.6	159.2 ± 49.3

Source: Table 6

Sponsor's Table p. 58 of submission

Determination of events (CHF or myocardial ischemia) was based on a retrospective blinded review of narratives for serious adverse events (SAEs), and blinded review of the individual investigator-provided verbatim terms for non-serious events.

SAEs were reviewed by physician members of a GSK Working Group as well as a cardiologist who was a member of the External Review Group. When there was insufficient data to definitively exclude the presence of myocardial ischemia, the event category defaulted to the investigator's diagnosis. Planned interventions, or cardiovascular adverse events with an onset prior to the initiation of study medication, were excluded from the analysis. Sudden deaths of unknown cause were assigned to the myocardial ischemia category. In cases where myocardial ischemia and CHF occurred in the same subject, the primary clinical event (either myocardial ischemia or CHF) was identified by the reviewing cardiologist, and the other event was excluded from the analysis.

Non-serious adverse events were identified from review of coded preferred terms thought to be relevant to myocardial ischemia or CHF diagnoses. Adverse events coded as chest pain were considered non-specific and were excluded from the analysis. No distinction was made between subjects with multiple adverse events of interest and those who had only a single adverse event.

The primary analysis for each regimen by control combination was based on SAEs and the "overall" comparison; i.e., one in which both RSG 4 mg and RSG 8 mg doses were combined. The primary methodology for the original dataset was the full logistic regression analysis. This analysis used data from all pertinent comparisons within a single model. It included various baseline risk factors as covariates and adjusted for exposure. An exact logistic regression, which requires fewer assumptions, was also pre-defined and performed as a secondary analysis. This analysis used data from each comparison separately and accounted only for number of major baseline risk factors and exposure.

Following the initial analysis, an additional exploratory recursive partitioning analysis was also conducted to assess whether any subgroup(s) of subjects were at particular risk for myocardial ischemic events. The recursive partitioning methodology was considered exploratory in the sense that the subject subgroups were not pre-defined, but were determined by the data; i.e. recursive partitioning was used to generate a hypothesis rather than to confirm a hypothesis.

Subsequently, further statistical analysis was conducted by the Sponsor on an updated integrated dataset in order to assess the consistency of results with the original analysis. The updated integrated dataset contained 5 additional clinical trials with statistical analysis completed on or before August 2005 and included data from a total of 14,237 subjects from 42 controlled double-blind studies. In addition, further statistical analysis was conducted on the original dataset to further explore on-therapy predictors of myocardial ischemic events.

For the original and the updated integrated dataset, separate comparisons were performed within seven comparison strata, representing different combinations of RSG treatment regimens and control groups.

- RSG monotherapy vs. Placebo
- RSG monotherapy vs. Sulfonylurea (SU) monotherapy / Metformin (MET) monotherapy
- SU+RSG vs. SU monotherapy
- MET+RSG vs. MET monotherapy
- MET+RSG vs. MET+SU
- SU+MET+RSG vs. SU+MET
- Insulin (INS) +RSG vs. INS monotherapy

Analyses on the updated integrated dataset included:

- Summary of key demographics and baseline characteristics of subject populations.
- Primary analysis: serious adverse events, CHF and myocardial ischemia separately, using exact logistic regression adjusting for exposure and number of major cardiovascular risk factors.
- Secondary analysis: total serious + non-serious adverse events, CHF and myocardial ischemia separately, using exact logistic regression adjusting for exposure and number of major cardiovascular risk factors.
- Proportional hazards regression comparing RSG vs. control in subgroups obtained by the exploratory recursive partitioning analysis.
- Cumulative incidence plots.

Several additional analyses were performed on the original dataset, but not for the updated integrated dataset, with the following rationale:

- Analysis by dose (one analysis for SAEs; one analysis for serious + non-serious): four out of the five new studies had either titrate to goal or titrate to tolerability designs, so new data by dose were minimal.
- Analysis of Treatment x Major Risk Factors interaction (one analysis for SAEs; one analysis for serious + non-serious): recursive partitioning subgroups were more helpful.
- Analysis excluding data from studies 211 and 352 (one analysis for SAEs; one analysis for serious + non-serious): results in original dataset were similar with and without studies 211 and 352.
- Full logistic regression analysis: in the original dataset, follow-up analysis demonstrated that some of the assumptions for the full logistic regression analysis were not supported by the data. In addition, adjustment for covariates other than number of major cardiovascular risk factors had relatively small impact on the results.

4.2 Results

4.2.1 Congestive Heart Failure

The Sponsor determined that results from the updated integrated dataset were generally similar to those observed in the original dataset. Overall, a total of 71/8604 (0.83%) RSG-treated subjects, and 33/5633 (0.59%) subjects in comparator groups were identified with CHF-related adverse events (serious + non-serious) in the updated integrated dataset. Of these, 30 (0.35%) RSG-treated subjects and 19 (0.34%) subjects in comparator groups experienced CHF-related events which were classified as serious.

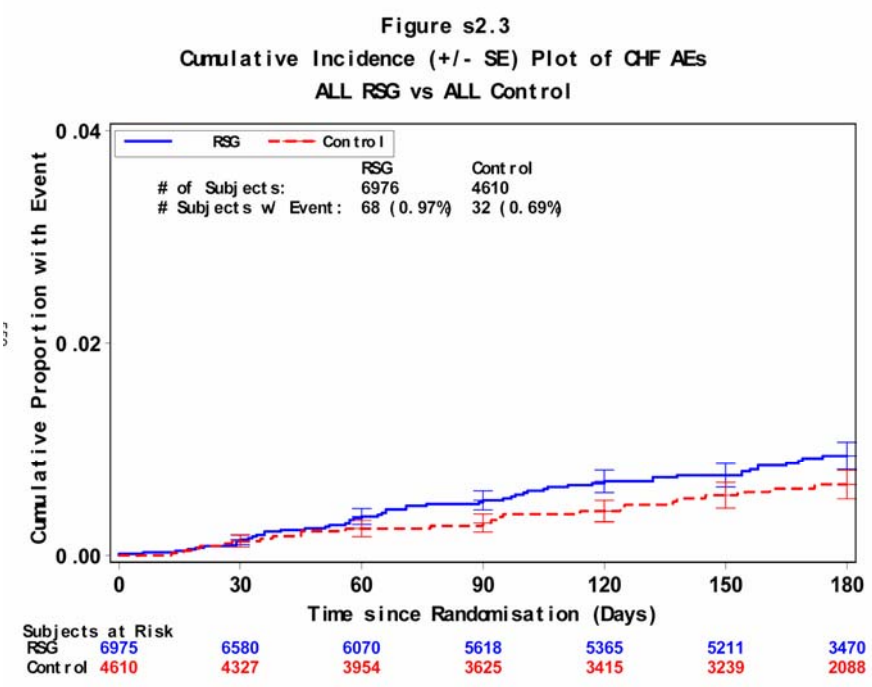
Across the treatment regimens evaluated in the updated integrated dataset, the incidence rate of CHF in the RSG treatment groups ranged from zero to 1.27% for SAEs and from 0.12% to 2.42% for total (serious + non-serious) adverse events pertaining to heart failure. Somewhat lower rates overall were noted in the control groups (range 0.07% to 0.75% for SAEs and 0.25% to 1.36% for total serious + non-serious adverse events).

An analysis of CHF adverse events was conducted with and without studies 211 (in subjects with established heart failure) and 352 (in subjects with established CHD), as these patients were not typical of the overall subject population recruited into other RSG studies. The Sponsor concluded that, when data from studies 211 and 352 were excluded, the results from the exact and the full logistic analysis of the original dataset were generally similar to the original data, both for SAEs and for total (serious + non-

serious) adverse events of CHF. The odds ratio point estimates remained close to the original values although the 95% confidence intervals were wider due to the smaller number of events.

The incidence of fatal CHF events in the updated integrated dataset was 0.05% (n = 4/8604) for RSG, and no fatal CHF events in the control groups.

Overall, the Sponsor concluded that odds ratio point estimates for CHF adverse events in the original and updated integrated datasets were higher for subjects using RSG in combination with sulfonylurea (SU) drugs, and in particular, for subjects receiving RSG in combination with insulin.



Sponsor's Figure p. 559 of submission

Figure s2.3 is reproduced from the Sponsor's submission. This graphic representation shows the cumulative proportion of subjects in the original dataset who developed congestive heart failure (serious + non-serious adverse events).

The blue line indicates subjects randomized to RSG therapy, and the dashed red line indicates subjects randomized to comparator groups. The trend shows an increased incidence of heart failure in RSG-treated subjects after Day 30, with significant between group differences at Days 90 and 120.

In the updated integrated dataset, four additional CHF adverse events were observed compared to the original dataset, three in RSG treatment groups, and one in a comparator group, and results of the analysis were similar to the original dataset. For all CHF adverse events (serious + non-serious) the odds ratio point estimates were greater than one for SU, and in particular for insulin-containing combinations with RSG, although the 95% CI was broad.

No consistent dose response relationship for CHF was observed across all treatment strata. However, for total (serious + non-serious) CHF adverse events, a high odds ratio point estimate which approached statistical significance (OR 5.23, 95% CI 0.93, 53.12) was observed for the INS+RSG vs. INS monotherapy

stratum, with 6/202 subjects (2.97%) receiving INS+ RSG 8 mg developing an adverse event identified as CHF, compared to 5/415 (1.20%) receiving INS+RSG 4 mg, and 2/415 (0.48%) in the insulin monotherapy group. The results for total (serious + non-serious) CHF adverse events by dose are summarized below in Table 27, reproduced from the Sponsor's submission.

Table 27 All CHF AEs - Results from Exact Logistic Regression Analysis by Dose (Original Dataset)

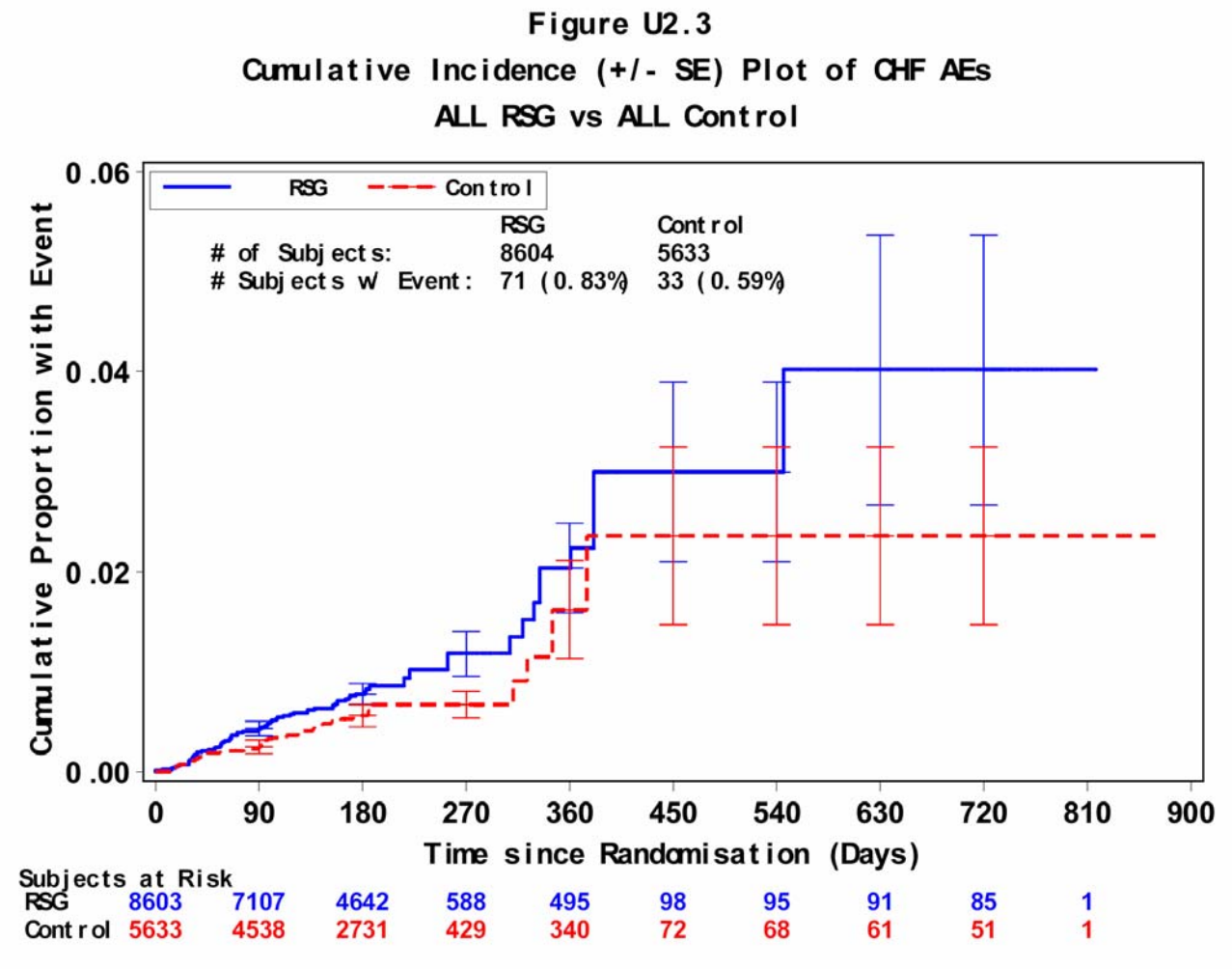
Treatment Comparison[2]	Dose of RSG	Odds Ratio Point Estimate[1] Exact Logistic (95% CI)	RSG Events / Subjects (%)	Control Events / Subjects (%)
RSG Mono vs. Placebo	4mg	0.66 (<0.01, 52.67)	1 / 822 (0.12%)	1 / 727 (0.14%)
RSG Mono vs. Placebo	8mg	0.61 (<0.01, 48.79)	1 / 849 (0.12%)	
RSG Mono vs. SU/MET Mono	4mg	1.26 (0.02, 99.26)	1 / 311 (0.32%)	1 / 461 (0.22%)
RSG Mono vs. SU/MET Mono	8mg	1.22 (0.02, 95.76)	1 / 336 (0.30%)	
MET+RSG vs. MET Mono	4mg	1.52 (0.00, 19.70)	0 / 191 (0)	2 / 667 (0.30%)
MET+RSG vs. MET Mono	8mg	0.91 (0.07, 12.55)	2 / 673 (0.30%)	
SU+RSG vs. SU Mono	4mg	1.68 (0.12, 23.17)	2 / 679 (0.29%)	2 / 1271 (0.16%)
SU+RSG vs. SU Mono	8mg	4.80 (0.91, 47.41)	7 / 944 (0.74%)	
SU+MET+RSG vs. SU+MET	4mg	5.43 (0.68, ∞)	4 / 281 (1.42%)	0 / 276 (0)
SU+MET+RSG vs. SU+MET	8mg	3.86 (0.41, ∞)	3 / 280 (1.07%)	
INS+RSG vs. INS Mono	4mg	2.16 (0.35, 22.79)	5 / 415 (1.20%)	2 / 415 (0.48%)
INS+RSG vs. INS Mono	8mg	5.23 (0.93, 53.12)	6 / 202 (2.97%)	

Source: Table 8.4

1. Covariates used in exact logistic regression: number of major CV risk factors.
2. All studies contributing to the MET+RSG vs. MET+SU analysis (137, 211, 282 and 352) were titrate to goal studies; therefore, there was no by-dose comparison in this case.

Sponsor's Table p. 78 of submission

Figure U2.3 from the Sponsor's submission (reproduced below) includes the updated integrated dataset, and also shows a persistent trend of increased heart failure in RSG-treated subjects up to Day 900, with a statistically significant between-group difference also noted at Day 270.

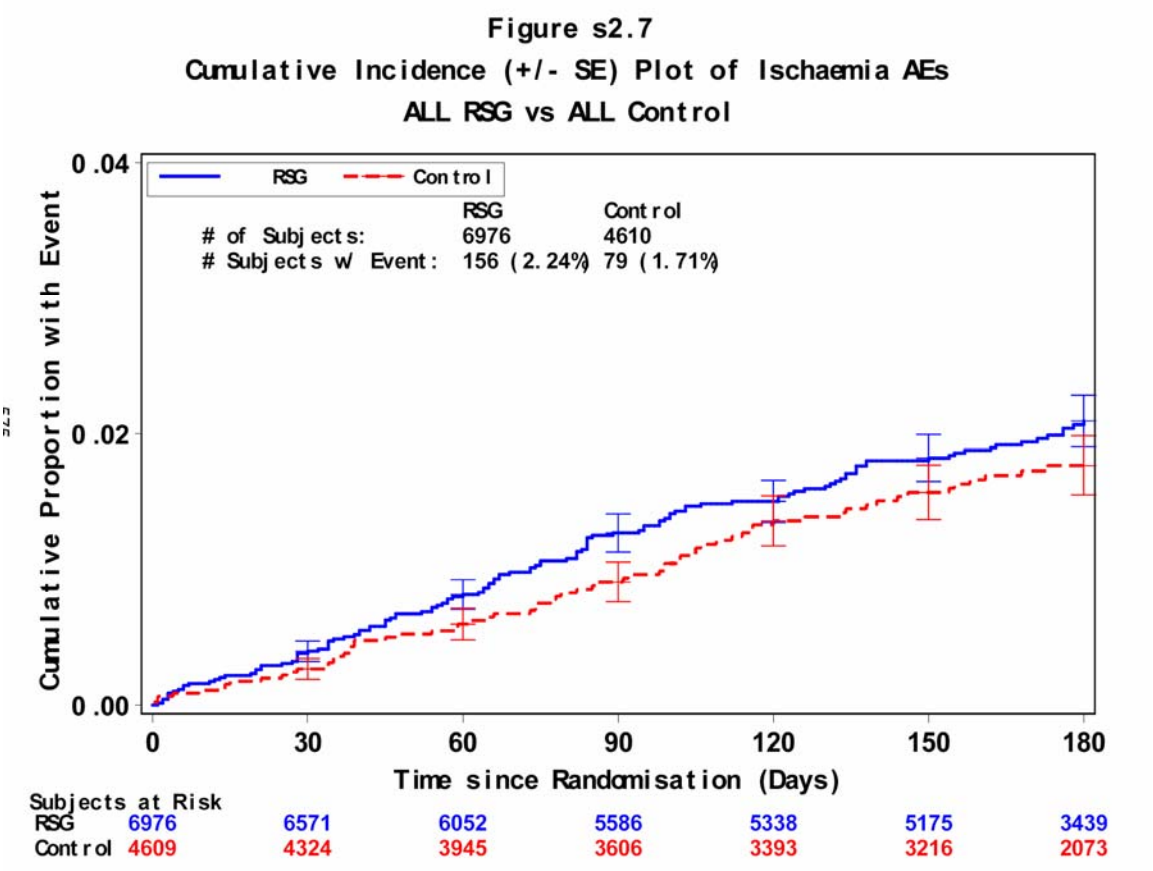


Sponsor's Figure p. 591 of submission

4.2.2 Myocardial Ischemia

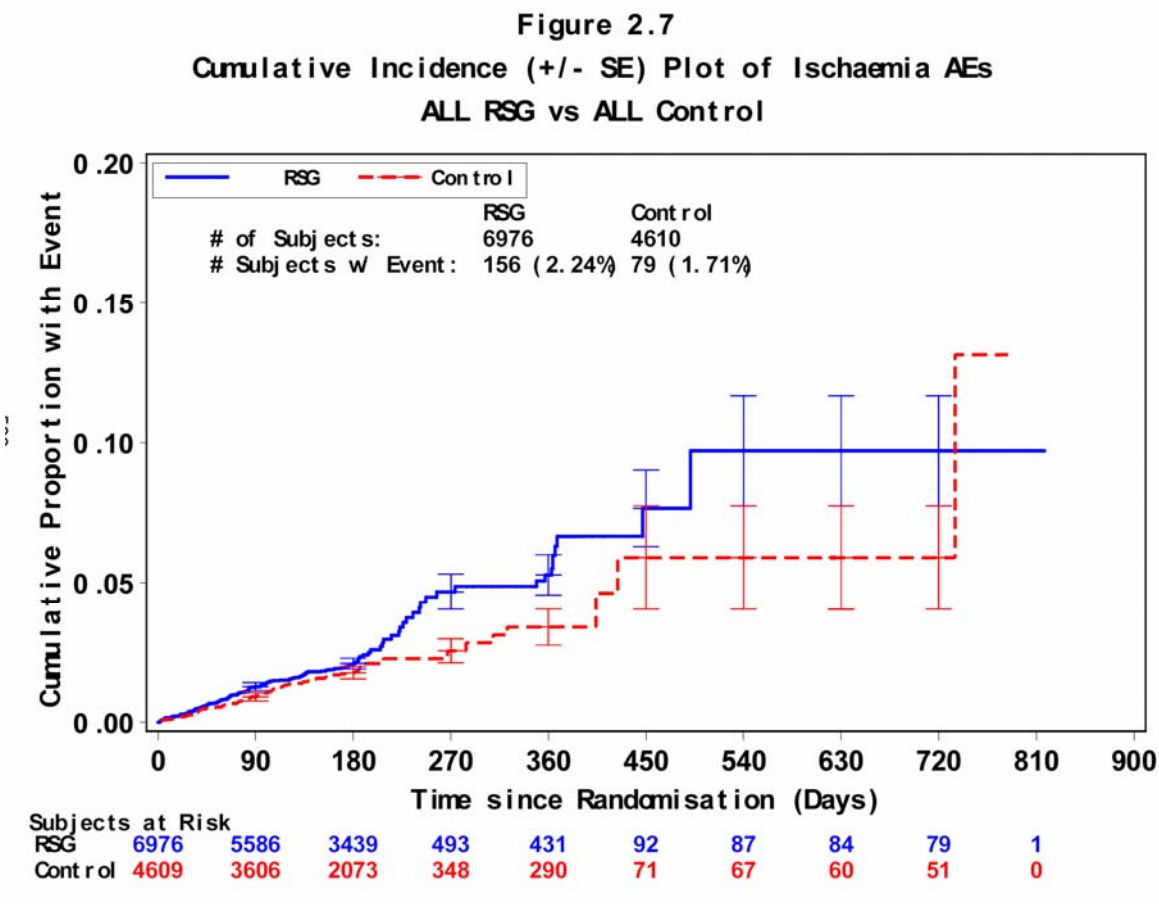
The Sponsor's analysis showed that the odds ratio point estimates for events relating to myocardial ischemia were generally slightly greater than one for all treatment combinations, although all but one of the seven treatment regimens had broad 95% CIs whose lower bounds were less than one. The exception occurred in the updated integrated dataset where the odds ratio point estimate in the MET+RSG vs. MET Mono treatment regimen was 2.72 (95% CI 1.17-7.03). RSG in combination with insulin was associated with a higher incidence of myocardial ischemia events, with an odds ratio point estimate greater than two. A subgroup of subjects with a history of CHD who were taking nitrates at baseline was identified using exploratory recursive partitioning methodology. This group overall had the highest incidence of myocardial ischemia events.

Figure s2.7 is reproduced below from the Sponsor's submission. This graphic representation shows the cumulative proportion of subjects in the original dataset who developed myocardial ischemia (serious + non-serious adverse events). The blue line indicates subjects randomized to RSG therapy, and the dashed red line indicates subjects randomized to comparator groups. The trend shows an increased incidence of myocardial ischemia in RSG-treated subjects which is seen starting before Day 30, with significant between group differences noted at Day 90.



Sponsor's Figure p. 575 of submission

Similarly, Figure 2.7 from the Sponsor's submission (reproduced below) shows a trend of increased myocardial ischemia in RSG-treated subjects up to Day 900, with statistically significant between-group differences noted at Days 270 and 360.



Sponsor's Figure p. 538 of submission

In the updated integrated dataset, there were 16 additional myocardial ischemia adverse events in the RSG treatment groups, and 12 additional myocardial ischemia adverse events in comparator groups. Results were consistent with the original dataset with one exception. The odds ratio point estimate of 2.72 (95% CI 1.17 – 7.03) for the MET+RSG vs. MET monotherapy group was statistically significant, and indicated more than a doubling of risk of myocardial ischemia-related events for RSG-treated subjects compared to metformin monotherapy. The Sponsor considered that this finding may reflect the "unusually low incidence of events in the MET control group (0.56%) which was 2 to 4 times lower than the other control groups."

Results from the exact logistic regression analysis for the original and updated integrated datasets are reproduced below in Sponsor's Table 48.

Table 48 All Myocardial Ischemia AEs (Serious and Non-Serious) – Results from Exact Logistic Regression Analysis (Original and Updated Integrated Datasets)

Treatment Comparison	Exact Logistic Analysis[2] - Odds Ratio Point Estimate (95% CI)		Updated Integrated Dataset Events / Subjects (%)	
	Original Integrated Data	Updated Integrated Data	RSG	Control
RSG Mono vs. Placebo[1]	1.05 (0.52, 2.25)	1.15 (0.58, 2.46)	32 / 1737 (1.84%)	12 / 792 (1.52%)
RSG Mono vs. SU/MET Mono[1]	1.21 (0.59, 2.53)	1.13 (0.60, 2.11)	25 / 1127 (2.22%)	22 / 1001 (2.20%)
MET+RSG vs. MET Mono[1]	1.89 (0.67, 6.10)	2.72 (1.17, 7.03)	23 / 1608 (1.43%)	8 / 1419 (0.56%)
MET+RSG vs. MET+SU	1.25 (0.34, 4.47)	1.25 (0.34, 4.47)	6 / 285 (2.11%)	7 / 294 (2.38%)
SU+RSG vs. SU Mono[1]	1.23 (0.80, 1.88)[3]	1.09 (0.72, 1.65)[3]	53 / 2505 (2.12%)	39 / 1926 (2.02%)
SU+MET+RSG vs. SU+MET	1.80 (0.55, 7.63)	1.80 (0.55, 7.63)	13 / 597 (2.18%)	4 / 310 (1.29%)
INS+RSG vs. INS Mono	2.02 (0.90, 4.94)	2.07[4] (0.93, 5.07)	24 / 867 (2.77%)	9 / 663 (1.36%)

Source: Table 8.9.2, Table 8.9.3,Table U8.4, and Table U8.4.1

1. indicates additional events in the updated integrated dataset.
2. Covariates used in exact logistic regression: number of major CV risk factors.
3. Computational burden for exact statistical methods increases with the number of events. Therefore, these results are from asymptotic analysis since the number of events is too large to allow computation of exact statistics.
4. Exact logistic regression results changed slightly for the INS+RSG vs. INS Mono comparisons, due to inadvertent omission of some of the medical history terms for major cv risk factors in the original analysis. As a result, the number of major cv risk factors changed from the original to the updated integrated dataset, impacting exact logistic regression results.

Sponsor's Table p. 118 of submission

A summary of demographic and baseline characteristics of subjects with and without on-therapy adverse events of myocardial ischemia is shown is Sponsor's Table 46, reproduced below. Differences were noted in the baseline characteristics of subjects who experienced ischemia-related adverse events in the RSG group compared to those in the control groups, in particular, a higher proportion of subjects with a history of heart failure (12.9% vs. 7.1%). There was also greater use of loop diuretics (15.2% vs. 8.2%) and nitrates (25.1% vs. 18.8%) in RSG-treated patients who went on to develop myocardial ischemia-related adverse events.

Table 46 Baseline Characteristics of Subjects With and Without On-Therapy AEs of Myocardial Ischemia in the RSG and Control Groups (Updated Integrated Dataset)

	RSG Subjects		Control Subjects	
	With on-therapy AE (N = 171)	Without on-therapy AE (N = 8433)	With on-therapy AE (N = 85)	Without on-therapy AE (N = 5548)
Age (yr; mean±SD)	61.3 ± 9.5	57.9 ± 10.2	61.0 ± 9.4	58.2 ±10.2
Males (%)	71.3	58.6	72.9	60.0
Major CV risk (% with at least one)	56.1	19.5	62.4	21.8
Cerebrovascular disease (%)	5.8	3.3	5.9	3.9
CHF (%)	12.9	2.6	7.1	3.5
CHD (%)	52.6	13.3	57.6	14.3
Peripheral Vascular Disease (%)	10.5	6.0	16.5	6.5
Serum creatinine (mg/dL; mean±SD)	86.7 ± 36.1	80.8 ± 22.6	86.2 ± 21.6	81.4 ± 25.3
Proportion using 3 or more CV medications (%)	45.6	23.9	44.6	26.1
ACEI or ARB n (%)	72 (42.1)	2840 (33.7)	34 (40.0)	2013 (36.3%)
CCB n (%)	49 (28.7)	1252 (14.8)	20 (23.5)	845 (15.2)
Beta blocker n (%)	52 (30.4)	1130 (13.4)	28 (32.9)	855 (15.4)
Nitrate n (%)	43 (25.1)	318 (3.8)	16 (18.8)	228 (4.1)
Loop diuretic n (%)	26 (15.2)	408 (4.8)	7 (8.2)	318 (5.7)
Antiplatelet n (%)	73 (42.7)	1811 (21.5)	43 (50.6)	1186 (21.4)
Statin n (%)	57 (33.3)	1556 (18.5)	27 (31.8)	1186 (21.4)

Source: Table U11.6.1 and Table U11.6.2

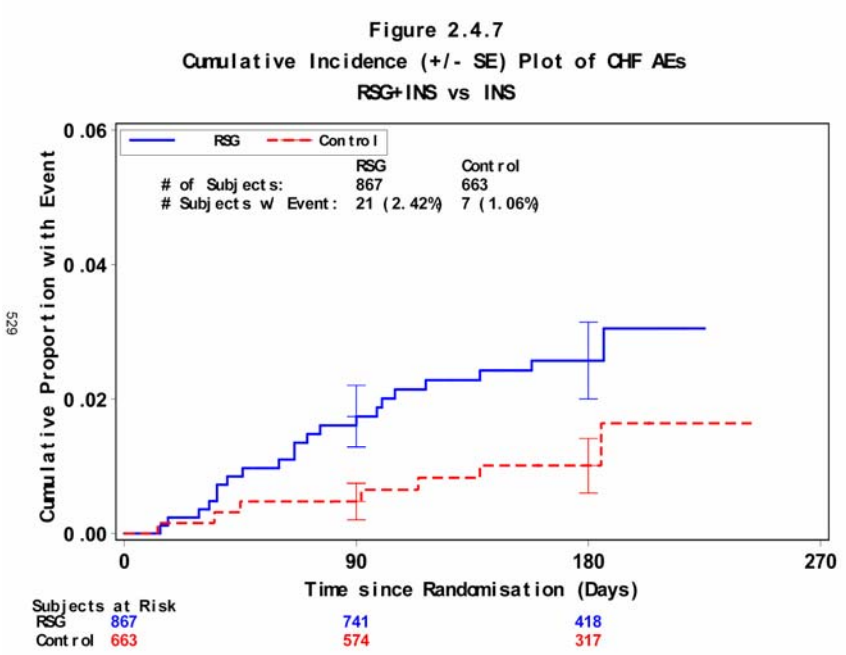
Sponsor's Table p. 115 of submission

The Sponsor conducted additional exploratory analyses to assess whether any subgroups of patients at particular risk for myocardial ischemic events could be identified. A recursive partitioning methodology was conducted using the original dataset. The results of the first stage of the analysis indicated that the best predictor of treatment emergent events of myocardial ischemia, regardless of treatment group assignment, was the presence of pre-existing coronary heart disease (CHD). Within subjects who had pre-existing CHD, the next best predictor of ischemic events was whether a subject was taking concomitant nitrates at screening. The second stage of the exploratory analysis used a Cox proportional hazards regression to compare the risk of ischemic events for RSG vs. comparator groups. The Sponsor found that, for subjects in the higher risk subgroup only (i.e., pre-existing CHD taking nitrates at screening), RSG-treated subjects had a higher risk of ischemic events relative to those in comparator groups, with an odds ratio point estimate of 2.45 (95% CI 1.34 – 4.49).

4.2.3 Special Populations with Increased Risk of Adverse Cardiovascular Events

4.2.3.1 Patients with Concomitant Insulin Therapy

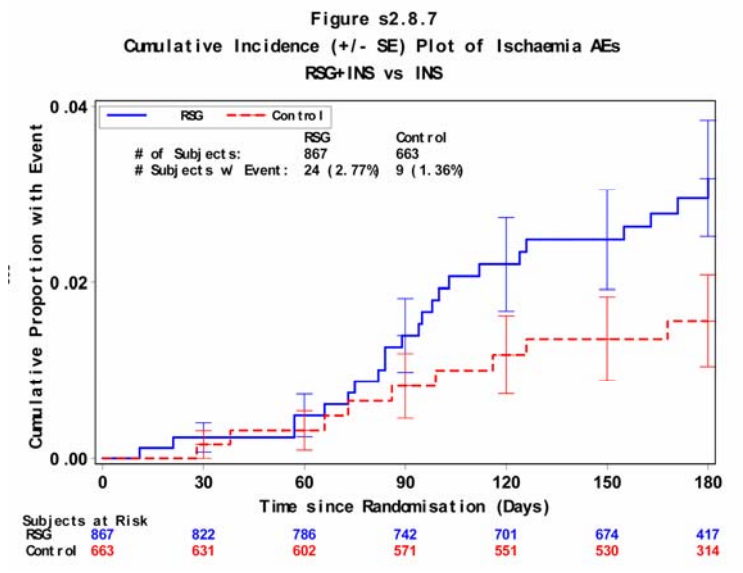
Figure s2.4.7 is reproduced from the Sponsor's submission. Five studies (082, 085, 095, 136, and 347) comprised patients receiving insulin in combination with RSG versus insulin monotherapy. The mean duration of exposure for the insulin monotherapy group was 159.2 days (SD 49.27), and for the insulin+RSG group was 157.7 days (SD 50.62). This graphic representation shows the cumulative proportion of subjects in the original dataset who developed congestive heart failure (serious + non-serious adverse events). The blue line indicates subjects randomized to RSG+INS therapy, and the dashed red line indicates subjects randomized to insulin monotherapy (INS). A striking trend is apparent, with a significantly increased incidence of heart failure in RSG+INS -treated subjects at Day 90, which persists thereafter.



Sponsor's Figure p. 529 of submission

Heart failure occurred more often in patients receiving rosiglitazone and concomitant insulin (2.42%) compared with insulin monotherapy (1.06%) in the pooled analysis (OR 2.50; 95%CI 1.06, 5.89).

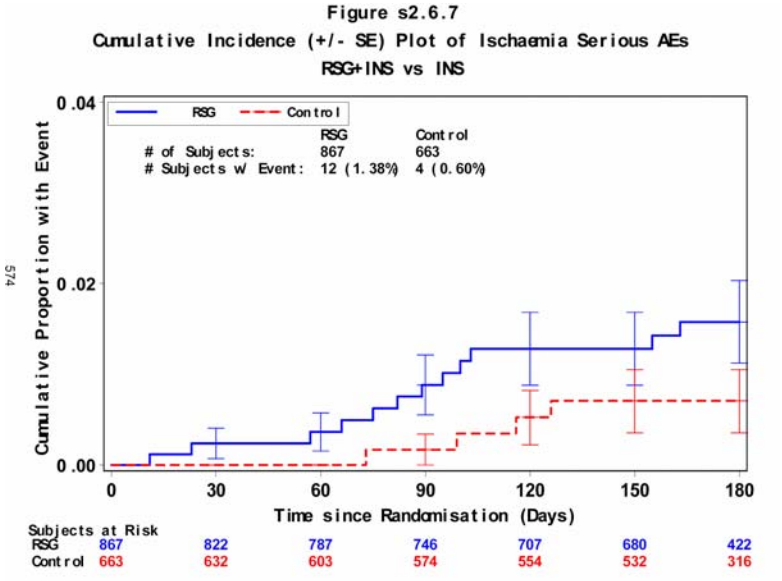
Similarly, as shown in the Sponsor's figure reproduced below, myocardial ischemia-related adverse events occurred more often in patients receiving rosiglitazone and concomitant insulin (2.77%) compared with insulin monotherapy (1.36%) in clinical trials (OR 2.02; 95%CI 0.90, 4.94). These data show roughly a doubling of risk of cardiovascular adverse effects in rosiglitazone-treated patients who require insulin therapy compared to patients receiving insulin monotherapy.



