Advisory Committee Briefing Document

Cardiovascular Safety of Rosiglitazone

Endocrinologic and Metabolic Drugs Advisory Committee

Drug Safety and Risk Management Advisory Committee

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List of Abbreviations

AACE	American Association of Clinical Endocrinologists
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin converting enzyme
ACR	Albumin Creatinine Ratio
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
AE	Adverse event
ALT/SGPT	Alanine Aminotransferase
BARI-2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial
BID	Twice a day
BMI	Body mass index
CAD	Coronary Artery Disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CR	Coronary Revascularization
CRP	C-reactive protein
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DREAM	Diabetes Reduction Assessment with ramipril and rosiglitazone Medication
DM	Diabetes mellitus
DSMB	Data Safety Monitoring Boards
EASD	European Association for the Study of Diabetes
EU	European Union
GCP	Good clinical practice
GLIB	Glibenclamide (glyburide)
GLY	Glyburide (glibenclamide)
GSK	GlaxoSmithKline
HbA1c	Glycated hemoglobin A_{1c}
HCL	Hydrochloric acid
HCP	Healthcare provider
Hct	Hematocrit
HDL-c	High density lipoprotein-cholesterol
HOMA-B	Homeostasis Model Assessment for β cell function
HOMA-S	Homeostasis Model Assessment for insulin sensitivity
HR	Hazard ratio
ICH	International Conference on Harmonization
ICT	integrated clinical trial

IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHCIS	Integrated Healthcare Information Services
IMT	Intimal medial thickness
INS	Insulin
ITT	Intent-to-treat
IVUS	Intravascular ultrasound
LDL-c	Low density lipoprotein-cholesterol
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular event
MCP	Monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metformin
MI	Myocardial infarction
MMP	matrix metalloproteinase
n	Number of patients
NA	Not applicable
NASH	nonalcoholic steatohepatitis
NDA	New Drug Application
NHANES	National Health and Nutrition Examination Surveys
NHLBI	National Heart, Lung and Blood Institute
NYHA	New York Heart Association
OAD	Oral anti-diabetic agent
OR	Odds ratio
PAI	Plasminogen activator inhibitor
PHRI	Population Health Research Institute
PI	Package insert or prescribing information
PIL	Patient information leaflet
PRO	Patient-reported outcomes
QD	Every day (once a day)
QOL	Quality of life
RAM	Ramipril
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes
RSG	Rosiglitazone
RR	Risk ratio
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SS/CBE	Special Supplements/Changes Being Effected
STARR	Study of Atherosclerosis with Ramipril and Rosiglitazone
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TID	Three times a day
TZD	Thiazolidinedione
U	Units
UKPDS	United Kingdom Prospective Diabetes Study
US	United States

VA DT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

1. SUMMARY

Rosiglitazone is an extensively studied oral anti-diabetic agent. To GSK's knowledge, the original NDA for rosiglitazone still represents the largest submitted dataset for a diabetic medicine at the time of first approval for use in the United States. Since the original regulatory approval in 1999, GSK have systematically expanded the knowledge base on rosiglitazone.

Throughout the clinical development program and with post-marketing experience, GSK have evaluated, on an ongoing basis, the safety profile of rosiglitazone, including the cardiovascular safety. GSK have worked consistently over the life of rosiglitazone, through regulatory submissions to the FDA, to add substantially to the cardiovascular safety information in the prescribing information.

Fluid retention which can lead to or exacerbate heart failure is a known effect of the TZD class of anti-diabetic agents. The potential for the exacerbation of heart failure during rosiglitazone therapy is highlighted in the current product labeling. At the request of the FDA, GSK have submitted a supplement to make information with regards to heart failure more prominent in labeling, thereby further assisting physicians in the appropriate use of TZDs.

Recently meta-analyses by GSK, FDA and others have raised the question whether rosiglitazone use results in an increased incidence of myocardial infarction in diabetic patients. Given the recognized limitations of this methodology, GSK have sought to answer this question by examining all available data, including long term, ongoing, prospective studies specifically designed to evaluate rosiglitazone cardiovascular safety, as well as large epidemiological studies reflecting actual clinical usage in the United States.

Across these multiple sources of data, there is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial infarction or cardiovascular death in comparison to other anti-diabetic agents.

The most robust data for assessing cardiovascular effects with rosiglitazone comes from the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study which was started in 2001 and was specifically designed to evaluate the cardiovascular safety of rosiglitazone, using well accepted adjudicated endpoints. An interim analysis has shown no statistically significant difference between rosiglitazone in combination with either metformin or sulfonylurea vs. the active comparators of metformin plus sulfonylurea, regarding myocardial infarction and death from cardiovascular causes or any cause.

ADOPT (A Diabetes Outcome Progression Trial), another active comparator study of rosiglitazone vs. standard therapy of metformin or sulfonylurea over 4-6 years, showed that rosiglitazone was superior with respect to durability of glycemic control. Overall, there was no meaningful difference among groups for myocardial infarction or death.

The DREAM study (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) demonstrated that rosiglitazone reduced the risk of progression to diabetes in a pre-diabetic population. The study was not designed to look at cardiovascular events and the number of events was small but there was no statistical difference between rosiglitazone and the placebo groups for myocardial infarction or cardiovascular death.

Several other long-term clinical trials with cardiovascular endpoints in diabetes subjects are currently underway and fully enrolled, including two large NHLBI-sponsored CV outcomes trials (BARI 2D and ACCORD), a Veterans Administration-sponsored diabetes trial on cardiovascular outcomes (VA DT), and a GSK-sponsored IVUS study (APPROACH). The large number of patients receiving rosiglitazone in these trials (estimated to be a total of approximately 4500 patients) will provide additional data on cardiovascular effects and further inform the benefit:risk profile of rosiglitazone for use in patients with type 2 diabetes. The independent Data Safety Monitoring Boards for these studies continue to review the accruing safety data in their study and the studies are continuing unaltered.

GSK have conducted numerous investigative/mechanistic studies with rosiglitazone and evaluated the effects on biomarkers and risk factors that may contribute to cardiovascular events. The overall data on cardiovascular risk markers do not suggest that rosiglitazone would lead to progression of atherosclerosis or increased plaque rupture, and therefore do not support a plausible biological hypothesis to link use of rosiglitazone with myocardial infarction.

GSK have also conducted three large epidemiological studies, encompassing over 500,000 patients with type 2 diabetes, to determine whether use of rosiglitazone in the real world setting is associated with an increase in myocardial infarction or coronary revascularization. The results of these studies show that rosiglitazone use is not associated with an increased risk of myocardial infarction vs. controls. Specifically in the largest and most recently performed study, there is no difference seen in the risk of myocardial infarction between rosiglitazone and pioglitazone.

The totality of the available data from large long term prospectively designed studies along with the three large epidemiological studies do not support the conclusion that rosiglitazone is associated with an increased risk of myocardial infarction.

Type 2 diabetes is a chronic progressive disease with short-term symptomatology and long-term devastating complications. It requires multiple therapeutic modalities to achieve optimal metabolic control. Rosiglitazone has demonstrated benefits on the underlying defects of type 2 diabetes, insulin resistance and beta cell dysfunction, which results in effective and durable glycemic control, with the absence of hypoglycemia. Rosiglitazone has an established efficacy and tolerability profile in a wide range of patients in whom other agents may not be suitable.

There is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial infarction or cardiovascular death in comparison to other anti-diabetic agents. Therefore, the benefit risk profile of rosiglitazone continues to be favorable. Rosiglitazone is an important therapeutic choice for physicians and their patients for the treatment of type 2 diabetes mellitus.

2. INTRODUCTION AND BACKGROUND

On June 6, 2007, FDA published a notice to announce a joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee plus the Drug Safety and Risk Management Advisory Committee to discuss the cardiovascular ischemic/thrombotic risks of the thiazolidinediones (TZDs), with particular focus on rosiglitazone. GSK accepted the invitation to present information to these Committees. We look forward to presentation and discussion of the data on cardiovascular ischemic events during treatment with RSG and other thiazolidinediones.

2.1. US Regulatory History of Rosiglitazone

A brief summary of the US regulatory history of rosiglitazone is provided here. The initial IND for rosiglitazone maleate tablets was submitted to FDA on September 22, 1993. Clinical development proceeded over the ensuing five years, resulting in submission of the original NDA 21-071 to FDA on November 25, 1998. During the review of the original NDA for this new chemical entity, FDA consulted with the Endocrinologic and Metabolic Drugs Advisory Committee on April 22, 1999. The Advisory Committee unanimously agreed that the benefits outweighed the risks for the use of rosiglitazone (alone or in combination with metformin) in the treatment of hyperglycemia in patients with type 2 diabetes mellitus. Subsequently, FDA granted approval for Avandia® (rosiglitazone maleate) Tablets on May 25, 1999. Avandia Tablets were introduced in the US as a new prescription drug product in June 1999.