Sponsor's Figure p. 582 of submission

Figure s2.8.7 is reproduced from the Sponsor's submission. This graphic representation shows the cumulative proportion of subjects receiving insulin therapy who developed myocardial ischemia (serious + non-serious adverse events). The blue line indicates subjects randomized to RSG+INS therapy, and the dashed red line indicates subjects randomized to insulin monotherapy (INS). The trend shows an increased incidence of myocardial ischemia in RSG+INS -treated subjects starting around Day 90, with significant between group differences noted at Day 120 and thereafter.

Similarly, Figure s2.6.7 (reproduced below) shows a significant trend of increased myocardial ischemia serious adverse events (SAEs) in RSG+INS -treated subjects up to Day 180, with statistically significant between-group differences first noted at Day 30.



Sponsor's Figure p. 574 of submission

4.2.3.2 Patients with Concomitant Sulfonylurea or Sulfonylurea plus Metformin

The pooled analysis showed that, similar to the effect observed with concomitant insulin therapy, an increased incidence of heart failure was observed when RSG was added to a SU or SU + MET. The results of the pooled analysis for the original dataset, and also the updated integrated dataset, for total (serious + non-serious) adverse events of CHF are reproduced below in Sponsor's Table 35.

Table 35 All CHF AEs (Serious and Non-Serious) – Results from Exact Logistic Regression Analysis (Original and Updated Integrated Datasets)

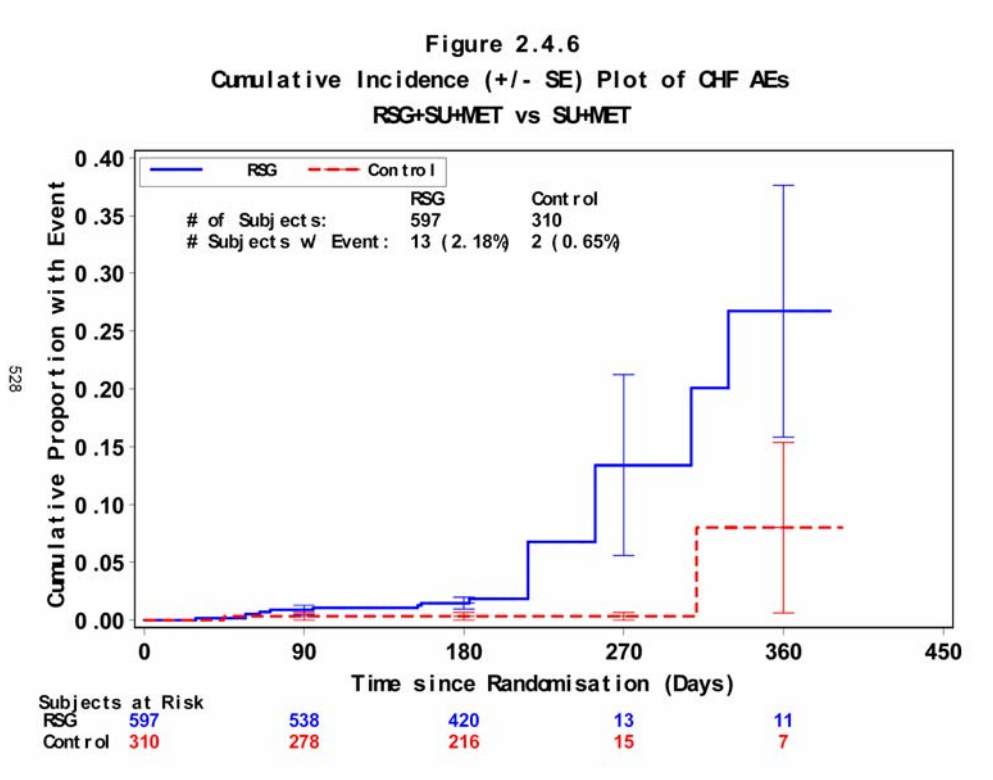
Treatment Comparison	Exact Logistic Analysis[2]--Odds Ratio Point Estimate (95% CI)		Updated Integrated Dataset: Events / Subjects (%)	
	Original Integrated Data	Updated Integrated Data	RSG	Control
RSG Mono vs. Placebo	0.45 (<0.03, 6.22)	0.46 (0.03, 6.40)	2 / 1737 (0.12%)	2 / 792 (0.25%)
RSG Mono vs. SU/MET Mono[1]	0.26 (0.03, 1.25)	0.38 (0.07, 1.48)	3 / 1127 (0.27%)	11 / 1001 (1.10%)
MET+RSG vs. MET Mono[1]	0.55 (0.05, 4.90)	0.70 (0.10, 4.12)	3 / 1608 (0.19%)	4 / 1419 (0.28%)
MET+RSG vs. MET+SU	0.95 (0.08, 6.97)	0.95 (0.08, 6.97)	2 / 285 (0.70%)	4 / 294 (1.36%)
SU+RSG vs. SU Mono[1]	1.53 (0.78, 3.12)	1.54 (0.79, 3.12)	27 / 2505 (1.08%)	15 / 1926 (0.78%)
SU+MET+RSG vs. SU+MET	4.36 (0.98, 40.00)	4.36 (0.98, 40.00)	13 / 597 (2.18%)	2 / 310 (0.65%)
INS+RSG vs. INS Mono	2.16 (0.88, 6.03)	2.26[3] (0.92, 6.29)	21 / 867 (2.42%)	7 / 663 (1.06%)

Source: Table 8.2.2 and Table U8.2

1. additional CHF AEs in the updated integrated dataset compared to the original dataset.
2. Covariates used in exact logistic regression: number of major CV risk factors.
3. Exact logistic regression results changed slightly for the INS+RSG vs. INS Mono comparisons, due to inadvertent omission of some of the medical history terms for major cv risk factors in the original analysis. As a result, the number of major cv risk factors changed from the original to the updated integrated dataset, impacting exact logistic regression results.

Sponsor's Table p. 88 of submission

A between-group comparison of subjects randomized to RSG+SU+MET vs. SU+MET showed a trend toward increased risk of heart failure in the RSG-treated group after Day 180. Figure 2.4.6 from the Sponsor's submission is reproduced below.



Sponsor's Figure p. 528 of submission

GSK proposes to add the following language to the Adverse Reactions section of the AVANDIA USPI: "Similarly, an increased incidence of heart failure has also been observed when AVANDIA was added to a sulfonylurea or to a sulfonylurea plus metformin. There were too few events to confirm a dose relationship; however, the incidence of heart failure appeared higher with AVANDIA 8 mg daily. (See WARNINGS, Cardiac Failure and Other Cardiac Effects.)"

Five of the seven strata in GSK's pooled analysis comprise various combinations of rosiglitazone, sulfonylureas, and metformin. An FDA biostatistical analysis of these data is currently in progress. It would be helpful to have results of between group comparisons of total cardiovascular adverse events (heart failure + myocardial ischemia), as well as further understanding of biostatistical effects of creating multiple strata containing various combinations of these three drugs on the results of the pooled analysis. A better understanding of the relative contribution of sulfonylurea drugs on adverse cardiovascular effects in the pooled data is needed. DDRE recommends further consideration of this issue after completion of the FDA Biostatistical review.

4.2.3.3 Patients with Pre-existing Coronary Heart Disease Requiring Nitrate Therapy

Table 59 from the Sponsor's submission (reproduced below) shows the results from a recursive partitioning analysis for the original and updated integrated datasets, as well as the number of events and total number of subjects for each treatment regimen in the updated integrated dataset. Subjects with pre-existing CHD who were taking nitrates at study baseline had a higher frequency of events of myocardial ischemia irrespective of whether they were receiving RSG or other anti-diabetic medications. Exploratory analyses conducted by the Sponsor on the original dataset identified a subgroup of RSG-treated patients (those with pre-existing CHD taking concomitant nitrates at screening) who demonstrated a significantly elevated risk of ischemic events relative to similar patients in the comparator groups (OR 2.45, 95% CI 1.34 – 4.49). The Sponsor found that results from the recursive partitioning analyses of the updated integrated dataset were consistent with those from the exploratory analysis conducted on the original dataset.

Table 59 All Myocardial Ischemia AEs (Serious and Non-Serious) – Results from Proportional Hazards Regression in Recursive Partitioning Subgroups (Original and Updated Integrated Datasets)

	Proportional Hazards Regression Hazard Ratio Point Est. (95% CI)		Updated Integrated Dataset Events / Subjects (%)	
Recursive Partitioning Subgroup	Original Integrated Data	Updated Integrated Data	RSG	Control
No pre-existing CHD	1.25 (0.84, 1.87)	1.42 (0.96, 2.11)	81 / 7395 (1.10%)	36 / 4788 (0.75%)
Pre-existing CHD, no nitrates	1.08 (0.67, 1.74)	1.06 (0.68, 1.65)	47 / 886 (5.30%)	33 / 622 (5.31%)
Pre-existing CHD, with nitrates	2.45 (1.34, 4.49)	2.14 (1.20, 3.81)	43 / 323 (13.31%)	16 / 223 (7.17%)
Overall	1.29 (0.99, 1.69)	1.31 (1.01, 1.70)	171 / 8604 (1.99%)	85 / 5633 (1.51%)

Source: Table 15.9 - Table 15.12 and Table U8.5.1 - Table U8.5.4

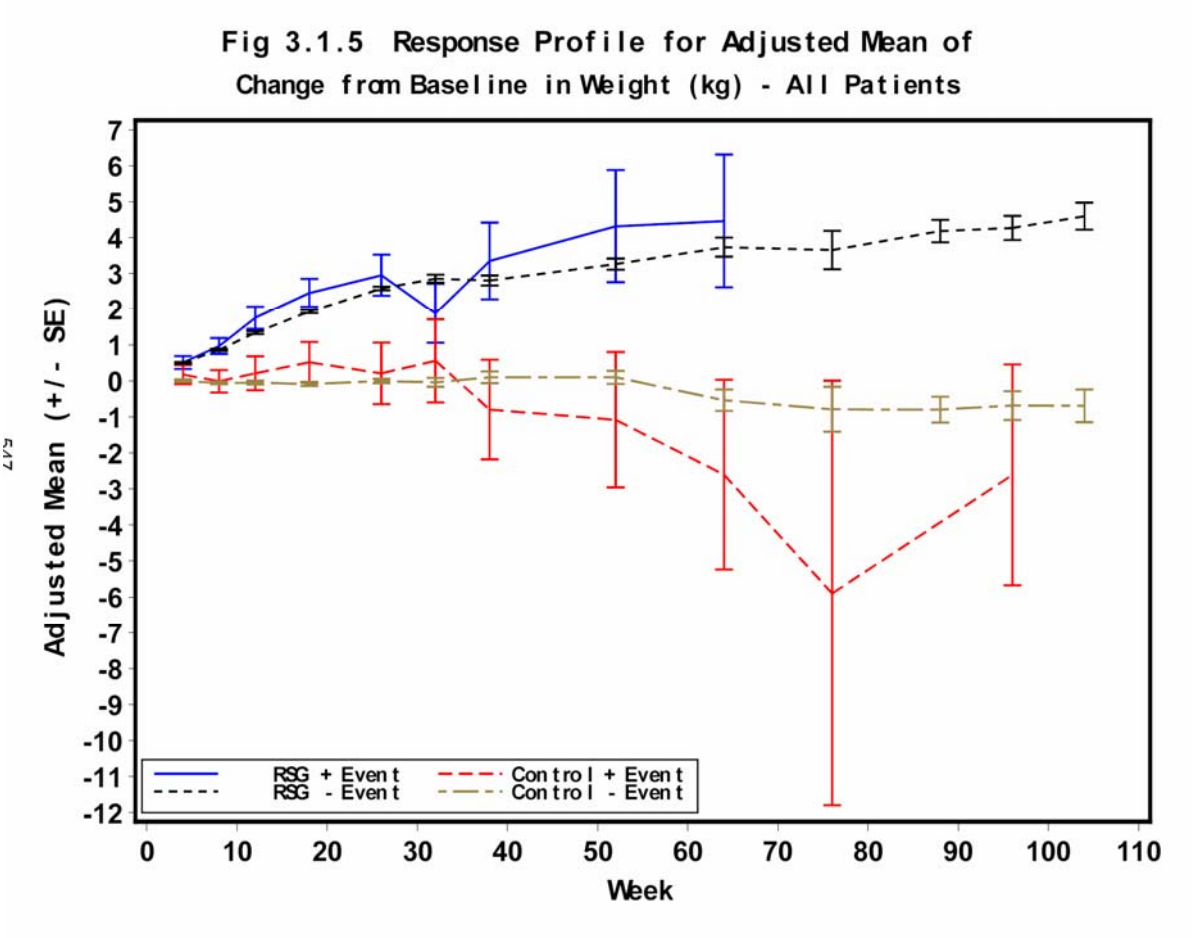
Sponsor's Table p. 132 of submission

The Sponsor determined that when subjects with a history of coronary heart disease were separated into those with and without concomitant nitrates, the nitrate using group was more likely to have a history of CHF at study entry, and was also more likely to be taking loop diuretics, beta blockers, calcium channel blockers and antiplatelet agents. The Sponsor concluded that, overall, subjects taking nitrates at study entry appear to have more severe or advanced underlying coronary disease.[31]

Other evaluation of on-therapy predictors for myocardial ischemic events included AEs of edema, laboratory values for hematocrit, weight, and blood pressure. There were small differences in the mean changes from baseline in both weight and hematocrit between subjects who developed myocardial ischemic events and those who did not, suggesting that small differences in the degree of fluid retention could potentially be contributing to the development of myocardial ischemic events in subjects with severe coronary heart disease (CHD).

[31] See Table 53, Section 7.1.4, in AVANDIA® Cardiovascular Event Modeling Project study report, submitted August 4, 2006.

Figure 3.1.5 (reproduced from the Sponsor's submission) shows a graphic display of mean change from baseline in weight for subjects randomized to RSG or comparator who experienced an adverse event of myocardial ischemia vs. those who did not experience such an event. A striking between-group difference is noted, with all RSG-treated subjects tending to gain weight, and comparator subjects with ischemia adverse events tending to lose weight.



Sponsor's Figure p. 547 of submission

4.2.4 Cardiovascular Deaths in the Pooled Analysis

The Sponsor identified 12 (0.14%) deaths related to myocardial ischemia in RSG-treated subjects and 6 (0.11%) deaths in comparator groups. Table 49 (reproduced below from the Sponsor's submission) shows the breakdown by treatment. In addition, there were four deaths related to CHF in RSG-treated subjects, and none in the comparator groups.

The overall total number of cardiovascular deaths identified in the pooled analysis is 16 (0.19%) in the RSG treatment group vs. 6 (0.11%) in comparator groups. Two additional cardiovascular deaths occurred after discontinuation of study drug, but were not counted in the death analysis as they occurred after the clinical trials database was closed.

Table 49 Summary of Deaths Related to Myocardial Ischemia (Updated Integrated Dataset)

Treatment Comparison	Treatment Group	
	RSG	CONTROL
RSG Mono vs. Placebo	2 / 1737 (0.12%)	1 / 792 (0.13%)
RSG Mono vs. SU/MET Mono	1 / 1127 (0.09%)	2 / 1001 (0.20%)
MET+RSG vs. MET Mono[1]	2 / 1608 (0.12%)	0 / 1419 (0)
MET+RSG vs. MET+SU	0 / 285 (0)	1 / 294 (0.34%)
SU+RSG vs. SU Mono	4 / 2505 (0.16%)	4 / 1926 (0.21%)
SU+MET+RSG vs. SU+MET	1 / 597 (0.17%)	0 / 310 (0)
INS+RSG vs. INS Mono	2 / 867 (0.23%)	0 / 663 (0)
Total	12 / 8604 (0.14%)	6 / 5633 (0.11%)

Source: Table U10.2

1. additional myocardial ischemia death in the updated integrated dataset compared to the original dataset

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Overall, there were nearly twice as many cardiovascular deaths (0.19% vs. 0.11%) in subjects randomized to rosiglitazone (16/8604) as there were in comparator groups (6/5633). Narrative summaries for all identified cardiovascular deaths are presented in Appendix 2.

Of the total cardiovascular deaths in RSG-treated subjects which were identified in the Sponsor's analysis, 12 cases (75% of the cardiovascular deaths in the RSG group) were consistent with sudden cardiac death. Of these, 11 were classified in the Sponsor's analysis as myocardial ischemia cases, and one was classified as CHF. Only two of these 12 sudden death cases included autopsy results. Of these, one case (A0239860A) stated that myocardial infarction was the cause of death, and one case (B0199699A) indicated the presence of myocardial infarction, as well as "severe pulmonary edema" in the autopsy report. Autopsy results were stated as "pending" in an additional case of sudden death (A0312591A). A reliable assessment of the relative contributing roles of heart failure and/or myocardial ischemia in these cases cannot be concluded on the basis of the incomplete information provided.

In comparator groups, four (67%) of the total six deaths were consistent with sudden cardiac death. Autopsy information was not provided for any of these cases.

The incidence of sudden cardiac death in RSG-treated subjects (11/8604 = 0.00128) is nearly twice that observed in the comparator groups (4/5633 = 0.00071).

As noted in Sponsor's Table 51 (reproduced below), relatively more RSG-treated subjects with no prior history of CHD (0.12%) experienced fatal myocardial ischemia compared to the proportion of subjects in control groups (0.02%).

Table 51 Reports of Fatal Events of Myocardial Ischemia by Recursive Partitioning Subgroup (Updated Integrated Dataset)

Subgroup	RSG Events / Subjects (%)	Control Events / Subjects (%)
No CHD	9 / 7395 (0.12%)	1 / 4788 (0.02%)
CHD without nitrates	1 / 886 (0.11%)	2 / 622 (0.32%)
CHD with nitrates	2 / 323 (0.62%)	3 / 223 (1.35%)
All Subjects	12 / 8604 (0.14%)	6 / 5633 (0.11%)

Source: Table U10.10

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4.3 Sponsor's Conclusions

Congestive Heart Failure –Results from the updated integrated dataset were generally similar to those observed in the original dataset. Across the treatment regimens evaluated, encompassing 14,237 subjects in 42 controlled double-blind studies in the updated integrated dataset, the incidence rate of CHF in the RSG and control treatment groups was generally low, although an increased incidence of CHF in both the original and updated integrated datasets was observed when RSG (at both 4 mg and 8 mg) was added to treatment regimens that included SU or insulin. There were too few events to confirm a dose relationship; however, the incidence of CHF appeared higher with 8 mg RSG compared to 4 mg RSG (total daily dose).

Myocardial ischemia –Results from the updated integrated dataset were generally similar to those observed in the original dataset. Across the treatment regimens evaluated, encompassing 14,237 subjects in 42 controlled double-blind studies in the updated integrated dataset, the incidence rate of myocardial ischemia events in the RSG and control treatment regimens was generally low. RSG in combination with insulin was associated with a higher incidence of myocardial ischemia events. A subgroup of subjects with a history of CHD who were taking nitrates at baseline was identified using exploratory recursive partitioning methodology. This group overall had the highest incidence of myocardial ischemia events, and the elevated risk estimate for RSG vs. control was similar in magnitude to that observed in insulin-treated subjects.

Although the evaluation of potential predictors for myocardial ischemia events was considered by the Sponsor to be inconclusive, there was a suggestion that slightly greater reductions in hematocrit and slightly greater weight gain may have occurred within the first 3 months of initiating RSG in subjects with subsequent ischemic events. These data support the hypothesis that small degrees of fluid retention may contribute to the development of worsening myocardial ischemia in higher risk subjects.

4.4 DDRE Reviewer Comments

The Sponsor's analysis is based on the assumption that serious cardiovascular adverse events of interest can be reliably adjudicated and classified *post hoc* as representing ***either*** cardiac ischemia ***or*** heart failure. A concern exists that this method likely results in misclassification. The rationale for this concern is that information about the serious adverse events included in this pooled analysis was derived from standard case report form pages which did not include targeted or specific data fields designed to facilitate adjudication of diagnostic criteria for confirmed disease conditions. Ischemic cardiomyopathy is an

important cause of heart failure, and its occult presence cannot be ruled out on the basis of the often incomplete information that is usually found in routine safety data collection. There is also a concern that cases identified as cardiac ischemia-related diagnoses on routine case report form pages may have occasionally failed to capture full information about relevant complications, such as heart failure.

Analysis of SAS datasets from pooled clinical trials submitted by GSK was also undertaken by FDA, and is described in a separate Office of Biostatistics review.[32] To address potential issues of misclassification, the FDA analysis compared total cardiovascular adverse events for the combination of CHF and myocardial ischemia events. The Sponsor's analysis retrospectively identified a total of 115 serious adverse cardiovascular events of interest (either ischemia or heart failure) in patients receiving RSG in controlled clinical trials (1.34% of 8604 subjects), and 59 such events (1.05%) in 5633 subjects randomized to comparator groups. Overall, subjects randomized to RSG treatment groups experienced a statistically significant 40% increased risk of serious cardiovascular adverse events, as identified in the Sponsor's analysis. Similarly, for total adverse cardiovascular events (serious + non-serious), the Sponsor identified 230 events (2.67%) in 8604 subjects receiving RSG, and 115 events (2.04%) in 5633 subjects in comparator groups, yielding a statistically significant odds ratio of 1.4 (95% CI 1.1, 1.8; p=0.003), corresponding to an overall 40% increased risk of cardiovascular adverse events in RSG-treated patients. In the FDA's analysis, increased risk for cardiovascular adverse events was consistently noted for RSG-treatment groups. Only the between-group comparison of SAEs classified as CHF failed to achieve statistical significance, although the odds ratio point estimate was greater than one. This may be due to the fact that subjects with SAEs with characteristics of CHF as well as myocardial ischemia could only be counted in one category. In the Sponsor's analysis, cases which included SAEs of both myocardial ischemia and congestive heart failure were, in each case, adjudicated as myocardial ischemia, and counted as such in the analysis. This convention likely resulted in under-ascertainment of SAEs classified as heart failure.

Results for Overall Study Population Using the Sponsor's Model [33]

	RSG Groups (n=8604)	**Comparators** (n=5633)	**OR** (95% CI)	**p-value**
AE				
Myocardial Ischemia	1.99% (171)	1.5% (85)	1.4 (1.1, 1.8)	0.012
CHF	0.83% (71)	0.6% (33)	1.6 (1.0, 2.4)	0.036
Either	2.67% (230)	2.04% (115)	1.4 (1.1, 1.8)	0.003
SAE				
Myocardial Ischemia	1.0% (86)	0.7% (40)	1.5 (1.0, 2.2)	0.035
CHF	0.35% (30)	0.34% (19)	1.1 (0.6, 2.0)	0.64
Either	1.34% (115)	1.05% (59)	1.4 (1.0, 1.9)	0.047

The FDA biostatistical analysis also found a statistically significant doubling of risk for total cardiovascular adverse events (serious + non-serious) in patients receiving RSG+INS compared to those receiving insulin monotherapy (16/663; 2.4%) OR 2.0 (95% CI 1.1, 3.6; p=0.02).

[32] Mele J. Draft results from analysis of SAS datasets included in GSK submission entitled "Analysis of Pooled Data from Randomized Controlled Trials with Rosiglitazone: Cardiovascular Event Modeling Project"; final document in preparation.
[33] Mele J., *ibid*.

5 Observational Balanced Cohort Study

Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents (HM2006/00497/00)

5.1 Methods

An observational balanced cohort study was conducted for GSK by the i3 Drug Safety Epidemiology division of Ingenix Pharmaceutical Services. The study design is outlined below:

- Enrollees of United Healthcare health plans with medical and prescription benefit coverage
- Identify drug initiators from JUL 2000 through DEC 2004
- Create matched cohorts using multivariate balancing procedure (propensity score matching) to match comparable initiators for each study group
- New cases of myocardial infarction or coronary revascularization were identified up to JUN 2005
- Analyses:
    - "As-balanced" (intent to treat)
        - K-M curves were calculated
        - Hazard ratios estimated from multivariate Cox proportional hazards models in each study group, adjusted for baseline covariates, for five pair-wise comparisons
        - Models were also adjusted for age, gender, and total baseline healthcare costs at baseline (surrogate for overall active disease burden)
    - "As-treated" (time-on-drug)
        - Periods of non-use were omitted from the analysis.
        - Poisson regression coefficients provided estimates of the relative incidence rates between current use periods for five pair-wise comparisons.
    - Multivariate models adjusted with baseline covariates to account for potential confounding
- Baseline characteristics included (based on 6-month look-back):
    - Age
    - Sex
    - Region of US
    - Date of initiation of drug (before or after JAN 2003)
    - Medical conditions: hyperlipidemia, myocardial infarction, coronary revascularization, angina, unstable angina, CHD, CHF, hypertension, smoking, obesity.
    - Prescriptions drug usage: nitrates, beta-blockers, CC-blockers, diuretics, anti-platelet drugs.
- Propensity score matching procedure is intended to balance the distribution of characteristics within each cohort that may have influenced a physician's choice of therapy for an individual patient.

5.2 Population Characteristics

- Monotherapy:
    - Identified 11,227 initiators of RSG of whom 8,977 (80%) were matched to 8,977 initiators of MET and 8,977 initiators of SU.

- Dual therapy:
    - Identified 2,075 initiators of RSG+SU of whom 1,362 (66%) were matched to 1,362 initiators of RSG+MET and 1,362 initiators of MET+SU.

- Combination with insulin:
    - Identified 1,236 initiators of RSG+insulin of whom 1,173 (95%) were matched to 1,173 initiators of other agents + insulin.

- Follow-up shifted between exposure classes on the basis of whether each day of follow-up fell within the period defined by the days supply associated with each dispensing of the study drugs.

5.3 Results: As-balanced Multivariate Analysis

Incidence rates per 1,000 person-years for the composite outcome (myocardial infarction + coronary revascularization) in the as-balanced multivariate analysis are presented in Table 2e below, reproduced from the Sponsor's study report.

Table 2e: Incidence rates for composite outcome

As-balanced analysis

	Full follow-up					Six-month follow-up				
	Events	Person-Years	IR[1]	95% C.I.[1]		Events	Person-Years	IR[1]	95% C.I.[1]	
Monotherapy										
Rosiglitazone	152	9,676	15.71	13.36	18.36	70	3,594	19.48	15.31	24.45
Metformin	149	10,722	13.90	11.80	16.27	57	3,772	15.11	11.56	19.43
Sulfonylurea	191	9,772	19.55	16.92	22.47	91	3,698	24.61	19.93	30.06
Dual therapy										
Rosiglitazone + Metformin	24	1,683	14.26	9.37	20.86	13	574	22.65	12.68	37.63
Rosiglitazone + Sulfonylurea	39	1,474	26.46	19.10	35.78	21	553	37.97	24.21	56.96
Metformin + Sulfonylurea	36	1,852	19.44	13.84	26.60	13	598	21.74	12.17	36.12
Insulin Therapy										
Rosiglitazone	44	1,997	22.03	16.22	29.29	15	539	27.83	16.26	44.74
Other[2]	51	1,957	26.06	19.62	33.97	16	528	30.30	18.03	48.04

Note:
[1] Incidence rates and 95% confidence intervals per 1,000 person-years.
[2] Other antidiabetic agents, excluding TZD's

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5.4 Results: As-treated Multivariate Analysis

Incidence rates per 1,000 person-years for the composite outcome (myocardial infarction + coronary revascularization) in the as-treated multivariate analysis are presented in Table 3e below, reproduced from the Sponsor's study report.

Table 3e: Incidence rates for composite outcome

As-treated analysis

Current Use of Drug	Events	Person-years	IR[1]	95% C.I.[1]	
Monotherapy					
Rosiglitazone	99	5,650	17.52	14.24	21.33
Metformin	85	6,256	13.59	10.85	16.80
Sulfonylurea	130	5,631	23.08	19.29	27.41
Dual therapy					
Rosiglitazone + Metformin	15	841	17.83	9.98	29.40
Rosiglitazone + Sulfonylurea	23	691	33.26	21.09	49.91
Metformin + Sulfonylurea	16	927	17.26	9.87	28.04
Insulin Therapy[2]					
Rosiglitazone	21	937	22.41	13.87	34.26
Other[3]	43	1,465	29.36	21.25	39.55

Note:
[1] Incidence rates and 95% confidence intervals per 1,000 person-years.
[2] Because of potential switching of therapy in the follow-up period, patients may be currently exposed to both drug classes, and therefore, person-years and outcome events are not mutually exclusive.
[3] Other antidiabetic agents, excluding TZD's

Sponsor's Table p. 48 of submission

5.5 Study Limitations

The Sponsor acknowledges that the statistical power of this study is limited. Also, the population in this study has relatively fewer elderly patients compared to the overall US population or the population of Type 2 diabetic patients. The Sponsor also acknowledges the limited generalizability of this study [34]

[34] See Discussion, page 29, Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents. Study Report, June 15, 2006.

5.6 DDRE Reviewer Comments

5.6.1 Statistical methods

A review of the observational study submitted by GSK was also conducted by an Office of Biostatistics Safety Reviewer 35 and is presented in a separate document.

A full statistical analysis plan was not provided for this study, including information about study population, study objectives/hypotheses, sample size, statistical methods (including the check of model assumptions and model diagnostics).

A sample size/power calculation demonstrating that the study has enough power to show similar rates of myocardial infarction (MI) and/or cardiac revascularization procedures (CR) between RSG and other anti-diabetic agents was not provided.

The use of the propensity score method for matching in this study as opposed to other alternatives (i.e., stratification or direct adjustment) was not adequately justified. A detailed derivation of the propensity score was not included in the study report, including: (a) the strategy of dealing with missing covariates in the logistic model for estimating the propensity scores; (b) the details of the matching procedure; and (c) a discussion of the limitations of the propensity score matching procedure, which precludes the possibility of analyzing treatment comparisons other than those proposed, and means that some data are discarded (mono-therapy group: 20%, dual-therapy group: 34%).

More detail is needed with regard to the CHD risk factor stratification analysis, and several questions remain. The final model included age, gender, total baseline healthcare costs, hyperlipidemia, nitrates, and cohort of origin. The study report does not state how the other baseline covariates were handled in the analysis of RSG versus non-RSG. Similar analyses should also be done for the as-treated population.

5.6.2 General design issues

The endpoint defined in this observational study is not adequate to address the cardiovascular safety issues raised by the pooled randomized controlled trial data. The outcome analysis was limited to myocardial infarction and coronary revascularization. Numerous other cardiac related events were excluded from this definition of outcome. Examples include sudden cardiac deaths due to myocardial ischemia, congestive heart failure, unstable angina or other forms of angina. In the pooled analysis of controlled clinical trials, the endpoint was defined as the overall incidence of "CHF or myocardial ischemia". Events of myocardial ischemia in RSG-treated subjects identified in the pooled analysis included at least eleven cases consistent with sudden cardiac death. However, in the observational cohort study, the endpoint was defined as the composite endpoint of MI and/or CR, and did not include sudden deaths. Since the majority of fatal cardiovascular adverse events in both treatment groups were consistent with sudden cardiac death, the omission of such cases from the observational study endpoints is an important limitation.

5.6.3 Potential biases in the study

There is no information about the loss-to-follow-up rate in the report. Differential loss-to-follow-up rate between study cohorts can possibly lead to selection bias. In addition, general problems in the United HealthCare database include: (a) Data on the use of inpatient drugs are not available; (b) If the cost of a

[35] Wu, Yu-Te. Draft review of Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents (HM2006/00497/00).

prescription drug is lower than the co-payment amount, the prescription may not be included in the database since no prescription claim may be submitted; and (c) No information on patient adherence with the therapeutic regimen was provided.

It is not clear how these limitations may affect the results of the study. However, it is clear that this observational study does not provide sufficient information to definitively impact the conclusions based on results of the pooled safety data analysis from randomized controlled trials with rosiglitazone.

5.7 Other Observational Studies Conducted by the Sponsor

Other observational studies submitted by GSK included a study entitled "Balanced Cohort Study of Thiazolidinediones (TZDs) and other Anti-diabetic Therapies and Coronary Heart Disease Outcomes".[36] This study focused on coronary heart disease (CHD) events among diabetics who use TZDs (i.e., pioglitazone or rosiglitazone), compared with diabetics who use SUs or MET. Two outcomes of interest were explored, fatal or non-fatal myocardial infarction (MI) and coronary revascularization (CR). The time period of interest was July 1, 1999 through June 30, 2002. Using a multivariate balancing procedure (propensity score matching) three sets of matched cohorts were created: TZD initiators matched to MET monotherapy initiators (10,269 per initiator group), TZD initiators matched to SU monotherapy initiators (7,881 per initiator group), and TZD initiators matched to MET-SU combination initiators (12,570 per initiator group). Variables were created for the propensity score model to represent characteristics in the six months before drug initiation that may have influenced a physician's choice of therapy for an individual patient. TZD initiators were older, had more diabetic complications, and more medical care utilization for cardiovascular disease than comparison drug initiators, an expected finding given the indications for TZDs. However, the matching process in this study, based on a propensity score derived from numerous pretreatment variables, resulted in cohorts that were well balanced in terms of patient characteristics, and did not exhibit the baseline differences evident before matching. Analysis of the "as-balanced" cohorts showed an incidence of acute MI in TZD initiators was 8.71 per 1,000 person-years and it was 7.20 per 1,000 person-years in the MET initiators; and the adjusted hazard ratio (HR) comparing TZD to MET initiators was 1.22 (95% confidence interval (CI): 0.93- 1.61). The incidence of an acute coronary revascularization (CR) event was 19.49 per 1,000 and 15.70 per 1,000 person-years in TZD and MET initiators, respectively; and the adjusted HR comparing TZD to MET initiators was 1.26 (95% CI: 1.05-1.52).

6 Published Literature: Brief Review

6.1 Consensus Statement

In August 2006, a consensus statement on the management of hyperglycemia in T2DM was published by the American Diabetes Association and the European Association for the Study of Diabetes.[37] The new recommendations state that "metformin therapy should be initiated concurrent with lifestyle intervention at diagnosis", as first line therapy, barring specific contraindications. The rationale provided for metformin as the drug of choice is "its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost." The guidelines state that "metformin treatment should be titrated to its maximally effective dose over 1-2 months, as tolerated." There is no clear

[36] Ingenix, Epidemiology Division. Final Report: Balanced Cohort Study of TZDs and other Anti-diabetic Therapies and Coronary Heart Disease Outcomes. August 9, 2004.

[37] Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, and Zinman B. Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care*; 29(8):1963-1972, 2006.

consensus regarding the second medication to be added if lifestyle intervention and maximal tolerated dose of metformin fail to "achieve or sustain glycemic goals", except that, for patients with symptomatic hyperglycemia or A1C >8.5%, consideration should be given to "the more effective glycemia-lowering agent, insulin".

With regard to thiazolidinediones (TZDs), the guidelines point out that the most common adverse effects are "weight gain and fluid retention", with an "increase in adiposity" and "fluid retention", which "usually manifests as peripheral edema, though new or worsened heart failure can occur." The authors comment that pioglitazone has a "more beneficial effect than rosiglitazone" on "atherogenic lipid profiles". The authors further comment that the PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) study showed "no significant effects of pioglitazone compared with placebo on the primary CVD outcome", but a "16% reduction in death, myocardial infarction, and stroke, a secondary endpoint, was reported with marginal statistical significance."[38]

6.2 Heart Failure and Thiazolidinediones

Numerous published case reports[39] [40] [41] [42] [43] [44] [45] [46] [47] as well as several published observational studies[48] [49] [50] [51] have described heart failure associated with TZD therapy.

One recent case report[52] describes a 74-year-old diabetic male with a history of coronary artery disease, heart failure (NYHA class II-III), and chronic renal insufficiency who developed weight gain, dyspnea, and was admitted to the hospital with exacerbation of heart failure one month after RSG was added to Glyburide 10 mg twice daily. Symptoms of heart failure resolved after five days with vigorous diuresis; however, RSG 8 mg daily was continued, and the patient was readmitted to the hospital five days later with marked weight gain and exacerbation of heart failure. The patient was subsequently discharged taking Glyburide, but not RSG. His weight was noted to be stabilized at two months and at three months after hospital discharge. A graphic representation of this patient's course is reproduced below:

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[38] 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.
[39] Kermani A and Garg A. Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc*. 78:1088-91, 2003.
[40] Jamieson A, Abousleiman Y. Thiazolidinedione-associated congestive heart failure and pulmonary edema [letter]. *Mayo Clin Proc*. 79:571, 2004.
[41] Wooltorton E. Rosiglitazone and pioglitazone and heart failure. *CMAJ*; 166:219, 2002.
[42] Thomas ML, Lloyd SJ. Pulmonary edema associated with rosiglitazone and troglitazone [letter]. *Ann Pharmacother*; 35:123-3, 2001.
[43] Cheng AY, Fantus IG. Thiazolidinedione-induced congestive heart failure. *Ann Pharmacother*. 38(5); 817-20, 2004.
[44] Page RL, Gozansky WS, Ruscin JM. Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy*. 23(7); 945-54, 2003.
[45] Ridderstrale M, Groop L. A case report: rosiglitazone treatment was highly effective yet had to be terminated [in Swedish]. *Lakartidningen*; 99:407-10, 2002.
[46] Singh N. Rosiglitazone and heart failure: long-term vigilance. *J Cardiovasc Pharmacol Ther*. 9(1); 21-5, 2004.
[47] Kennedy FP. Do thiazolidinediones cause congestive heart failure? [editorial] *Mayo Clin Proc*; 78:1076-1077, 2003.
[48] Delea TE, Edelsberg JS, Hagiwara M, *et al*. Use of thiazolidinediones and risk of heart failure in people with Type 2 diabetes. A retrospective cohort study. *Diabetes Care*; 26(11):2983-89, 2003.
[49] Hartung DM, Touchette DR, Bultemeier NC, Haxby DG. Risk of hospitalization for heart failure associated with thiazolidinedione therapy: a Medicaid claims-based case-control study. *Pharmacotherapy* 25(10):1329-36, 2005.
[50] Marceille JR, Goins JA, Soni R, Biery JC, Lee TA. Chronic heart failure related interventions after starting rosiglitazone in patients receiving insulin. *Pharmacotherapy*; 24:1317-22, 2004.
[51] Masoudi FA, Inzucchi SE, Wang Y, Havranek EP et al. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation*; 111:583-90, 2005.
[52] Page RL, Gozansky WS, Ruscin JM. 2003, *Op cit*.

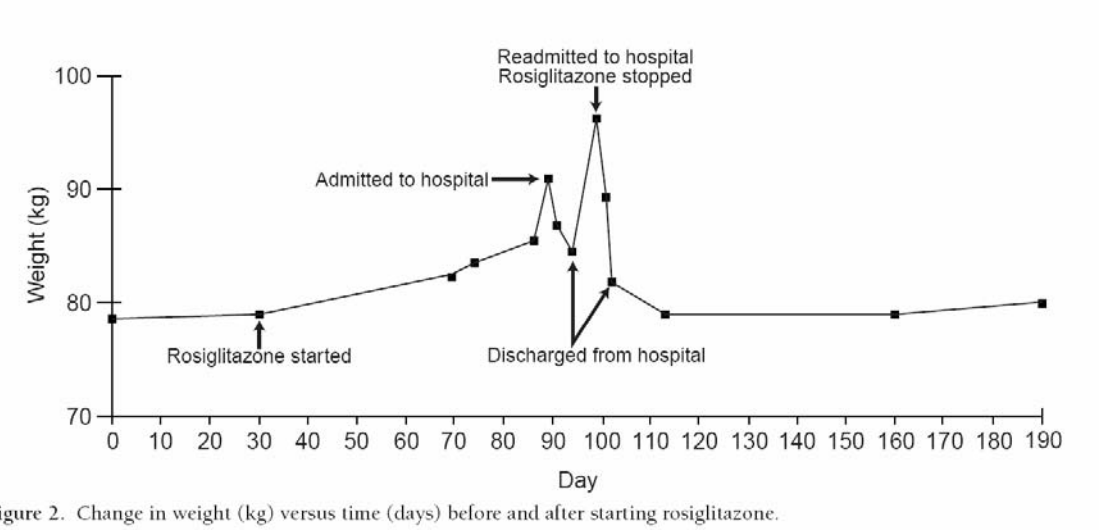

Figure 2. Change in weight (kg) versus time (days) before and after starting rosiglitazone.

Figure reproduced from Page RL, Gozansky WS, and Ruscin JM. Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. *Pharmacotherapy*. 23(7); 945-54, 2003.

Other published case reports have noted that, despite treatment with potent diuretics, symptomatic heart failure resolved only after RSG therapy was stopped. For instance, two of the six cases (Case 3 and Case 4) of TZD-associated heart failure described by Kermani and Garg [53] improved only after RSG was discontinued.

GSK acknowledges in their review of relevant published observational data[54] that "published observational studies have generally demonstrated an increased risk for heart failure among users of TZDs with the magnitude of the measured risk being variable depending upon the patient population examined and the methodology employed."

6.3 Cardiovascular Outcomes with Antidiabetic Agents

6.3.1 United Kingdom Prospective Diabetes Study (UKPDS)[55] [56]

The United Kingdom Prospective Diabetes Study (UKPDS) included 5,102 patients newly diagnosed with T2DM in the UK between 1977 and 1991. Patients were followed for an average of ten years to determine 1) whether intensive use of pharmacological therapy to lower blood glucose levels would result in clinical benefits (i.e., reduced cardiovascular and microvascular complications) and 2) whether the use of various SU drugs, MET, or insulin have specific therapeutic advantages or disadvantages. The main conclusions described in the Position Statement of the American Diabetes Association[57] included:

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[53] Kermani A and Garg A. *op cit*. 2003

[54] AVANDIA Cardiovascular Event Modeling Project, ZM2005/00181/01, Section 8.3, Summary of Observational Studies, page 136.

[55] UK Prospective Diabetes Study (UKPDS) Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837-853, 1998.

[56] UK Prospective Diabetes (UKPDS) Group: Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854-865, 1998.

[57] Genuth S, Eastman R, Kahn R, *et al*. Implications of the United Kingdom Prospective Diabetes Study. Position Statement, American Diabetes Association. *Diabetes Care*; 25, *Suppl* 1: 528-532, 2002.

- "The UKPDS results establish that retinopathy, nephropathy, and possibly neuropathy are benefited by lowering blood glucose levels in T2DM with intensive therapy, which achieved a median HbA1c of 7.0% compared with conventional therapy with a median HbA1c of 7.9%. The overall microvascular complication rate was reduced by 25%."
- "No significant effect of lowering blood glucose on cardiovascular complications was observed. A 16% reduction (which was not statistically significant, p=0.052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death was observed."
- Patients assigned to intensive therapy with MET had "decreased risks of combined diabetes-related end points, diabetes-related deaths, all-cause deaths, and myocardial infarction compared with the conventionally treated patients. These risks were significantly reduced by about one-third (p< 0.0023-0.017)."

6.3.2 Cohort Studies of Diabetic Patients from Saskatchewan and Tayside

Several recent studies have demonstrated results consistent with those of the UKPDS, in which overweight and obese subjects who were randomized to initial monotherapy with metformin experienced significant reductions in myocardial infarction and diabetes-related deaths. [58]

A retrospective cohort analysis using the Saskatchewan Health administrative database found that "metformin therapy, alone or in combination with SU, was associated with reduced all-cause and cardiovascular mortality compared with SU monotherapy among new users of these agents"[59]

This finding was subsequently confirmed by the same study group using standard multivariate techniques, including propensity scores, to adjust for potential confounding, and additional analyses showed that metformin monotherapy was also associated with a lower risk of nonfatal cardiovascular-related hospitalizations compared to SU monotherapy.[60]

Also recently, an observational study was conducted in the UK to evaluate the risk of adverse cardiovascular outcomes in patients with T2DM newly treated with SUs or metformin.[61] This study utilized data from the Diabetes Audit and Research in Tayside, Scotland (DARTS), which incorporates health care data routinely collected by the UK National Health Service for approximately 400,000 people residing in Tayside. The authors found that "in this cohort study of patients newly treated with oral hypoglycemic agents, those treated with SUs only, or combinations of SUs and metformin, were at higher risk of adverse cardiovascular outcomes than those treated with metformin alone."

6.3.3 PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive Study)

Heart failure was identified as a safety issue in a recent large randomized controlled trial of PIO vs. placebo in 5238 patients with T2DM[62]. The study included patients 35 to 79 years of age with HgbA1c levels greater than 6.5% despite treatment with diet alone or with oral glucose-lowering agents with or without

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[58] UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood glucose control with metformin on complication in overweight patients with T2DM (UKPDS 34). *Op.cit.*.

[59] Johnson JA, Simpson SH, Majumdar SR, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in Type 2 Diabetes. Diabetes Care; 25(12):2244-2248, 2002.

[60] Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 Diabetes. 2005 Diabetes UK. *Diabetic Medicine*; 22:497-502, 2005.

[61] Evans JMM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia* 49: 930-936, 2006.

[62] Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, et al. *Op. cit.* 2005.

insulin. Patients had to have evidence of "extensive macrovascular disease" to qualify for enrollment in the study; however, patients with NYHA class II heart failure or above were excluded from study participation.

A statistically significant excess risk of heart failure was observed in the PIO treatment group, with 11% of subjects randomized to PIO experiencing heart failure, compared to 8% of subjects in the placebo group ($p<0.0001$). Despite this concern, pioglitazone reduced the composite endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke in these high risk diabetic patients, many of whom were taking concomitant insulin, by about 16%.[63]

Table 9 from the published article describes between group differences in heart failure occurrence, and is reproduced below.

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any report of heart failure*	417	281 (11%)	302	198 (8%)	<0·0001
Heart failure not needing hospital admission*	160	132 (5%)	117	90 (3%)	0·003
Heart failure needing hospital admission*	209	149 (6%)	153	108 (4%)	0·007
Fatal heart failure†	25	25 (1%)	22	22 (1%)	0·634

*Not adjudicated. †Adjudicated cause of death.

Table 9: **Reports of heart failure**

Figure reproduced from Dormandy JA, Charbonnel B, Eckland DJA, Erdman E, et al. PROactive Investigators: Secondary prevention of microvascular events in patients with type 2 diabetes in the PROactive (PROspective pioglitazone Clinical Trial in macroVascular Events): a randomized controlled trial. *Lancet*. 366: 1279-1289, 2005.

6.3.4 Prevention of Type 2 Diabetes

6.3.4.1 Diabetes Prevention Program[64]

In the Diabetes Prevention Program, 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations were randomized to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week. The average follow-up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. Lifestyle intervention was more effective than metformin.

[63] Yki-Jarvinen H. The PROactive study: some answers, many questions. *Lancet* 2005; 366:1241-1242.
[64] Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346: 393-403, 2002.

6.3.4.2 Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial

The recently published DREAM study[65], an international, randomized, double-blind, 2x2 factorial trial involving 5,269 participants with impaired glucose tolerance and/or impaired fasting glucose (considered to represent pre-diabetes), showed a statistically significant increased risk of confirmed heart failure in subjects receiving RSG therapy compared to placebo (0.5% vs. 0.1%, p=0.01). Although not statistically significant, a consistent trend toward increased cardiovascular adverse events was noted in the RSG-treated group, including myocardial infarction (0.6% vs. 0.3%), cardiovascular death (0.5% vs. 0.4%), new angina (0.9% vs. 0.8%), and revascularization (1.3% vs. 1.0%). A between group comparison of overall composite cardiovascular events showed a hazard ratio of 1.37 (95% CI 0.97-1.94) which approached statistical significance. These findings are particularly troubling in that patients with a history of cardiovascular disease, including heart failure, were excluded from the trial.

7 Postmarketing Experience

7.1 Proportion of Cardiovascular Adverse Events: FDA AERS Safety Database

In the six years post approval of glitazones, concerns over continued submissions of reports of cardiac events remained high. However, in a passive surveillance database such as AERS and as stated in a previous consult dated July 16, 2002,[66] it is difficult to discern the drug effect associated with reported cardiac events in a non-randomized controlled trial setting. Nevertheless, Table 7.1 presents the percent of all reports of serious outcomes that are cardiac events each year for each of the six oral hypoglycemic agents. In Table 7.1, from 2000 to 2005 both TZDs consistently showed that about 20% more of the serious outcomes are cardiac events compared to the other four hypoglycemic agents; data for years 1999 and 2006 were not considered because they represent less than 12 months of data. The finding supports an association of cardiac events with TZDs as a signal.

Table 7.1 Proportion of Cardiac Events* Over all Events by Serious Outcome, Year, and Product

	Rosiglitazone Cardiac/All%	***Pioglitazone Cardiac/All%***	***Metformin Cardiac/All%***	***Glipizide Cardiac/All%***	***Glyburide Cardiac/All%***	***Glimepiride Cardiac/All%***
Approval date	**May-99**	**July-99**	**May-95**	**June-84**	**June-85**	**July-97**
1999	24	32	29	14	18	13
2000	**47**	**51**	**28**	**15**	**21**	**22**
2001	**51**	**53**	**28**	**15**	**22**	**21**
2002	**52**	**50**	**26**	**28**	**24**	**17**
2003	**55**	**50**	**22**	**18**	**25**	**19**
2004	**45**	**48**	**21**	**18**	**20**	**20**
2005	**45**	**50**	**23**	**29**	**16**	**20**
2006	39	41	29	23	27	24

* Include duplicates

[65] 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*; 368:1096-1105, 2006.

[66] Green L, Shaffer D. PID # D010431: Congestive heart failure requiring hospitalization associated with Actos and Avandia.

7.2 Postmarketing Spontaneous Reports of Fatal Heart Failure

A search of the FDA Adverse Event Reporting System (AERS) database using pertinent MedDRA (Medical Dictionary for Regulatory Activities) terms was conducted for the 5-year period (1999 – 2004) with the following selection criteria for CHF: reported clinical diagnosis of CHF or clinical documentation of CHF (physical, laboratory, autopsy findings), and exclusion of cases with a primary hepatic diagnosis or other major confounding factor(s).

A total of 98 fatal cases with a primary diagnosis of CHF in patients with Type 2 diabetes mellitus treated with rosiglitazone (n=67) or pioglitazone (n=31) were reported.[67] A rapid increase in weight was described in a number of these reports. Several reported a 4-9 kg gain in 2 months, and a few cases reported a 14-32 kg gain in 9 months. Patients who developed CHF in this series (n=98) were elderly with a mean age of 69 years. They were treated with multiple medications, in addition to a TZD, including insulin and/or a sulfonylurea or metformin. A prior history of CHF was identified in fewer than 20% of the cases. One-third of the patients received diuretic therapy, but some failed to improve with increased doses of diuretics when CHF was identified or exacerbated. One case with positive dechallenge and positive rechallenge for symptoms of heart failure was identified in the search.

7.3 Utilization Data

7.3.1 Projected Total Prescriptions Dispensed

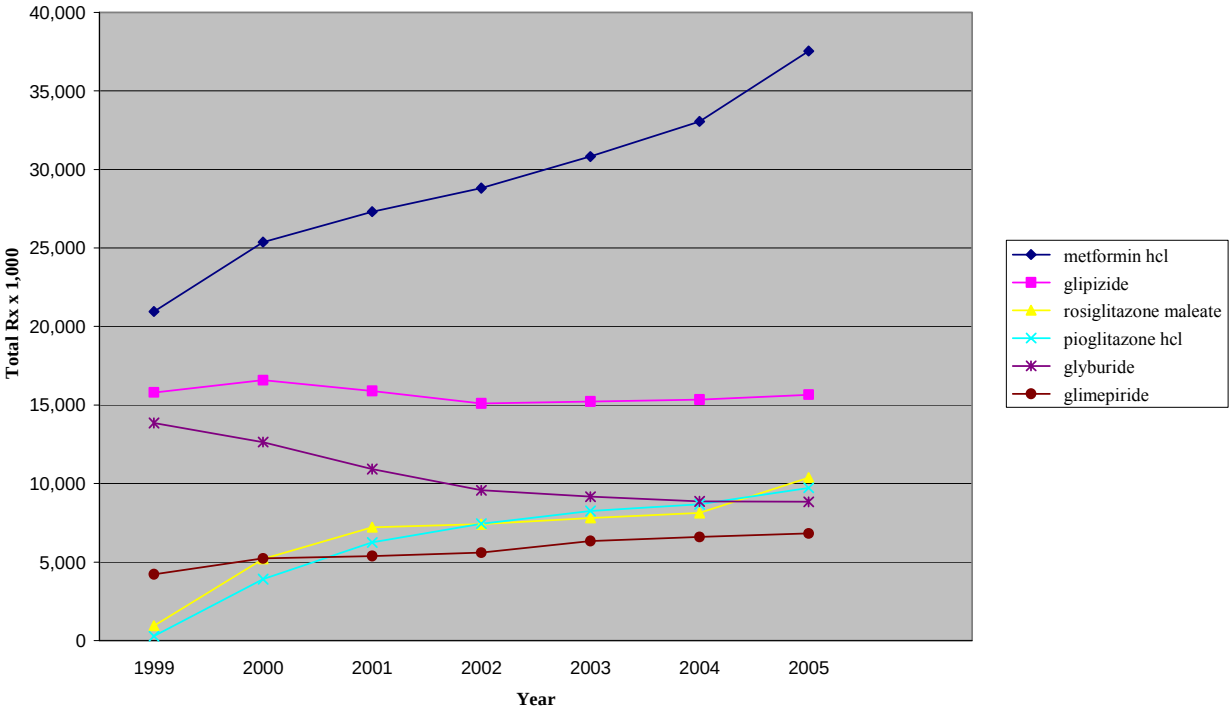
The utilization data for the six selected antidiabetic agents (metformin, glipizide, rosiglitazone, pioglitazone, glyburide, and glimepiride) were provided by Vicky Borders-Hemphill, PharmD, Division of Surveillance, Research and Communication Support (DSRCS).[68]

As shown in Figure 7.1 below, metformin (blue) ranks first in sales with a projected number of total prescriptions dispensed about 2.5 times greater than that of rosiglitazone (yellow) and pioglitazone (aqua). Glipizide (magenta) has maintained second place in sales through 2005 with a declining sales trend. Although sales of glitazones have increased since approval in 1999, a larger yearly increment is observed from approval in 1999 to 2001 than in the following years; in 2005, sales of rosiglitazone ranked third, slightly ahead of pioglitazone which ranked fourth. Glyburide is the only agent that has had declining sales since 1999. In 2005, glyburide (purple) ranked fifth in sales, lower than the TZDs. Sales for glimepiride (maroon) closely follows that of TZDs, just below their yearly sales; glimepiride ranks last among these six agents. Note: 2006 was not included because there are only 6 months of data.

[67] Zawadzki JK, Green L, Gelperin K. Association of rapid weight gain and fatal congestive heart failure with thiazolidinedione use. Poster Presentation at The Endocrine Society's 87th Annual Meeting, San Diego, California. June 4-7, 2005.

[68] Borders-Hemphill, Vicky, PID # D060129-A060294 VONA 8-16-06 Antidiabetics Duration

Figure 7.1 Projected Total Dispensed Prescriptions for Antidiabetic Products in U.S. Retail Pharmacies by Year, 1999-2005



Verispan Vector One®: National, Years 1999 through 2005 and year to date 2006, data extracted 8-16-2006

Data Source
Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One™ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector one receives over 1.8 billion prescription claims per year, representing over 150 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S., and this number represents approximately half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

7.3.2 Concurrent Drug Utilization

In August 2006, the consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes mentioned "More than one medication will be necessary for the majority of patients over time." Therefore, DDRE has requested, an analysis of concurrent use (all brands and dosage forms) of sulfonylureas and biguanides with RSG and PIO to better understand the current practice of management of hyperglycemia in T2DM. Vicky Borders-Hemphill, PharmD. of DSRCS provided this concurrency analysis. 69

[69] Borders-Hemphill, Vicky, Concurrency analysis VOCON: Actos and Avandia with sulfonylureas and biguanides AIMS No 2006-210

The Vector One: Concurrency (VOCON) tool from Verispan's longitudinal prescription data was the source for this concurrency analysis for the years of 2002 to 2005 and year to date, September 2006. The annual number of patients who filled a prescription for PIO increased from 602,863 in 2002 to 804,245 in 2005. Similarly for RSG, the annual number of patients increased from 609,149 to 872,381 for the same period. The concurrent usage of glimepiride, glyburide, and glipizide with RSG and PIO was found, per year, to be at approximately 10%, 10% and 14%, respectively. In contrast, higher percentages of concurrent use of metformin with RSG and PIO were observed per year at about 47% and 36%, respectively.[69] (*Note: Information about insulin utilization is not available from the VOCON tool.*)

8 Labeling Considerations

8.1 GSK Proposed Labeling - AVANDIA®

GSK's August 4, 2006 Prior Approval Labeling Supplement proposes that the following language be added to the ADVERSE REACTIONS section of the AVANDIA® USPI, based on the Sponsor's integrated clinical trials analysis and the final report for an observational balanced cohort study which focused on myocardial infarction and coronary revascularization procedures:

> *In a retrospective analysis of data from pooled controlled clinical studies, which included patients on combination therapy with insulin as well as patients with NYHA Class 1 and 2 heart failure (see WARNINGS, Cardiac Failure and Other Cardiovascular Effects), the overall incidence of myocardial ischemic adverse events was higher for regimens containing AVANDIA, 1.99% versus comparators, 1.51% (Hazard ratio 1.31; 95% confidence interval 1.01, 1.70). However, in a large observational study where patients were well-matched at baseline, the incidence of the composite endpoint of myocardial infarction and/or coronary revascularization was 1.75 events per 100 person years for regimens containing AVANDIA and 1.76 events per 100 person years for other anti-diabetic agents (Hazard ratio 0.93; 95% confidence interval 0.80, 1.10). The nature of the relationship, if any, of AVANDIA to events related to myocardial ischemia is not clear.*

For reference, copies of current approved labeling (USPI) for AVANDIA® [70] and ACTOS® [71] can be accessed via the links provided on this page.

8.2 DDRE Reviewer Comment

GSK's proposal to describe the results of the pooled data analysis in the ADVERSE REACTIONS section of the label does not provide sufficient emphasis considering the impact of identified cardiovascular risks on the benefit / risk balance of rosiglitazone. Prevention of macrovascular complications of diabetes is a desired benefit of antidiabetic therapy, and the demonstration of a failure to achieve this goal denotes a serious limitation of anticipated therapeutic benefit. Information about adverse cardiovascular effects of rosiglitazone should be prominently communicated in a BOXED WARNING.

Patient sub-groups at special risk of adverse cardiovascular effects associated with rosiglitazone, such as patients with a diagnosis of heart disease, heart failure, or requiring insulin therapy, should also be clearly

[70] USPI for AVANDIA available at http://us.gsk.com/products/assets/us_avandia.pdf (accessed January 8, 2007).
[71] USPI for ACTOS available at http://www.fda.gov/cder/foi/label/2006/021073s027lbl.pdf (accessed January 5, 2007).

identified in the BOXED WARNING. The results of observational studies conducted by the Sponsor do not resolve the overall concerns about potential serious cardiovascular risks with rosiglitazone.

8.3 Comparison with EU Label

Recent changes relevant to this review have been made to prescribing information for rosiglitazone and pioglitazone in the EU. Links to the EMEA website which includes copies of these new Summaries of Product Characteristics (SPCs) are provided here for reference. [72] [73]

9 Conclusions / Recommendations

9.1 TZD Class – Heart Failure

9.1.1 Consistent evidence shows that TZDs (rosiglitazone and pioglitazone) can cause weight gain, fluid retention, and lead to new or worsening heart failure. This is not a rare occurrence, and has included cases with serious and fatal outcomes.

9.1.2 Based on review of AERS cases, as well as published case reports, it appears that not all prescribers understand the importance of stopping TZD therapy when fluid retention, excessive weight gain, or heart failure occurs.

9.1.3 DDRE recommends a BOXED WARNING with a clear statement of the increased risk of congestive heart failure associated with the TZD class (rosiglitazone and pioglitazone), the importance of careful monitoring for rapid or excessive weight gain, and the recommendation that prescribers stop the drug if this occurs.

9.1.4 Although currently approved labeling for both AVANDIA and ACTOS include WARNINGS under a bolded heading "Cardiac Failure and Other Cardiac Effects", DDRE recommends that information about adverse cardiac effects be given additional prominence by adding a BOXED WARNING describing the information about risk of heart failure. The rationale for this emphasis is that adverse cardiovascular effects with thiazolidinediones may be avoided or mitigated with proper patient selection and adequate monitoring of patients for weight gain and fluid retention.

9.2 Rosiglitazone – Myocardial Ischemia

9.2.1 In GSK's retrospective analysis of data from pooled clinical trials with rosiglitazone, the overall incidence of myocardial ischemia was higher for patients receiving rosiglitazone (1.99%) versus comparators (1.51%), with a hazard ratio of 1.31 (95% CI, 1.01-1.70). Information about increased risks of myocardial ischemia with rosiglitazone warrants prominent placement in the labeling to ensure proper patient selection and appropriate monitoring for risk factors such as rapid or excessive weight gain. DDRE recommends that this information be included in a BOXED WARNING for rosiglitazone.

9.2.2 Patients receiving concurrent therapy with rosiglitazone and insulin were shown to be at increased risk of adverse cardiovascular effects. Myocardial ischemia-related adverse events occurred more

[72] SmPC for AVANDIA available at http://www.emea.eu.int/humandocs/Humans/EPAR/avandia/avandia.htm (accessed January 5, 2007).
[73] SmPC for ACTOS available at http://www.emea.eu.int/humandocs/Humans/EPAR/actos/actos.htm (accessed January 5, 2007).

often in patients receiving rosiglitazone and concomitant insulin (2.77%) compared with insulin monotherapy (1.36%) in the pooled clinical trials. These data support the conclusion that treatment with rosiglitazone should be avoided in patients receiving insulin.

9.2.3 The presence of pre-existing coronary heart disease or heart failure, especially in patients receiving nitrate therapy at baseline, was associated with increased risk of myocardial ischemia in the rosiglitazone pooled data analysis. This finding supports the conclusion that rosiglitazone therapy should be avoided in patients with heart failure, or serious heart disease. DDRE recommends that information about increased risk of myocardial ischemia in patients with a history serious heart disease or heart failure should be included in a BOXED WARNING for rosiglitazone.

9.2.4 Information about increased risks of myocardial ischemia with rosiglitazone warrants prominent placement in the labeling to ensure proper patient selection and appropriate monitoring for risk factors such as rapid or excessive weight gain. DDRE recommends that the following information be included in a BOXED WARNING for rosiglitazone:

- In a retrospective analysis of data from pooled controlled clinical studies, an increased risk of myocardial ischemia was observed in patients treated with rosiglitazone (Hazard ratio 1.31; 95% confidence interval 1.01, 1.70). Higher levels of risk were noted in patients with pre-existing serious heart disease, including heart failure, as well as in patients receiving insulin therapy.
- Rosiglitazone is not recommended in patients receiving insulin.
- Rosiglitazone is not recommended in patients with heart failure, or serious heart disease, including symptomatic coronary artery disease.

GSK's proposed labeling which states that risk of myocardial ischemia with rosiglitazone is not clear based on results of an observational study is not acceptable. The results of the observational study conducted by the Sponsor do not resolve the concerns about potential serious cardiovascular risks with rosiglitazone, and do not warrant inclusion in the product label.

9.3 Rosiglitazone in Combinations with Sulfonylureas and/or Metformin

GSK also proposes to add the following to the AVANDIA Adverse Reactions section: "Similarly, an increased incidence of heart failure has also been observed when AVANDIA was added to a sulfonylurea or to a sulfonylurea plus metformin. There were too few events to confirm a dose relationship; however, the incidence of heart failure appeared higher with AVANDIA 8 mg daily. (See WARNINGS, Cardiac Failure and Other Cardiac Effects.)"

Five of the seven strata in GSK's pooled analysis comprise various combinations of rosiglitazone, sulfonylureas, and metformin. An FDA biostatistical analysis of these data is currently in progress. It would be helpful to have results of between group comparisons of total cardiovascular adverse events (heart failure + myocardial ischemia), as well as further understanding of biostatistical effects of creating multiple strata containing various combinations of these three drugs on the results of the pooled analysis. A better understanding of the relative contribution of sulfonylurea drugs on adverse cardiovascular effects in the pooled data is needed. DDRE recommends further consideration of this issue after completion of the FDA Biostatistical review.

9.4 Cardiovascular Risk versus Benefit

Antidiabetic treatment with rosiglitazone in patients with pre-existing serious coronary heart disease or heart failure, as well as in patients requiring concomitant therapy with insulin, is associated with increased cardiovascular risk, including heart failure or myocardial ischemia, which is not off-set by the magnitude of

the demonstrated benefit. GSK's proposal to describe the results of the pooled data analysis in the ADVERSE REACTIONS section of the label does not provide sufficient emphasis considering the impact of identified cardiovascular risks on the benefit / risk balance of rosiglitazone. Prevention of macrovascular complications of diabetes is a desired benefit of antidiabetic therapy, and the demonstration of a failure to achieve this goal denotes a serious limitation of anticipated therapeutic benefit. Information about adverse cardiovascular effects of rosiglitazone, including heart failure and myocardial ischemia, should be prominently communicated in a BOXED WARNING.

In contrast, treatment with pioglitazone, although clearly associated with increased risk of heart failure, has not been shown to result in increased risk of myocardial ischemia, even in patients receiving concomitant insulin therapy. A pooled analysis of cardiovascular safety data from randomized controlled trials with pioglitazone has been submitted by Takeda and is currently under review by DMEP. Information about risk of heart failure with pioglitazone should be prominently communicated in a BOXED WARNING in order to assure proper patient selection and monitoring.

10 APPENDIX 1

STUDIES INCLUDED IN THE AVANDIA CARDIOVASCULAR EVENT MODELING PROJECT

ORIGINAL DATASET

Table 1 Studies Included, Listed by Comparison Strata to Which they Contributed (Original Dataset)

RSG Regimen	Control	Study	RSG Doses	Notes
RSG Mono	Placebo	006[1]	4mg	Exclude doses of RSG<4mg
		011[1]	4mg, 8mg	
		024[1]	4mg, 8mg	
		025	8mg	
		083	8mg	
		090[1]	4mg, 8mg	Exclude RSG 12mg regimen
		098[1]	4mg, 8mg	Exclude RSG 12mg regimen
		140	8mg	
		211	Titrate to glycemic target	This study enrolled only NYHA Class I & II CHF subjects.
		311	4mg, 8mg	
		352	Titrate to glycemic target	This study enrolled only coronary heart disease (CHD) subjects.
RSG Mono	SU/MET Mono	020[1]	4mg, 8mg	
		025	8mg	
		079[1]	4mg	
		093[1]	8mg	
		211	Titrate to glycemic target	This study enrolled only NYHA Class I & II CHF subjects.
		311	4mg, 8mg	
		352	Titrate to glycemic target	This study enrolled only CHD subjects.
		369	Titrate to glycemic target	
SU+RSG	SU Mono	015[1]	4mg	Exclude SU+RSG 2mg regimen
		079[1]	4mg	
		096[1]	4mg	Exclude SU+RSG 2mg regimen
		127	8mg	
		132	4mg, 8mg	
		135	Titrate to glycemic target	
		136	Titrate to tolerability	
		143	8mg	
		145	8mg	
		147	8mg	
		162	8mg	
		211	Titrate to glycemic target	This study enrolled only NYHA Class I & II CHF subjects.
		234	4mg, 8mg	
		325	Titrate to glycemic target	

Sponsor's Table page 25 of submission (continued on next page)

Table 1 (continued)
Studies Included, Listed by Comparison Strata to which they Contributed (Original Dataset)

RSG Regimen	Control	Study	RSG Doses	Notes
		352	Titrate to glycemic target	This study enrolled only CHD subjects.
MET+RSG	MET Mono	044	4mg, 8mg	
		093[1]	8mg	
		094[1]	4mg, 8mg	
		211	Titrate to glycemic target	This study enrolled only NYHA Class I & II CHF subjects.
		284	8mg	
		311	4mg, 8mg	
		352	Titrate to glycemic target	This study enrolled only CHD subjects.
MET+RSG	MET+SU	137	Titrate to glycemic target	
		211	Titrate to glycemic target	This study enrolled only NYHA Class I & II CHF subjects.
		282	Titrate to glycemic target	
		352	Titrate to glycemic target	This study enrolled only CHD subjects.
SU+MET+RSG	SU+MET	134	4mg, 8mg	
		211	Titrate to glycemic target	This study enrolled only NYHA Class I & II CHF subjects.
		352	Titrate to glycemic target	This study enrolled only CHD subjects.
INS+RSG	INS Mono	082[1]	4mg, 8mg	
		085	Titrate to glycemic target	
		095[1]	4mg, 8mg	
		136	Titrate to tolerability	
		347	4mg	Exclude INS+RSG 2mg regimen

1. Indicates studies where the last dose of study medication was prior to approval of the initial United States New Drug Application (US NDA) for AVANDIA (25-May-1999). Division of studies into before / after categories was used as a way to model study effect for inclusion as a potential covariate into the model

Sponsor's Table page 25 of submission (continued from previous page)

STUDIES INCLUDED IN THE AVANDIA CARDIOVASCULAR EVENT MODELING PROJECT

UPDATED INTEGRATED DATASET

Table 5 Additional Studies Included Listed by Comparison Strata to Which they Contributed (Updated Integrated Dataset)

RSG Regimen	Control	Study	RSG Doses	Notes
RSG Mono	Placebo	334[1]	8mg	Only T2DM cohort was included in this analysis
RSG Mono	SU/MET Mono	334[1]	8mg	Only T2DM cohort was included in this analysis
		AVR004	Titrate to glycemic goal	Drug naïve subjects
		AVM007	Titrate to glycemic goal	Drug naïve subjects
SU+RSG	SU Mono	334[1]	8mg	Only T2DM cohort was included in this analysis
		AVR004	4mg or Titrate to glycemic goal	Drug naïve subjects
MET+RSG	MET Mono	334[1]	8mg	Only T2DM cohort was included in this analysis
		AVM002	Titrate to tolerability[2]	
		AVM003	Titrate to tolerability[2]	
		AVM007	Titrate to glycemic goal	Drug naïve subjects

AVM = AVANDAMET, AVR = AVANDARYL

1. This study enrolled both type 2 diabetic subjects and non-diabetic subjects with insulin resistance syndrome
2. Titrate to tolerability: subjects in these studies were titrated to maximum tolerated dose of RSG and were allowed to downtitrate study medication based on tolerability (e.g. GI symptoms or edema).