Subsequently, the safety and efficacy of rosiglitazone (RSG) were assessed in other combination regimens, in various patient populations, in adequate and well-controlled studies, thereby enabling updates to labeling to add further information on safety and efficacy of RSG in these additional settings. Data examining the benefit:risk of RSG as add-on therapy to patients not obtaining adequate glycemic control on sulfonylurea therapy was submitted to FDA in June 1999 and approved in April 2000. Subsequently, data examining the benefit:risk of RSG as add-on to patients not obtaining adequate glycemic control on insulin therapy and the benefit:risk of RSG as add-on therapy to patients not obtaining adequate glycemic control on combination therapy of sulfonylurea and metformin were submitted to FDA and approval of these additional uses was obtained in February 2003 and February 2005, respectively. From the time of initial availability of RSG for prescription use (May 1999) to June 2007, the labeling of Avandia Tablets had multiple updates in accordance with the additional data submitted by GSK in Supplemental NDAs and reviewed by FDA. Overall, the benefits continued to outweigh the risks for the use of RSG as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus

As of June 2007, the FDA-approved INDICATIONS AND USAGE section of the prescribing information for Avandia (rosiglitazone maleate) Tablets is shown below:

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.

In the years since the approval of Avandia Tablets, GSK have submitted and gained approval of two additional New Drug Applications in order to obtain FDA's approval of two fixed-dose combination products, i.e., Avandamet® (rosiglitazone maleate and metformin HCl) Tablets and Avandaryl® (rosiglitazone maleate and glimepiride) Tablets, as approved on October 10, 2002 and November 23, 2005, respectively.

2.2. Chronology of Additions of Cardiovascular Safety Information to Labeling of Avandia Tablets

A brief review of the history of prescribing information changes for Avandia Tablets is relevant here. The original FDA-approved prescribing information for AVANDIA (on May 25, 1999) contained some information on cardiovascular safety of RSG. The PRECAUTIONS section stated that edema has been observed in some patients receiving AVANDIA. The PRECAUTIONS section also noted that AVANDIA is not indicated for use in patients with New York Heart Association (NYHA) Class 3 or 4 cardiac status (based in part on preclinical evidence of a risk of heart failure and lack of clinical data in such patients). No clinical adverse events in the cardiovascular organ system were noted in the ADVERSE REACTIONS section.

From May 25, 1999 through June 30, 2007, 8 Supplements have been submitted by GSK to add cardiovascular safety information to labeling for Avandia Tablets. Six of the 8 Supplements have attained approval by FDA. Five of the 6 FDA-approved Supplements

were submitted as Special Supplements/Changes Being Effected (SS/CBE) to expedite the new safety information into labeling. These additions to labeling have been substantive and their implementation has been timely. The contents of these Supplements are summarized in the table below.

Supplement No.	Summary of Change	Submission Date	Approval Date
002 CBE	PRECAUTIONS: Revisions to Edema subsection to state that fluid retention can exacerbate heart failure	Oct 27, 1999	July 11, 2000
006 CBE	WARNINGS: Added a new subsection on "Cardiac Failure"; added new paragraph on monitoring CV adverse events during use of AVANDIA + insulin	May 26, 2000	Feb 8, 2001
008 CBE	PRECAUTIONS: Added new information from postmarketing reports of patients with unusually rapid weight gain; such patients should be assessed for excessive edema and heart failure	June 7, 2002	Dec 3, 2002
014 CBE	PRECAUTIONS: Added a new subsection on "Drug Interactions" to caution about interaction between RSG and inhibitors (gemfibrozil) or inducers (rifampin) of CYP 2C8	July 28, 2004	Jan 4, 2005
016	WARNINGS: Added text and table of results to labeling for a 52-week, double-blind, placebo-controlled study in 224 patients with NYHA Class 1 or 2 heart failure	June 21, 2005	April 21, 2006
019 CBE	PRECAUTIONS: Added a new subsection on "Macular Edema" based on postmarketing reports	Dec 15, 2005 April 26, 2006	June 16, 2006
022	Proposed addition of the results of the Integrated Clinical Trials analysis and balanced cohort epidemiologic study to labeling	August 4, 2006	pending
028	WARNINGS: added a boxed warning and contraindication regarding heart failure	May 31, 2007	pending

In February 2007, the long-term safety and efficacy results of our Phase 4 Commitment study, ADOPT, were submitted to FDA in a supplemental New Drug Application (S-026) and are currently under review. In addition, note that GSK obtained FDA approval on May 12, 2005 to provide an FDA-approved "Patient Information" item of labeling to accompany the complete Prescribing Information for healthcare professionals.

Taken together, these Supplements show that GSK have worked consistently over the product lifecycle of Avandia Tablets to add substantially to the cardiovascular safety information in the prescribing information. GSK fully intends to work with FDA to propose further expansion in the cardiovascular safety information in labeling, as the results of additional clinical trials become available.

2.3. Other Background Information on Rosiglitazone

GSK established and maintains a program to monitor and assess the safety of RSG, including cardiovascular safety. A large number of preclinical, clinical and observational studies have been performed that have assessed fluid and CV effects. Echocardiography has been used in 5 studies in patients with type 2 diabetes; one of these studies was in patients with heart failure (meeting criteria for NYHA class 1 or 2 at entry). Large trials directed at disease prevention or at early disease modification have been conducted. Several trials directed at cardiovascular (CV) outcomes are ongoing. Finally, there has been ongoing evaluation of clinical trial data and postmarketing experience. When appropriate, revisions to the label have been undertaken to convey relevant and meaningful information to prescribers.

Substantial data on patients treated for at least 1 year (>2000 patients) were included in the original NDA, and these data were expanded with longer term studies designed to compare against active comparators started soon after initial approval of Avandia Tablets. ADOPT (A Diabetes Outcome Progression Trial) was initiated in April 2000 to examine long-term safety and efficacy of RSG in patients with recently diagnosed type 2 diabetes. A long-term trial RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) was initiated in April 2001 to specifically examine cardiovascular death and hospitalization outcomes in later stage type 2 diabetic patients, i.e., those not adequately controlled on metformin (MET) or sulfonylurea (SU) monotherapy [Home, 2005; Appendix A]. In addition, DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication), was initiated in 2001 (with support from GSK and other sponsors) by Population Health Research Institute (PHRI) at McMaster University. DREAM used a two-by-two factorial design to evaluate the safety and efficacy of RSG and ramipril (RAM) in the prevention of T2DM in subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) over an average three year period.

RSG is being used as a therapy in cardiovascular outcome studies (BARI 2D, ACCORD, VA DT) designed and sponsored by other organizations (e.g., National Heart, Lung, and Blood Institute). Other studies are evaluating the effects of RSG in high-risk populations (APPROACH). The designs and key dates for initiation of enrollment, completion of

enrollment, and availability of results for each of these studies are summarized in section 5.12 of this Briefing Document.

Throughout the development program, GSK evaluated investigator reported CV events in clinical studies with RSG. Typically, events rates were very low in individual studies and also in summary reports across studies supporting indicated uses for RSG. Although low in numbers, the incidence of heart failure and events typically associated with myocardial ischemia was higher in patients treated with a combination of RSG plus insulin than with insulin alone. The US label was updated to include this insulin safety data in February 2001.

In January 2004, the World Health Organization's (WHO) Uppsala Drug Monitoring Center published a notification of a review of postmarketing safety reports on "Thiazolidinediones and cardiac disease" in the WHO newsletter SIGNAL. This review was undertaken in response to elevated reporting ratios for a variety of cardiac events (e.g. cardiac failure, cardiomegaly, myocardial ischemia, myocardial infarction, and angina pectoris) for patients receiving TZDs (both pioglitazone and rosiglitazone).

In 2005, GSK took the initiative to design and conduct a retrospective exploratory patient-level analysis of an integrated clinical trial (ICT) database to evaluate the association (if any) between RSG and heart failure and, separately, events of myocardial ischemia, with respect to the various treatment regimens in which RSG is prescribed. Preliminary results were submitted to FDA in October 2005. As this analysis was, by design, retrospective and integrated across a variety of different studies, it was recognized that its results would be hypothesis generating, rather than conclusive. In June 2006, the results of a balanced cohort observational study examining a composite endpoint of hospitalizations for myocardial infarction and/or coronary revascularization comparing RSG to other anti-diabetic agents became available. This study was conducted in 33,363 patents in a large managed care setting treated with anti-diabetic therapy. On August 4, 2006, the final results of the ICT of 42 studies, the results of the balanced cohort observational trial, and a proposed update to the prescribing information of AVANDIA (to describe the observations of the ICT and the balanced cohort study) were submitted as a supplemental New Drug Application (S-022).

Following responses to a number of requests during the review cycle of those submissions, GSK met with FDA on May 16, 2007 to present data on myocardial ischemic events and therapy with RSG. At this meeting, GSK reviewed data from all available sources, including data from long-term trials of DREAM and ADOPT which were completed after the submission of the ICT and observational study, to assess the risk of myocardial ischemic events with RSG.

From the pooled analysis of the ICT dataset, the incidence of myocardial ischemic events was 1.99% (171/8604 patients) for RSG containing regimens and 1.51% (85/5633) for comparator regimens (Hazard ratio 1.31, 95% CI 1.01-1.70). Importantly, this observation has not been confirmed in subsequent studies, i.e. epidemiological studies, ADOPT or DREAM. Further, recognizing the clear potential of RECORD to directly inform the cardiovascular profile of RSG, given its key design as a CV outcome trial, the RECORD Steering Committee recommended that a safety interim analysis be conducted.