Sponsor's Table page 49 of submission

11 APPENDIX 2

CARDIOVASCULAR DEATHS IN ROSIGLITAZONE POOLED ANALYSIS

Narrative Summaries of Cardiovascular Deaths in Rosiglitazone-treated Subjects

Overall, there were nearly twice as many cardiovascular deaths (0.19% vs. 0.11%) in subjects randomized to RSG (16/8604) as there were in comparator groups (6/5633). Narrative summaries for all identified cardiovascular deaths in RSG-treated subjects are presented below. Information about cases with a fatal outcome is obtained from the relevant line-listings[74], narrative summaries, and the AdHoc Listing 1675.1 "Listing of Rosiglitazone Treated Patients with Serious AE Included in Avandia CV Modeling Analysis".

A0239860A Acute myocardial infarction
A 52-year-old male with a history of hypertension and left ventricular dysfunction (baseline LVEF =35%) was found dead in his bed after 34 days of double-blind treatment with RSG 4 mg daily for T2DM. An autopsy stated the cause of death was myocardial infarction. Six days prior to his death, the patient was seen in the clinic for his week seven study visit. Blood pressure was 120/78 mm/Hg, and he was asymptomatic. Concomitant medications included captopril and hydrochlorothiazide. Baseline weight was 83.9 kg. Last recorded weight was 83.9 kg.

A0267010A Acute myocardial infarction
A 67-year-old female with a history of hypertension, hypothyroidism, and hypercholesterolemia, died in her sleep after 138 days of double-blind treatment with RSG 4 mg daily for T2DM. The death certificate lists the cause of death as acute myocardial infarction related to diabetes and hypertension. Eleven days prior to her death the patient had "appeared well" at her study visit, with blood pressure 144/82 and pulse 68 bpm. Concomitant medications included conjugated estrogens, gemfibrozil, levothyroxine, metoprolol, and pravastatin. Baseline weight was 95.1 kg. Last recorded weight was 97.6 kg (difference = +2.5 kg).

A0270243A Acute myocardial infarction
A 69-year-old male with a history of myocardial infarction, chronic unstable angina, hypercholesterolemia, and status post CABG, was found slumped in his chair and was pronounced dead on arrival at the hospital after 136 days of double-blind treatment with RSG 4 mg daily for T2DM. Concomitant medications included aspirin, Mylanta, and nitroglycerin. Prior therapy included Glyburide. Baseline weight was 96.7 kg. Last recorded weight was 90.8 kg (difference = -5.9 kg).

A0274880A Acute myocardial infarction
A 63-year-old female with a history of hypertension, malignant nerve sheath tumor and Herpes Zoster, was found dead in a chair clutching her chest after 185 days of double-blind treatment with MET + RSG 4 mg daily for T2DM. The diagnosis was reported as acute myocardial infarction. An autopsy was not performed. Concomitant medications included atenolol, dextropropoxyphene, and paracetamol. Baseline weight was 65.8 kg. Last recorded weight was 71.3 kg (difference = +5.5 kg).

A0276423A Myocardial infarction
A 71-year-old male with a history of splenectomy, cholecystectomy, pancreatitis, hypothyroidism, and arthritis experienced a fatal myocardial infarction after 89 days of double-blind treatment with INS + RSG 4 mg for T2DM. An autopsy was not performed. Concomitant medications included levothyroxine and vitamins. Baseline weight was 88.3 kg. Last recorded weight was 90.4 kg (difference = +2.1 kg).

A0312591A Cardiac arrest
A 51-year-old female with a history of hypertension, hyperlipidemia, anemia and bladder repair experienced a cardiac arrest during physical activity and could not be resuscitated after 54 days of double-blind treatment with SU + MET + RSG 4 mg daily for T2DM. Autopsy results were reported to be pending. Concomitant medications included atorvastatin, metoprolol, potassium chloride, furosemide, labetalol, and estradiol. Baseline weight was 102.6 kg. Last recorded weight was 102.5 kg (difference = -0.1 kg).

[74] M5.3.5.3 Safety Line Listings

A0535933A Myocardial infarction, Cardiac failure, Ischaemic cardiomyopathy
A 61-year-old female with a history of cataract developed dyspnea and pulmonary congestion and was diagnosed with ischemic cardiomyopathy and myocardial infarction after 214 days of double-blind treatment with RSG 8 mg for T2DM. Concomitant medications included simvastatin and bamethan sulfate. Treatment for cardiomyopathy included digoxin, furosemide and captopril. The subject's last dose of investigational drug was reportedly taken ten days later. Approximately two months later, the subject died from an acute myocardial infarction with subsequent pulmonary edema and respiratory failure as determined by autopsy. Information was not provided about what medications were being taken at the time of death. Baseline weight was 57 kg. Last recorded weight was 61.2 kg (difference = +4.2 kg). *Please note: this case is not included in the cardiovascular death analysis as death occurred after the clinical trials database was closed. The patient completed study drug in November and death occurred in January.*[75]

B0199699A Myocardial infarction, Ventricular fibrillation
A 67-year-old male with a history of hypertension, retinopathy, and possible urinary tract infection, collapsed while shopping, and was found to be in ventricular fibrillation with respiratory arrest after 6 days of double-blind treatment with SU + RSG 4 mg daily for T2DM. He was admitted to the hospital, and died the next day despite treatment with inotropes. Concomitant medications included lisinopril. Autopsy showed recent full thickness inferior myocardial infarction, severe triple vessel coronary artery disease, enlarged heart, and generalized severe pulmonary edema. Baseline weight was 80.5 kg, which was also the last recorded weight.

B0228804A Acute myocardial infarction
A 56-year-old male with a history of cerebral thrombosis and hyperlipidemia developed chest distress, dyspnea, loss of consciousness, and circulatory collapse after 100 days of double-blind treatment with SU + RSG 8 mg for T2DM. Death was attributed to myocardial infarction. An autopsy was not done. Concomitant medications included simvastatin, nitroglycerine, metformin, Gingko Biloba and sorbitol. Baseline weight was 73 kg. Last recorded weight was 74 kg (difference = +1 kg).

B0230354A Myocardial infarction
A 78-year-old male with a history of myocardial infarction, status post CABG, chronic renal failure, atrial flutter, and hypertension, died from a suspected myocardial infarction after 25 days of double-blind treatment with SU + RSG 4 mg daily for T2DM. Concomitant medications included allopurinol, enalapril, furosemide, hydrochlorothiazide, isosorbide mononitrate, metoprolol, pravastatin, and warfarin. An autopsy was not done. Baseline weight was 94.8 kg, which was also the last recorded weight.

B0231254A Myocardial infarction
A 69-year-old male with a history of myocardial infarction, status post CABG, peripheral vascular disease, status post embolectomy and aortic graft, and chronic bronchitis, developed chest pain and died from a myocardial infarction after 64 days of double-blind treatment with SU + RSG 8 mg daily for T2DM. An autopsy was not done. Concomitant medications included aspirin, diltiazem, perindopril, ranitidine, and simvastatin. Baseline weight was 86 kg, which was also the last recorded weight.

B0238615A Pneumonia, Cardiac failure, Angina pectoris
A 72-year-old male with a history of chronic renal failure, hyperlipidemia, myocardial infarction, hypertension, and right bundle branch block, developed pneumonia and cardiac insufficiency, and subsequently died ten days later, after 117 days of double-blind treatment with Ins + RSG 4 mg for T2DM. Episodes of chest pain a few weeks earlier had resolved with glyceryl trinitrate. Concomitant medications included aspirin, allopurinol, cephalexin, enalapril, erythropoietin, felodipine, furosemide, glyceryl trinitrate, isosorbide mononitrate, metoprolol, simvastatin. Baseline weight was 85 kg. Last recorded weight was 86 kg (difference = +1 kg).

B0239957A Myocardial infarction
A 66-year-old female with a history of asthma, hypertension and spondylosis developed angina pectoris and underwent angiography after 100 days of double-blind treatment with INS + RSG 8 mg for T2DM. During the angiography procedure, the patient experienced acute myocardial infarction and cardiorespiratory arrest. The patient died five days later due to myocardial infarction. An autopsy was not done. Concomitant medications included aspirin,

[75] GSK Response to FDA Safety Data Request, November 14, 2006; Module 5.3.5.3 – Response Summary.

bromazepam, dipotassium clorazepate, enoxaparin, glyceryl trinitrate, losartan, nimesulide, and piroxicam. Baseline weight was 75.5 kg. Last recorded weight was 77.1 kg (difference = +1.6 kg).

B0244564A Ventricular fibrillation, Left ventricular failure, Pulmonary edema
A 51-year-old male with a history of hypertension developed pulmonary edema and died from "sudden heart failure, probably ventricular fibrillation" after 32 days of double-blind treatment with SU + RSG 8 mg for T2DM. Concomitant medications included bisoprolol, fosinopril, and torasemide. Prior treatment included metformin and glibenclamide. An autopsy was not done.
Baseline weight was 77.3 kg, which was also the last recorded weight.

B0256125A Cardiac failure, Chest pain
A 79-year-old male with a history of heart failure, myocardial infarction, status post CABG, hyperlipidemia, and hypothyroidism, developed worsening heart failure requiring hospital admission after 39 days of double-blind treatment with SU + RSG 4 mg daily for T2DM. The events did not resolve. Study drug was discontinued. The patient died 70 days after the last dose of study medication due to congestive heart failure. An autopsy was not done. Concomitant medications included captopril, digoxin, furosemide, levothyroxine, potassium chloride, and simvastatin. Baseline weight was 69 kg, which was also the last recorded weight.

B0309553A Sudden death
A 66-year-old male with a history of central apnea syndrome, hypertension, and ventricular hypertrophy died in his sleep after 20 days of double-blind treatment with MET + RSG 4 mg daily for T2DM. Concomitant medications included amlodipine and metoprolol. An autopsy was not done. Baseline weight was 110.7 kg, which was also his last recorded weight.

B0283856A Cardiac failure congestive
A 66-year-old female with a history of myocardial infarction, heart failure, hypertension, and obesity developed worsening heart failure and subsequently expired after 157 days of double-blind treatment with SU + MET + RSG 8 mg for T2DM. A previous episode of worsening heart failure had occurred after 71 days of double-blind treatment, and had been treated with enalapril, furosemide, and fosinopril. Study medication had not been stopped. Concomitant medications included isosorbide dinitrate, indapamide, trimetazidine, aspirin, metoprolol, and fosinopril. Baseline weight was 90.7 kg. Last recorded weight was 94 kg (difference = +3.3 kg).

Narrative Summaries of Cardiovascular Deaths in Comparator-treated Subjects

Of the 59 cardiovascular SAEs identified by the Sponsor in subjects randomized to comparator groups, six cases indicated a fatal outcome. An additional case (B0226871A) describes a patient whose death due to progressively worsening left ventricular failure and terminal ventricular fibrillation occurred more than six months after the patient's last dose of study medication. For completeness, that case is also described in this section.

A0266313A Ventricular tachycardia, Myocardial infarction
A 70-year-old male with a history of diverticulitis, ischemic bowel status post resection, hypertension, and diabetic neuropathy, was admitted to the hospital and was diagnosed with myocardial infarction after 82 days of double-blind treatment with placebo for T2DM. Concomitant medications included aspirin, multivitamins, and zinc. Study medication was discontinued at the time of hospital admission. The investigator stated the event could have been associated with unspecified congenital heart disease. Nine days later, the patient developed sepsis and decreased urinary output. Subsequently, the patient developed third degree heart block, hypotension, loss of consciousness, cardiogenic shock, and acute renal failure. An intra-aortic balloon pump was placed. Eighteen days after the last dose of study medication, the patient developed ventricular tachycardia and expired. The patient's baseline weight was 91.3 kg. His last recorded weight was 90.8 kg (difference = -0.5 kg).

A0265831A Myocardial infarction
A 71-year-old male with a history of hypertension and angina pectoris died suddenly "of an apparent heart attack" after 81 days of double-blind treatment with placebo for T2DM. No autopsy was performed. Concomitant medications

included glibenclamide, amlodipine, and carisoprodol. Baseline weight was 93.1 kg. Last recorded weight was 90.8 kg (difference = -2.3 kg).

A0339112A Cardiac arrest
A 70-year-old male with a history of angina pectoris, myocardial infarction status post CABG, and COPD, developed dyspnea and was pronounced dead on arrival at the hospital after 186 days of double-blind treatment with placebo for T2DM. Concomitant medications included glipizide, atorvastatin, and metoprolol. The cause of death was reported to be cardiac arrest. An autopsy was not performed. Baseline weight was 81.2 kg. Last recorded weight was 80.7 kg (difference = -0.5 kg).

A0331390A Myocardial infarction
A 71-year-old female with a history of blocked carotid right side, triple bypass surgery, hypertension, hypercholesterolemia, bradycardia, ventricular tachycardia, cardiomegaly, congestive heart failure, sulfa allergy, edema lower extremities, and anemia, developed substernal chest pain, hypotension, and heart failure, underwent emergency angioplasty complicated by cardiac arrest, and expired the next day, after 240 days of double-blind treatment with placebo for T2DM. Concomitant medications included glibenclamide, metoprolol, furosemide, isosorbide mononitrate, atorvastatin, glyceryl trinitrate, lisinopril, metformin, metolazone, rebaprazole, spironolactone, torasemide, aspirin, allopurinol, conjugated estrogens, propoxyphene with acetaminophen, cyclobenzaprin, and metoclopramide. Prior to this event, after 137 days of double-blind treatment, the patient had been diagnosed with myocardial infarction which was treated medically with metoprolol. Baseline weight was 73.4 kg. Last recorded weight was 75.7 kg (difference = +2.3 kg).

B0226871A Congestive heart failure, Ventricular fibrillation
A 72-year-old male with a history of chronic renal failure, coronary heart disease, NYHA Class 2 heart failure, occlusive arterial disease, hypertension, hyperuricemia, hyperlipidemia, and prostatic hyperplasia, developed congestive heart failure after 45 days of double-blind therapy with placebo in addition to 128 units of subcutaneous insulin daily in accordance with the protocol, a study in patients with chronic renal failure. Study medication was discontinued due to this event. Concomitant medications included carvedilol, allopurinol, atorvastatin, clopidogrel, digitoxin, enalapril, isosorbide dinitrate, molsidomine, and torasemide. Subsequently, 3 months and 6 months after the last dose of study medication, the patient was admitted to the hospital with progressively worsening left ventricular failure. The patient was found dead in the bathroom approximately three weeks after the last hospital admission. The treating physician considered that the cause of death was terminal ventricular fibrillation with known coronary heart disease. Baseline weight was 97.9 kg. Last recorded weight was 98.2 kg (difference = +0.3 kg). *Please note: this case is not included in the cardiovascular death analysis as the patient died six months after study drug was discontinued.*

A0352432A Myocardial infarction
A 78-year-old male with a history of stroke, coronary artery disease, hypertension, Parkinson's disease, and TIA, collapsed at home and could not be resuscitated after 185 days of double-blind treatment with glibenclamide and metformin for T2DM. The cause of death was considered to be myocardial infarction. Concomitant medications included carbidopa, levodopa, ibuprofen, hydroxyzine, amlodipine, aspirin, terazosin, lisinopril, isosorbide dinitrate, and hydrochlorothiazide. Baseline weight was 112.3 kg. Last recorded weight was 111.4 kg (difference = -0.9 kg).

B0267435A Myocardial infarction
A 72-year-old male with a history of congestive heart failure, myocardial infarction, and peripheral arterial occlusive disease, was diagnosed with myocardial infarction, cardiogenic shock, and died the same day, after 77 days of double-blind treatment with placebo for T2DM. An autopsy was not done. Concomitant medications included glibenclamide, aspirin, captopril, and atenolol. Baseline weight was 73.5 kg. Last recorded weight was 72 kg (difference = -1.5 kg).

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/s/

Kate Gelperin
2/6/2007 01:43:22 PM
DRUG SAFETY OFFICE REVIEWER

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2/6/2007 02:45:38 PM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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Office of Biostatistics

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SUBJECT: Review of the epidemiology report HM2006/00497/00 entitled, "Coronary Heart Disease Outcomes in Patients Receiving Anti-diabetic Agents". Document submitted to NDA 21-071.

Background:

Avandia (Rosiglitazone) tablet is an anti-diabetic agent for treating patients with type 2 diabetes and was approved on May 29, 1999. In a retrospective analysis of data from pooled controlled clinical studies, which included patients on combination therapy with insulin as well as patients with New York Heart Association (NYHA) Class 1 and 2 heart failure, the overall incidence of myocardial ischemic adverse events was higher for regimens containing Avandia, 1.99% versus comparators 1.51% (hazard ratio 1.31; 95% CI: 1.01 – 1.70). The sponsor, GSK, referred to results from a an observational study in

which it was estimated that the incidence of the composite endpoint of myocardial infaraction (MI) and/or coronary revascularization (CR) was 1.75 (per 100 person years) for regimens containing Avandia and 1.76 (per 100 person years) for other anti-diabetic agents (hazard ratio 0.93; 95% CI: 0.80 – 1.10). This was to support their claim that "the nature of the relationship, if any, of Avandia to events related to myocardial ischemia is not clear".

The current consult is to provide comments on the appropriateness of the study design and analytic methods used in the conduct and analysis as presented in the sponsor's study reports. Essentially, the question is whether there is sufficient evidence from the observational study to dispute the findings from the clinical trials data.

Reviewer Comments:

Statistical methods

- Although propensity score matching is a statistical method that may be used in the setting of observational studies to adjust for covariate imbalance between study cohorts, we would like the sponsor to provide details regarding the derivation of the propensity scores with specific reference to the following topics:

    1. The strategy for dealing with missing covariates in the logistic model for estimating the propensity scores.

    2. The details of the matching procedure used.

    3. The limitations of propensity score matching procedure including:
        - Precludes the possibility of analyzing treatment comparisons other than proposed

        - Discards data (mono-therapy group: 20%, dual-therapy group: 34%)

    4. Please justify the use of propensity score method on matching in this study as opposed to other alternatives, i.e., stratification or direct adjustment.

- Please provide details to support sample size/power calculation and the impact on the conclusions of the study. In particular, did the study have sufficient power to show the similar rates of MI and/or CR between rosiglitazone and other anti-diabetic agents?

- More detail is needed with regard to the CHD risk factor stratification analysis. Please address the following questions/issues:

1. How is the balance of baseline coronary risk factors (other than the ones mentioned in the analysis) controlled for in the analysis of rosiglitazone versus non-rosiglitazone?

2. Repeat the same analysis in the as-treated population. This is important because differences that were seen in as balanced analyses (Study report, Table 2e) disappear when looking at the same analysis done on the as treated population Study report, Table 3e).

- Please provide clarification of the following issues:

1. The distribution of baseline covariates for those subjects identified but excluded from the matching procedure.

2. Are the non-study oral anti-diabetic medications accounted for in the baseline covariates? Although the study report mentioned this information, this was not among the factors listed in the appendix B of the Sponsor's report.

3. What was the effect of the under-representation of the over 65 year old age group in the baseline characteristics of the dual therapy group?

4. What is the impact of over-counting issue on the results from the as treated analysis in the combination-with-insulin study group?

5. Please provide the justification for "6" month follow-up analysis, i.e., why this duration of exposure is specifically important to the study hypothesis.

General design issues

- Please provide more details regarding the endpoint definition and justify why this endpoint definition was chosen in the study

1. Why was the outcome analysis limited to myocardial infarction and coronary revascularization? Numerous other cardiac related events were excluded from this definition of outcome. Examples include fatal MIs, congestive heart failure, unstable angina or other forms of angina. Please comment on the potential effect of the exclusion of these events on the analysis.

2. In the pooled analysis of control clinical studies, the endpoint was defined as the overall incidence of "myocardial ischemia", and included cases of fatal myocardial infarction. However, in the observational cohort study, the endpoint was defined as the composite endpoint of MI and/or CR.

- Potential biases in the study

1. There is no information about the loss-to-follow-up rate in the report. Differential loss-to-follow-up rate between study cohorts can possibly lead to selection bias.

2. General issues in the use of United HealthCare database:

    - Data on the use of drugs during inpatient periods are not available.

    - If the cost of a prescription drug is lower than the co-payment amount, the prescription may not be included in the database sine no prescription claim may be submitted.

- Lack of information on patient adherence with the therapeutic regimen.

- Additional baseline factors to be considered:

    Family history
    Ethnicity,
    Menopause
    Physical inactivity
    Alcohol use
    Use of a statin drug

Thank you for asking us to comment on this report. If you need further assistance please do not hesitate to contact us at (301) 796-0986.

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/s/

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2/2/2007 01:03:12 PM
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U.S. Department of Health and Human Services
Food and Drug Administration
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SUBJECT: Review of the section 3 of study report entitled, "Rosiglitazone and CV events: Further analysis of the integrated clinical trial dataset and long-term outcome studies". Document submitted to NDA 21-071\S_022\2007-05-31.

Background:

The current consult is to provide comments on the section 3 of the sponsor's study reports.

Avandia (Rosiglitazone) tablet is an anti-diabetic agent for treating patients with type 2 diabetes and was approved on May 29, 1999. In 2005, the sponsor conducted a retrospective analysis of data from 42 controlled double-blinded clinical studies, which contained a total of 14,237 subjects. Most of the clinical studies included in the analysis

were approximately six months in duration. Mean duration of exposure to study medication was 180 days. The results showed that the overall incidence of myocardial ischemic adverse events (including serious and non-serious AEs) was higher for regimens containing Avandia, 1.99% (171/8604) versus comparators 1.51% (85/5633) (hazard ratio 1.31; 95% CI: 1.01 – 1.70).

In the current submission, the sponsor (GSK) performed an additional analysis of data from a previously-submitted ('original') post-marketing cohort observational study – Coronary Heart Disease Outcomes in Patients Receiving Anti-diabetic Agent (study report – June 15, 2006). In the current submission, the sponsor claims that the incidence rate of MI (expressed as events per 100 person-years of exposure) was similar in the Rosiglitazone group and the non- Rosiglitazone group.

The post-marketing observational study of 33,000 subjects was originally designed to balance the study cohort, using a propensity score matching method, within monotherapy study group, dual-therapy study group and combination-with-insulin study group. The balanced cohorts within each study group were as follow:

Monotherapy

- Rosiglitazone(RSG) vs Sulfonylurea(SU)
- Rosiglitazone(RSG) vs. Metformin(MET)

Dual therapy

- Rosiglitazone(RSG) + Metformin(MET) vs. Sulfonylurea(SU) +Metformin(MET)
- Rosiglitazone(RSG)+ Sulfondlurea(SU) vs. Sulfonulurea(SU) + Metformin(MET)

Combination with insulin

- Rosiglitazone(RSG) current-use time in either insulin cohort vs. Other-oral-antidiabetic-agents (excluding other TZDs) current-used time in either insulin cohort

In the current submission, the sponsor performed a post-hoc analysis to compare the incidence rates of MIs between RSG and non- RSG regimens. The RSG group combined RSG monotherapy, dual therapy with RSG+MET, dual therapy with RSG+SU, and INS+RSG. The "non-RSG" group combined all remaining cohorts. The details of statistical method used in the post-hoc analysis were not provided in the submission.

Reviewer's Comment:

A review of the original post-marketing cohort study was previously conducted jointly by Office of Surveillance and Epidemiology and Office of Biostatistics, and is presented in a separate document[1]. The major criticisms and limitations of the original study were as follows:

- The endpoint defined in the study was not adequate to address the cardiovascular safety issues raised by the pooled randomized clinical trials.
- Selection and information biases are likely to affect the internal validity of the study.

[1] A formal review by Kate Gelperin (FDA's medical epidemiologist) on the subject of Thiasolidinediones and Cardiovascular Adverse Effects,. The document was in the DFS under NDA21071\N000.

- The population in the study had relatively fewer elderly patients compared to the overall US population or the population of Type II diabetic patients. Therefore, the generalizability of the study was limited.

In the current submission, the sponsor's claim that "the incidence rate of MI was similar in the RSG and the non-RSG groups in the balanced cohort study" was not supported by the post-hoc analysis conducted on the observational balanced cohort study. The propensity score matching procedure only adjusted for covariate imbalances between cohorts *within each study group*. **By combining study cohorts to form RSG and non-RSG groups, the RSG and non-RSG groups were no longer balanced.** The baseline incomparability between two groups can lead to biased results, confounded by those measured and unobserved covariates. The validity of the post-hoc analysis/results is therefore questionable. Thus, the current submission does not provide any additional information to definitely impact the conclusions based on the results of the original observational balanced cohort study. In order to compare the risk of MI between RSG-users and non-RSG users, the sponsor needs to conduct another well-designed study to address the issue.

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Yu-Te Wu
6/20/2007 03:25:09 PM
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George Rochester
6/20/2007 03:42:01 PM
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Yi Tsong
6/20/2007 03:44:55 PM
BIOMETRICS

Stella Machado
6/20/2007 04:26:12 PM
BIOMETRICS

TAB 6

Publications

1] Kahn, SE, Haffner, SM, Heise, MA, et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. N Engl J Med 2006; 23: 2427-2443.

2] 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. www.thelancet.com 2006; 368: 1096-1105 (published online September 15, 2006).

3] The DREAM Trial Investigators. Rationale, design and recruitment characteristics of a large, simple international trial of diabetes prevention: the DREAM trial. Diabetologia 2004 47: 1519-1527 (published online August 21, 2004).

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5] Home, PD, Pocock, SJ, Beck-Nielsen, H et al. Rosiglitazone evaluated for cardiac outcomes and regulation of glylcaemia in diabetes (RECORD): study design and protocol. Diabetologia 2005 48: 1726-1735. (published online July 16, 2005).

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12] The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998; 116: 874-886.

13] Johannes, CB, Koro, CE, Quinn, SG, et al. The risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy. Pharmacoepidemiology and Drug Safety 2007; 16: 504-512.