The results of the interim analysis of RECORD were published in the New England Journal of Medicine in June 2007 by the RECORD Steering Committee [Home, 2007b, Appendix B]. The authors stated that there was no evidence in the RSG group of any increase in death from either cardiovascular causes or all causes.

2.4. Study Level Meta-analysis

Nissen and Wolski published the results of a study-level meta-analysis to explore the relationship, if any, between rosiglitazone and the risk of myocardial infarction and cardiovascular death [Nissen, 2007]. This analysis was designed and conducted independent of GSK. Publicly available summary results from 42 clinical studies were selected for inclusion based on having a randomized comparison of rosiglitazone versus a control, similar duration of treatment in all groups, more than 24 weeks of drug exposure, and at least one report of myocardial infarction or death. Studies of patients without type 2 diabetes were included if other criteria were met. Results of the study-level meta-analysis showed an absolute frequency of myocardial infarction of 0.553% of patients (86/15,565 patients) with RSG and 0.586% of patients (72/12,282 patients) on controls, with an odds ratio of 1.43 (95% CI = 1.03-1.98) for rosiglitazone compared with controls. Also, results showed frequencies of cardiovascular death of 0.25% (39/15,565 patients) with rosiglitazone and 0.18% (22/12,282 patients) with controls, with an odds ratio of 1.64 (95% CI = 0.98-2.74). The authors stated key limitations of this analysis, including the "relatively small" number of events, lack of availability of patient-level source data for review, and lack of centrally adjudicated cardiovascular outcomes. The authors stated an "urgent need for comprehensive evaluation to clarify the cardiovascular risks of rosiglitazone".

2.5. Prologue

GSK have undertaken a comprehensive evaluation of the cardiovascular risks of rosiglitazone. This evaluation has been done in a manner that overcomes many of the limitations of the meta-analysis in that we utilized patient-level data, we examined source records underlying the databases, and we carefully assessed the totality of evidence in concert with the strength of each source of evidence (considering, for example, features of study design, objective of the study, and whether cardiovascular events were adjudicated).

The remainder of this Briefing Document summarizes key features of Type 2 diabetes, presents and discusses data from the ICT, 3 epidemiologic studies, ADOPT, interim data on RECORD, and data from the DREAM and the PPAR studies (studies in non-diabetic populations that specifically examined CV effects) to consider the available data on RSG therapy and CV events. This document also presents and discusses the benefit:risk of RSG therapy, given the currently available data and within the context of current management of type 2 diabetes and available therapeutic approaches. GSK appreciates the opportunity for a careful review and consideration of all data to allow for an informed judgment on the benefit:risk profile of RSG.

3. TYPE 2 DIABETES MELLITUS IN THE UNITED STATES:

3.1. Prevalence and Incidence of Diabetes

In the US in 2005, the prevalence of diabetes across all age groups was 20.8 million individuals, or 7% of the US population [Blonde, 2007], approximately two thirds of which, or 14.6 MM cases, are diagnosed. Type 2 diabetes mellitus (T2DM) accounts for 90-95% of all diagnosed diabetes cases (i.e. 13.4 to 13.9 million). Prevalence is highest in adults aged 60 years or older, with approximately 21% of all people in this age group having diabetes [CDC, 2005]. With respect to gender, 10.5% of men 20 yr or older (10.9 million) have diabetes, as compared to 8.8% of women in the same age group (9.7million). Diabetes is more prevalent in all minority populations in adults aged 20 years or older compared to Non-Hispanic Whites [CDC, 2005].

The incidence of new cases of diabetes increased 41% from 1997 to 2003, largely due to a rise in obesity, a common risk factor in development of type 2 diabetes [Blonde, 2007]. In the US from 2000 to 2030, diabetes is projected to increase from 17.7 to 30.3 million people, largely due an aging population, along with a rise in obesity and sedentary lifestyle [Wild, 2004]. By 2030, the US is expected to be one of the top three countries with the highest number of people with diabetes [Wild 2004, Mohan 2007].

3.2. Mortality

In the US, diabetes ranks 6th among leading causes of death [CDC, 2005], with approximately half of all diabetes-related deaths occurring in adults under 70 years of age [WHO, 2007]. In a single year in the US, 213,000 people die from diabetes and its complications [CDC, 2005]. The most common cause of mortality in people with diabetes is cardiovascular disease [Zimmet, 1997, O'Keefe, 1999]; coronary heart disease and stroke account for 65% of deaths [CDC, 2005]. Kidney failure is responsible for death in approximately 10-20% of people with diabetes [CDC, 2005].

Studies have shown that diabetic patients *without* a history of prior cardiovascular disease have the same event rates as non-diabetic patients *with* a history of myocardial infarction [Haffner, 1998, Malmberg, 2000]. The risk of mortality after an initial myocardial infarction in diabetic patients is twice that of non-diabetic patients, and patients with diabetes are more likely to die from sudden death before hospitalization [Mittinen, 1998]. The number of cardiovascular risk factors significantly influences age adjusted cardiovascular death rates [Nesto, 2001]. Studies have shown that systolic blood pressure, cholesterol levels, HbA1c and cigarette smoking are significant predictors of cardiovascular death in people with diabetes [Stamler, 1993]. Treatment of modifiable cardiovascular risk factors in the diabetic population is an important means for prevention of coronary events [UKPDS 38, 1998].

The United Kingdom Prospective Diabetes Study (UKPDS) provides the longest term data examining the impact of glucose control on death due to cardiovascular reasons. Despite attempts to maintain glucose control, there was progressive decline in glucose control, even in the intensive treatment group. Therefore, while intensive efforts to lower

HbA1c have been demonstrated to favorably affect the clinical course of T2DM in terms of microvascular complications, the optimal hyperglycemia management strategy with regard to macrovascular outcomes is unknown. Two studies of rosiglitazone (BARI-2D and ACCORD) are currently ongoing to examine the impact of management of hyperglycemia on macrovascular complications. The designs and key dates for initiation of enrollment, completion of enrollment, and availability of results are summarized in section 5.12 of this Briefing Document.

3.3. Morbidity

Type 2 diabetes mellitus is a metabolic disorder characterized by hyperglycemia. Untreated or inadequately-treated T2DM is associated with polydipsia, polyuria and progressive weight loss. In the extreme, the progressive hyperglycemia of untreated or inadequately treated T2DM will lead to dehydration and development of hyperosmolar coma. Treatment of T2DM is indicated for the acute management of these symptoms.

The chronic and progressive nature of T2DM is reflected in the relentless deterioration of glycemic control and the development and progression of both micro- and macrovascular complications [Lebovitz, 1999; UKPDS 16, 1995]. The higher rates of morbidity and mortality observed in people with T2DM are largely consequences of the long-term macrovascular (coronary, cerebral and peripheral vasculatures) and microvascular complications of diabetes [DeFronzo, 1999; Blonde, 2007].

Of the typical, and indeed pathognomonic, microvascular complications of diabetes (retinopathy, neuropathy and nephropathy), retinopathy is the most common. Retinopathy is one of the leading causes of blindness worldwide and in the US, causes up to 24,000 new cases of blindness each year [Fong 2004; CDC, 2005; Girach 2007]. Neuropathy is present in the majority of people with diabetes (60-70%) and can range in severity. Approximately 30% of people with diabetes aged 40 years or older have severe peripheral neuropathy of the feet which can lead to amputations [CDC, 2005]. In the US, T2DM is responsible for 82,000 amputations annually. Diabetes is the leading cause of end-stage renal disease (ESRD). In a single year in the US, 41,000 people with diabetes begin treatment for ESRD. Diabetes accounts for one out of every three patients treated with dialysis or who enter a transplant program. Of those patients receiving dialysis, nearly 1 in 5 patients die annually [DeFronzo 1999]. There are no approved therapies for established microvascular disease. Therefore, proper management of hyperglycemia with resulting prevention of these complications is the key to limiting the serious morbidity associated with these conditions. A 1% reduction has been associated with a 37% reduction in risk of microvascular complications [Stratton, 2000].

It is well established that T2DM is a major independent risk factor for cardiovascular disease [Grundy, 1999]. The risk of macrovascular complications including coronary heart disease and stroke in people with diabetes is 2- to 4-fold above that of the normal adult population [CDC, 2005], and people with diabetes have a significantly higher incidence of multi-vessel disease [Nesto, 2001]. Ischemic heart disease accounts for death in approximately 25% to 45% of people with diabetes [Bonow, 2004]. Atherosclerotic coronary disease is the leading cause of diabetes-related deaths.

Previous studies reported poor control of CV risk factors among people with T2DM in the US. Among diabetic individuals in the US, 80% have dyslipidemia, 70% are obese, and 60% are hypertensive. In the National Health Nutrition Examination Survey (NHANES) 1999-2000, 37% of subjects achieved HbA1c <7%, 36% of subjects achieved targets for systolic and diastolic blood pressure (<130/80mmHg) and 52% of subjects had cholesterol levels <200mg/dL. Only 7% of adults with diabetes achieved the recommended treatment goals for HbA1c and blood pressure and total cholesterol [Saydah, 2004]. Intensive long-term intervention of multiple modifiable risk factors in T2DM patients with microalbuminuria (one-third of the diabetes population), lowered the risk of cardiovascular and microvascular events by approximately 50% [Gaede P, 2003]. In addition to aggressive management of hyperglycemia, guidelines recommend that treating comorbid conditions is also essential to lower the risk of CV morbidity and mortality in people with T2DM [ADA, 2007b; NCEP-ATPIII, 2001].

3.4. Costs of Diabetes in the United States

Diabetes and its microvascular and macrovascular complications inflict significant economic consequences on individuals, families, health systems and countries. In 2002, the US total annual economic healthcare costs attributed to diabetes was estimated to be $132 billion [ADA, 2003]. Direct medical expenditures totaled $92 billion and comprised $23.2 billion for diabetes care, $24.6 billion for diabetes-related complications, and $44 billion for excess prevalence of general medical conditions. Of all diabetes complications, CV disease is the most costly, accounting for more than $17.6 billion of the total direct medical costs for diabetes in 2002 [ADA, 2003]. Microvascular complications of eye damage, foot problems and chronic kidney disease represent a considerable cost burden, in addition to the macrovascular complications.

Indirect costs resulting from lost workdays, restricted activity days, mortality, and permanent disability due to diabetes totaled $40.8 billion. In the US, almost $1 out of every $5 spent on healthcare is for a person with diabetes. Acute hospitalization contributes to 44% of diabetes-related costs followed by 22% for outpatient care, 19% for drugs and supplies, and 15% for nursing care [ADA, 2003]. Diabetes-related hospitalizations totaled 16.9 million days in 2002. Rates of outpatient care were highest for physician office visits, which included 62.6 million visits to treat diabetes patients [ADA, 2003].

3.5. Treatment of Diabetes

3.5.1. Treatment of Hyperglycemia

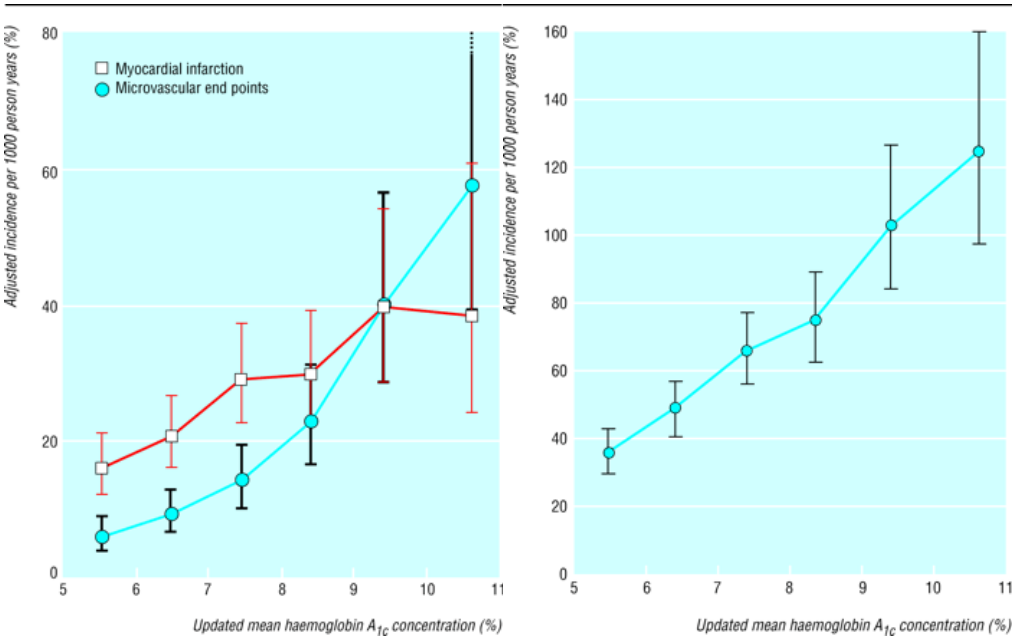
Inadequate glycemic control among individuals with diabetes constitutes a major public health problem in the US. Uncontrolled diabetes is associated with premature death and disability, decreased quality of life, and significantly adds to national medical health care expenditures. The relentless progression of the key metabolic defects in T2DM, decreasing beta-cell function on a background of insulin resistance, was evidenced by the progressive increases in glycemia in the UKPDS which occurred in spite of intensive efforts to control glycemia. Glycemic control remains the major therapeutic objective

and challenge for the prevention of complications and accompanying target organ damage arising from diabetes. Treatment with diet and exercise, insulin, and oral hypoglycemic agents are known to improve glycemia, and approaches to disease management that include greater patient self-participation are recommended. Furthermore, studies have shown that a comprehensive and aggressive management approach is effective in decreasing the rate of progression of microvascular complications.

People with type 2 diabetes have a reduced quality of life compared to the normal population [Kilillea, 2002]. Addition of pharmacotherapy to diet compared to placebo for 15 weeks has shown reductions in HbA1c and had a favorable impact on the quality of life with significant reductions in symptoms of hyperglycemia including frequent urination, thirst, nocturia, and fatigue [Testa, 1998]. Additionally, the improvement in glycemic control as measured by HbA1c, was associated with substantial improvements in mental health, cognitive function, general perceived health and symptom distress [Kilillea, 2002].

Under current treatment guidelines, the treatment of hyperglycemia aims to reduce blood sugar to a level as close to normal as is practical [ADA, 2007b]. The improved outcomes on microvascular complications were demonstrated using HbA1c as a surrogate for mean glucose levels, in both the Diabetes Control and Complications Trial (DCCT) and the UKPDS [DCCT, 1993; UKPDS 33, 1998]. The UKPDS study, in patients with T2DM, found that for a 0.9% decrease in HbA1c there was about a 25% decrease in the incidence of microvascular endpoints (such as retinopathy, albuminuria and need for retinal photocoagulation) [UKPDS 33, 1998] over the 10 year duration of the study. Additionally, in the Kumamoto study, intensive glycemic control, lowering HbA1c to less than 6.5%, fasting blood glucose to less than 110mg/dL, and 2-hour post-prandial glucose to less than 180mg/dL was shown to delay the onset and progression of retinopathy, neuropathy and nephropathy in Japanese patients treated with intensive insulin therapy [Ohkubo, 1995]. The UKPDS, DCCT and Kumamoto studies are the only published studies which evaluated the impact of glycemic control on the complications of diabetes.

An observational study using the UKPDS data [Stratton, 2000] evaluated the relationships between glycemic control and complications of diabetes. The figures shown below exemplify these data for white males; the original analysis demonstrated similar results for females and other ethnic groups.



Incidence rate and 95% CI for myocardial infarction and microvascular complications by category of updated mean hemoglobin A1c, expressed for white men age 50-54 years at diagnosis and with mean duration of diabetes of 10 years	Incidence rate and 95% CI for any endpoint related to diabetes by category of updated mean hemoglobin A1c, expressed for white men age 50 - 54 years at diagnosis and with mean duration of diabetes of 10 yrs

The evidence to support the impact of reducing glucose levels to near normal on macrovascular outcomes is less definitive than for microvascular outcomes. Nonetheless, in the UKPDS, there was a borderline significant 16% reduction in myocardial infarction in the intensive treatment group despite the progressive increases in HbA1c that occurred. The relatively greater impact of improvements in glycemic control on microvascular as opposed to CV endpoints is reflected in the Figure above. A relatively small impact of increasing glucose on CV risk was also apparent in a retrospective analysis of data from the HOPE trial [Gerstein, 2005].

A recent analysis of UKPDS linked past elevations in HbA1c to increased cardiac mortality [UKPDS 66, 2004]. Long-term follow-up of the DCCT in Type 1 Diabetes, also suggests that there may be long-term cardiovascular benefit long after prolonged periods of near normalization of blood glucose [Nathan, 2005]. A sub-analysis of the Heart Protection Study showed that the incidence of coronary events, non-fatal myocardial infarction or coronary death, was lower among diabetes patients with HbA1c below 7% [HPSCG, 2003, Heinig, 2006]. This suggests that long-term glycemic control should provide significant CV benefits, but that even short-term achievement of glycemic goals may yield longer term benefit.

The UKPDS is generally considered the foundation for contemporary guidelines for T2DM treatment. Guidelines for the treatment of hyperglycemia in T2DM are provided

by the American Diabetes Association (ADA), American Association of Clinical Endocrinologists, and the European Association for the Study of Diabetes (EASD). The guidelines now acknowledge the relentless progression of the disease and therefore advise a progression of therapeutic choices to manage progressive increases in glycemia. MET is recommended for initial pharmacotherapy as it provides proven efficacy, a favorable safety profile with no hypoglycemia and is associated with no weight gain or modest weight loss [DeFronzo, 1999]. With the inevitable worsening of glycemic control despite monotherapy with MET, current ADA/EASD guidelines [Nathan, 2006] suggest the addition of a second agent to be chosen among insulin, SU or TZD. According to these guidelines, the treatment choice for a second agent may depend on medical and patient considerations, including degree of hyperglycemia, side effects, cost and adherence to therapy. Among the features that could be considered for the three agents that the guidelines identify for combination with MET are the superior efficacy of insulin, the low cost of SU and the absence of hypoglycemia with TZD. The third line of therapy for worsening HbA1c can include the use of a third oral agent, or second oral agent for patients who were given insulin at the second stage. The guideline favors the addition of insulin when glycemia is uncontrolled on oral monotherapy (HbA1c is >8.5%) and rapid glycemic control is needed, or in situations when target glycemic control is not achieved on two oral agents.