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
TOTAL	965	(66.28%)	19.48	1023	(70.99%)	24.11	990	(68.09%)	20.18	2978	(68.44%)	21.12
CV	201	(13.81%)	4.06	170	(11.80%)	4.01	237	(16.30%)	4.83	608	(13.97%)	4.31
AFib	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Acute coronary syndrome	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Acute heart failure	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Acute myocardial infarction	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Acute myocardial infarction, of anterolateral wall	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Acute myocardial infarction, of other anterior wall	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Acute myocardial infarction, of other inferior wall	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Acute pulmonary edema	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Aneurysm atrial	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Angina at rest	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Angina on exercise	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Angina pectoris	23	(1.58%)	0.46	17	(1.18%)	0.40	26	(1.79%)	0.53	66	(1.52%)	0.47
Angina pectoris aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Angina pectoris unstable	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Angina syndrome	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Anginal pain	1	(0.07%)	0.02	0			4	(0.28%)	0.08	5	(0.12%)	0.04
Anterior myocardial infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Aortic regurgitation	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Aortic valve disease	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Aortic valve incompetence	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Aortic valve sclerosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Aortic valve stenosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Arrhythmia	0			6	(0.42%)	0.14	2	(0.14%)	0.04	8	(0.18%)	0.06
Arrhythmia absoluta	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Asystole	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Atrial arrhythmia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Atrial fibrillation	19	(1.31%)	0.38	14	(0.97%)	0.33	20	(1.38%)	0.41	53	(1.22%)	0.38
Atrial fibrillation aggravated	4	(0.28%)	0.08	1	(0.07%)	0.02	0			5	(0.12%)	0.04
Atrial fibrillation with rapid ventricular response	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Atrial flutter	2	(0.14%)	0.04	2	(0.14%)	0.05	3	(0.21%)	0.06	7	(0.16%)	0.05
Atrial tachycardia	1	(0.07%)	0.02	3	(0.21%)	0.07	0			4	(0.09%)	0.03
Atrial thrombosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Atrioventricular block	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Auricular fibrillation	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Bi-ventricular failure	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Bigeminy	2	(0.14%)	0.04	0			1	(0.07%)	0.02	3	(0.07%)	0.02
Bradyarrhythmia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Bradycardia	7	(0.48%)	0.14	5	(0.35%)	0.12	6	(0.41%)	0.12	18	(0.41%)	0.13
Cardiac arrest	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Cardiac arrhythmia	1	(0.07%)	0.02	7	(0.49%)	0.16	2	(0.14%)	0.04	10	(0.23%)	0.07
Cardiac catheterisation abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiac dysrhythmias	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Cardiac failure	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Cardiac insufficiency	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Cardiac pain	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Cardiac tamponade	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cardiac valve disease	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiac ventricular thrombosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cardiomegaly	4	(0.28%)	0.08	1	(0.07%)	0.02	1	(0.07%)	0.02	6	(0.14%)	0.04
Cardiomyopathy	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Cardiovascular deconditioning	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiovascular disease, unspecified	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cardiovascular disorder	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Chest pain - cardiac	32	(2.20%)	0.65	27	(1.87%)	0.64	29	(1.99%)	0.59	88	(2.02%)	0.62
Complete right bundle branch block	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Congestive cardiac failure aggravated	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Congestive heart failure	7	(0.48%)	0.14	3	(0.21%)	0.07	7	(0.48%)	0.14	17	(0.39%)	0.12
Cor pulmonale	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Coronary artery atherosclerosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Coronary artery disease	15	(1.03%)	0.30	12	(0.83%)	0.28	18	(1.24%)	0.37	45	(1.03%)	0.32
Coronary artery disease aggravated	7	(0.48%)	0.14	2	(0.14%)	0.05	6	(0.41%)	0.12	15	(0.35%)	0.11
Coronary artery occlusion	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Coronary artery restenosis	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Coronary artery stenosis	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Coronary atheroma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Coronary atherosclerosis	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Coronary disease	6	(0.41%)	0.12	4	(0.28%)	0.09	7	(0.48%)	0.14	17	(0.39%)	0.12
Coronary insufficiency	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
Cyanosis peripheral	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Decompensation cardiac	2	(0.14%)	0.04	0			3	(0.21%)	0.06	5	(0.12%)	0.04
Defect conduction intraventricular	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Diastolic dysfunction	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Dilatation ventricular	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Dilated cardiomyopathy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Disorder circulatory system	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Dysrhythmias	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
ECG signs of myocardial ischemia	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
ECG signs of ventricular hypertrophy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Early systolic murmur	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Effusion pericardial	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Ejection fraction abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Ejection fraction decreased	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Electrocardiogram Q wave abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram QRS complex abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Electrocardiogram QT prolonged	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram ST segment depression	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Electrocardiogram ST-T change	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Electrocardiogram ST-T segment abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram T wave abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Electrocardiogram T wave inversion	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Electrocardiogram abnormal	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Electrocardiogram repolarization abnormality	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Exercise induced angina	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Extrasystoles	2	(0.14%)	0.04	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.09%)	0.03
Extrasystoles atrial	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
First degree atrioventricular block	10	(0.69%)	0.20	3	(0.21%)	0.07	5	(0.34%)	0.10	18	(0.41%)	0.13
Heart attack	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart block AV second degree	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart block first degree	3	(0.21%)	0.06	4	(0.28%)	0.09	2	(0.14%)	0.04	9	(0.21%)	0.06
Heart disease, unspecified	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Heart disorder	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart enlarged	2	(0.14%)	0.04	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.09%)	0.03
Heart fluttering	2	(0.14%)	0.04	0			1	(0.07%)	0.02	3	(0.07%)	0.02
Heart murmur	8	(0.55%)	0.16	6	(0.42%)	0.14	6	(0.41%)	0.12	20	(0.46%)	0.14
Heart pounding	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart rate irregular	2	(0.14%)	0.04	2	(0.14%)	0.05	0			4	(0.09%)	0.03
Heart throbbing	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Heart valve insufficiency	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heartbeats irregular	1	(0.07%)	0.02	6	(0.42%)	0.14	2	(0.14%)	0.04	9	(0.21%)	0.06
Hypertensive heart disease	0			2	(0.14%)	0.05	5	(0.34%)	0.10	7	(0.16%)	0.05
Incomplete right bundle branch block	0			0			3	(0.21%)	0.06	3	(0.07%)	0.02
Inferior myocardial infarction	1	(0.07%)	0.02	0			3	(0.21%)	0.06	4	(0.09%)	0.03
Irregular pulse	0			1	(0.07%)	0.02	3	(0.21%)	0.06	4	(0.09%)	0.03
Ischemic cardiomyopathy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ischemic heart disease	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Left anterior fascicular block	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Left anterior hemiblock	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Left atrial enlargement	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Left atrial hypertrophy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Left bundle branch block	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Left ventricular dilatation	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Left ventricular dysfunction	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Left ventricular ejection fraction decreased	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Left ventricular failure	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Left ventricular hypertrophy	5	(0.34%)	0.10	6	(0.42%)	0.14	5	(0.34%)	0.10	16	(0.37%)	0.11
Mitral insufficiency	2	(0.14%)	0.04	0			2	(0.14%)	0.04	4	(0.09%)	0.03
Mitral regurgitation	5	(0.34%)	0.10	2	(0.14%)	0.05	3	(0.21%)	0.06	10	(0.23%)	0.07
Mitral valve disease	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Mitral valve prolapse	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Mixed aortic valve disease	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Myocardial infarction	18	(1.24%)	0.36	9	(0.63%)	0.21	12	(0.83%)	0.24	39	(0.90%)	0.28
Myocardial ischemia	6	(0.41%)	0.12	3	(0.21%)	0.07	5	(0.34%)	0.10	14	(0.32%)	0.10
Non-Q wave MI	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Nonspecific ST segment change	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Old myocardial infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
PQ interval prolonged	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Palpitation	23	(1.58%)	0.46	19	(1.32%)	0.45	35	(2.41%)	0.71	77	(1.77%)	0.55
Paroxysmal atrial fibrillation	0			0			5	(0.34%)	0.10	5	(0.12%)	0.04
Paroxysmal atrial flutter	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Paroxysmal supraventricular tachycardia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Pericardial calcification	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Pericardial effusion	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Pericarditis	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Posterior myocardial infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Postinfarction angina	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Premature beat atrial	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Premature beats	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Premature ventricular contractions	6	(0.41%)	0.12	4	(0.28%)	0.09	3	(0.21%)	0.06	13	(0.30%)	0.09
Pulmonary edema	3	(0.21%)	0.06	3	(0.21%)	0.07	2	(0.14%)	0.04	8	(0.18%)	0.06
Pulmonary valve regurgitation	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
RBBB	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Right bundle branch block	2	(0.14%)	0.04	3	(0.21%)	0.07	3	(0.21%)	0.06	8	(0.18%)	0.06
Right bundle branch block and left anterior fascicular block	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Right heart failure	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Right ventricular hypertrophy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
ST depressed	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Septal myocardial infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Sick sinus syndrome	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Silent myocardial infarction	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Silent myocardial ischemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Sinoatrial node dysfunction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Sinus arrhythmia	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Sinus bradycardia	6	(0.41%)	0.12	2	(0.14%)	0.05	6	(0.41%)	0.12	14	(0.32%)	0.10
Sinus tachycardia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Stable angina pectoris	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Stenocardia	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Subendocardial myocardial infarction	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Sudden death	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Supraventricular extrasystoles	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Supraventricular tachycardia	2	(0.14%)	0.04	6	(0.42%)	0.14	3	(0.21%)	0.06	11	(0.25%)	0.08
T wave flattening of	2	(0.14%)	0.04	1	(0.07%)	0.02	2	(0.14%)	0.04	5	(0.12%)	0.04
Tachyarrhythmia	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Tachyarrhythmia absoluta	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Tachycardia	8	(0.55%)	0.16	10	(0.69%)	0.24	7	(0.48%)	0.14	25	(0.58%)	0.18
Tachycardia irregular	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Tachycardia paroxysmal	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Third degree AV block	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Tricuspid regurgitation	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Triple vessel disease	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Type I second degree atrioventricular block	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Unstable angina	6	(0.41%)	0.12	7	(0.49%)	0.16	7	(0.48%)	0.14	20	(0.46%)	0.14
Ventricular arrhythmia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Ventricular bigeminy	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Ventricular dyskinesia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ventricular fibrillation	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Ventricular hypokinesia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Ventricular tachycardia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
CV - Arrhythmia/Conduction	79	(5.43%)	1.59	71	(4.93%)	1.67	85	(5.85%)	1.73	235	(5.40%)	1.67
AFib	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Arrhythmia	0			6	(0.42%)	0.14	2	(0.14%)	0.04	8	(0.18%)	0.06
Arrhythmia absoluta	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Atrial arrhythmia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Atrial fibrillation	19	(1.31%)	0.38	14	(0.97%)	0.33	20	(1.38%)	0.41	53	(1.22%)	0.38
Atrial fibrillation aggravated	4	(0.28%)	0.08	1	(0.07%)	0.02	0			5	(0.12%)	0.04
Atrial fibrillation with rapid ventricular response	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Atrial flutter	2	(0.14%)	0.04	2	(0.14%)	0.05	3	(0.21%)	0.06	7	(0.16%)	0.05
Atrial tachycardia	1	(0.07%)	0.02	3	(0.21%)	0.07	0			4	(0.09%)	0.03
Atrioventricular block	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Auricular fibrillation	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Bigeminy	2	(0.14%)	0.04	0			1	(0.07%)	0.02	3	(0.07%)	0.02
Bradyarrhythmia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Bradycardia	7	(0.48%)	0.14	5	(0.35%)	0.12	6	(0.41%)	0.12	18	(0.41%)	0.13
Cardiac arrhythmia	1	(0.07%)	0.02	7	(0.49%)	0.16	2	(0.14%)	0.04	10	(0.23%)	0.07
Cardiac dysrhythmias	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Complete right bundle branch block	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Defect conduction intraventricular	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Dysrhythmias	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Electrocardiogram QT prolonged	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram repolarization abnormality	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Extrasystoles	2	(0.14%)	0.04	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.09%)	0.03
Extrasystoles atrial	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
First degree atrioventricular block	10	(0.69%)	0.20	3	(0.21%)	0.07	5	(0.34%)	0.10	18	(0.41%)	0.13
Heart block AV second degree	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart block first degree	3	(0.21%)	0.06	4	(0.28%)	0.09	2	(0.14%)	0.04	9	(0.21%)	0.06
Heart fluttering	2	(0.14%)	0.04	0			1	(0.07%)	0.02	3	(0.07%)	0.02
Heart rate irregular	2	(0.14%)	0.04	2	(0.14%)	0.05	0			4	(0.09%)	0.03
Heartbeats irregular	1	(0.07%)	0.02	6	(0.42%)	0.14	2	(0.14%)	0.04	9	(0.21%)	0.06
Incomplete right bundle branch block	0			0			3	(0.21%)	0.06	3	(0.07%)	0.02
Irregular pulse	0			1	(0.07%)	0.02	3	(0.21%)	0.06	4	(0.09%)	0.03
Left anterior fascicular block	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Left anterior hemiblock	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Left bundle branch block	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
PQ interval prolonged	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Paroxysmal atrial fibrillation	0			0			5	(0.34%)	0.10	5	(0.12%)	0.04
Paroxysmal atrial flutter	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Paroxysmal supraventricular tachycardia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Premature beat atrial	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Premature beats	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Premature ventricular contractions	6	(0.41%)	0.12	4	(0.28%)	0.09	3	(0.21%)	0.06	13	(0.30%)	0.09
RBBB	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Right bundle branch block	2	(0.14%)	0.04	3	(0.21%)	0.07	3	(0.21%)	0.06	8	(0.18%)	0.06
Right bundle branch block and left anterior fascicular block	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Sick sinus syndrome	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Sinoatrial node dysfunction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Sinus arrhythmia	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Sinus bradycardia	6	(0.41%)	0.12	2	(0.14%)	0.05	6	(0.41%)	0.12	14	(0.32%)	0.10
Sinus tachycardia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Supraventricular extrasystoles	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Supraventricular tachycardia	2	(0.14%)	0.04	6	(0.42%)	0.14	3	(0.21%)	0.06	11	(0.25%)	0.08
Tachyarrhythmia	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Tachyarrhythmia absoluta	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Tachycardia	8	(0.55%)	0.16	10	(0.69%)	0.24	7	(0.48%)	0.14	25	(0.58%)	0.18
Tachycardia irregular	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Tachycardia paroxysmal	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Third degree AV block	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Type I second degree atrioventricular block	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Ventricular arrhythmia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Ventricular bigeminy	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Ventricular fibrillation	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Ventricular tachycardia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
CV - CHF/Pulmonary Edema	22	(1.51%)	0.44	9	(0.63%)	0.21	19	(1.31%)	0.39	50	(1.15%)	0.35
Acute heart failure	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Acute pulmonary edema	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Bi-ventricular failure	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Cardiac failure	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Congestive cardiac failure aggravated	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Congestive heart failure	7	(0.48%)	0.14	3	(0.21%)	0.07	7	(0.48%)	0.14	17	(0.39%)	0.12
Decompensation cardiac	2	(0.14%)	0.04	0			3	(0.21%)	0.06	5	(0.12%)	0.04
Diastolic dysfunction	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Ejection fraction abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ejection fraction decreased	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Left ventricular dysfunction	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Left ventricular ejection fraction decreased	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Left ventricular failure	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Pulmonary edema	3	(0.21%)	0.06	3	(0.21%)	0.07	2	(0.14%)	0.04	8	(0.18%)	0.06
Right heart failure	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Ventricular dyskinesia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ventricular hypokinesia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
CV - Myocardial Ischaemia	106	(7.28%)	2.14	82	(5.69%)	1.93	111	(7.63%)	2.26	299	(6.87%)	2.12
Acute coronary syndrome	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Acute myocardial infarction	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Acute myocardial infarction, of anterolateral wall	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Acute myocardial infarction, of other anterior wall	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Acute myocardial infarction, of other inferior wall	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Angina at rest	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Angina on exercise	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Angina pectoris	23	(1.58%)	0.46	17	(1.18%)	0.40	26	(1.79%)	0.53	66	(1.52%)	0.47
Angina pectoris aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Angina pectoris unstable	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Angina syndrome	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Anginal pain	1	(0.07%)	0.02	0			4	(0.28%)	0.08	5	(0.12%)	0.04
Anterior myocardial infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Asystole	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cardiac arrest	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Cardiac catheterisation abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiac insufficiency	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Cardiac pain	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Chest pain - cardiac	32	(2.20%)	0.65	27	(1.87%)	0.64	29	(1.99%)	0.59	88	(2.02%)	0.62
Coronary artery atherosclerosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Coronary artery disease	15	(1.03%)	0.30	12	(0.83%)	0.28	18	(1.24%)	0.37	45	(1.03%)	0.32
Coronary artery disease aggravated	7	(0.48%)	0.14	2	(0.14%)	0.05	6	(0.41%)	0.12	15	(0.35%)	0.11
Coronary artery occlusion	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Coronary artery restenosis	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Coronary artery stenosis	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Coronary atheroma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Coronary atherosclerosis	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Coronary disease	6	(0.41%)	0.12	4	(0.28%)	0.09	7	(0.48%)	0.14	17	(0.39%)	0.12
Coronary insufficiency	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
ECG signs of myocardial ischemia	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Electrocardiogram ST segment depression	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Electrocardiogram ST-T change	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Electrocardiogram ST-T segment abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram T wave inversion	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Exercise induced angina	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Heart attack	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Inferior myocardial infarction	1	(0.07%)	0.02	0			3	(0.21%)	0.06	4	(0.09%)	0.03
Ischemic cardiomyopathy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ischemic heart disease	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Myocardial infarction	18	(1.24%)	0.36	9	(0.63%)	0.21	12	(0.83%)	0.24	39	(0.90%)	0.28
Myocardial ischemia	6	(0.41%)	0.12	3	(0.21%)	0.07	5	(0.34%)	0.10	14	(0.32%)	0.10
Non-Q wave MI	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Nonspecific ST segment change	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Old myocardial infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Posterior myocardial infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Postinfarction angina	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
ST depressed	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Septal myocardial infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Silent myocardial infarction	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Silent myocardial ischemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Stable angina pectoris	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Stenocardia	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Subendocardial myocardial infarction	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Sudden death	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
T wave flattening of	2	(0.14%)	0.04	1	(0.07%)	0.02	2	(0.14%)	0.04	5	(0.12%)	0.04
Triple vessel disease	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Unstable angina	6	(0.41%)	0.12	7	(0.49%)	0.16	7	(0.48%)	0.14	20	(0.46%)	0.14
CV - Myocardial Ischaemia - Angina	64	(4.40%)	1.29	45	(3.12%)	1.06	69	(4.75%)	1.41	178	(4.09%)	1.26
Acute coronary syndrome	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Angina at rest	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Angina on exercise	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Angina pectoris	23	(1.58%)	0.46	17	(1.18%)	0.40	26	(1.79%)	0.53	66	(1.52%)	0.47
Angina pectoris aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Angina pectoris unstable	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Angina syndrome	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Anginal pain	1	(0.07%)	0.02	0			4	(0.28%)	0.08	5	(0.12%)	0.04
Cardiac pain	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Chest pain - cardiac	32	(2.20%)	0.65	27	(1.87%)	0.64	29	(1.99%)	0.59	88	(2.02%)	0.62
Exercise induced angina	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Postinfarction angina	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Stable angina pectoris	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Stenocardia	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Unstable angina	6	(0.41%)	0.12	7	(0.49%)	0.16	7	(0.48%)	0.14	20	(0.46%)	0.14
CV - Myocardial Ischaemia - CAD	39	(2.68%)	0.79	33	(2.29%)	0.78	48	(3.30%)	0.98	120	(2.76%)	0.85
Cardiac catheterisation abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiac insufficiency	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Coronary artery atherosclerosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Coronary artery disease	15	(1.03%)	0.30	12	(0.83%)	0.28	18	(1.24%)	0.37	45	(1.03%)	0.32
Coronary artery disease aggravated	7	(0.48%)	0.14	2	(0.14%)	0.05	6	(0.41%)	0.12	15	(0.35%)	0.11
Coronary artery restenosis	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Coronary artery stenosis	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Coronary atheroma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Coronary atherosclerosis	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Coronary disease	6	(0.41%)	0.12	4	(0.28%)	0.09	7	(0.48%)	0.14	17	(0.39%)	0.12
Coronary insufficiency	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
ECG signs of myocardial ischemia	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Electrocardiogram ST segment depression	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Electrocardiogram ST-T change	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Electrocardiogram ST-T segment abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram T wave inversion	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Ischemic cardiomyopathy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ischemic heart disease	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Myocardial ischemia	6	(0.41%)	0.12	3	(0.21%)	0.07	5	(0.34%)	0.10	14	(0.32%)	0.10
Nonspecific ST segment change	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
ST depressed	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Silent myocardial ischemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
T wave flattening of	2	(0.14%)	0.04	1	(0.07%)	0.02	2	(0.14%)	0.04	5	(0.12%)	0.04
Triple vessel disease	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
CV - Myocardial Ischaemia - MI	27	(1.85%)	0.55	18	(1.25%)	0.42	23	(1.58%)	0.47	68	(1.56%)	0.48
Acute myocardial infarction	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Acute myocardial infarction, of anterolateral wall	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Acute myocardial infarction, of other anterior wall	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Acute myocardial infarction, of other inferior wall	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Anterior myocardial infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Asystole	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cardiac arrest	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Coronary artery occlusion	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Heart attack	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Inferior myocardial infarction	1	(0.07%)	0.02	0			3	(0.21%)	0.06	4	(0.09%)	0.03
Myocardial infarction	18	(1.24%)	0.36	9	(0.63%)	0.21	12	(0.83%)	0.24	39	(0.90%)	0.28
Non-Q wave MI	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Old myocardial infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Posterior myocardial infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Septal myocardial infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Silent myocardial infarction	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Subendocardial myocardial infarction	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Sudden death	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
CV - Other	63	(4.33%)	1.27	46	(3.19%)	1.08	73	(5.02%)	1.49	182	(4.18%)	1.29
Aneurysm atrial	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Aortic regurgitation	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Aortic valve disease	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Aortic valve incompetence	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Aortic valve sclerosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Aortic valve stenosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Atrial thrombosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cardiac tamponade	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cardiac valve disease	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiac ventricular thrombosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cardiomegaly	4	(0.28%)	0.08	1	(0.07%)	0.02	1	(0.07%)	0.02	6	(0.14%)	0.04
Cardiomyopathy	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Cardiovascular deconditioning	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cardiovascular disease, unspecified	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cardiovascular disorder	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cor pulmonale	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cyanosis peripheral	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Dilatation ventricular	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Dilated cardiomyopathy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Disorder circulatory system	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
ECG signs of ventricular hypertrophy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Early systolic murmur	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Effusion pericardial	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Electrocardiogram Q wave abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Electrocardiogram QRS complex abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Electrocardiogram T wave abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Electrocardiogram abnormal	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Heart disease, unspecified	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Heart disorder	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart enlarged	2	(0.14%)	0.04	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.09%)	0.03
Heart murmur	8	(0.55%)	0.16	6	(0.42%)	0.14	6	(0.41%)	0.12	20	(0.46%)	0.14
Heart pounding	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Heart throbbing	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Heart valve insufficiency	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hypertensive heart disease	0			2	(0.14%)	0.05	5	(0.34%)	0.10	7	(0.16%)	0.05
Left atrial enlargement	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Left atrial hypertrophy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Left ventricular dilatation	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Left ventricular hypertrophy	5	(0.34%)	0.10	6	(0.42%)	0.14	5	(0.34%)	0.10	16	(0.37%)	0.11
Mitral insufficiency	2	(0.14%)	0.04	0			2	(0.14%)	0.04	4	(0.09%)	0.03
Mitral regurgitation	5	(0.34%)	0.10	2	(0.14%)	0.05	3	(0.21%)	0.06	10	(0.23%)	0.07
Mitral valve disease	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Mitral valve prolapse	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Mixed aortic valve disease	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Palpitation	23	(1.58%)	0.46	19	(1.32%)	0.45	35	(2.41%)	0.71	77	(1.77%)	0.55
Pericardial calcification	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Pericardial effusion	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Pericarditis	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Pulmonary valve regurgitation	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Right ventricular hypertrophy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Tricuspid regurgitation	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Cerebrovascular	25	(1.72%)	0.50	24	(1.67%)	0.57	31	(2.13%)	0.63	80	(1.84%)	0.57
Apoplexy	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Carotid artery occlusion	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cerebellar infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cerebral arterial aneurysm	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cerebral arteriosclerosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cerebral hemorrhage	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Cerebral infarction	0			0			3	(0.21%)	0.06	3	(0.07%)	0.02
Cerebral ischemia	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
Cerebral vascular disturbance	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cerebrovascular accident	7	(0.48%)	0.14	3	(0.21%)	0.07	5	(0.34%)	0.10	15	(0.35%)	0.11
Cerebrovascular disorder	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cerebrovascular insufficiency	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cerebrovascular spasm	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hemorrhagic cerebral infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Ischemia cerebrovascular	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Late effects of cerebral stroke	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Stroke	2	(0.14%)	0.04	4	(0.28%)	0.09	5	(0.34%)	0.10	11	(0.25%)	0.08
Subarachnoid hemorrhage	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Transient cerebral ischemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Transient ischemic attacks	7	(0.48%)	0.14	5	(0.35%)	0.12	11	(0.76%)	0.22	23	(0.53%)	0.16
Cerebrovascular - Stroke	16	(1.10%)	0.32	17	(1.18%)	0.40	19	(1.31%)	0.39	52	(1.20%)	0.37
Apoplexy	3	(0.21%)	0.06	2	(0.14%)	0.05	2	(0.14%)	0.04	7	(0.16%)	0.05
Carotid artery occlusion	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cerebellar infarction	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cerebral arterial aneurysm	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cerebral hemorrhage	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Cerebral infarction	0			0			3	(0.21%)	0.06	3	(0.07%)	0.02
Cerebral ischemia	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
Cerebrovascular accident	7	(0.48%)	0.14	3	(0.21%)	0.07	5	(0.34%)	0.10	15	(0.35%)	0.11
Hemorrhagic cerebral infarction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Ischemia cerebrovascular	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Late effects of cerebral stroke	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Stroke	2	(0.14%)	0.04	4	(0.28%)	0.09	5	(0.34%)	0.10	11	(0.25%)	0.08
Subarachnoid hemorrhage	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Cerebrovascular - Transient Ischaemic Attack	7	(0.48%)	0.14	6	(0.42%)	0.14	11	(0.76%)	0.22	24	(0.55%)	0.17
Transient cerebral ischemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Transient ischemic attacks	7	(0.48%)	0.14	5	(0.35%)	0.12	11	(0.76%)	0.22	23	(0.53%)	0.16
Dyslipidemia	411	(28.23%)	8.30	261	(18.11%)	6.15	269	(18.50%)	5.48	941	(21.63%)	6.67
Blood cholesterol increased	31	(2.13%)	0.63	18	(1.25%)	0.42	25	(1.72%)	0.51	74	(1.70%)	0.52
Cholesterol total increased	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Dyslipidemia	38	(2.61%)	0.77	25	(1.74%)	0.59	26	(1.79%)	0.53	89	(2.05%)	0.63
Fredrickson Type II lipidemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
HDL cholesterol decreased	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
HDL low	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
High density lipoprotein cholesterol decreased	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
High density lipoprotein decreased	3	(0.21%)	0.06	1	(0.07%)	0.02	1	(0.07%)	0.02	5	(0.12%)	0.04
Hypercholesterolemia	155	(10.65%)	3.13	92	(6.38%)	2.17	94	(6.47%)	1.92	341	(7.84%)	2.42
Hypercholesterolemia aggravated	19	(1.31%)	0.38	17	(1.18%)	0.40	16	(1.10%)	0.33	52	(1.20%)	0.37
Hyperlipidemia	144	(9.89%)	2.91	74	(5.14%)	1.74	79	(5.43%)	1.61	297	(6.83%)	2.11
Hypertriglyceridemia	8	(0.55%)	0.16	18	(1.25%)	0.42	16	(1.10%)	0.33	42	(0.97%)	0.30
LDL raised	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Lipid metabolism disorder	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Lipids abnormal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Lipids increased	7	(0.48%)	0.14	4	(0.28%)	0.09	5	(0.34%)	0.10	16	(0.37%)	0.11

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Low HDL	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Low density lipoprotein abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Low density lipoprotein cholesterol increased	7	(0.48%)	0.14	5	(0.35%)	0.12	2	(0.14%)	0.04	14	(0.32%)	0.10
Low density lipoprotein increased	6	(0.41%)	0.12	5	(0.35%)	0.12	1	(0.07%)	0.02	12	(0.28%)	0.09
Pure hypercholesterolemia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Serum cholesterol increased	1	(0.07%)	0.02	2	(0.14%)	0.05	1	(0.07%)	0.02	4	(0.09%)	0.03
Triglyceride increased	25	(1.72%)	0.50	15	(1.04%)	0.35	24	(1.65%)	0.49	64	(1.47%)	0.45
Triglycerides high	1	(0.07%)	0.02	0			3	(0.21%)	0.06	4	(0.09%)	0.03
Edema	205	(14.08%)	4.14	123	(8.54%)	2.90	104	(7.15%)	2.12	432	(9.93%)	3.06
Ankle edema	46	(3.16%)	0.93	25	(1.74%)	0.59	19	(1.31%)	0.39	90	(2.07%)	0.64
Dependent edema	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Edema	19	(1.31%)	0.38	9	(0.63%)	0.21	10	(0.69%)	0.20	38	(0.87%)	0.27
Edema aggravated	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Edema extremities	5	(0.34%)	0.10	3	(0.21%)	0.07	4	(0.28%)	0.08	12	(0.28%)	0.09
Edema lower limb	21	(1.44%)	0.42	8	(0.56%)	0.19	10	(0.69%)	0.20	39	(0.90%)	0.28
Edema of lower extremities	36	(2.47%)	0.73	15	(1.04%)	0.35	19	(1.31%)	0.39	70	(1.61%)	0.50
Fluid retention	7	(0.48%)	0.14	0			4	(0.28%)	0.08	11	(0.25%)	0.08
Generalized edema	10	(0.69%)	0.20	2	(0.14%)	0.05	0			12	(0.28%)	0.09
Leg edema	31	(2.13%)	0.63	24	(1.67%)	0.57	23	(1.58%)	0.47	78	(1.79%)	0.55
Malleolus edema	4	(0.28%)	0.08	2	(0.14%)	0.05	1	(0.07%)	0.02	7	(0.16%)	0.05
Pedal edema	24	(1.65%)	0.48	13	(0.90%)	0.31	9	(0.62%)	0.18	46	(1.06%)	0.33
Peripheral edema	16	(1.10%)	0.32	9	(0.63%)	0.21	4	(0.28%)	0.08	29	(0.67%)	0.21
Peripheral swelling	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Pitting edema	4	(0.28%)	0.08	5	(0.35%)	0.12	0			9	(0.21%)	0.06
Pretibial edema	7	(0.48%)	0.14	3	(0.21%)	0.07	0			10	(0.23%)	0.07
Swelling of feet	8	(0.55%)	0.16	5	(0.35%)	0.12	5	(0.34%)	0.10	18	(0.41%)	0.13
Swelling of legs	13	(0.89%)	0.26	12	(0.83%)	0.28	9	(0.62%)	0.18	34	(0.78%)	0.24
Swelling of limb	1	(0.07%)	0.02	0			4	(0.28%)	0.08	5	(0.12%)	0.04
Water retention	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Eye Disorders	10	(0.69%)	0.20	11	(0.76%)	0.26	12	(0.83%)	0.24	33	(0.76%)	0.23
Background diabetic retinopathy	3	(0.21%)	0.06	0			1	(0.07%)	0.02	4	(0.09%)	0.03
Cystoid macular edema	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Diabetic macular retinopathy	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Diabetic retinopathy	6	(0.41%)	0.12	4	(0.28%)	0.09	5	(0.34%)	0.10	15	(0.35%)	0.11
Fundus hypertonicus	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hypertensive retinopathy	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Macular edema	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Non-proliferative diabetic retinopathy	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Retinopathy	0			4	(0.28%)	0.09	3	(0.21%)	0.06	7	(0.16%)	0.05
Eye Disorders - Macular Edema	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Cystoid macular edema	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Macular edema	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Eye Disorders - Retinopathy	10	(0.69%)	0.20	11	(0.76%)	0.26	10	(0.69%)	0.20	31	(0.71%)	0.22
Background diabetic retinopathy	3	(0.21%)	0.06	0			1	(0.07%)	0.02	4	(0.09%)	0.03
Diabetic macular retinopathy	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Diabetic retinopathy	6	(0.41%)	0.12	4	(0.28%)	0.09	5	(0.34%)	0.10	15	(0.35%)	0.11
Fundus hypertonicus	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hypertensive retinopathy	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Non-proliferative diabetic retinopathy	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Retinopathy	0			4	(0.28%)	0.09	3	(0.21%)	0.06	7	(0.16%)	0.05
GI	376	(25.82%)	7.59	371	(25.75%)	8.74	605	(41.61%)	12.33	1352	(31.07%)	9.59
Abdominal bloating	4	(0.28%)	0.08	5	(0.35%)	0.12	14	(0.96%)	0.29	23	(0.53%)	0.16
Abdominal colic	0			2	(0.14%)	0.05	4	(0.28%)	0.08	6	(0.14%)	0.04
Abdominal cramp	6	(0.41%)	0.12	10	(0.69%)	0.24	17	(1.17%)	0.35	33	(0.76%)	0.23
Abdominal crampy pains	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Abdominal discomfort	9	(0.62%)	0.18	6	(0.42%)	0.14	10	(0.69%)	0.20	25	(0.58%)	0.18
Abdominal distension	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Abdominal distension gaseous	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Abdominal distress	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Abdominal fullness	2	(0.14%)	0.04	2	(0.14%)	0.05	1	(0.07%)	0.02	5	(0.12%)	0.04
Abdominal pain	63	(4.33%)	1.27	62	(4.30%)	1.46	72	(4.95%)	1.47	197	(4.53%)	1.40
Abdominal pain aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Abdominal tenderness	0			0			4	(0.28%)	0.08	4	(0.09%)	0.03
Acute diarrhea	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Acute gastritis	3	(0.21%)	0.06	0			1	(0.07%)	0.02	4	(0.09%)	0.03
Bloated feeling	4	(0.28%)	0.08	2	(0.14%)	0.05	3	(0.21%)	0.06	9	(0.21%)	0.06
Bloating	7	(0.48%)	0.14	5	(0.35%)	0.12	6	(0.41%)	0.12	18	(0.41%)	0.13
Bowel motility disorder	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Constipation	64	(4.40%)	1.29	73	(5.07%)	1.72	75	(5.16%)	1.53	212	(4.87%)	1.50
Constipation aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	5	(0.34%)	0.10	7	(0.16%)	0.05
Constipation chronic	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cramp in lower abdomen	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Defecation frequency decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Defecation frequency increased	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Defecation urgency	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Diarrhea	111	(7.62%)	2.24	126	(8.74%)	2.97	296	(20.36%)	6.03	533	(12.25%)	3.78
Diarrhea aggravated	0			1	(0.07%)	0.02	8	(0.55%)	0.16	9	(0.21%)	0.06
Distress gastrointestinal	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Dry heaves	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Epigastric pain	14	(0.96%)	0.28	22	(1.53%)	0.52	23	(1.58%)	0.47	59	(1.36%)	0.42
Flatulence	25	(1.72%)	0.50	17	(1.18%)	0.40	29	(1.99%)	0.59	71	(1.63%)	0.50
Flatulent dyspepsia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Flatus increased	4	(0.28%)	0.08	5	(0.35%)	0.12	5	(0.34%)	0.10	14	(0.32%)	0.10
Frequent bowel movements	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Gas	5	(0.34%)	0.10	1	(0.07%)	0.02	9	(0.62%)	0.18	15	(0.35%)	0.11
Gas evolution in intestine	2	(0.14%)	0.04	2	(0.14%)	0.05	1	(0.07%)	0.02	5	(0.12%)	0.04
Gas in stomach	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Gas pain	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Gastric irritation	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Gastric spasm	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Gastrointestinal cramps	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Gastrointestinal discomfort	1	(0.07%)	0.02	2	(0.14%)	0.05	2	(0.14%)	0.04	5	(0.12%)	0.04
Gastrointestinal pain	2	(0.14%)	0.04	0			4	(0.28%)	0.08	6	(0.14%)	0.04
Gastrointestinal upset	3	(0.21%)	0.06	7	(0.49%)	0.16	11	(0.76%)	0.22	21	(0.48%)	0.15
Hyperemesis	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hypochondrial pain	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Hypogastric pain	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Iliac fossa pain	0			4	(0.28%)	0.09	0			4	(0.09%)	0.03
Increased bowel frequency	1	(0.07%)	0.02	3	(0.21%)	0.07	4	(0.28%)	0.08	8	(0.18%)	0.06
Increased stool frequency	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Intestinal cramps	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Intestinal hypermotility	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Irritable bowel	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Irritable bowel syndrome	2	(0.14%)	0.04	3	(0.21%)	0.07	10	(0.69%)	0.20	15	(0.35%)	0.11
Irritable colon	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Left lower quadrant pain	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Loose bowel	1	(0.07%)	0.02	1	(0.07%)	0.02	10	(0.69%)	0.20	12	(0.28%)	0.09
Loose motions	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Loose stools	9	(0.62%)	0.18	6	(0.42%)	0.14	32	(2.20%)	0.65	47	(1.08%)	0.33
Lower abdominal pain	4	(0.28%)	0.08	5	(0.35%)	0.12	14	(0.96%)	0.29	23	(0.53%)	0.16
Nausea	112	(7.69%)	2.26	99	(6.87%)	2.33	168	(11.55%)	3.42	379	(8.71%)	2.69
Nausea aggravated	1	(0.07%)	0.02	0			3	(0.21%)	0.06	4	(0.09%)	0.03
Pain hunger	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Postprandial nausea	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Queasy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Right lower quadrant pain	3	(0.21%)	0.06	4	(0.28%)	0.09	4	(0.28%)	0.08	11	(0.25%)	0.08
Soft stools	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Spastic colon	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Stomach cramps	9	(0.62%)	0.18	6	(0.42%)	0.14	6	(0.41%)	0.12	21	(0.48%)	0.15
Stomach discomfort	0			3	(0.21%)	0.07	6	(0.41%)	0.12	9	(0.21%)	0.06
Stomach fullness	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Stomach heaviness	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Stomach pain	23	(1.58%)	0.46	18	(1.25%)	0.42	38	(2.61%)	0.77	79	(1.82%)	0.56
Stools hard	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Stools watery	0			0			6	(0.41%)	0.12	6	(0.14%)	0.04
Swelling abdomen	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Tenderness epigastric	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Upper abdominal pain	8	(0.55%)	0.16	13	(0.90%)	0.31	5	(0.34%)	0.10	26	(0.60%)	0.18
Vomiting	57	(3.92%)	1.15	45	(3.12%)	1.06	82	(5.64%)	1.67	184	(4.23%)	1.30
Vomiting aggravated	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
GI - Abdominal Discomfort	161	(11.06%)	3.25	163	(11.31%)	3.84	224	(15.41%)	4.57	548	(12.60%)	3.89
Abdominal bloating	4	(0.28%)	0.08	5	(0.35%)	0.12	14	(0.96%)	0.29	23	(0.53%)	0.16
Abdominal colic	0			2	(0.14%)	0.05	4	(0.28%)	0.08	6	(0.14%)	0.04
Abdominal cramp	6	(0.41%)	0.12	10	(0.69%)	0.24	17	(1.17%)	0.35	33	(0.76%)	0.23
Abdominal crampy pains	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Abdominal discomfort	9	(0.62%)	0.18	6	(0.42%)	0.14	10	(0.69%)	0.20	25	(0.58%)	0.18
Abdominal distension	1	(0.07%)	0.02	2	(0.14%)	0.05	3	(0.21%)	0.06	6	(0.14%)	0.04
Abdominal distension gaseous	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Abdominal distress	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Abdominal fullness	2	(0.14%)	0.04	2	(0.14%)	0.05	1	(0.07%)	0.02	5	(0.12%)	0.04
Abdominal pain	63	(4.33%)	1.27	62	(4.30%)	1.46	72	(4.95%)	1.47	197	(4.53%)	1.40
Abdominal pain aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Abdominal tenderness	0			0			4	(0.28%)	0.08	4	(0.09%)	0.03
Acute gastritis	3	(0.21%)	0.06	0			1	(0.07%)	0.02	4	(0.09%)	0.03
Bloated feeling	4	(0.28%)	0.08	2	(0.14%)	0.05	3	(0.21%)	0.06	9	(0.21%)	0.06
Bloating	7	(0.48%)	0.14	5	(0.35%)	0.12	6	(0.41%)	0.12	18	(0.41%)	0.13
Cramp in lower abdomen	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Distress gastrointestinal	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Epigastric pain	14	(0.96%)	0.28	22	(1.53%)	0.52	23	(1.58%)	0.47	59	(1.36%)	0.42
Gas	5	(0.34%)	0.10	1	(0.07%)	0.02	9	(0.62%)	0.18	15	(0.35%)	0.11
Gas evolution in intestine	2	(0.14%)	0.04	2	(0.14%)	0.05	1	(0.07%)	0.02	5	(0.12%)	0.04
Gas in stomach	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Gas pain	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Gastric irritation	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Gastric spasm	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Gastrointestinal cramps	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Gastrointestinal discomfort	1	(0.07%)	0.02	2	(0.14%)	0.05	2	(0.14%)	0.04	5	(0.12%)	0.04
Gastrointestinal pain	2	(0.14%)	0.04	0			4	(0.28%)	0.08	6	(0.14%)	0.04
Gastrointestinal upset	3	(0.21%)	0.06	7	(0.49%)	0.16	11	(0.76%)	0.22	21	(0.48%)	0.15
Hypochondrial pain	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Hypogastric pain	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Iliac fossa pain	0			4	(0.28%)	0.09	0			4	(0.09%)	0.03
Intestinal cramps	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Left lower quadrant pain	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Lower abdominal pain	4	(0.28%)	0.08	5	(0.35%)	0.12	14	(0.96%)	0.29	23	(0.53%)	0.16
Pain hunger	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Right lower quadrant pain	3	(0.21%)	0.06	4	(0.28%)	0.09	4	(0.28%)	0.08	11	(0.25%)	0.08
Stomach cramps	9	(0.62%)	0.18	6	(0.42%)	0.14	6	(0.41%)	0.12	21	(0.48%)	0.15
Stomach discomfort	0			3	(0.21%)	0.07	6	(0.41%)	0.12	9	(0.21%)	0.06