Despite the current recommendations and the acknowledged importance of maintaining glycemic control, only 36% and 33% of type 2 diabetes patients in US are at the recommended treatment goals for HbA1c <7% and ≤6.5%, respectively [Koro, 2004a; Blonde, 2007].

3.5.2. Treatment of Other Risk Factors

The contribution of other risk factors to the development of CV complications in T2DM is well established and acknowledged in current standards of care for T2DM. Smoking cessation, aspirin use and treatment of lipids and hypertension are advised in the standards. Specific treatment algorithms for hypertension and lipids are prescribed in the ADA Standards of Medical Care in Diabetes. The goal for treatment of hypertension is blood pressure ≤130/80 mm Hg and for lipids, LDLc <100mg/dL or <70mg/dL (patients with overt cardiovascular disease), triglycerides <150 mg/dL, and HLDc >40 mg/dL for men and >50 mg/dL for women. The impact of this type of multifactorial intervention along with aggressive glycemic control was evaluated in the STENO-2 study [Gaede, 2003] in which there was approximately a 50% decrease in microvascular and CV outcomes. Despite the evidence in support of aggressively treating modifiable risk factors for cardiovascular disease, according to 1999-2000 NHANES, only 7% of adults with diabetes achieved recommended treatment goals for HbA1c and blood pressure and total cholesterol [Saydah, 2004].

3.6. Summary

Treatment of hyperglycemia, along with diet and exercise, can help ease the overall burden of disease in people with diabetes. Evidence has accumulated regarding the benefits of maintaining glycemia close to normal values in patients with T2DM. Current

standards of care recommend aggressive glycemic targets to attain HbA1c levels <7% or ≤6.5%, or near-normal blood glucose levels without significant risk of hypoglycemia [ADA, 2007b; AACE, 2002]. Furthermore, in view of the increasing cardiovascular burden of T2DM, current guidelines now recommend the concurrent aggressive treatment of all CV risk factors, including blood pressure and lipids, to further lower the risk of cardiovascular morbidity and mortality in people with type 2 diabetes.

Individualized management of T2DM will continue to provide a challenge to healthcare providers. Availability of therapeutic options, particularly those with different mechanisms of action and those which maintain longer-term glycemic control, will be important for patients who will require change in therapy or multiple therapies to help them maintain glycemic control over time.

4. BACKGROUND ON ROSIGLITAZONE

4.1. Mechanism of Action

Rosiglitazone maleate is a potent and orally active anti-hyperglycemic compound of the thiazolidinedione (TZD) chemical class, developed by GlaxoSmithKline (formerly SmithKline Beecham Pharmaceuticals). TZDs act by reducing insulin resistance and sensitizing the liver, muscle, and adipose tissue to the actions of circulating insulin. They exert their effects by binding to and activating the nuclear peroxisome proliferator activated receptor-gamma (PPARγ), thus modifying transcriptional regulation of numerous genes including those involved in the regulation of insulin action. PPARγ receptors are present in adipose tissue, skeletal muscle, liver, pancreatic beta cells and vascular endothelium.

4.2. Effects on Glycemic Control

GSK have undertaken a comprehensive program investigating RSG across the spectrum of T2DM patient populations from early disease to patients with advanced disease and failing insulin therapy. RSG has been shown to produce significant glucose lowering effects in drug-naïve patients, as alternative monotherapy in patients washed-out from previous anti-diabetic drugs, as additive glycemic benefit in patients failing one or 2 oral agents, and as additive glycemic benefit in patients failing insulin therapy. As such, RSG has been shown to be an effective glucose lowering agent, generally safe and well tolerated and indicated for use in patients with T2DM when given as monotherapy [Charbonnel, 1999], in dual or triple combination with a sulphonylurea [Wolffenbuttel, 2000] and/or MET [Fonseca, 2000], or in combination with insulin [Raskin, 2001].

In clinical studies, treatment with RSG resulted in an improvement in glycemic control, as measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c), with a concurrent reduction in hyperinsulinemia as measured by circulating levels of insulin and C-peptide. This is consistent with the mechanism of action of RSG as an insulin sensitizer. Short-term improvement in glycemic control with RSG is consistent with the most effective oral anti-diabetic agents. In the long-term, RSG monotherapy has demonstrated superior glycemic control to monotherapy with these same agents, MET and SU.

4.2.1. Rosiglitazone Monotherapy

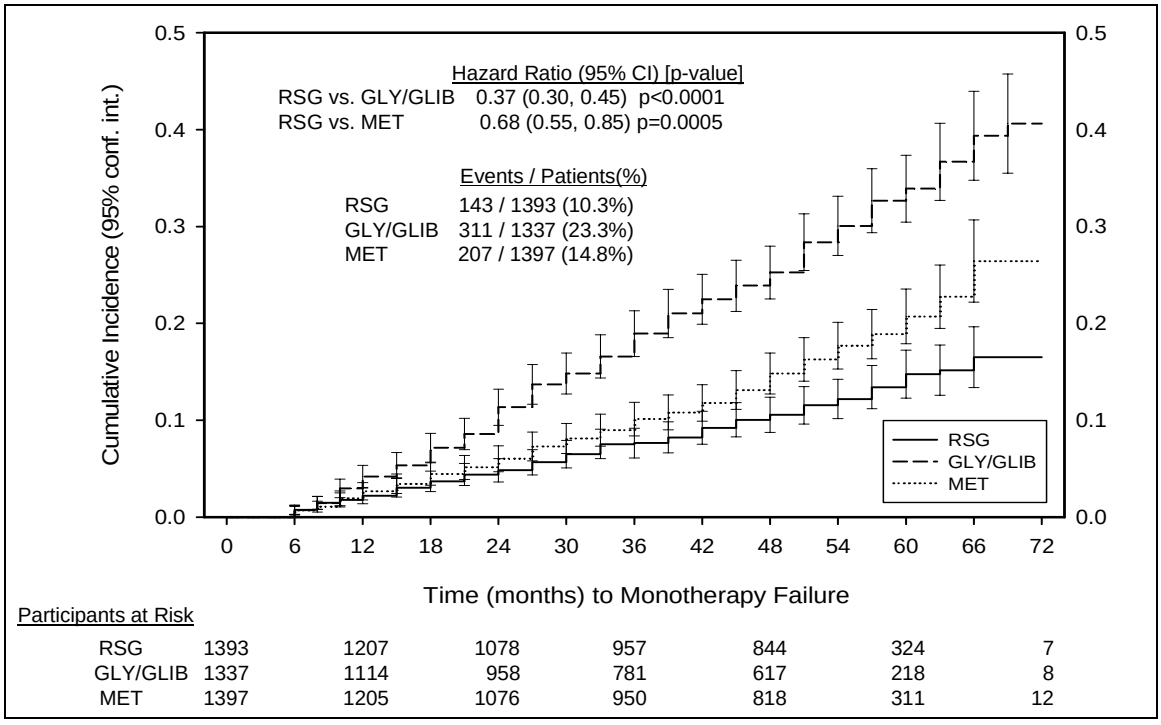
The glucose-lowering efficacy of RSG monotherapy has previously been demonstrated in six double-blind trials in 2315 subjects with type 2 diabetes previously treated with diet alone or anti-diabetic medication(s). This included two 26-week, placebo-controlled studies, one 52-week glyburide-controlled study, and three placebo-controlled dose-ranging studies of 8 to 12 weeks duration. In the two 26-week studies, 1,401 subjects 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%]), treatment with

RSG produced statistically significant decreases in HbA1c (up to -1.5%) and FPG (decreases up to -76mg/dL).

The long-term durability of effect of RSG monotherapy was initially demonstrated in the 52-week, glyburide-controlled study. Improvement in glycemic control seen with RSG 4 mg bid at week 26 was maintained through week 52 of the study. The most compelling evidence for long-term durable anti-hyperglycemic efficacy of RSG comes from the recently completed ADOPT study [Kahn, 2006]. This landmark study in patients with newly diagnosed T2DM investigated the efficacy of RSG directly compared to that of MET and to SU in maintaining fasting blood glucose levels over a median of four years. The primary endpoint of the ADOPT study was the time to monotherapy failure while on maximal tolerated dose of randomized study medication. ADOPT was a post-approval Phase 4 commitment study in the US, and as such, the protocol was agreed with the FDA, and the definition of monotherapy failure was aligned with US treatment guidelines in place at the time of initiation of the study [ADA, 1998].

Over the 4-6 year period of ADOPT, RSG provided the best long-term glycemic control, as evidenced by time to monotherapy failure, HbA1c and FPG, compared to either MET or SU. In ADOPT, RSG significantly reduced the risk of reaching monotherapy failure by 63% relative to SU and by 32% relative to MET during the course of the study, thus demonstrating a greater benefit in maintaining glycemic control relative to both MET and SU (Figure 1). At the time of treatment failure, 99.3% of patients in the RSG group, 98.6% in the MET group, and 99.0% in the SU group were receiving the maximum (target) dose of study drug, suggesting that monotherapy failures were due to disease progression and not the lack of up-titration to optimal doses. There was a higher withdrawal rate due to therapy failure in the GLY/GLIB group compared to both RSG and MET, apparent beginning at 12 months of therapy.

Figure 1 Cumulative Incidence of Monotherapy Failures in ADOPT (ITT population)



Mean HbA1c and FPG reductions from baseline were significantly greater with RSG compared to SU and MET at 48 months (Table 1).

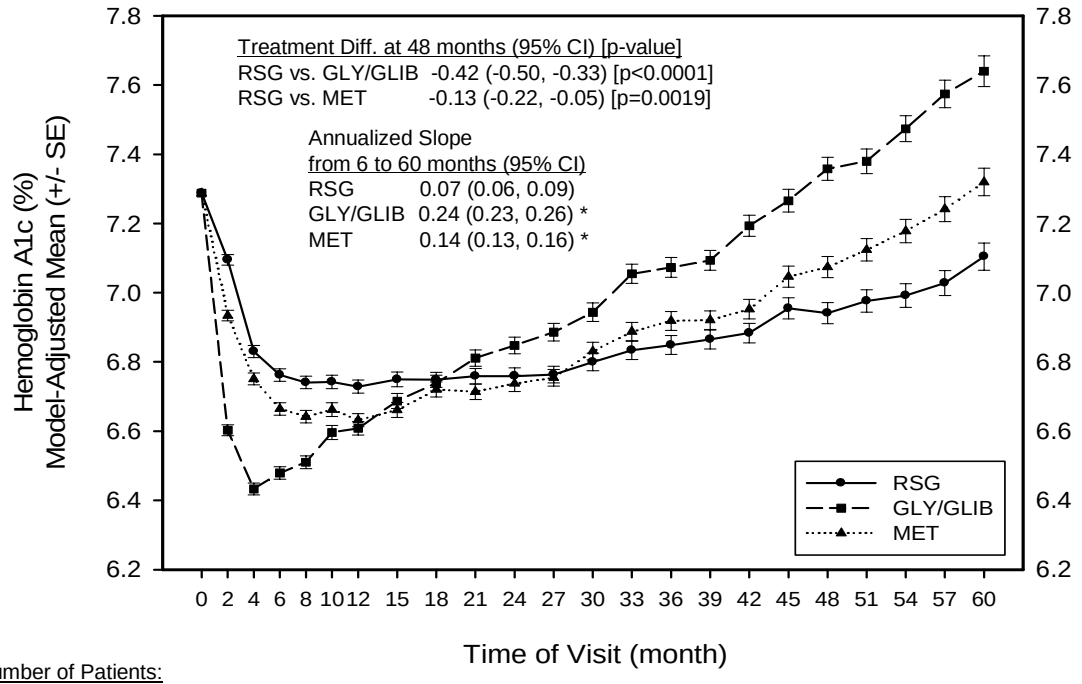
Table 1 Change in HbA1c and FPG from Baseline to 48 Months

	RSG	MET	GLY/GLIB
HbA1c (%), n	1350	1352	1310
Baseline, Mean±SD	7.36±0.92	7.35±0.93	7.36±0.93
Adjusted Mean±SE for Change from Baseline	-0.35±0.03	-0.22±0.03	0.07±0.03
Adjusted Mean Difference	-	-0.13, p=0.0018	-0.42, p<0.0001
FPG (mg/dL), n	1390	1394	1334
Baseline, Mean±SD	151.6±25.7	151.3±25.3	152.6±27.4
Adjusted Mean±SE for Change from Baseline	-19.0±1.03	-9.2±1.04	-1.6±1.14
Adjusted Mean Difference	-	-9.8, p<0.0001	-17.4, p<0.0001

Adjusted means are at 48 months and are from a repeated measures model utilizing all on-therapy dta through the 48 month visit

Within the first six months, HbA1c decreased in all treatment groups, with SU showing the greatest initial decline, but subsequently increased in all treatment groups (Figure 2). The rate of increase in HbA1c from 6 to 60 months was greatest for SU, intermediate for MET, and least for RSG. RSG showed a more durable effect on glucose control by maintaining a mean HbA1c <7% for a longer period (54.25 months) than with either MET (44.50 months, p=0.0009) or SU (32.25 months, p<0.0001).

Figure 2 Model Adjusted Mean HbA1c (%) Values (Plus or minus SE) in ADOPT (ITT Population)



Number of Patients:						
RSG	1350	1123	1032	912	808	308
GLY/GLIB	1310	1060	923	758	604	214
MET	1352	1125	1036	913	785	300

The importance of achieving and maintaining normoglycemia continues to gain widespread recognition due to its impact on reducing the risk of long-term complications of diabetes. In ADOPT, at 4 years, significantly more subjects were adequately controlled (HbA1c <7% or ≤6.5%) with RSG (40% and 26%) than with either SU (26% and 18%, p<0.0001 for both) or MET (36%, p=0.0224 and 23%, p=0.0383). The findings that RSG treatment allows more patient to reach and maintain glycemic targets than SU or MET supports the proposition that RSG therapy may delay or avoid the complications associated with poor glycemic control.

4.2.2. Rosiglitazone in Combination Therapy

4.2.2.1. Rosiglitazone in Combination with Metformin

The efficacy of RSG as additive therapy to MET has been demonstrated in three 26-week, double-blind studies that included 784 subjects with T2DM inadequately controlled on a maximum dose (2.5 grams/day) of MET. Subjects were treated with RSG 4mg or 8mg in addition to MET or with MET monotherapy. RSG in combination with MET demonstrated statistically and clinically significant reductions in mean HbA1c (ranging from -0.8% to -1.4%) and FPG (ranging from -40 to -62mg/dL) compared to subjects continued on MET monotherapy. The glycemic efficacy of RSG 8mg/day in combination with sub-maximal MET (1g/day) versus the maximal effective dose of MET (2g/day) has also been demonstrated in a 24-week study in 573 subjects with T2DM.

Reductions in HbA1c and FPG were consistent with that observed with RSG 8mg/day plus MET 2.5mg/day.

4.2.2.2. Rosiglitazone and Metformin Fixed-Dose Combination (AVANDAMET)

RSG and MET have been evaluated as a fixed-dose combination (AVANDAMET) in a 32-week, double-blind study in 468 drug-naïve subjects with T2DM inadequately controlled with diet and exercise alone. Subjects were titrated to a maximum of 8mg/2,000 mg of AVANDAMET, 8mg of RSG, and 2000mg for MET to reach a target mean daily glucose ≤110 mg/dL. Significant improvements in glycemic parameters were observed in patients treated with the fixed-dose combination compared to either RSG or MET montherapy ($p<0.001$). Significantly more subjects treated with AVANDAMET reached HbA1c <7% (77%) compared to RSG (58%) and MET (57%).

Drug-naive subjects with uncontrolled hyperglycemia (HbA1c >11% and FPG >270mg/dl) were treated for 32 weeks with open-label AVANDAMET (titrated to a maximum of 8mg/2,000 mg based on a glycemic target of MDG ≤110mg/dL. Significant improvements in HbA1c (-4.0%, $p< 0.0001$) and FPG (-139.4mg/dL, $p<0.0001$) were observed in subjects treated with AVANDAMET. In this study, 44.0% of subjects reached HbA1c <7%.

This study demonstrated that RSG provides additive glycemic benefit to that of MET, even in an initial treatment setting.

4.2.2.3. Rosiglitazone in Combination with Sulfonylureas

A total of 3457 patients inadequately controlled on a sub-maximal or maximal dose of SU were studied in eleven 24-to 26-week randomized, double-blind, placebo/active-controlled studies and one 2-year double-blind, active-controlled study. In the short-term studies, the addition of RSG 4mg or 8mg daily to a SU significantly improved glycemic control compared to SU monotherapy or further up-titration of the SU. The addition of RSG to SU resulted in reduction in HbA1c of 0.55% to 1.4% and FPG from 18mg/dL to 71.5mg/dL compared to SU.

The long-term effectiveness of RSG added to a SU on glycemic control was demonstrated in a two-year study in elderly subjects who were inadequately controlled on glipizide (10mg bid). Subjects were randomized to RSG (4 mg qd) combined with glipizide (10 mg bid) or uptitration of glipizide monotherapy. Subjects were required to uptitrate study medication when FPG levels were ≥180 mg/dL to a maximum dose of 40 mg/day glipizide and 8 mg/day RSG or placebo. HbA1c (-0.79%) and FPG (-37.7mg/dL) significantly decreased with RSG and SU combination therapy compared to SU monotherapy. In this two-year period, only 2% subjects treated with RSG plus glipizide experienced therapeutic failure (FPG > 180 mg/dL on maximum dose) compared with 29% subjects treated with glipizide alone ($p<0.0001$). Significantly more subjects treated with RSG + glipizide reached a HbA1c <7% (50%) compared to glipizide alone (22%).