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Stomach fullness	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Stomach heaviness	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Stomach pain	23	(1.58%)	0.46	18	(1.25%)	0.42	38	(2.61%)	0.77	79	(1.82%)	0.56
Swelling abdomen	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Tenderness epigastric	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Upper abdominal pain	8	(0.55%)	0.16	13	(0.90%)	0.31	5	(0.34%)	0.10	26	(0.60%)	0.18
GI - Constipation	66	(4.53%)	1.33	74	(5.14%)	1.74	79	(5.43%)	1.61	219	(5.03%)	1.55
Constipation	64	(4.40%)	1.29	73	(5.07%)	1.72	75	(5.16%)	1.53	212	(4.87%)	1.50
Constipation aggravated	1	(0.07%)	0.02	1	(0.07%)	0.02	5	(0.34%)	0.10	7	(0.16%)	0.05
Constipation chronic	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Defecation frequency decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Stools hard	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
GI - Diarrhea	129	(8.86%)	2.60	142	(9.85%)	3.35	345	(23.73%)	7.03	616	(14.16%)	4.37
Acute diarrhea	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Bowel motility disorder	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Defecation frequency increased	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Defecation urgency	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Diarrhea	111	(7.62%)	2.24	126	(8.74%)	2.97	296	(20.36%)	6.03	533	(12.25%)	3.78
Diarrhea aggravated	0			1	(0.07%)	0.02	8	(0.55%)	0.16	9	(0.21%)	0.06
Frequent bowel movements	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Increased bowel frequency	1	(0.07%)	0.02	3	(0.21%)	0.07	4	(0.28%)	0.08	8	(0.18%)	0.06
Increased stool frequency	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Intestinal hypermotility	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Irritable bowel	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.21%)	0.06	5	(0.12%)	0.04
Irritable bowel syndrome	2	(0.14%)	0.04	3	(0.21%)	0.07	10	(0.69%)	0.20	15	(0.35%)	0.11
Irritable colon	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Loose bowel	1	(0.07%)	0.02	1	(0.07%)	0.02	10	(0.69%)	0.20	12	(0.28%)	0.09
Loose motions	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Loose stools	9	(0.62%)	0.18	6	(0.42%)	0.14	32	(2.20%)	0.65	47	(1.08%)	0.33
Soft stools	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.28%)	0.08	6	(0.14%)	0.04
Spastic colon	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Stools watery	0			0			6	(0.41%)	0.12	6	(0.14%)	0.04
GI - Flatus	30	(2.06%)	0.61	21	(1.46%)	0.49	34	(2.34%)	0.69	85	(1.95%)	0.60
Flatulence	25	(1.72%)	0.50	17	(1.18%)	0.40	29	(1.99%)	0.59	71	(1.63%)	0.50
Flatulent dyspepsia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Flatus increased	4	(0.28%)	0.08	5	(0.35%)	0.12	5	(0.34%)	0.10	14	(0.32%)	0.10
GI - Nausea	112	(7.69%)	2.26	99	(6.87%)	2.33	170	(11.69%)	3.47	381	(8.76%)	2.70
Nausea	112	(7.69%)	2.26	99	(6.87%)	2.33	168	(11.55%)	3.42	379	(8.71%)	2.69
Nausea aggravated	1	(0.07%)	0.02	0			3	(0.21%)	0.06	4	(0.09%)	0.03
Postprandial nausea	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Queasy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
GI - Vomiting	58	(3.98%)	1.17	45	(3.12%)	1.06	84	(5.78%)	1.71	187	(4.30%)	1.33
Dry heaves	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hyperemesis	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Vomiting	57	(3.92%)	1.15	45	(3.12%)	1.06	82	(5.64%)	1.67	184	(4.23%)	1.30
Vomiting aggravated	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hematologic	103	(7.07%)	2.08	37	(2.57%)	0.87	53	(3.65%)	1.08	193	(4.44%)	1.37
Anemia	68	(4.67%)	1.37	18	(1.25%)	0.42	31	(2.13%)	0.63	117	(2.69%)	0.83
Anemia aggravated	2	(0.14%)	0.04	0			3	(0.21%)	0.06	5	(0.12%)	0.04
Blood iron decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Decreased white cell count	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Eosinophilia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Erythrocytes decreased	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hematocrit decreased	7	(0.48%)	0.14	3	(0.21%)	0.07	7	(0.48%)	0.14	17	(0.39%)	0.12
Hemoglobin decreased	5	(0.34%)	0.10	4	(0.28%)	0.09	4	(0.28%)	0.08	13	(0.30%)	0.09
Hemoglobin low	13	(0.89%)	0.26	5	(0.35%)	0.12	4	(0.28%)	0.08	22	(0.51%)	0.16
Hypochromic microcytic anemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Iron deficiency anemia	7	(0.48%)	0.14	1	(0.07%)	0.02	5	(0.34%)	0.10	13	(0.30%)	0.09
Leukopenia	4	(0.28%)	0.08	2	(0.14%)	0.05	2	(0.14%)	0.04	8	(0.18%)	0.06
Lymphocyte count decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Macrocytic anemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Microcytic anemia	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Neutropenia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Neutrophil count low	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Pancytopenia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Pernicious anemia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Platelet count decreased	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Platelet count low	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Platelets decreased	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Red blood cell count decreased	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Thrombocytopenia	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Thrombopenia	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
White blood cell count decreased	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
White blood cell count low	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
White blood cell decreased	3	(0.21%)	0.06	0			0			3	(0.07%)	0.02
Hematologic - Anemia	94	(6.46%)	1.90	27	(1.87%)	0.64	48	(3.30%)	0.98	169	(3.88%)	1.20
Anemia	68	(4.67%)	1.37	18	(1.25%)	0.42	31	(2.13%)	0.63	117	(2.69%)	0.83
Anemia aggravated	2	(0.14%)	0.04	0			3	(0.21%)	0.06	5	(0.12%)	0.04
Blood iron decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Erythrocytes decreased	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hematocrit decreased	7	(0.48%)	0.14	3	(0.21%)	0.07	7	(0.48%)	0.14	17	(0.39%)	0.12

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Hemoglobin decreased	5	(0.34%)	0.10	4	(0.28%)	0.09	4	(0.28%)	0.08	13	(0.30%)	0.09
Hemoglobin low	13	(0.89%)	0.26	5	(0.35%)	0.12	4	(0.28%)	0.08	22	(0.51%)	0.16
Hypochromic microcytic anemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Iron deficiency anemia	7	(0.48%)	0.14	1	(0.07%)	0.02	5	(0.34%)	0.10	13	(0.30%)	0.09
Macrocytic anemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Microcytic anemia	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Pernicious anemia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Red blood cell count decreased	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Hematologic - Non-red cell	14	(0.96%)	0.28	11	(0.76%)	0.26	9	(0.62%)	0.18	34	(0.78%)	0.24
Decreased white cell count	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Eosinophilia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Leukopenia	4	(0.28%)	0.08	2	(0.14%)	0.05	2	(0.14%)	0.04	8	(0.18%)	0.06
Lymphocyte count decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Neutropenia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Neutrophil count low	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Platelet count decreased	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Platelet count low	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Platelets decreased	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Thrombocytopenia	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Thrombopenia	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
White blood cell count decreased	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
White blood cell count low	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
White blood cell decreased	3	(0.21%)	0.06	0			0			3	(0.07%)	0.02
Hematologic - Non-red cell - Leukocytopenia	11	(0.76%)	0.22	5	(0.35%)	0.12	6	(0.41%)	0.12	22	(0.51%)	0.16
Decreased white cell count	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Eosinophilia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Leukopenia	4	(0.28%)	0.08	2	(0.14%)	0.05	2	(0.14%)	0.04	8	(0.18%)	0.06
Lymphocyte count decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Neutropenia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Neutrophil count low	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
White blood cell count decreased	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
White blood cell count low	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
White blood cell decreased	3	(0.21%)	0.06	0			0			3	(0.07%)	0.02
Hematologic - Non-red cell - Thrombocytopenia	5	(0.34%)	0.10	6	(0.42%)	0.14	4	(0.28%)	0.08	15	(0.35%)	0.11
Platelet count decreased	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Platelet count low	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Platelets decreased	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Thrombocytopenia	2	(0.14%)	0.04	1	(0.07%)	0.02	4	(0.28%)	0.08	7	(0.16%)	0.05
Thrombopenia	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Hematologic - Pancytopenia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Pancytopenia	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Hepatic	46	(3.16%)	0.93	63	(4.37%)	1.48	88	(6.05%)	1.79	197	(4.53%)	1.40
Alanine aminotransferase increased	8	(0.55%)	0.16	14	(0.97%)	0.33	17	(1.17%)	0.35	39	(0.90%)	0.28
Alkaline phosphatase increased	1	(0.07%)	0.02	2	(0.14%)	0.05	7	(0.48%)	0.14	10	(0.23%)	0.07
Aspartate aminotransferase increased	6	(0.41%)	0.12	4	(0.28%)	0.09	6	(0.41%)	0.12	16	(0.37%)	0.11
Bilirubin increased	0			0			7	(0.48%)	0.14	7	(0.16%)	0.05
Bilirubin total increased	0			2	(0.14%)	0.05	1	(0.07%)	0.02	3	(0.07%)	0.02
Elevated liver enzymes	12	(0.82%)	0.24	13	(0.90%)	0.31	18	(1.24%)	0.37	43	(0.99%)	0.30
Esophageal varices	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Esophageal varices hemorrhage	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Fatty liver	3	(0.21%)	0.06	3	(0.21%)	0.07	4	(0.28%)	0.08	10	(0.23%)	0.07
Gamma-glutamyltransferase abnormal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Gamma-glutamyltransferase increased	20	(1.37%)	0.40	21	(1.46%)	0.49	29	(1.99%)	0.59	70	(1.61%)	0.50
Hepatic cirrhosis	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Hepatic disease	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hepatic enzymes increased	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Hepatic fibrosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hepatic function abnormal	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Hepatic lesion	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Hepatic necrosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hepatic shock	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hepatic steatosis	3	(0.21%)	0.06	6	(0.42%)	0.14	5	(0.34%)	0.10	14	(0.32%)	0.10
Hepatitis	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Hepatomegaly	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Hepatosplenomegaly	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hyperbilirubinemia	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Icteric conjunctivae	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Liver disorder	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Liver enlargement	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Liver fatty infiltration	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Liver function test abnormal	1	(0.07%)	0.02	2	(0.14%)	0.05	6	(0.41%)	0.12	9	(0.21%)	0.06
Non-alcoholic fatty liver	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Serum transaminase increased	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Transaminases increased	0			0			5	(0.34%)	0.10	5	(0.12%)	0.04
Transaminitis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Hypoglycaemia	142	(9.75%)	2.87	557	(38.65%)	13.13	168	(11.55%)	3.42	867	(19.93%)	6.15
Blood glucose decreased	0			4	(0.28%)	0.09	0			4	(0.09%)	0.03
Blood sugar decreased	3	(0.21%)	0.06	3	(0.21%)	0.07	0			6	(0.14%)	0.04
Fasting blood glucose decreased	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Glucose decreased	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Hypoglycemia	128	(8.79%)	2.58	510	(35.39%)	12.02	148	(10.18%)	3.02	786	(18.07%)	5.57

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Hypoglycemia aggravated	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Hypoglycemia night	0			3	(0.21%)	0.07	0			3	(0.07%)	0.02
Hypoglycemic episode	13	(0.89%)	0.26	76	(5.27%)	1.79	22	(1.51%)	0.45	111	(2.55%)	0.79
Hypoglycemic reaction	2	(0.14%)	0.04	3	(0.21%)	0.07	2	(0.14%)	0.04	7	(0.16%)	0.05
Plasma glucose decreased	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Neoplasms/Cancer	206	(14.15%)	4.16	209	(14.50%)	4.93	235	(16.16%)	4.79	650	(14.94%)	4.61
Abdominal neoplasm	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Acanthosis nigricans	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
Acoustic neuroma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Acute lymphocytic leukemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Acute myeloid leukemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Adenocarcinoma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Adenocarcinoma gastric	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Adenocarcinoma of colon	1	(0.07%)	0.02	2	(0.14%)	0.05	1	(0.07%)	0.02	4	(0.09%)	0.03
Adenocarcinoma of esophagus	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Adenocarcinoma of prostate	2	(0.14%)	0.04	0			1	(0.07%)	0.02	3	(0.07%)	0.02
Adenoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Adrenal adenoma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Adrenal cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Adrenal metastases	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Angiomyolipoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Arachnoid cyst	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Baker's cyst	2	(0.14%)	0.04	3	(0.21%)	0.07	4	(0.28%)	0.08	9	(0.21%)	0.06
Basal cell carcinoma	10	(0.69%)	0.20	13	(0.90%)	0.31	10	(0.69%)	0.20	33	(0.76%)	0.23
Basal cell epithelioma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Benign basal cell papilloma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Benign breast neoplasm	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Benign colonic polyp	5	(0.34%)	0.10	2	(0.14%)	0.05	4	(0.28%)	0.08	11	(0.25%)	0.08
Benign gastric polyp	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Benign lip neoplasm	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Benign meningioma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Benign neoplasm	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Benign neoplasm of bladder	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Benign neoplasm of pleura	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Benign neoplasm of skin	3	(0.21%)	0.06	2	(0.14%)	0.05	3	(0.21%)	0.06	8	(0.18%)	0.06
Benign neoplasm of vulva	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Benign ovarian cyst	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Benign parotid tumor	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Benign polyp of uterus	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Benign soft tissue neoplasm	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Benign thyroid nodule	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Benign uterine neoplasm	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Bladder cancer	2	(0.14%)	0.04	2	(0.14%)	0.05	0			4	(0.09%)	0.03

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Bladder cyst	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Bladder neoplasm	1	(0.07%)	0.02	2	(0.14%)	0.05	2	(0.14%)	0.04	5	(0.12%)	0.04
Bladder papilloma	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Bone metastases	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Bowen's disease	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Brain metastases	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Brain neoplasm	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Brain neoplasm benign	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Breast cancer	2	(0.14%)	0.04	1	(0.07%)	0.02	3	(0.21%)	0.06	6	(0.14%)	0.04
Breast cancer female	1	(0.07%)	0.02	2	(0.14%)	0.05	2	(0.14%)	0.04	5	(0.12%)	0.04
Breast cyst	2	(0.14%)	0.04	1	(0.07%)	0.02	6	(0.41%)	0.12	9	(0.21%)	0.06
Breast fibrocystic change	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Breast lump (benign)	4	(0.28%)	0.08	6	(0.42%)	0.14	1	(0.07%)	0.02	11	(0.25%)	0.08
Breast neoplasm benign female	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cancer pain	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Carcinoma endometrial stage I	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Carcinoma of the prostate recurrent	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Carcinoma of tongue	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Carcinoma uterine cervix	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Carcinoma vocal cord	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cecal cancer	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Cecal polyp	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cervical cyst	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cervical polyp	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Chondromatosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Chronic lymphatic leukemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Chronic lymphocytic leukemia	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Colon adenoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Colon cancer	2	(0.14%)	0.04	4	(0.28%)	0.09	2	(0.14%)	0.04	8	(0.18%)	0.06
Colon carcinoma	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Colon carcinoma Duke's C	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Colonic polyp	10	(0.69%)	0.20	10	(0.69%)	0.24	12	(0.83%)	0.24	32	(0.74%)	0.23
Colonic tubular adenoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Colorectal hyperplastic polyp	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Compound nevus	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Cutaneous T-cell lymphoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Cyst	15	(1.03%)	0.30	10	(0.69%)	0.24	15	(1.03%)	0.31	40	(0.92%)	0.28
Dermal inclusion cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Dermatofibroma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Dysplastic nevus	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Endocervical polyp	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Endometrial adenocarcinoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Endometrial carcinoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Endometrial polyp	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Epidermal inclusion cyst	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Epidermoid carcinoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Epididymal cyst	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Epiglottic carcinoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Epithelioma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Esophageal cancer	1	(0.07%)	0.02	2	(0.14%)	0.05	0			3	(0.07%)	0.02
Esophageal carcinoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Esophageal polyp	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Fibroadenoma of breast	0			4	(0.28%)	0.09	0			4	(0.09%)	0.03
Fibrocystic breast	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Fibrocystic breast disease	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Fibroma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Fibrous mastopathy	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Flat warts	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Follicular cyst of ovary	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Gastric cancer	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Gastric carcinoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Gastric polyps	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Genital labial cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Glioblastoma multiforme	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Glomus tumor	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hemangioma	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Hemangioma of liver	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Hemangioma of skin	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Hemangiopericytoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hepatic cyst	1	(0.07%)	0.02	2	(0.14%)	0.05	1	(0.07%)	0.02	4	(0.09%)	0.03
Histiocytoma	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Horner's syndrome	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Hyperplastic intestine polyp	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Infected cyst	3	(0.21%)	0.06	2	(0.14%)	0.05	4	(0.28%)	0.08	9	(0.21%)	0.06
Infected epidermal cyst	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Infected sebaceous cyst	3	(0.21%)	0.06	1	(0.07%)	0.02	3	(0.21%)	0.06	7	(0.16%)	0.05
Infected skin atheroma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Infiltrating ductal breast cancer	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Inflamed seborrheic keratosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Intestinal adenoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Intestinal polyp	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Intraductal papilloma of breast	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Invasive bladder cancer	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Invasive ductal breast cancer	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Inverting papilloma of the nasal cavity	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Jaw cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Laryngeal squamous cell carcinoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Leiomyoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Lip basal cell carcinoma	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Lipoma	9	(0.62%)	0.18	11	(0.76%)	0.26	8	(0.55%)	0.16	28	(0.64%)	0.20
Lipoma of breast	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Liver carcinoma	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Liver nodule	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Liver, cancer of	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Lung cancer	3	(0.21%)	0.06	2	(0.14%)	0.05	1	(0.07%)	0.02	6	(0.14%)	0.04
Lung cancer metastatic	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Lung carcinoma	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Lung neoplasm	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Lung neoplasm malignant	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Lung nodule	0			1	(0.07%)	0.02	4	(0.28%)	0.08	5	(0.12%)	0.04
Lymph node metastases	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Lymphoma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Malignant breast neoplasm	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Malignant melanoma	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Malignant melanoma in situ	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Malignant neoplasm of abdomen	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Malignant neoplasm of bladder	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Malignant neoplasm of esophagus	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Malignant neoplasm of female breast	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Malignant neoplasm of head of pancreas	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Malignant neoplasm of pancreas	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Malignant neoplasm of parotid gland	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Malignant neoplasm of testis	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Mastopathy	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Mediastinal cyst	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Melanoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Meningioma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Mesothelioma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Metastases to abdominal cavity	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Metastases to liver	1	(0.07%)	0.02	3	(0.21%)	0.07	1	(0.07%)	0.02	5	(0.12%)	0.04
Metastases to the mediastinum	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Metastatic bone pain	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Mole changes	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Mole of skin	6	(0.41%)	0.12	5	(0.35%)	0.12	10	(0.69%)	0.20	21	(0.48%)	0.15
Monoclonal paraproteinemia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Morton's neuroma	3	(0.21%)	0.06	2	(0.14%)	0.05	0			5	(0.12%)	0.04
Mouth cyst	1	(0.07%)	0.02	2	(0.14%)	0.05	1	(0.07%)	0.02	4	(0.09%)	0.03
Mucinous breast cancer	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Multiple myeloma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Myeloma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Nasal cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Nasal neoplasm	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Nasal polyp	2	(0.14%)	0.04	2	(0.14%)	0.05	3	(0.21%)	0.06	7	(0.16%)	0.05
Neoplasm	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Nervous system neoplasm benign	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Neuroma	1	(0.07%)	0.02	3	(0.21%)	0.07	0			4	(0.09%)	0.03
Nevus	4	(0.28%)	0.08	0			1	(0.07%)	0.02	5	(0.12%)	0.04
Nipple neoplasm	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Non-Hodgkin's lymphoma	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Non-small cell lung cancer	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Osteoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Ovarian cancer	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Ovarian carcinoma	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Ovarian cyst	5	(0.34%)	0.10	5	(0.35%)	0.12	6	(0.41%)	0.12	16	(0.37%)	0.11
Ovarian cystadenoma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Palmar fibromatosis	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Pancreas cancer	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Pancreatic cancer metastatic	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Papilloma of face	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Parathyroid adenoma	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Parathyroid tumour benign	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Peritoneal cyst	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Pituitary adenoma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Pituitary gland neoplasm	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Pituitary microadenoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Plantar fascial fibromatosis	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Plantar warts	4	(0.28%)	0.08	3	(0.21%)	0.07	3	(0.21%)	0.06	10	(0.23%)	0.07
Polyp	3	(0.21%)	0.06	4	(0.28%)	0.09	2	(0.14%)	0.04	9	(0.21%)	0.06
Polyp colorectal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Popliteal cyst	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Prostate cancer	6	(0.41%)	0.12	8	(0.56%)	0.19	8	(0.55%)	0.16	22	(0.51%)	0.16
Prostate cancer metastatic	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Prostatic adenoma	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Prostatic carcinoma	3	(0.21%)	0.06	1	(0.07%)	0.02	1	(0.07%)	0.02	5	(0.12%)	0.04
Prostatic nodule	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Pulmonary hamartoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Radicular cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Rectal adenocarcinoma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Rectal carcinoma	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Rectal polyp	6	(0.41%)	0.12	2	(0.14%)	0.05	4	(0.28%)	0.08	12	(0.28%)	0.09
Rectosigmoid cancer	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Renal cancer	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Renal carcinoma	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Renal cyst	6	(0.41%)	0.12	6	(0.42%)	0.14	6	(0.41%)	0.12	18	(0.41%)	0.13
Renal neoplasm	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Retention cyst	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Rodent ulcer	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Sarcoma	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Scrotal cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Sebaceous cyst	12	(0.82%)	0.24	6	(0.42%)	0.14	7	(0.48%)	0.14	25	(0.58%)	0.18
Seborrheic keratosis	7	(0.48%)	0.14	8	(0.56%)	0.19	6	(0.41%)	0.12	21	(0.48%)	0.15
Seborrheic wart	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Senile lentigo	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Sigmoid polyp	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Sinus polyp	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Skin cancer	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
Skin cysts	3	(0.21%)	0.06	1	(0.07%)	0.02	2	(0.14%)	0.04	6	(0.14%)	0.04
Skin growth NOS	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Skin melanoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Skin neoplasm malignant	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Skin tags	6	(0.41%)	0.12	6	(0.42%)	0.14	9	(0.62%)	0.18	21	(0.48%)	0.15
Small cell lung cancer	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Small cell lung cancer extensive stage	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Small intestine cancer (excl sarcoma and lymphoma)	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Small intestine carcinoma	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Solar lentigo	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Squamous cell carcinoma	1	(0.07%)	0.02	2	(0.14%)	0.05	7	(0.48%)	0.14	10	(0.23%)	0.07
Squamous cell carcinoma of skin	0			0			3	(0.21%)	0.06	3	(0.07%)	0.02
Squamous cell carcinoma of the tongue	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Synovial cyst	0			0			2	(0.14%)	0.04	2	(0.05%)	0.01
Tarlov's cyst	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Thyroid adenoma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Thyroid cyst	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Thyroid nodule	2	(0.14%)	0.04	7	(0.49%)	0.16	7	(0.48%)	0.14	16	(0.37%)	0.11
Uterine fibroid	5	(0.34%)	0.10	8	(0.56%)	0.19	5	(0.34%)	0.10	18	(0.41%)	0.13
Uterine fibroid cyst	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Uterine fibroids aggravated	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Uterine leiomyoma	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Uterine myoma	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Uterine polyp	2	(0.14%)	0.04	2	(0.14%)	0.05	1	(0.07%)	0.02	5	(0.12%)	0.04
Vaginal cyst	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Verruca	6	(0.41%)	0.12	5	(0.35%)	0.12	6	(0.41%)	0.12	17	(0.39%)	0.12
Verruca vulgaris	0			3	(0.21%)	0.07	1	(0.07%)	0.02	4	(0.09%)	0.03
Viral warts	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Vocal cord polyp	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Wart	9	(0.62%)	0.18	11	(0.76%)	0.26	8	(0.55%)	0.16	28	(0.64%)	0.20
Parotid/Salivary Gland Enlargement	5	(0.34%)	0.10	6	(0.42%)	0.14	3	(0.21%)	0.06	14	(0.32%)	0.10
Parotid gland enlargement	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8) n	%	Rate/ 100 PY	GLY/GLIB (N=1441, PY=4243.6) n	%	Rate/ 100 PY	METFORMIN (N=1454, PY=4905.6) n	%	Rate/ 100 PY	TOTAL (N=4351, PY=14103.1) n	%	Rate/ 100 PY
Parotid swelling	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Parotitis	3	(0.21%)	0.06	3	(0.21%)	0.07	2	(0.14%)	0.04	8	(0.18%)	0.06
Salivary gland enlargement	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Salivary gland swelling	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Peripheral Vascular Disease	36	(2.47%)	0.73	31	(2.15%)	0.73	27	(1.86%)	0.55	94	(2.16%)	0.67
Abdominal aortic bruit	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Abdominal bruit	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Aortic sclerosis	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Aortic stenosis	6	(0.41%)	0.12	2	(0.14%)	0.05	3	(0.21%)	0.06	11	(0.25%)	0.08
Arterial insufficiency peripheral	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Arterial murmur	2	(0.14%)	0.04	0			0			2	(0.05%)	0.01
Arterial occlusion	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Arterial occlusive disease	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Arterial stenosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Arterial thrombosis	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Arteriosclerosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Atherosclerosis	1	(0.07%)	0.02	1	(0.07%)	0.02	1	(0.07%)	0.02	3	(0.07%)	0.02
Carotid artery atheroma	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Carotid artery disease	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Carotid artery stenosis	3	(0.21%)	0.06	7	(0.49%)	0.16	6	(0.41%)	0.12	16	(0.37%)	0.11
Carotid bruit	4	(0.28%)	0.08	3	(0.21%)	0.07	4	(0.28%)	0.08	11	(0.25%)	0.08
Carotid murmur	1	(0.07%)	0.02	0			2	(0.14%)	0.04	3	(0.07%)	0.02
Claudication	2	(0.14%)	0.04	4	(0.28%)	0.09	3	(0.21%)	0.06	9	(0.21%)	0.06
Femoral artery stenosis	2	(0.14%)	0.04	1	(0.07%)	0.02	0			3	(0.07%)	0.02
Femoral bruit	0			2	(0.14%)	0.05	0			2	(0.05%)	0.01
Iliac artery stenosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Intermittent claudication	4	(0.28%)	0.08	2	(0.14%)	0.05	0			6	(0.14%)	0.04
Ischemic limb pain	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Peripheral arterial occlusive disease	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Peripheral artery occlusion	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Peripheral ischemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Peripheral vascular disease	2	(0.14%)	0.04	5	(0.35%)	0.12	3	(0.21%)	0.06	10	(0.23%)	0.07
Poor peripheral circulation	2	(0.14%)	0.04	1	(0.07%)	0.02	1	(0.07%)	0.02	4	(0.09%)	0.03
Poor peripheral perfusion	1	(0.07%)	0.02	1	(0.07%)	0.02	0			2	(0.05%)	0.01
Popliteal arterial obstruction	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Vascular atheroma	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Vascular calcification	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Vascular stenosis	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Visceral arterial ischaemia	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Renal	37	(2.54%)	0.75	32	(2.22%)	0.75	47	(3.23%)	0.96	116	(2.67%)	0.82
Acute renal failure	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Albuminuria	4	(0.28%)	0.08	1	(0.07%)	0.02	3	(0.21%)	0.06	8	(0.18%)	0.06

Note: PY = Patient Years

Data Source Table 8.2.4.3
Summary of On-Therapy Adverse Experiences of Special Interest
All Randomized Patients

AE Special Interest Group MedDRA Lower Level Term	ROSIGLITAZONE (N=1456, PY=4953.8)			GLY/GLIB (N=1441, PY=4243.6)			METFORMIN (N=1454, PY=4905.6)			TOTAL (N=4351, PY=14103.1)		
	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY	n	%	Rate/ 100 PY
Azotemia prerenal	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Blood creatinine increased	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Chronic kidney disease	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Chronic renal insufficiency	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Creatine increased	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Creatinine decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Creatinine high	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Creatinine increased	5	(0.34%)	0.10	6	(0.42%)	0.14	12	(0.83%)	0.24	23	(0.53%)	0.16
Diabetic nephropathy	2	(0.14%)	0.04	0			1	(0.07%)	0.02	3	(0.07%)	0.02
Function kidney decreased	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Impaired renal function	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Kidney atrophy	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Microalbuminuria	8	(0.55%)	0.16	9	(0.63%)	0.21	18	(1.24%)	0.37	35	(0.80%)	0.25
Nephropathy	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Oliguria	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Proteinuria	9	(0.62%)	0.18	7	(0.49%)	0.16	3	(0.21%)	0.06	19	(0.44%)	0.13
Renal failure	3	(0.21%)	0.06	0			0			3	(0.07%)	0.02
Renal insufficiency	4	(0.28%)	0.08	2	(0.14%)	0.05	5	(0.34%)	0.10	11	(0.25%)	0.08
Serum creatinine increased	2	(0.14%)	0.04	4	(0.28%)	0.09	2	(0.14%)	0.04	8	(0.18%)	0.06
Toxicity renal	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Urea nitrogen increased	0			1	(0.07%)	0.02	2	(0.14%)	0.04	3	(0.07%)	0.02
Uremia	0			0			1	(0.07%)	0.02	1	(0.02%)	0.01
Urine albumin/creatinine ratio increased	1	(0.07%)	0.02	0			1	(0.07%)	0.02	2	(0.05%)	0.01
Urine microalbumin present	0			1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.05%)	0.01
Urine production scanty	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Weight Gain	100	(6.87%)	2.02	47	(3.26%)	1.11	18	(1.24%)	0.37	165	(3.79%)	1.17
Adipositas	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Adipositas per magna	0			1	(0.07%)	0.02	0			1	(0.02%)	0.01
Morbid obesity	1	(0.07%)	0.02	0			0			1	(0.02%)	0.01
Obesity	15	(1.03%)	0.30	10	(0.69%)	0.24	1	(0.07%)	0.02	26	(0.60%)	0.18
Overweight	1	(0.07%)	0.02	1	(0.07%)	0.02	2	(0.14%)	0.04	4	(0.09%)	0.03
Weight gain	68	(4.67%)	1.37	27	(1.87%)	0.64	15	(1.03%)	0.31	110	(2.53%)	0.78
Weight increased	17	(1.17%)	0.34	8	(0.56%)	0.19	0			25	(0.58%)	0.18

Note: PY = Patient Years

AV:LFS-023

PRESCRIBING INFORMATION

AVANDIA®

(rosiglitazone maleate)

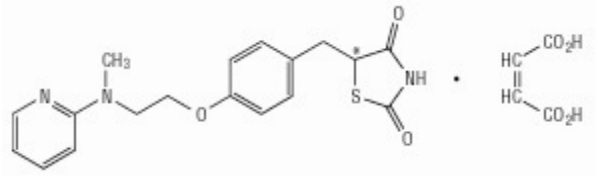
Tablets

DESCRIPTION

AVANDIA (rosiglitazone maleate) is an oral antidiabetic agent which acts primarily by increasing insulin sensitivity. AVANDIA is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). AVANDIA improves glycemic control while reducing circulating insulin levels.

Pharmacological studies in animal models indicate that rosiglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Rosiglitazone maleate is not chemically or functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecule has a single chiral center and is present as a racemate. Due to rapid interconversion, the enantiomers are functionally indistinguishable. The structural formula of rosiglitazone maleate is:



The molecular formula is $C_{18}H_{19}N_3O_3S \cdot C_4H_4O_4$. Rosiglitazone maleate is a white to off-white solid with a melting point range of 122° to 123°C. The pKa values of rosiglitazone maleate are 6.8 and 6.1. It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Each pentagonal film-coated TILTAB® tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are: Hypromellose 2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and 1 or more of the following: Synthetic red and yellow iron oxides and talc.

CLINICAL PHARMACOLOGY

Mechanism of Action: Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the

transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive genes also participate in the regulation of fatty acid metabolism.

Insulin resistance is a common feature characterizing the pathogenesis of type 2 diabetes. The antidiabetic activity of rosiglitazone has been demonstrated in animal models of type 2 diabetes in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues. Rosiglitazone reduces blood glucose concentrations and reduces hyperinsulinemia in the ob/ob obese mouse, db/db diabetic mouse, and fa/fa fatty Zucker rat.

In animal models, rosiglitazone's antidiabetic activity was shown to be mediated by increased sensitivity to insulin's action in the liver, muscle, and adipose tissues. The expression of the insulin-regulated glucose transporter GLUT-4 was increased in adipose tissue. Rosiglitazone did not induce hypoglycemia in animal models of type 2 diabetes and/or impaired glucose tolerance.

Pharmacokinetics and Drug Metabolism: Maximum plasma concentration (C_{max}) and the area under the curve (AUC) of rosiglitazone increase in a dose-proportional manner over the therapeutic dose range (see Table 1). The elimination half-life is 3 to 4 hours and is independent of dose.

Table 1. Mean (SD) Pharmacokinetic Parameters for Rosiglitazone Following Single Oral Doses (N = 32)

Parameter	1 mg Fasting	2 mg Fasting	8 mg Fasting	8 mg Fed
$AUC_{0\text{-}inf}$ [ng•hr/mL]	358 (112)	733 (184)	2,971 (730)	2,890 (795)
C_{max} [ng/mL]	76 (13)	156 (42)	598 (117)	432 (92)
Half-life [hr]	3.16 (0.72)	3.15 (0.39)	3.37 (0.63)	3.59 (0.70)
CL/F* [L/hr]	3.03 (0.87)	2.89 (0.71)	2.85 (0.69)	2.97 (0.81)

* CL/F = Oral clearance.

Absorption: The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in C_{max} and a delay in T_{max} (1.75 hours). These changes are not likely to be clinically significant; therefore, AVANDIA may be administered with or without food.

Distribution: The mean (CV%) oral volume of distribution (Vss/F) of rosiglitazone is approximately 17.6 (30%) liters, based on a population pharmacokinetic analysis. Rosiglitazone is approximately 99.8% bound to plasma proteins, primarily albumin.

Metabolism: Rosiglitazone is extensively metabolized with no unchanged drug excreted in the urine. The major routes of metabolism were N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. All the circulating metabolites are considerably less potent than parent and, therefore, are not expected to contribute to the insulin-sensitizing activity of rosiglitazone.

In vitro data demonstrate that rosiglitazone is predominantly metabolized by Cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 contributing as a minor pathway.

Excretion: Following oral or intravenous administration of [^{14}C]rosiglitazone maleate, approximately 64% and 23% of the dose was eliminated in the urine and in the feces, respectively. The plasma half-life of [^{14}C]related material ranged from 103 to 158 hours.

Population Pharmacokinetics in Patients with Type 2 Diabetes: Population pharmacokinetic analyses from 3 large clinical trials including 642 men and 405 women with type 2 diabetes (aged 35 to 80 years) showed that the pharmacokinetics of rosiglitazone are not influenced by age, race, smoking, or alcohol consumption. Both oral clearance (CL/F) and oral steady-state volume of distribution (Vss/F) were shown to increase with increases in body weight. Over the weight range observed in these analyses (50 to 150 kg), the range of predicted CL/F and Vss/F values varied by <1.7-fold and <2.3-fold, respectively. Additionally, rosiglitazone CL/F was shown to be influenced by both weight and gender, being lower (about 15%) in female patients.

Special Populations: ***Geriatric:*** Results of the population pharmacokinetic analysis (n = 716 <65 years; n = 331 ≥65 years) showed that age does not significantly affect the pharmacokinetics of rosiglitazone.

Gender: Results of the population pharmacokinetics analysis showed that the mean oral clearance of rosiglitazone in female patients (n = 405) was approximately 6% lower compared to male patients of the same body weight (n = 642).

As monotherapy and in combination with metformin, AVANDIA improved glycemic control in both males and females. In metformin combination studies, efficacy was demonstrated with no gender differences in glycemic response.

In monotherapy studies, a greater therapeutic response was observed in females; however, in more obese patients, gender differences were less evident. For a given body mass index (BMI), females tend to have a greater fat mass than males. Since the molecular target PPARγ is expressed in adipose tissues, this differentiating characteristic may account, at least in part, for the greater response to AVANDIA in females. Since therapy should be individualized, no dose adjustments are necessary based on gender alone.

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound C_{max} and $AUC_{0\text{-}inf}$ were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline (see PRECAUTIONS, General, *Hepatic Effects*).

Pediatric: Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Renal Impairment: There are no clinically relevant differences in the pharmacokinetics of rosiglitazone in patients with mild to severe renal impairment or in hemodialysis-dependent patients compared to subjects with normal renal function. No dosage adjustment is therefore required in such patients receiving AVANDIA. Since metformin is contraindicated in patients with renal impairment, coadministration of metformin with AVANDIA is contraindicated in these patients.

Race: Results of a population pharmacokinetic analysis including subjects of Caucasian, black, and other ethnic origins indicate that race has no influence on the pharmacokinetics of rosiglitazone.

Drug Interactions:

Drugs that Inhibit, Induce, or are Metabolized by Cytochrome P450: In vitro drug metabolism studies suggest that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. In vitro data demonstrate that rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, 2C9.