4.2.2.4. Rosiglitazone and Glimepiride Fixed-Dose Combination (AVANDARYL)

RSG and glimepiride (GLIM) have been evaluated as a fixed-dose combination (AVANDARYL) in a 28-week, double-blind clinical study in 901 drug-naïve subjects with T2DM inadequately controlled with diet and exercise alone. Subjects were titrated to a maximum of 4 mg/4 mg or 8 mg/4 mg of AVANDARYL, 8mg of RSG, or 4mg of GLIM to reach a target mean daily glucose of ≤110 mg/dL. Significant improvements in HbA1c (-0.6 to -0.8%) and FPG (-16 to -37 mg/dL) were observed in patients treated with AVANDARYL compared to either RSG or GLIM monotherapy ($p<0.0001$). A greater percentage of subjects treated with AVANDARYL achieved ADA HbA1c target of <7.0% compared to RSG or GLIM monotherapy ($p<0.0001$).

This study demonstrates that RSG provides additive glycemic benefit to that of SU even in an initial treatment setting.

4.2.2.5. Rosiglitazone in Combination with Metformin and Sulfonylurea

In two double-blind studies, triple combination of RSG (4mg/day and 8mg/day) with MET and SU demonstrated statistically and clinically significant reductions in HbA1c compared with the use of MET+SU only (ranging from -0.6 to -1.1%) [Dailey, 2004]. In an open-label study, RSG+MET+SU resulted in durable glycemic control as determined by both HbA1c and FPG over a period of 44 weeks with a low incidence of withdrawals due to lack of efficacy (1.8%), suggesting that for patients staying on therapy, the triple combination of RSG+MET+SU offers sustained glycemic control.

4.2.2.6. Rosiglitazone in Combination with Insulin

RSG (2mg, 4mg and 8mg) in combination with insulin has been evaluated in three randomized, double-blind, controlled studies in 1166 subjects with type 2 diabetes inadequately controlled on a standardized twice daily insulin monotherapy. Compared to insulin monotherapy, 4-8mg/day RSG added to insulin significantly reduced HbA1c (-0.4 to -1.3%). Approximately 40% of all patients reduced their insulin dose when RSG was added.

The effect of RSG (4mg to 8mg/day) in combination with insulin and/or a SU versus insulin and/or SU therapy was evaluated in 92 subjects with T2DM and mild to severe renal failure. RSG plus insulin and/or a SU produced a significant decrease in HbA1c (-0.5%) compared to insulin and/or SU in T2DM subjects with renal impairment. Reduction in HbA1c was similar irrespective of the degree of renal impairment.

4.2.2.7. Rosiglitazone and Metformin (AVANDAMET) Plus Insulin

The effect of AVANDAMET in combination with insulin was evaluated in a study of 319 subjects with T2DM. Unlike previous insulin combination studies, insulin was added to AVANDAMET and up-titrated to achieve target pre-meal capillary blood glucose values.

When insulin was added to AVANDAMET, there was a significant decrease in HbA1c (-0.7%) and FPG (-26 mg/dL) compared to switching subjects to insulin monotherapy ($p<0.0001$). Significantly more subjects treated with AVANDAMET plus insulin (70%)

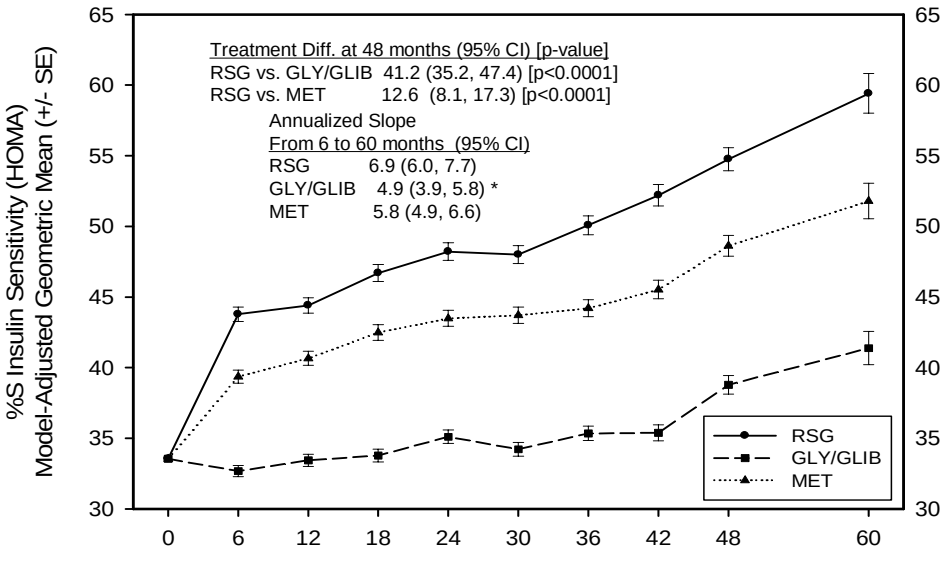
achieved ADA target HbA1c <7% compared to subjects switched to insulin (34%) monotherapy (p<0.0001).

4.3. Insulin Sensitivity and Beta-cell Function

Throughout the development program, RSG has consistently demonstrated improvement in measures of insulin resistance and estimates of β-cell function, two core defects in T2DM. The longest duration data on these effects comes from ADOPT, which in addition to comparing glycemic control, also allowed a direct comparison of RSG, MET and SU with regard to their effects on these measures of underlying disease progression.

ADOPT demonstrated that insulin sensitivity, as estimated by the homeostasis model assessment (HOMA-S), was significantly greater with RSG compared to SU and MET when assessed at 48 months. These data demonstrate the potent effect of RSG on improving insulin sensitivity relative to the other agents (Figure 3).

Figure 3 Mean HOMA-S Values by Visit

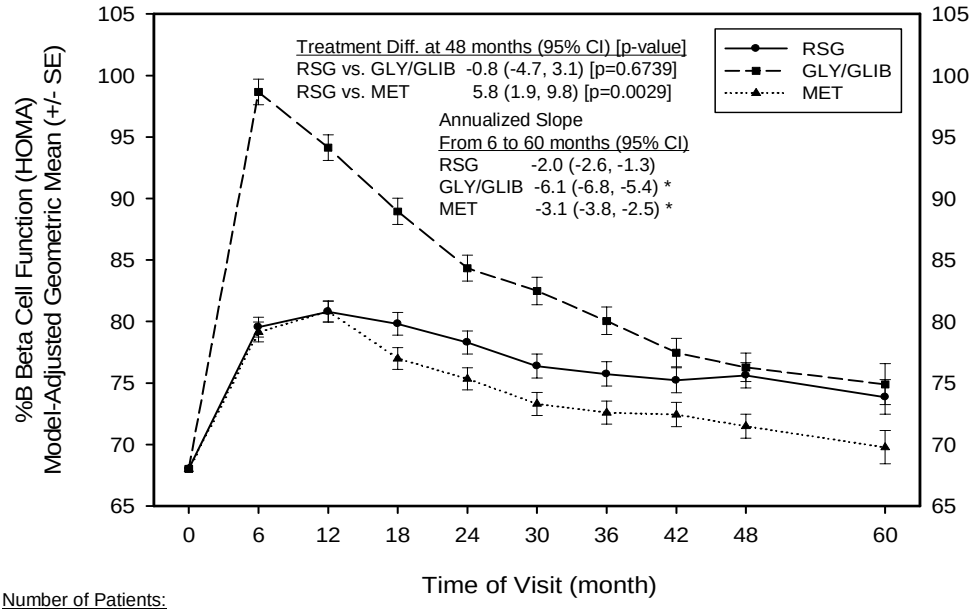


Number of Patients:						
RSG	1234	1095	970	838	752	316
GLY/GLIB	1160	1003	850	689	545	208
MET	1240	1095	956	840	728	296

Estimates of β-cell function (HOMA-B) were statistically significantly increased in the RSG group relative to MET at 48 months but were not different from GLY. There was a significantly slower rate of decline in HOMA β-cell function in the RSG group relative to GLY and MET and this is reflected in the overall improved durability of glycemic control (Figure 4). The long-term maintenance of glycemic control that accompanies the

improved β-cell function and insulin sensitivity with RSG treatment could have a significant favorable impact on the long-term micro- and macrovascular complications of T2DM, as currently being evaluated in cardiovascular outcome studies.

Figure 4 Mean HOMA -B Values (±SE) by Visit



Number of Patients:						
RSG	1240	1105	976	836	701	297
GLY/GLIB	1166	1017	857	685	527	202
MET	1246	1105	963	832	690	277

It is important to recognize the interrelationship between HOMA-S, HOMA-B and glycemia when interpreting the effects of SU, MET and RSG on beta-cell function.

- For SU, the data show a rapid decline in HOMA-B, no change in HOMA-S, both in the context of the higher glucose levels, indicating that there is progressive beta-cell failure. The HOMA-B values with SU after the 6 month time point are in fact too low to support maintenance of normoglycemia, as was the case at the peak of the HOMA-B (6 months) with accompanying nadir in glucose.
- In contrast, the results with MET and RSG show that normoglycemia is achieved at lower HOMA-B values but higher HOMA-S values (6 to 12 months). Both MET and RSG therapies demonstrate progressive increases in HOMA-S with similar slopes from month 6 forward.
- The decline in glycemic control with MET is greater than with RSG as is the decline in HOMA-B, which is consistent with differing rates of beta-cell failure against a background of increasing insulin sensitivity (HOMA-S). These data strongly suggest that RSG has a beneficial effect in maintaining beta-cell function relative to MET and especially SU.