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily), an inhibitor of CYP2C8, and rosiglitazone (4 mg once daily) for 7 days increased rosiglitazone AUC by 127%, compared to the administration of rosiglitazone (4 mg once daily) alone. Given the potential for dose-related adverse events with rosiglitazone, a decrease in the dose of rosiglitazone may be needed when gemfibrozil is introduced (see PRECAUTIONS).

Rifampin: Rifampin administration (600 mg once a day), an inducer of CYP2C8, for 6 days is reported to decrease rosiglitazone AUC by 66%, compared to the administration of rosiglitazone (8 mg) alone (see PRECAUTIONS).[1]

AVANDIA (4 mg twice daily) was shown to have no clinically relevant effect on the pharmacokinetics of nifedipine and oral contraceptives (ethinyl estradiol and norethindrone), which are predominantly metabolized by CYP3A4.

Glyburide: AVANDIA (2 mg twice daily) taken concomitantly with glyburide (3.75 to 10 mg/day) for 7 days did not alter the mean steady-state 24-hour plasma glucose concentrations in diabetic patients stabilized on glyburide therapy. Repeat doses of AVANDIA (8 mg once daily) for 8 days in healthy adult Caucasian subjects caused a decrease in glyburide AUC and C_{max} of approximately 30%. In Japanese subjects, glyburide AUC and C_{max} slightly increased following coadministration of AVANDIA.

Glimepiride: Single oral doses of glimepiride in 14 healthy adult subjects had no clinically significant effect on the steady-state pharmacokinetics of AVANDIA. No clinically significant reductions in glimepiride AUC and C_{max} were observed after repeat doses of AVANDIA (8 mg once daily) for 8 days in healthy adult subjects.

Metformin: Concurrent administration of AVANDIA (2 mg twice daily) and metformin (500 mg twice daily) in healthy volunteers for 4 days had no effect on the steady-state pharmacokinetics of either metformin or rosiglitazone.

Acarbose: Coadministration of acarbose (100 mg three times daily) for 7 days in healthy volunteers had no clinically relevant effect on the pharmacokinetics of a single oral dose of AVANDIA.

Digoxin: Repeat oral dosing of AVANDIA (8 mg once daily) for 14 days did not alter the steady-state pharmacokinetics of digoxin (0.375 mg once daily) in healthy volunteers.

Warfarin: Repeat dosing with AVANDIA had no clinically relevant effect on the steady-state pharmacokinetics of warfarin enantiomers.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in type 2 diabetes mellitus patients treated with AVANDIA.

Ranitidine: Pretreatment with ranitidine (150 mg twice daily for 4 days) did not alter the pharmacokinetics of either single oral or intravenous doses of rosiglitazone in healthy volunteers. These results suggest that the absorption of oral rosiglitazone is not altered in conditions accompanied by increases in gastrointestinal pH.

CLINICAL STUDIES

In clinical studies, treatment with AVANDIA resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), with a concurrent reduction in insulin and C-peptide. Postprandial glucose and insulin were also reduced. This is consistent with the mechanism of action of AVANDIA as an insulin sensitizer. The improvement in glycemic control was durable, with maintenance of effect for 52 weeks. The maximum recommended daily dose is 8 mg. Dose-ranging studies suggested that no additional benefit was obtained with a total daily dose of 12 mg.

The addition of AVANDIA to either metformin, a sulfonylurea, or insulin resulted in significant reductions in hyperglycemia compared to any of these agents alone. These results are consistent with an additive effect on glycemic control when AVANDIA is used as combination therapy.

Patients with lipid abnormalities were not excluded from clinical trials of AVANDIA. In all 26-week controlled trials, across the recommended dose range, AVANDIA as monotherapy was associated with increases in total cholesterol, LDL, and HDL and decreases in free fatty acids. These changes were statistically significantly different from placebo or glyburide controls (see Table 2).

Increases in LDL occurred primarily during the first 1 to 2 months of therapy with AVANDIA and LDL levels remained elevated above baseline throughout the trials. In contrast, HDL

continued to rise over time. As a result, the LDL/HDL ratio peaked after 2 months of therapy and then appeared to decrease over time. Because of the temporal nature of lipid changes, the 52-week glyburide-controlled study is most pertinent to assess long-term effects on lipids. At baseline, week 26, and week 52, mean LDL/HDL ratios were 3.1, 3.2, and 3.0, respectively, for AVANDIA 4 mg twice daily. The corresponding values for glyburide were 3.2, 3.1, and 2.9. The differences in change from baseline between AVANDIA and glyburide at week 52 were statistically significant.

The pattern of LDL and HDL changes following therapy with AVANDIA in combination with other hypoglycemic agents were generally similar to those seen with AVANDIA in monotherapy.

The changes in triglycerides during therapy with AVANDIA were variable and were generally not statistically different from placebo or glyburide controls.

Table 2. Summary of Mean Lipid Changes in 26-Week Placebo-Controlled and 52-Week Glyburide-Controlled Monotherapy Studies

	Placebo-Controlled Studies Week 26			Glyburide-Controlled Study Week 26 and Week 52			
	Placebo	AVANDIA		Glyburide Titration		AVANDIA 8 mg	
		4 mg daily*	8 mg daily*	Wk 26	Wk 52	Wk 26	Wk 52
Free Fatty Acids							
N	207	428	436	181	168	166	145
Baseline (mean)	18.1	17.5	17.9	26.4	26.4	26.9	26.6
% Change from baseline (mean)	+0.2%	-7.8%	-14.7%	-2.4%	-4.7%	-20.8%	-21.5%
LDL							
N	190	400	374	175	160	161	133
Baseline (mean)	123.7	126.8	125.3	142.7	141.9	142.1	142.1
% Change from baseline (mean)	+4.8%	+14.1%	+18.6%	-0.9%	-0.5%	+11.9%	+12.1%
HDL							
N	208	429	436	184	170	170	145
Baseline (mean)	44.1	44.4	43.0	47.2	47.7	48.4	48.3
% Change from baseline (mean)	+8.0%	+11.4%	+14.2%	+4.3%	+8.7%	+14.0%	+18.5%

* Once daily and twice daily dosing groups were combined.

Monotherapy: A total of 2,315 patients with type 2 diabetes, previously treated with diet alone or antidiabetic medication(s), were treated with AVANDIA as monotherapy in 6 double-blind studies, which included two 26-week placebo-controlled studies, one 52-week

glyburide-controlled study, and 3 placebo-controlled dose-ranging studies of 8 to 12 weeks duration. Previous antidiabetic medication(s) were withdrawn and patients entered a 2 to 4 week placebo run-in period prior to randomization.

Two 26-week, double-blind, placebo-controlled trials, in patients with type 2 diabetes (n = 1,401) with inadequate glycemic control (mean baseline FPG approximately 228 mg/dL [101 to 425 mg/dL] and mean baseline HbA1c 8.9% [5.2% to 16.2%]), were conducted. Treatment with AVANDIA produced statistically significant improvements in FPG and HbA1c compared to baseline and relative to placebo. Data from one of these studies are summarized in Table 3.

Table 3. Glycemic Parameters in a 26-Week Placebo-Controlled Trial

		AVANDIA		AVANDIA	
	Placebo	4 mg once daily	2 mg twice daily	8 mg once daily	4 mg twice daily
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31*	-43*	-49*	-62*
% of patients with ≥30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8*	-0.9*	-1.1*	-1.5*
% of patients with ≥0.7% decrease from baseline	9%	28%	29%	39%	54%

* $p<0.0001$ compared to placebo.

When administered at the same total daily dose, AVANDIA was generally more effective in reducing FPG and HbA1c when administered in divided doses twice daily compared to once daily doses. However, for HbA1c, the difference between the 4 mg once daily and 2 mg twice daily doses was not statistically significant.

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glyburide-controlled trial in patients with type 2 diabetes. Patients were randomized to treatment with AVANDIA 2 mg twice daily (N = 195) or AVANDIA 4 mg twice daily (N = 189) or glyburide (N = 202) for 52 weeks. Patients receiving glyburide were given an initial dosage of either 2.5 mg/day or 5.0 mg/day. The dosage was then titrated in 2.5 mg/day increments over the next 12 weeks, to a maximum dosage of 15.0 mg/day in order to optimize glycemic control. Thereafter the glyburide dose was kept constant.

The median titrated dose of glyburide was 7.5 mg. All treatments resulted in a statistically significant improvement in glycemic control from baseline (see Figure 1 and Figure 2). At the end of week 52, the reduction from baseline in FPG and HbA1c was -40.8 mg/dL and -0.53% with AVANDIA 4 mg twice daily; -25.4 mg/dL and -0.27% with AVANDIA 2 mg twice daily; and -30.0 mg/dL and -0.72% with glyburide. For HbA1c, the difference between AVANDIA 4 mg twice daily and glyburide was not statistically significant at week 52. The initial fall in FPG with glyburide was greater than with AVANDIA; however, this effect was less durable over time. The improvement in glycemic control seen with AVANDIA 4 mg twice daily at week 26 was maintained through week 52 of the study.

Figure 1. Mean FPG Over Time in a 52-Week Glyburide-Controlled Study

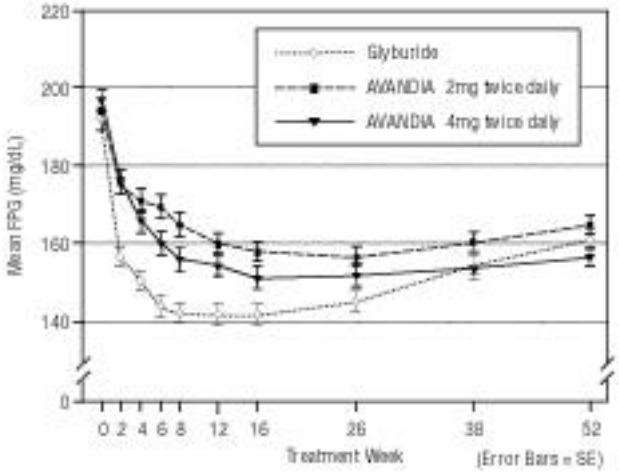
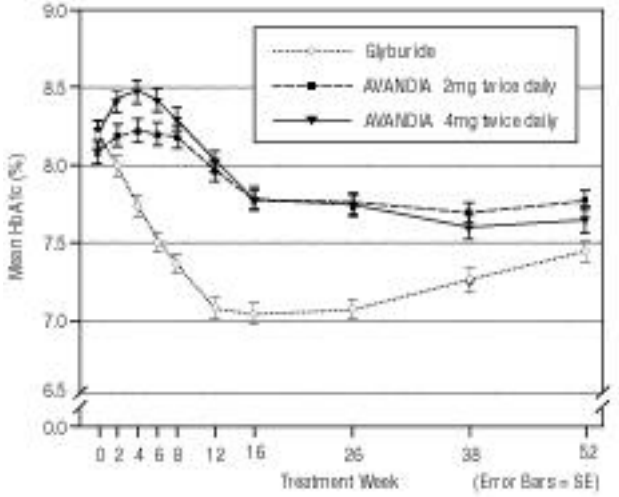


Figure 2. Mean HbA1c Over Time in a 52-Week Glyburide-Controlled Study



Hypoglycemia was reported in 12.1% of glyburide-treated patients versus 0.5% (2 mg twice daily) and 1.6% (4 mg twice daily) of patients treated with AVANDIA. The improvements in

glycemic control were associated with a mean weight gain of 1.75 kg and 2.95 kg for patients treated with 2 mg and 4 mg twice daily of AVANDIA, respectively, versus 1.9 kg in glyburide-treated patients. In patients treated with AVANDIA, C-peptide, insulin, pro-insulin, and pro-insulin split products were significantly reduced in a dose-ordered fashion, compared to an increase in the glyburide-treated patients.

Combination With Metformin: A total of 670 patients with type 2 diabetes participated in two 26-week, randomized, double-blind, placebo/active-controlled studies designed to assess the efficacy of AVANDIA in combination with metformin. AVANDIA, administered in either once daily or twice daily dosing regimens, was added to the therapy of patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin.

In one study, patients inadequately controlled on 2.5 grams/day of metformin (mean baseline FPG 216 mg/dL and mean baseline HbA1c 8.8%) were randomized to receive 4 mg of AVANDIA once daily, 8 mg of AVANDIA once daily, or placebo in addition to metformin. A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of metformin and 4 mg of AVANDIA once daily and 8 mg of AVANDIA once daily, versus patients continued on metformin alone (see Table 4).

Table 4. Glycemic Parameters in a 26-Week Combination Study of AVANDIA Plus Metformin

	Metformin	AVANDIA 4 mg once daily + metformin	AVANDIA 8 mg once daily + metformin
N	113	116	110
FPG (mg/dL)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
Difference from metformin alone (adjusted mean)	–	-40*	-53*
% of patients with ≥30 mg/dL decrease from baseline	20%	45%	61%
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-0.6	-0.8
Difference from metformin alone (adjusted mean)	–	-1.0*	-1.2*
% of patients with ≥0.7% decrease from baseline	11%	45%	52%

* $p<0.0001$ compared to metformin.

In a second 26-week study, patients with type 2 diabetes inadequately controlled on 2.5 grams/day of metformin who were randomized to receive the combination of AVANDIA 4 mg twice daily and metformin (N = 105) showed a statistically significant improvement in glycemic control with a mean treatment effect for FPG of -56 mg/dL and a mean treatment effect for HbA1c of -0.8% over metformin alone. The combination of metformin and AVANDIA resulted in lower levels of FPG and HbA1c than either agent alone.

Patients who were inadequately controlled on a maximum dose (2.5 grams/day) of metformin and who were switched to monotherapy with AVANDIA demonstrated loss of glycemic control, as evidenced by increases in FPG and HbA1c. In this group, increases in LDL and VLDL were also seen.

Combination With a Sulfonylurea: A total of 3,457 patients with type 2 diabetes participated in ten 24- to 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study in elderly patients designed to assess the efficacy and safety of AVANDIA in combination with a sulfonylurea. AVANDIA 2 mg, 4 mg, or 8 mg daily, was administered either once daily (3 studies) or in divided doses twice daily (7 studies), to patients inadequately controlled on a submaximal or maximal dose of sulfonylurea.

In these studies, the combination of AVANDIA 4 mg or 8 mg daily (administered as single or twice daily divided doses) and a sulfonylurea significantly reduced FPG and HbA1c compared to placebo plus sulfonylurea or further up-titration of the sulfonylurea. Table 5 shows pooled data for 8 studies in which AVANDIA added to sulfonylurea was compared to placebo plus sulfonylurea.

Table 5. Glycemic Parameters in 24- to 26-Week Combination Studies of AVANDIA Plus Sulfonylurea

Twice Daily Divided Dosing (5 Studies)	Sulfonylurea	AVANDIA 2 mg twice daily + sulfonylurea	Sulfonylurea	AVANDIA 4 mg twice daily + sulfonylurea
N	397	497	248	346
FPG (mg/dL)				
Baseline (mean)	204	198	188	187
Change from baseline (mean)	11	-29	8	-43
Difference from sulfonylurea alone (adjusted mean)	-	-42*	-	-53*
% of patients with ≥30 mg/dL decrease from baseline	17%	49%	15%	61%
HbA1c (%)				
Baseline (mean)	9.4	9.5	9.3	9.6
Change from baseline (mean)	0.2	-1.0	0.0	-1.6
Difference from sulfonylurea alone (adjusted mean)	-	-1.1*	-	-1.4*
% of patients with ≥0.7% decrease from baseline	21%	60%	23%	75%
Once Daily Dosing (3 Studies)	Sulfonylurea	AVANDIA 4 mg once daily + sulfonylurea	Sulfonylurea	AVANDIA 8 mg once daily + sulfonylurea
N	172	172	173	176
FPG (mg/dL)				
Baseline (mean)	198	206	188	192
Change from baseline (mean)	17	-25	17	-43
Difference from sulfonylurea alone (adjusted mean)	-	-47*	-	-66*
% of patients with ≥30 mg/dL decrease from baseline	17%	48%	19%	55%
HbA1c (%)				
Baseline (mean)	8.6	8.8	8.9	8.9
Change from baseline (mean)	0.4	-0.5	0.1	-1.2
Difference from sulfonylurea alone (adjusted mean)	-	-0.9*	-	-1.4*
% of patients with ≥0.7% decrease from baseline	11%	36%	20%	68%

* $p<0.0001$ compared to sulfonylurea alone.

One of the 24- to 26-week studies included patients who were inadequately controlled on maximal doses of glyburide and switched to 4 mg of AVANDIA daily as monotherapy; in this group, loss of glycemic control was demonstrated, as evidenced by increases in FPG and HbA1c.

In a 2-year double-blind study, elderly patients (aged 59 to 89 years) on half-maximal sulfonylurea (glipizide 10 mg twice daily) were randomized to the addition of AVANDIA (n = 115, 4 mg once daily to 8 mg as needed) or to continued up-titration of glipizide (n = 110), to a maximum of 20 mg twice daily. Mean baseline FPG and HbA1c were 157 mg/dL and 7.72%, respectively, for the AVANDIA plus glipizide arm and 159 mg/dL and 7.65%, respectively, for the glipizide up-titration arm. Loss of glycemic control (FPG ≥180 mg/dL) occurred in a significantly lower proportion of patients (2%) on AVANDIA plus glipizide compared to patients in the glipizide up-titration arm (28.7%). About 78% of the patients on combination therapy completed the 2 years of therapy while only 51% completed on glipizide monotherapy. The effect of combination therapy on FPG and HbA1c was durable over the 2-year study period, with patients achieving a mean of 132 mg/dL for FPG and a mean of 6.98% for HbA1c compared to no change on the glipizide arm.

Combination With Insulin: In two 26-week randomized, double-blind, fixed-dose studies designed to assess the efficacy and safety of AVANDIA in combination with insulin, patients inadequately controlled on insulin (65 to 76 units/day, mean range at baseline) were randomized to receive AVANDIA 4 mg plus insulin (n = 206) or placebo plus insulin (n = 203). The mean duration of disease in these patients was 12 to 13 years.

Compared to insulin plus placebo, single or divided doses of AVANDIA 4 mg daily plus insulin significantly reduced FPG (mean reduction of 32 to 40 mg/dL) and HbA1c (mean reduction of 0.6% to 0.7%). Approximately 40% of all patients treated with AVANDIA reduced their insulin dose.

Combination With Sulfonylurea and Metformin: In two 24- to 26-week, double-blind, placebo-controlled, studies designed to assess the efficacy and safety of AVANDIA in combination with sulfonylurea plus metformin, AVANDIA 4 mg or 8 mg daily, was administered in divided doses twice daily, to patients inadequately controlled on submaximal (10 mg) and maximal (20 mg) doses of glyburide and maximal dose of metformin (2 g/day). A statistically significant improvement in FPG and HbA1c was observed in patients treated with the combinations of sulfonylurea plus metformin and 4 mg of AVANDIA and 8 mg of AVANDIA versus patients continued on sulfonylurea plus metformin, as shown in Table 6.

Table 6. Glycemic Parameters in a 26-Week Combination Study of AVANDIA Plus Sulfonylurea and Metformin

	Sulfonylurea + metformin	AVANDIA 2 mg twice daily + sulfonylurea + metformin	AVANDIA 4 mg twice daily + sulfonylurea + metformin
N	273	276	277
FPG (mg/dL)			
Baseline (mean)	189	190	192
Change from baseline (mean)	14	-19	-40
Difference from sulfonylurea plus metformin (adjusted mean)	-	-30*	-52*
% of patients with ≥30 mg/dL decrease from baseline	16%	46%	62%
HbA1c (%)			
Baseline (mean)	8.7	8.6	8.7
Change from baseline (mean)	0.2	-0.4	-0.9
Difference from sulfonylurea plus metformin (adjusted mean)	-	-0.6*	-1.1*
% of patients with ≥0.7% decrease from baseline	16%	39%	63%

* $p<0.0001$ compared to placebo.

INDICATIONS AND USAGE

AVANDIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

- AVANDIA is indicated as monotherapy.
- AVANDIA is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, AVANDIA should be added to, rather than substituted for, a sulfonylurea or metformin.
- AVANDIA is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycemic control.

Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2

diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation of therapy with AVANDIA, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated.

CONTRAINDICATIONS

AVANDIA is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects: AVANDIA, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. In combination with insulin, thiazolidinediones may also increase the risk of other cardiovascular adverse events. AVANDIA should be discontinued if any deterioration in cardiac status occurs.

Patients with congestive heart failure (CHF) New York Heart Association (NYHA) Class 1 and 2 treated with AVANDIA have an increased risk of cardiovascular events. A 52-week, double-blind, placebo-controlled echocardiographic study was conducted in 224 patients with type 2 diabetes mellitus and NYHA Class 1 or 2 CHF (ejection fraction ≤45%) on background antidiabetic and CHF therapy. An independent committee conducted a blinded evaluation of fluid-related events (including congestive heart failure) and cardiovascular hospitalizations according to predefined criteria (adjudication). Separate from the adjudication, other cardiovascular adverse events were reported by investigators. Although no treatment difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with AVANDIA treatment compared to placebo during the 52-week study. (See Table 7.)

Table 7. Emergent Cardiovascular Adverse Events in Patients with Congestive Heart Failure (NYHA Class 1 and 2) treated with AVANDIA or Placebo (in Addition to Background Antidiabetic and CHF Therapy)

	Placebo	**AVANDIA**
Events	N = 114 n (%)	N = 110 n (%)
Adjudicated		
Cardiovascular Deaths	4 (4)	5 (5)
CHF Worsening	4 (4)	7 (6)
• with overnight hospitalization	4 (4)	5 (5)
• without overnight hospitalization	0 (0)	2 (2)
New or Worsening Edema	10 (9)	28 (25)
New or Worsening Dyspnea	19 (17)	29 (26)
Increases in CHF Medication	20 (18)	36 (33)
Cardiovascular Hospitalization*	15 (13)	21 (19)
Investigator-reported, Non-adjudicated		
Ischemic Adverse Events	5 (4)	10 (9)
• Myocardial Infarction	2 (2)	5 (5)
• Angina	3 (3)	6 (5)

* Includes hospitalization for any cardiovascular reason

Patients with NYHA Class 3 and 4 cardiac status were not studied during the clinical trials. AVANDIA is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In three 26-week trials in patients with type 2 diabetes, 216 received 4 mg of AVANDIA plus insulin, 322 received 8 mg of AVANDIA plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy, retinopathy, ischemic heart disease, vascular disease, and congestive heart failure. In these clinical studies an increased incidence of edema, cardiac failure, and other cardiovascular adverse events was seen in patients on AVANDIA and insulin combination therapy compared to insulin and placebo. Patients who experienced cardiovascular events were on average older and had a longer duration of diabetes. These cardiovascular events were noted at both the 4 mg and 8 mg daily doses of AVANDIA. In this population, however, it was not possible to determine specific risk factors that could be used to identify all patients at risk of heart failure and other cardiovascular events on combination therapy. Three of 10 patients who developed cardiac failure on combination therapy during the double-blind part of the fixed-dose studies had no known prior evidence of congestive heart failure, or pre-existing cardiac condition.

In a double-blind study in type 2 diabetes patients with chronic renal failure (112 received 4 mg or 8 mg of AVANDIA plus insulin and 108 received insulin control), there was no

difference in cardiovascular adverse events with AVANDIA in combination with insulin compared to insulin control.

Patients treated with combination AVANDIA and insulin should be monitored for cardiovascular adverse events. This combination therapy should be discontinued in patients who do not respond as manifested by a reduction in HbA1c or insulin dose after 4 to 5 months of therapy or who develop any significant adverse events. (See ADVERSE REACTIONS.)

PRECAUTIONS

General: Due to its mechanism of action, AVANDIA is active only in the presence of endogenous insulin. Therefore, AVANDIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving AVANDIA in combination with other hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Edema: AVANDIA should be used with caution in patients with edema. In a clinical study in healthy volunteers who received 8 mg of AVANDIA once daily for 8 weeks, there was a statistically significant increase in median plasma volume compared to placebo.

Since thiazolidinediones, including rosiglitazone, can cause fluid retention, which can exacerbate or lead to congestive heart failure, AVANDIA should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see WARNINGS, Cardiac Failure and Other Cardiac Effects and PRECAUTIONS, Information for Patients).

In controlled clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with AVANDIA, and may be dose related. Patients with ongoing edema are more likely to have adverse events associated with edema if started on combination therapy with insulin and AVANDIA (see ADVERSE REACTIONS).

Macular Edema: Macular edema has been reported in postmarketing experience in some diabetic patients who were taking AVANDIA or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Most patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings. (See ADVERSE REACTIONS, Adult.)

Weight Gain: Dose-related weight gain was seen with AVANDIA alone and in combination with other hypoglycemic agents (see Table 8). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

In postmarketing experience, there have been reports of unusually rapid increases in weight and increases in excess of that generally observed in clinical trials. Patients who experience such increases should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

Table 8. Weight Changes (kg) From Baseline During Clinical Trials With AVANDIA

		Control Group		AVANDIA 4 mg	AVANDIA 8 mg
Monotherapy	Duration		Median (25^{th}, 75^{th} percentile)	Median (25^{th}, 75^{th} percentile)	Median (25^{th}, 75^{th} percentile)
	26 weeks	placebo	-0.9 (-2.8, 0.9) n = 210	1.0 (-0.9, 3.6) n = 436	3.1 (1.1, 5.8) n = 439
	52 weeks	sulfonylurea	2.0 (0, 4.0) n = 173	2.0 (-0.6, 4.0) n = 150	2.6 (0, 5.3) n = 157
Combination therapy					
sulfonylurea	24-26 weeks	sulfonylurea	0 (-1.0, 1.3) n = 1,155	2.2 (0.5, 4.0) n = 613	3.5 (1.4, 5.9) n = 841
metformin	26 weeks	metformin	-1.4 (-3.2, 0.2) n = 175	0.8 (-1.0, 2.6) n = 100	2.1 (0, 4.3) n = 184
insulin	26 weeks	insulin	0.9 (-0.5, 2.7) n = 162	4.1 (1.4, 6.3) n = 164	5.4 (3.4, 7.3) n = 150
sulfonylurea + metformin	26 weeks	sulfonylurea + metformin	0.2 (-1.2, 1.6) n = 272	2.5 (0.8, 4.6) n = 275	4.5 (2.4, 7.3) n = 276

In a 24-week study in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to 8 mg daily, a median weight gain of 2.8 kg (25^{th}, 75^{th} percentiles: 0.0, 5.8) was reported.

Hematologic: Across all controlled clinical studies in adults, decreases in hemoglobin and hematocrit (mean decreases in individual studies ≤1.0 gram/dL and ≤3.3%, respectively) were observed for AVANDIA alone and in combination with other hypoglycemic agents. The changes occurred primarily during the first 3 months following initiation of therapy with AVANDIA or following a dose increase in AVANDIA. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with AVANDIA. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities, *Hematologic*).

Ovulation: Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA (see PRECAUTIONS, Pregnancy, *Pregnancy*

Category C). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Although hormonal imbalance has been seen in preclinical studies (see PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility), the clinical significance of this finding is not known. If unexpected menstrual dysfunction occurs, the benefits of continued therapy with AVANDIA should be reviewed.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, was associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death were reported during clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations in liver enzymes (ALT >3X upper limit of normal) compared to placebo. Very rare cases of reversible jaundice were also reported.

In pre-approval clinical studies in 4,598 patients treated with AVANDIA, encompassing approximately 3,600 patient years of exposure, there was no signal of drug-induced hepatotoxicity or elevation of ALT levels. In the pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible and were not clearly causally related to therapy with AVANDIA.

In postmarketing experience with AVANDIA, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established. Rosiglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death during clinical use. Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with AVANDIA undergo periodic monitoring of liver enzymes.

Liver enzymes should be checked prior to the initiation of therapy with AVANDIA in all patients and periodically thereafter per the clinical judgement of the healthcare professional. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels ≤2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with AVANDIA in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDIA should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDIA should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

There are no data available from clinical trials to evaluate the safety of AVANDIA in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. AVANDIA should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests: Periodic fasting blood glucose and HbA1c measurements should be performed to monitor therapeutic response.

Liver enzyme monitoring is recommended prior to initiation of therapy with AVANDIA in all patients and periodically thereafter (see PRECAUTIONS, General, *Hepatic Effects* and ADVERSE REACTIONS, Laboratory Abnormalities, *Serum Transaminase Levels*).

Information for Patients: Patients should be informed of the following: Management of type 2 diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but in maintaining the efficacy of drug therapy.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. Patients should be advised that it can take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see full effect. Patients should be informed that blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgement of the healthcare professional. Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician. Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on AVANDIA should immediately report these symptoms to their physician.

AVANDIA can be taken with or without meals.

When using AVANDIA in combination with other hypoglycemic agents, the risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with AVANDIA, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking AVANDIA (see PRECAUTIONS, Pregnancy, *Pregnancy Category C*). Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been specifically investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions: An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during

treatment with rosiglitazone, changes in diabetes treatment may be needed based upon clinical response. (See CLINICAL PHARMACOLOGY, Drug Interactions.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** A 2-year carcinogenicity study was conducted in Charles River CD-1 mice at doses of 0.4, 1.5, and 6 mg/kg/day in the diet (highest dose equivalent to approximately 12 times human AUC at the maximum recommended human daily dose). Sprague-Dawley rats were dosed for 2 years by oral gavage at doses of 0.05, 0.3, and 2 mg/kg/day (highest dose equivalent to approximately 10 and 20 times human AUC at the maximum recommended human daily dose for male and female rats, respectively).

Rosiglitazone was not carcinogenic in the mouse. There was an increase in incidence of adipose hyperplasia in the mouse at doses ≥1.5 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). In rats, there was a significant increase in the incidence of benign adipose tissue tumors (lipomas) at doses ≥0.3 mg/kg/day (approximately 2 times human AUC at the maximum recommended human daily dose). These proliferative changes in both species are considered due to the persistent pharmacological overstimulation of adipose tissue.

Mutagenesis: Rosiglitazone was not mutagenic or clastogenic in the in vitro bacterial assays for gene mutation, the in vitro chromosome aberration test in human lymphocytes, the in vivo mouse micronucleus test, and the in vivo/in vitro rat UDS assay. There was a small (about 2-fold) increase in mutation in the in vitro mouse lymphoma assay in the presence of metabolic activation.

Impairment of Fertility: Rosiglitazone had no effects on mating or fertility of male rats given up to 40 mg/kg/day (approximately 116 times human AUC at the maximum recommended human daily dose). Rosiglitazone altered estrous cyclicity (2 mg/kg/day) and reduced fertility (40 mg/kg/day) of female rats in association with lower plasma levels of progesterone and estradiol (approximately 20 and 200 times human AUC at the maximum recommended human daily dose, respectively). No such effects were noted at 0.2 mg/kg/day (approximately 3 times human AUC at the maximum recommended human daily dose). In juvenile rats dosed from 27 days of age through to sexual maturity (at up to 40 mg/kg/day), there was no effect on male reproductive performance, or on estrous cyclicity, mating performance or pregnancy incidence in females (approximately 68 times human AUC at the maximum recommended daily dose). In monkeys, rosiglitazone (0.6 and 4.6 mg/kg/day; approximately 3 and 15 times human AUC at the maximum recommended human daily dose, respectively) diminished the follicular phase rise in serum estradiol with consequential reduction in the luteinizing hormone surge, lower luteal phase progesterone levels, and amenorrhea. The mechanism for these effects appears to be direct inhibition of ovarian steroidogenesis.

Animal Toxicology: Heart weights were increased in mice (3 mg/kg/day), rats (5 mg/kg/day), and dogs (2 mg/kg/day) with rosiglitazone treatments (approximately 5, 22, and 2 times human AUC at the maximum recommended human daily dose, respectively). Effects in juvenile rats were consistent with those seen in adults. Morphometric measurement indicated that there was

hypertrophy in cardiac ventricular tissues, which may be due to increased heart work as a result of plasma volume expansion.

Pregnancy: Pregnancy Category C. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Careful monitoring of glucose control is essential in such patients. Most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Human Data: Rosiglitazone has been reported to cross the human placenta and be detectable in fetal tissue. The clinical significance of these findings is unknown. There are no adequate and well-controlled studies in pregnant women. AVANDIA should not be used during pregnancy.

Animal Studies: There was no effect on implantation or the embryo with rosiglitazone treatment during early pregnancy in rats, but treatment during mid-late gestation was associated with fetal death and growth retardation in both rats and rabbits. Teratogenicity was not observed at doses up to 3 mg/kg in rats and 100 mg/kg in rabbits (approximately 20 and 75 times human AUC at the maximum recommended human daily dose, respectively). Rosiglitazone caused placental pathology in rats (3 mg/kg/day). Treatment of rats during gestation through lactation reduced litter size, neonatal viability, and postnatal growth, with growth retardation reversible after puberty. For effects on the placenta, embryo/fetus, and offspring, the no-effect dose was 0.2 mg/kg/day in rats and 15 mg/kg/day in rabbits. These no-effect levels are approximately 4 times human AUC at the maximum recommended human daily dose. Rosiglitazone reduced the number of uterine implantations and live offspring when juvenile female rats were treated at 40 mg/kg/day from 27 days of age through to sexual maturity (approximately 68 times human AUC at the maximum recommended daily dose). The no-effect level was 2 mg/kg/day (approximately 4 times human AUC at the maximum recommended daily dose). There was no effect on pre- or post-natal survival or growth.

Labor and Delivery: The effect of rosiglitazone on labor and delivery in humans is not known.

Nursing Mothers: Drug-related material was detected in milk from lactating rats. It is not known whether AVANDIA is excreted in human milk. Because many drugs are excreted in human milk, AVANDIA should not be administered to a nursing woman.

Pediatric Use: After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m^2, were randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, fasting plasma glucose (FPG) decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of AVANDIA-treated patients and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with

AVANDIA and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table 9).

Table 9. Week 24 FPG and HbA1c Change from Baseline Last-Observation-Carried Forward in Children with Baseline HbA1c >6.5%

	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
N	40	45	43	32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted Treatment Difference* (rosiglitazone–metformin)†		8		21
(95% CI)		(-15, 30)		(-9, 51)
% of patients with ≥30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted Treatment Difference* (rosiglitazone – metformin)†		0.2		0.5
(95% CI)		(-0.6, 0.9)		(-0.2, 1.3)
% of patients with ≥0.7% decrease from baseline	63%	52%	54%	31%

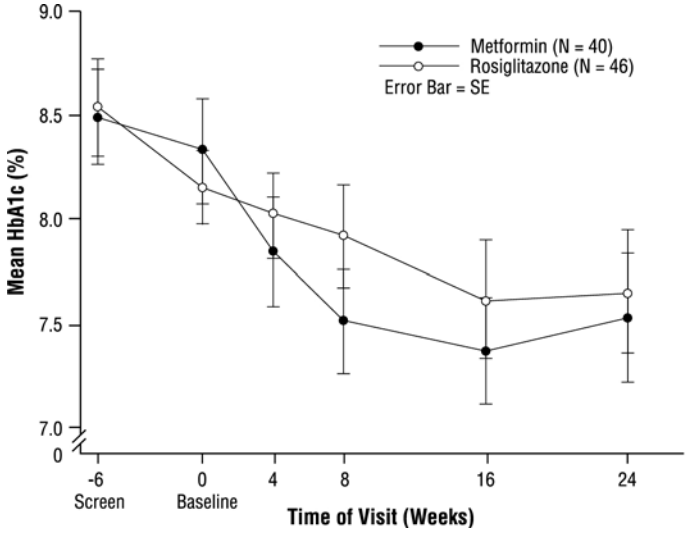
* Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.

† Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of AVANDIA and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin (see PRECAUTIONS, General, *Weight Gain*). Fifty four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on study.

Adverse events observed in this study are described in ADVERSE REACTIONS.

Figure 3. Mean HbA1c Over Time in a 24-Week Study of AVANDIA and Metformin in Pediatric Patients — Drug-Naïve Subgroup



Geriatric Use: Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of rosiglitazone (see CLINICAL PHARMACOLOGY, Special Populations). Therefore, no dosage adjustments are required for the elderly. In controlled clinical trials, no overall differences in safety and effectiveness between older (≥65 years) and younger (<65 years) patients were observed.

ADVERSE REACTIONS

Adult: In clinical trials, approximately 8,400 patients with type 2 diabetes have been treated with AVANDIA; 6,000 patients were treated for 6 months or longer and 3,000 patients were treated for 12 months or longer.

Trials of AVANDIA as Monotherapy and in Combination With Other Hypoglycemic Agents:

The incidence and types of adverse events reported in clinical trials of AVANDIA as monotherapy are shown in Table 10.

Table 10. Adverse Events (≥5% in Any Treatment Group) Reported by Patients in Double-Blind Clinical Trials With AVANDIA as Monotherapy

Preferred Term	AVANDIA Monotherapy N = 2,526	Placebo N = 601	Metformin N = 225	Sulfonylureas* N = 626
	%	%	%	%
Upper respiratory tract infection	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
Fatigue	3.6	5.0	4.0	1.9
Sinusitis	3.2	4.5	5.3	3.0
Diarrhea	2.3	3.3	15.6	3.0
Hypoglycemia	0.6	0.2	1.3	5.9

* Includes patients receiving glyburide (N = 514), gliclazide (N = 91) or glipizide (N = 21).

Overall, the types of adverse experiences reported when AVANDIA was used in combination with a sulfonylurea or metformin were similar to those during monotherapy with AVANDIA. Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with AVANDIA.

In double-blind studies, anemia was reported in 1.9% of patients receiving AVANDIA as monotherapy compared to 0.7% on placebo, 0.6% on sulfonylureas, and 2.2% on metformin. Reports of anemia were greater in patients treated with a combination of AVANDIA and metformin (7.1%) and with a combination of AVANDIA and a sulfonylurea plus metformin (6.7%) compared to monotherapy with AVANDIA or in combination with a sulfonylurea (2.3%). Lower pre-treatment hemoglobin/hematocrit levels in patients enrolled in the metformin combination clinical trials may have contributed to the higher reporting rate of anemia in these studies (see ADVERSE REACTIONS, Laboratory Abnormalities, *Hematologic*).

In clinical trials, edema was reported in 4.8% of patients receiving AVANDIA as monotherapy compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin. The reporting rate of edema was higher for AVANDIA 8 mg in sulfonylurea combinations (12.4%) compared to other combinations, with the exception of insulin. Edema was reported in 14.7% of patients receiving AVANDIA in the insulin combination trials compared to 5.4% on insulin alone. Reports of new onset or exacerbation of congestive heart failure occurred at rates of 1% for insulin alone, and 2% (4 mg) and 3% (8 mg) for insulin in combination with AVANDIA.

In controlled combination therapy studies with sulfonylureas, mild to moderate hypoglycemic symptoms, which appear to be dose related, were reported. Few patients were withdrawn for

hypoglycemia (<1%) and few episodes of hypoglycemia were considered to be severe (<1%). Hypoglycemia was the most frequently reported adverse event in the fixed-dose insulin combination trials, although few patients withdrew for hypoglycemia (4 of 408 for AVANDIA plus insulin and 1 of 203 for insulin alone). Rates of hypoglycemia, confirmed by capillary blood glucose concentration ≤50 mg/dL, were 6% for insulin alone and 12% (4 mg) and 14% (8 mg) for insulin in combination with AVANDIA. (See PRECAUTIONS, General, *Hypoglycemia* and DOSAGE AND ADMINISTRATION, Combination Therapy.)

Postmarketing Experience: In addition to adverse reactions reported from clinical trials, the events described below have been identified during post-approval use of AVANDIA. Because these events are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or to always establish a causal relationship to drug exposure.

In postmarketing experience in patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema, and pleural effusions) have been reported. (See WARNINGS, Cardiac Failure and Other Cardiac Effects.)

Rash, pruritus, urticaria, angioedema, anaphylactic reaction, and Stevens-Johnson syndrome have been reported rarely.

Reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see PRECAUTIONS, Macular Edema).

Pediatric: AVANDIA has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were treated with metformin. In this study, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of ~300 mg/dL, 2+ ketonuria, and an elevated anion gap. The incidence and type of adverse events reported in ≥5% of patients for each treatment group are shown in Table 11.

Table 11. Adverse Events Reported by ≥5% of Patients in a Double-Blind, Active-Controlled, Clinical Trial With AVANDIA or Metformin as Monotherapy in Pediatric Patients

Preferred Term	AVANDIA N = 99	Metformin N = 101
	%	%
Headache	17.2	13.9
Influenza	7.1	5.9
Upper Respiratory Tract Infection	6.1	5.9
Cough	6.1	5.0
Hyperglycemia	8.1	6.9
Dizziness	5.1	2.0
Back Pain	5.1	1.0
Nausea	4.0	10.9
Hypoglycemia	4.0	5.0
Nasopharyngitis	3.0	11.9
Vomiting	3.0	8.9
Abdominal Pain	3.0	6.9
Pharyngolaryngeal pain	2.0	5.0
Diarrhea	1.0	12.9
Sinusitis	1.0	5.0
Dysmenorrhea	0	6.9

Laboratory Abnormalities: ***Hematologic:*** Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patients treated with AVANDIA (mean decreases in individual studies up to 1.0 gram/dL hemoglobin and up to 3.3% hematocrit). The time course and magnitude of decreases were similar in patients treated with a combination of AVANDIA and other hypoglycemic agents or AVANDIA monotherapy. Pre-treatment levels of hemoglobin and hematocrit were lower in patients in metformin combination studies and may have contributed to the higher reporting rate of anemia. In a single study in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported. White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA.

Lipids: Changes in serum lipids have been observed following treatment with AVANDIA in adults (see CLINICAL STUDIES). Small changes in serum lipid parameters were reported in children treated with AVANDIA for 24 weeks.

Serum Transaminase Levels: In clinical studies in 4,598 patients treated with AVANDIA encompassing approximately 3,600 patient years of exposure, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels.

In controlled trials, 0.2% of patients treated with AVANDIA had reversible elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators.

In the clinical program including long-term, open-label experience, the rate per 100 patient years exposure of ALT increase to >3X the upper limit of normal was 0.35 for patients treated with AVANDIA, 0.59 for placebo-treated patients, and 0.78 for patients treated with active comparator agents.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. In postmarketing experience with AVANDIA, reports of hepatic enzyme elevations 3 or more times the upper limit of normal and hepatitis have been received (see PRECAUTIONS, General, *Hepatic Effects*).

OVERDOSAGE

Limited data are available with regard to overdosage in humans. In clinical studies in volunteers, AVANDIA has been administered at single oral doses of up to 20 mg and was well-tolerated. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status.

DOSAGE AND ADMINISTRATION

The management of antidiabetic therapy should be individualized. All patients should start AVANDIA at the lowest recommended dose. Further increases in the dose of AVANDIA should be accompanied by careful monitoring for adverse events related to fluid retention. (See WARNINGS, Cardiac Failure and Other Cardiac Events.)

AVANDIA may be administered either at a starting dose of 4 mg as a single daily dose or divided and administered in the morning and evening. For patients who respond inadequately following 8 to 12 weeks of treatment, as determined by reduction in FPG, the dose may be increased to 8 mg daily as monotherapy or in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Reductions in glycemic parameters by dose and regimen are described under CLINICAL STUDIES. AVANDIA may be taken with or without food.

Monotherapy: The usual starting dose of AVANDIA is 4 mg administered either as a single dose once daily or in divided doses twice daily. In clinical trials, the 4 mg twice daily regimen resulted in the greatest reduction in FPG and HbA1c.

Combination Therapy: When AVANDIA is added to existing therapy, the current dose(s) of the agent(s) can be continued upon initiation of AVANDIA therapy.

Sulfonylurea: When used in combination with sulfonylurea, the usual starting dose of AVANDIA is 4 mg administered as either a single dose once daily or in divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: The usual starting dose of AVANDIA in combination with metformin is 4 mg administered as either a single dose once daily or in divided doses twice daily. It is unlikely that

the dose of metformin will require adjustment due to hypoglycemia during combination therapy with AVANDIA.

Insulin: For patients stabilized on insulin, the insulin dose should be continued upon initiation of therapy with AVANDIA. AVANDIA should be dosed at 4 mg daily. Doses of AVANDIA greater than 4 mg daily in combination with insulin are not currently indicated. It is recommended that the insulin dose be decreased by 10% to 25% if the patient reports hypoglycemia or if FPG concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Sulfonylurea Plus Metformin: The usual starting dose of AVANDIA in combination with a sulfonylurea plus metformin is 4 mg administered as either a single dose once daily or divided doses twice daily. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Maximum Recommended Dose: The dose of AVANDIA should not exceed 8 mg daily, as a single dose or divided twice daily. The 8 mg daily dose has been shown to be safe and effective in clinical studies as monotherapy and in combination with metformin, sulfonylurea, or sulfonylurea plus metformin. Doses of AVANDIA greater than 4 mg daily in combination with insulin are not currently indicated.

AVANDIA may be taken with or without food.

Special Populations: ***Geriatric:*** No dosage adjustments are required for the elderly.

Renal Impairment: No dosage adjustment is necessary when AVANDIA is used as monotherapy in patients with renal impairment. Since metformin is contraindicated in such patients, concomitant administration of metformin and AVANDIA is also contraindicated in patients with renal impairment.

Hepatic Impairment: Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, General, *Hepatic Effects* and CLINICAL PHARMACOLOGY, Special Populations, *Hepatic Impairment*). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDIA and periodically thereafter (see PRECAUTIONS, General, *Hepatic Effects*).

Pediatric: Data are insufficient to recommend pediatric use of AVANDIA.

HOW SUPPLIED

Tablets: Each pentagonal film-coated TILTAB tablet contains rosiglitazone as the maleate as follows: 2 mg–pink, debossed with SB on one side and 2 on the other; 4 mg–orange, debossed with SB on one side and 4 on the other; 8 mg–red-brown, debossed with SB on one side and 8 on the other.

2 mg bottles of 60: NDC 0029-3158-18
4 mg bottles of 30: NDC 0029-3159-13
4 mg bottles of 90: NDC 0029-3159-00
4 mg bottles of 100: NDC 0029-3159-20

8 mg bottles of 30: NDC 0029-3160-13
8 mg bottles of 90: NDC 0029-3160-59
8 mg bottles of 100: NDC 0029-3160-20

STORAGE

Store at 25°C (77°F); excursions 15°–30°C (59°–86°F). Dispense in a tight, light-resistant container.

REFERENCE

1. Park JY, Kim KA, Kang MH, et al. Effect of rifampin on the pharmacokinetics of rosiglitazone in healthy subjects. *Clin Pharmacol Ther* 2004;75:157-162.

GlaxoSmithKline
Research Triangle Park, NC 27709

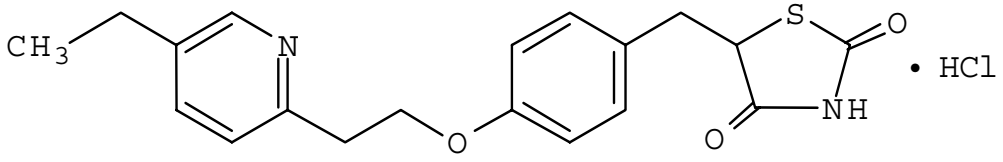
April 2007 AV:LFS-023

ACTOS®
(pioglitazone hydrochloride) Tablets

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the □-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert *in vivo*. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90 daltons. It is soluble in *N,N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. *In vivo* studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see **Drug Interactions**). Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with ACTOS showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see **PRECAUTIONS**, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Oral Contraceptives: Co-administration of ACTOS (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 - 0.95) for C_{max} and 0.88 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ACTOS for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for C_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

Atorvastatin Calcium: Co-administration of ACTOS for 7 days with atorvastatin calcium (LIPITOR®) 80 mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57 - 0.85) for C_{max}, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See **PRECAUTIONS**

Gemfibrozil: Concomitant administration of gemfibrozil (oral 600 mg twice daily), an inhibitor of CYP2C8, with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 2 days prior with gemfibrozil (oral 600 mg twice daily) resulted in pioglitazone exposure (AUC_{0-24}) being 226% of the pioglitazone exposure in the absence of gemfibrozil (see **PRECAUTIONS**).[1]

Rifampin: Concomitant administration of rifampin (oral 600 mg once daily), an inducer of CYP2C8 with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 5 days prior with rifampin (oral 600 mg once daily) resulted in a decrease in the AUC of pioglitazone by 54% (see **PRECAUTIONS**).[2]

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (**Table 1**).

Table 1 Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

	Placebo	**ACTOS 15 mg Once Daily**	**ACTOS 30 mg Once Daily**	**ACTOS 45 mg Once Daily**
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL in patients treated with ACTOS. A similar pattern of results was seen in 24-week combination therapy studies of ACTOS with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with ACTOS with insulin.

Clinical Studies

Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week, dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) at endpoint compared to placebo (**Figure 1, Table 2**).

Figure 1 shows the time course for changes in FPG and HbA_{1c} for the entire study population in this 26-week study.

FIGURE 1 MEAN CHANGE FROM BASELINE FOR FPG AND HbA_{1C} IN A 26-WEEK PLACEBO-CONTROLLED DOSE-RANGING STUDY

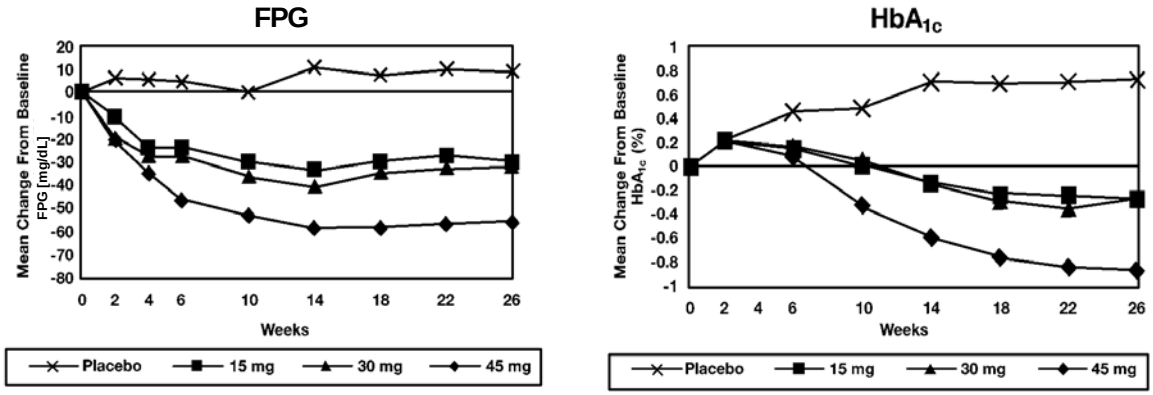


Table 2 shows HbA_{1c} and FPG values for the entire study population.

Table 2 **Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study**

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
	Total Population			
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean[+])	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean[+])		-1.0*	-1.0*	-1.6*
FPG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean[+])	9	-30	-32	-56
Difference from placebo (adjusted mean[+])		-39*	-41*	-65*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously-treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FPG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FPG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FPG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

Table 3 **Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study**

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FPG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FPG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week, placebo-controlled study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (**Table 4**).

Table 4 **Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study**

	Placebo	ACTOS 30 mg[+] Once Daily	ACTOS 45 mg[+] Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean[++])	0.9	-0.6	-0.6
Difference from placebo (adjusted mean[++])		-1.5*	-1.5*
FPG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean[++])	18	-44	-50
Difference from placebo (adjusted mean[++])		-62*	-68*

[+] Final dose in forced titration

[++] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.2% and mean FPG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FPG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.7% and mean FPG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FPG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (**Table 5**).

Table 5 **Glycemic Parameters in a 16-Week Placebo-Controlled Study**

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean[+])	0.8	-0.6
Difference from placebo (adjusted mean[+])		-1.4*
FPG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean[+])	8	-50
Difference from placebo (adjusted mean[+])		-58*

[+] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.4% and

mean FPG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FPG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.6% and mean FPG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FPG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

Combination Therapy

Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week, randomized, double-blind, dose-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

ACTOS Plus Sulfonylurea Studies

Two clinical studies were conducted with ACTOS in combination with a sulfonylurea. Both studies included patients with type 2 diabetes on a sulfonylurea, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 560 patients were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current sulfonylurea regimen. When compared to placebo at Week 16, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% and mean FPG by 39 mg/dL and 58 mg/dL for the 15 mg and 30 mg doses, respectively.

In the second study, 702 patients were randomized to receive 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current sulfonylurea regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea.

ACTOS Plus Metformin Studies

Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 328 patients were randomized to receive either 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current metformin regimen. When compared to placebo at Week 16, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FPG by 38 mg/dL.

In the second study, 827 patients were randomized to receive either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current metformin regimen.

The mean reductions from baseline at Week 24 in HbA_{1c} were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin.

ACTOS Plus Insulin Studies

Two clinical studies were conducted with ACTOS in combination with insulin. Both studies included patients with type 2 diabetes on insulin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 566 patients receiving a median of 60.5 units per day of insulin were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their insulin regimen. When compared to placebo at Week 16, the addition of ACTOS to insulin significantly reduced both HbA_{1c} by 0.7% and 1.0% and FPG by 35 mg/dL and 49 mg/dL for the 15 mg and 30 mg dose, respectively.

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin.

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM).

ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see **Information for Patients**). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see **PRECAUTIONS**, Cardiovascular).

In one 16-week, U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study, two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week, dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

Analysis of data from these studies did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

In type 2 diabetes and congestive heart failure (systolic dysfunction)

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1c} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

ACTOS should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation.

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg once daily, or placebo (n=2633) (see **ADVERSE REACTIONS**). The percentage of patients who had an event of serious heart failure was higher for patients treated with ACTOS (5.7%, n=149) than for patients treated with placebo (4.1%, n=108). The incidence of death subsequent to a report of serious heart failure was 1.5% (n=40) in patients treated with ACTOS and 1.4% (n=37) in placebo-treated patients.

PRECAUTIONS

General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events

related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see **WARNINGS**). Patients with NYHA Class III and IV cardiac status were not studied in these ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related (see **ADVERSE REACTIONS**). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (**Table 6**). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 **Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS**

		Control Group (Placebo)	**ACTOS 15 mg**	**ACTOS 30 mg**	**ACTOS 45 mg**
		Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9(-0.5/3.4) n = 79	1.0(-0.9/3.4) n=188	2.6 (0.2/5.4) n = 79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	3.1 (1.1/5.4) n=528	4.1 (1.8/7.3) n=333
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	0.9(-0.3/3.2) n=567	1.8(-0.9/5.0) n=407
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.3 (0.9/6.3) n=522	4.1 (1.4/6.8) n=338

Note: Trial durations of 16 to 26 weeks

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see **ADVERSE REACTIONS**, **Laboratory Abnormalities**).

Hepatic Effects: In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

Macular Edema: Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Some patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings (see **ADVERSE REACTIONS**).

Laboratory Tests

FPG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional (see **PRECAUTIONS**, **General**, Hepatic Effects and **ADVERSE REACTIONS**, **Serum Transaminase Levels**).

Information for Patients

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate (see **CLINICAL PHARMACOLOGY**, **Metabolism** and **Drug-Drug Interactions**).

An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response (see **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**).

Carcinogenesis, **Mutagenesis**, **Impairment of Fertility**

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in*

vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers
Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use
Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use
Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS
Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials. This includes 2605 high-risk patients with type 2 diabetes treated with ACTOS from the PROactive clinical trial. Over 6000 patients have been treated for 6 months or longer, and over 4500 patients for one year or longer. Over 3000 patients have received ACTOS for at least 2 years.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7

Placebo-Controlled Clinical Studies of ACTOS Monotherapy:
Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see **PRECAUTIONS**, **General**, Hypoglycemia and **DOSAGE and ADMINISTRATION, Combination Therapy**).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see **PRECAUTIONS**, **General**, Hematologic).

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS**, **General**, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see **WARNINGS**, **Cardiac Failure and Other Cardiac Effects**).

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily, or placebo (n=2633), in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA1c 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see table 8 below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 8

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint				
	Placebo N=2633		**ACTOS N=2605**	
Cardiovascular Events	First Events (N)	Total events	First Events	Total events
Any event	572	900	514	803
All-cause mortality	122	186	110	177
Non-fatal MI	118	157	105	131
Stroke	96	119	76	92
ACS	63	78	42	65
Cardiac intervention	101	240	101	195
Major leg amputation	15	28	9	28
Leg revascularization	57	92	71	115

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General,** Macular Edema).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS**, **General**, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates.

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics and Drug Metabolism**).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see **PRECAUTIONS**, **General**, Hepatic Effects and **CLINICAL PHARMACOLOGY**, **Special Populations**, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see **PRECAUTIONS**, **General**, Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:
NDC 64764-151-04 Bottles of 30
NDC 64764-151-05 Bottles of 90
NDC 64764-151-06 Bottles of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:
NDC 64764-301-14 Bottles of 30
NDC 64764-301-15 Bottles of 90
NDC 64764-301-16 Bottles of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:
NDC 64764-451-24 Bottles of 30
NDC 64764-451-25 Bottles of 90
NDC 64764-451-26 Bottles of 500

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

REFERENCES

1. Deng, LJ, et al. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol* 2005; 61: 831-836, Table 1.
2. Jaakkola, T, et al. Effect of rifampicin on the pharmacokinetics of pioglitazone. *Clin Pharmacol Brit Jour* 2006; 61:1 70-78.

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Takeda Pharmaceutical Company Limited
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Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Janet Norden at 301-796-2270, or (CBER) Toni Stifano at 301-827-6190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2006
Labeling

Guidance for Industry

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2006
Labeling

TABLE OF CONTENTS

Guidance for Industry[1]

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format[2]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants and reviewers in drafting the WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING sections of labeling, as described in the final rule amending the requirements for the content and format of labeling for human prescription drug and biological products (21 CFR 201.56 and 201.57).[3] The recommendations in this guidance are intended to help ensure that the labeling is clear, useful, informative, and to the extent possible, consistent in content and format.

This guidance provides recommendations on the following:

- How to decide which adverse reactions are significant enough to warrant inclusion in the WARNINGS AND PRECAUTIONS section; what information to include when describing those adverse reactions; and how to organize the section

[1] This guidance has been prepared by the Medical Policy Coordinating Committees in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs.

[3] See the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in the *Federal Register* in January 2006.

- What situations warrant a contraindication; what information to provide in those situations when the use of the product is contraindicated; and how to organize the CONTRAINDICATIONS section
- When to include a boxed warning; and what information to include in the BOXED WARNING section

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. WARNINGS AND PRECAUTIONS SECTION (§ 201.57(c)(6))

A. Adverse Reactions and Information to Include

1. Observed Adverse Reactions

This section includes clinically significant adverse reactions observed in association with the use of a drug for which there is reasonable evidence of a causal association between the drug and the adverse reaction (a causal relationship need not have been established):

IF

- The adverse reaction is serious (see glossary for definition of serious adverse reaction).

OR

- The adverse reaction does not meet the definition of a serious adverse reaction, but is still considered clinically significant (*otherwise clinically significant*). Adverse reactions that are considered *otherwise clinically significant* could include:

  — Adverse reactions that require discontinuation, dosage or regimen adjustment, or addition of another drug

  — Adverse reactions that could be prevented or managed with appropriate patient selection or avoidance of concomitant therapy

  — Adverse reactions that significantly affect patient compliance

OR

- The product interferes with a laboratory test.

2. Expected Adverse Reactions

There are circumstances in which an adverse reaction can be expected to occur with a drug, despite its not having been observed with that drug, based on observations from

other members of the drug class or animal studies. An expected adverse reaction may not be observed, for example, in clinical trials for newer drugs in a class where the trials are designed to exclude populations that were determined to be vulnerable to the adverse reaction with earlier members of the drug class.

The WARNINGS AND PRECAUTIONS section includes adverse reactions that are expected to occur with a drug, but have yet to be observed if:

- The reaction is *serious* or *otherwise clinically significant* as discussed above

AND EITHER

- Based on what is known about the pharmacology, chemistry, or class of the drug, it appears likely that the adverse reaction will occur with the drug.

OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects).

In these cases, the labeling should acknowledge that the adverse reaction has not been observed, but may be expected to occur.

3. Additional Considerations

The following factors should also be considered in determining whether to include an adverse reaction in the WARNINGS AND PRECAUTIONS section of labeling:

- Indication

The relative seriousness of the disease or condition for which a drug is indicated will influence whether an adverse reaction would be considered clinically significant and thus appropriate for inclusion in the WARNINGS AND PRECAUTIONS section. For example, for a drug intended to treat a minor, self-limiting condition (e.g., allergic rhinitis, cosmetic conditions, transient insomnia), a nonserious adverse reaction (e.g., nausea, pruritis, alopecia) may be considered clinically significant and, therefore, appropriate for inclusion in the section. For a drug intended to treat a serious or life-threatening condition (e.g., cancer), the same adverse reaction may be considered much less clinically significant and not appropriate for inclusion in the section.

- Incidence

Typically, the nature of an adverse reaction and a drug's indication are the most influential factors in determining whether an adverse reaction should be included in the WARNINGS AND PRECAUTIONS section. In some cases, however, the absolute risk or rate of an adverse reaction can be an important factor when deciding whether to include the reaction in this section (e.g., when the risk or rate is high).

- Ability to Manage or Prevent an Adverse Reaction

The ability to manage or prevent an adverse reaction through patient monitoring, proper dose selection or titration, or avoidance of concomitant therapy can also be an important factor in deciding whether to discuss an adverse reaction in the WARNINGS AND PRECAUTIONS section.

4. Adverse Reactions Associated with Unapproved Uses

FDA may require a specific warning relating to an unapproved use if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard (§ 201.57(c)(6)(i)). Clinically significant adverse reactions that appear to be linked primarily to an unapproved use of a drug (e.g., use for a disease, condition, or population not included in the INDICATIONS AND USE section, use of an unapproved dose or regimen) should be identified and discussed in the WARNINGS AND PRECAUTIONS section. The discussion should include a statement indicating that safety and effectiveness have not been established in that setting and that the use is not approved by FDA.

5. Drug Interactions

The WARNINGS AND PRECAUTIONS section should include a discussion of any known or predicted drug interactions with serious or otherwise clinically significant outcomes, with a cross-reference to any additional information in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections.

6. Monitoring

The WARNINGS AND PRECAUTIONS section must identify any laboratory tests helpful in following the patient's response or in identifying possible adverse reactions (§ 201.57(c)(6)(iii)), and, if appropriate, information about the frequency of testing and expected ranges of normal and abnormal values.

B. Information to Provide

The WARNINGS AND PRECAUTIONS section should contain the following information for each adverse reaction, if such information is known:

- A description of the adverse reaction and outcome (e.g., time to resolution, significant sequelae)
- An estimate of risk or adverse reaction rate[4]
- A discussion of known risk factors for the adverse reaction (e.g., age, gender, race, comorbid conditions, dose, duration of use, coadministered drugs)
- A discussion of steps to take to reduce the risk of, decrease the likelihood of, shorten the duration of, or minimize the severity of an adverse reaction. These steps could include, for example, necessary evaluation prior to use, titration and other kinds of dose adjustment, monitoring during dose adjustment or prolonged use, avoidance of other drugs or substances, or special care during comorbid events (e.g., dehydration, infection)
- A discussion of how to treat, or otherwise manage, an adverse reaction that has occurred

Although the following issues would typically be discussed elsewhere in labeling, they can also be mentioned in the WARNINGS AND PRECAUTIONS section when such information would help prescribers understand the clinical significance of an adverse reaction:

- A discussion of the mechanism of the adverse reaction
- The source of information about the adverse reaction (e.g., it may be informative to know whether the information is from clinical trials or postmarketing reports, or whether an adverse reaction was seen only in foreign experience with the drug)

The information and advice provided in this section should be reasonably qualified, where appropriate, to convey whatever uncertainties may exist about judgments and conclusions made (e.g., concerning causality assessments, estimated adverse reaction rates, and value of proposed monitoring).

C. Format

1. Subheadings

FDA recommends that each adverse reaction, syndrome, or constellation of reactions (e.g., thrombotic events, hemorrhagic events) included in the WARNINGS AND PRECAUTIONS section have its own subheading. There would ordinarily be no reason

[4] When the risk for an adverse reaction is highest during early exposure, crude risk (# of adverse reactions/# patients exposed) may be the best estimate. For adverse reactions that occur after prolonged exposure, there should be an adjustment for duration of exposure by use of either overall exposed person time if the risk is constant over time, or by calculation of cumulative incidence for a specified exposure time in a survival analysis.

to further subcategorize adverse reactions (e.g., separating observed and expected adverse reactions by placing them under different subheadings).

2. Order of Adverse Reactions

The order in which adverse reactions are presented should reflect the relative public health significance of the adverse reactions. Factors to consider include the relative seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction, the likelihood of occurrence, and the size of the population that is potentially affected. In general, the relative seriousness of the adverse reaction and the ability to prevent or mitigate it weigh more heavily than the likelihood of occurrence or the size of the affected population.

3. Emphasis in Text

Bolded text, or other emphasis, can be used to highlight particular adverse reactions or parts of the discussion of particular adverse reactions (e.g., steps to be taken to avoid a problem, subpopulations at particular risk). Emphasis should be used sparingly so that its impact is not diminished. When information is to be emphasized, also consider whether that information should be in a boxed warning (see section IV on BOXED WARNING section).

4. Cross-Referencing

Information discussed in the WARNINGS AND PRECAUTIONS section often is discussed or mentioned in other sections of the labeling (e.g., ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS). Information appearing in other locations should be appropriately cross-referenced.

III. CONTRAINDICATIONS SECTION (§ 201.57(c)(5))

A. When to Contraindicate

A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, must be listed. If there are no known contraindications for a drug, this section must state "None."

1. Observed Adverse Reactions

For observed adverse reactions, the following would ordinarily be reason to contraindicate a drug:

- The risk of the adverse reaction in the clinical situation to which the contraindication will apply, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to the patient.

AND

- The causal relationship between exposure to the drug and the adverse reaction is well established.

2. Expected Adverse Reactions

Adverse reactions that are expected to occur when a drug is used in a specific clinical situation can be the basis for a contraindication.[5] The following would ordinarily be reason to contraindicate a drug on the basis of an expected adverse reaction.

The risk of the adverse reaction in the clinical situation to which the contraindication will apply, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to the patient

AND EITHER

- Based on what is known about the pharmacology, chemistry, or class of the drug, it appears highly likely that the adverse reaction will occur with the drug.

OR

- Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrating that a drug has teratogenic effects).

The labeling should acknowledge that the adverse reaction has not yet been observed, but is expected to occur.

3. Likely Clinical Situations

A contraindication usually involves one or more of the following clinical situations:

- Comorbid condition or coexistent physiological state (e.g., existing hepatic disease, renal disease, congenital long QT syndrome, hypokalemia, pregnancy or childbearing potential, CYP 2D6 poor metabolizer[6])

- Demographic risk factor (e.g., age, sex, race, genetic vulnerability)

[5] Expected adverse reactions are distinguishable from "theoretical possibilities" because there are data (e.g., from class, chemistry, animal studies) to support the expected adverse reaction.

[6] Use of a particular drug in a patient with a slow metabolizer status would be contraindicated only if there were no way to lower the dose to adjust for the compromised metabolic state.

- The risks of the drug are such that the drug should never be used in a selected subset of the larger population with a disease[7]

- Coadministered drug where the combination is dangerous (e.g., MAO inhibitor and sympathomimetic drug, a drug known to prolong the QT interval and a drug known to interfere with the metabolism of that drug)[8]

Contraindications based on drug interactions with serious outcomes should be described in the CONTRAINDICATIONS section and cross-referenced to more detailed information in the DRUG INTERACTIONS or CLINICAL PHARMACOLOGY sections.

B. Information to Provide

For each listed contraindication, provide the following information:

- Brief description of the contraindicated situation or scenario, including any pertinent demographic or identifiable predisposing characteristics

- Description of anticipated consequences of the contraindicated use

C. Format

1. Subheadings

FDA recommends that each contraindication be identified by its own subheading.

2. Order of Contraindications

The order in which contraindications are presented should reflect the relative public health significance of the listed contraindications. Factors to consider include the likelihood of occurrence and the size of the population that is potentially affected.

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[7] The INDICATIONS AND USAGE section must contain information about use of the drug when safety considerations are such that the drug should be reserved for certain patients (e.g., patients with severe disease) or situations (e.g., patients refractory to other drugs) (§ 201.57(c)(2)(i)(B) and (E)). In rare cases, when the risks of the drug clearly outweigh any possible therapeutic benefit and the drug should never be used in a selected patient subset, a contraindication for use of the drug in that subset should also be described in the CONTRAINDICATIONS section.

[8] There should be consistency across labeling for contraindicated products (i.e., if use of drug A with drug B is contraindicated in the labeling for drug A, the use of drug B with drug A should be contraindicated in the labeling for drug B). For drugs that are regulated in different reviewing divisions, there should be cross-divisional coordination and agreement on contraindicated coadministration of drugs.

3. Text Emphasis

Bolded text, or other emphasis, can be used to highlight particular contraindicated situations or parts of the discussions of these situations. Emphasis should be used sparingly so that its impact is not diminished. When information is to be emphasized, also consider whether that information should be in a boxed warning (see BOXED WARNING below).

IV. BOXED WARNING (§ 201.57(c)(1))

A. When to Use a Boxed Warning

A boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug

OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

OR

- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR part 314, subpart H, § 314.520 "Approval with restrictions to assure safe use").

A boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber. Information included in the WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections should therefore be evaluated to determine whether it should also be placed in a boxed warning.

Boxed warnings are more likely to be based on observed adverse reactions, but there are instances when a boxed warning based on an expected adverse reaction would be appropriate. For example, a contraindication during pregnancy based on evidence in humans that drugs in a pharmacologic class pose a serious risk of developmental toxicity during that time would usually be in a boxed warning for all drugs in that class, even those in which the adverse reaction has not been seen.

A boxed warning can also be considered for a drug that has important risk/benefit information that is unique among drugs in a drug class (e.g., to note that a drug is the

only one in its class to have a particular risk that makes it inappropriate for use as a first line therapy).

B. Information to Provide

A boxed warning provides a brief, concise summary of the information that is critical for a prescriber to be aware of, including any restriction on distribution or use. If there is a more detailed discussion of the concern in either the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section, or any other labeling section that contains pertinent information (e.g., DOSAGE AND ADMINISTRATION), a cross-reference to that section must be provided (§ 201.57(c)(1)).

C. Format

FDA recommends the information in the boxed warning be presented in a bulleted format (or some alternative format, such as subheadings) that helps to make the information visually accessible.

GLOSSARY

Adverse Reaction (21 CFR 201.57(c)(7)): For purposes of prescription drug labeling and this guidance, an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and electrocardiogram (ECG).

Adverse Event (or adverse experience): For the purposes of this guidance, an *adverse event* refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related.

Serious Adverse Reaction: For purposes of this guidance, the term *serious adverse reaction* refers to any reaction occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug reactions when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.