4.4. Factors Associated with CV Risk

The effect of RSG on cardiovascular risk factors and biomarkers has been extensively studied. RSG has been studied on both established risk factors such as cholesterol and other lipid parameters, weight, blood pressure and microalbuminuria as well as novel risk factors for atheroma such as inflammatory mediators including CRP. Furthermore the effect of RSG on atheroma over time has been assessed in both IMT and restenosis studies. The effect of RSG on key thrombotic factors that drive cardiovascular events in diabetics have also been studied. In addition, RSG has been evaluated in studies examining both cardiac structure and function.

4.4.1. Effects on Lipids

Changes in lipids have been evaluated during the clinical development program for RSG and the lipid effects of RSG have been well described when used as monotherapy or in combination with other antidiabetic agents [Malinowski, 2000; Wagstaff, 2002]. In 26 week, placebo-controlled studies utilizing 4mg and 8 mg of RSG, a 14.1-18.6% increase in LDL-c level and a 11.4 – 14.2% increase in HDL-c level was observed, without a clinically significant increase in LDL-c/HDL-c ratio. Further evaluation has shown that the increases in LDL-c are associated with a shift in particle size toward the more buoyant and less atherogenic LDL particles. Importantly, the increase in HDL is especially pronounced in patients with low baseline HDL-c levels. Changes in triglycerides have been less consistent and not significantly different from controls.

In the longest duration study of RSG in type 2 diabetes patients to date (ADOPT) where use of statins with appropriate individualization of dosage was encouraged, the LDL-c concentration was lower at 48 months than at baseline in all treatment groups. Notably although the LDL-c level was significantly higher in the RSG group than the MET and GLY groups by about 8% and 5%, respectively, there was no clinically significant difference between RSG, GLY and MET treatment groups in LDLc/HDLc ratio at the end of the study. There were no clinically significant changes in triglycerides in any of the treatment groups.

Increasingly, guidelines mandate use of statin therapy in subjects with type 2 diabetes. In a randomized study exploring the effects of RSG on lipid parameters, treatment with RSG 8mg for 8 weeks was associated with a 9% increase in LDLc [Freed, 2002], and an accompanying shift from small, dense LDL particles to less atherogenic large buoyant LDL particles. When atorvastatin 10mg or 20mg was added to RSG, there was a substantial reduction in both LDL-c (31.5-38.8%) and triglycerides (18.5-27.2%) and the beneficial effects of RSG on HDL-c was maintained. A study to evaluate the effects of RSG or placebo on lipids in well-controlled type 2 diabetic subjects who had predominantly small dense LDL and were on stable dose of a statin was also conducted. At 12 weeks following addition of RSG to statins, there was a complementary effect with LDL particles shifting toward less atherogenic large buoyant LDL and reductions in several biomarkers for CVD risk [Yu, 2006].

4.4.2. Effects on Inflammatory Mediators

Vascular inflammation is a critical component in the pathophysiology of atherosclerosis and its associated complications, and multiple biomarkers of vascular inflammation have been recognized as potential risk factors predictive of cardiovascular events. These include markers such as monocyte chemoattractant protein-1 (MCP-1), C-reactive protein (CRP), CD40 ligand, plasminogen activator inhibitor-type 1 (PAI-1), and matrix metalloproteinase-9 (MMP-9), relating to inflammation, thrombosis, fibrinolysis, and plaque vulnerability. RSG treatment has been associated with improvements in these circulating CV biomarkers [Martens, 2002; Plutzky, 2003].

Furthermore, there is a body of evidence demonstrating positive effects of RSG on endothelial function. RSG has been associated with a 45% larger increase in maximal forearm blood flow than that observed in patients using nateglinide, and this effect was independent of glycemic control [Pistrosch, 2004].

4.4.3. Effects on Blood Pressure

Across the clinical trial program, consistent reductions in blood pressure, low in magnitude, have been observed with RSG therapy. These decreases in blood pressure have been observed in those RSG studies in which ambulatory blood pressure monitoring (ABPM) has been used [Barnett, 2003; Natali, 2004; Negro, 2005; Raji, 2003; Sarafidis, 2004; St John Sutton, 2002]. RSG has been shown to reproducibly decrease blood pressure, alone or in combination with MET or SU. Reductions in blood pressure are not seen with MET, SU or insulin.

In general, reductions in blood pressure in diabetics are associated with reduction in risk of stroke [Stratton, 2006].

4.4.4. Effects on Prothrombotic Markers

The fibrinolytic system is predominantly regulated by PAI-1, and increased activity of PAI-1 is considered an independent risk factor for cardiovascular disease such as CAD, restenosis, myocardial infarction, and other vascular diseases. Inhibition of plasminogen activation to plasmin by PAI-1 reduces proteolysis of fibrin, and increases its deposition, contributing to thrombus formation. Increased levels of PAI-1 have been associated with insulin resistance and components of the metabolic syndrome and increased plasma fibrinogen concentrations have been increasingly recognized as a risk factor for cardiovascular disease.

Fibrinolytic activities have been evaluated in several clinical studies. In a 26-week study, plasma PAI-1 antigen level and PAI-1 activity decreased from baseline in the RSG-treated group. In contrast, PAI-1 antigen increased and PAI-1 activity was unchanged in the control group. In addition, PAI-1 levels also decreased with RSG treatment in a pilot study in non-diabetic patients with essential hypertension and insulin resistance [Raji, 2003].

Although some studies have demonstrated no change from baseline in some markers of platelet activation or thrombosis, there is no evidence of a potential exacerbation of the pro-thrombotic state with the use of RSG.

4.4.5. Effect on cIMT and Restenosis

The atherosclerotic process can be assessed non-invasively by measuring the intimal-medial thickness of the carotid arterial wall (cIMT).

Treatment with RSG has been shown to slow the progression of carotid atherosclerosis, as measured by changes in carotid intimal-media thickness (cIMT). In a double-blind, randomized controlled study of subjects with insulin resistance, the progression cIMT was significantly reduced (mean change: -0.005 mm vs. 0.021 mm, p=0.007) in the common carotid artery in the diabetic group. There was also a trend toward slower progression (p=0.07) in the composite cIMT endpoints [Hedblad, 2007]. This observation was confirmed in a second study in diabetic patients randomized to receive either RSG or MET with both mean and maximal cIMT measurements from the common carotid artery [Stocker, 2007]. The effects of rosiglitazone on cIMT progression are in general consistent although less definitive in patents without diabetes [Sidhu, 2004; Bhatt, 2007]. The largest study of cIMT in non-diabetic subjects came from STARR (Study of Atherosclerosis with Ramipril and Rosiglitazone), a cIMT substudy of DREAM trial, where cIMT were evaluated in more than 1400 subjects at risk for developing diabetes for an average follow up duration of 3 years [Lonn, 2006]. In this STARR study, RSG treatment resulted in a significant reduction of cIMT progression in the common carotid artery and a trend toward slower progression in the composite cIMT endpoint.

The effect of RSG on in-stent stenosis after coronary stent placement was evaluated. After 6 months treatment with RSG, diabetic subjects had a restenosis frequency of 17.6% as compared to 38.2% in the conventional anti-diabetic agent group [Choi, 2004]. The observed effect of RSG on coronary stent restenosis was also associated with a marked reduction in CRP levels, and was independent of its hypoglycemic effects as both control and RSG groups achieved similar glycemic control

4.5. Effects on Albuminuria

Development of microalbuminuria heralds progression to overt diabetic nephropathy and end-stage renal disease [Bakker, 1999], which are among the characteristic microvascular complications of diabetes. Furthermore microalbuminuria is associated with increased cardiovascular risk. Microalbuminuria is a relatively common complication of diabetes mellitus, affecting between 15% and 60% of subjects with type 2 diabetes mellitus (T2DM). Urinary albumin excretion rate between 30mg/day (considered the upper limit of the normal range) and 300mg/day define the presence of microalbuminuria. Urinary albumin creatinine ratio (ACR) is often substituted for direct measurement of microabuminuria, in clinical trials, due to the simplicity of sample collection.

The UKPDS and DCCT studies have clearly shown that tight glycemic control significantly improves urinary albumin excretion and reduces progression to nephropathy [UKPDS 38, 1998; DCCT, 1993]. In 3 trials which measured ACR, there was a reproducible and consistent decrease from baseline in ACR for RSG-treated subjects with T2DM [Bakris, 2003; Lebovitz, 2001; Bakris, 2006] as would be expected in response to glucose lowering. In addition to the glycemic reductions observed with long-term RSG treatment in the ADOPT study, ACR also decreased. The mean change in ACR from baseline with RSG was not significantly different from GLY, but was significantly lower compared to MET. These data are consistent with the expected effect that lowering glucose with rosiglitazone should have on the progression of albuminuria, and likely other microvascular complications, as demonstrated in DCCT and UKPDS.

4.6. Safety of Rosiglitazone

4.6.1. Fluid Effects

RSG, like other TZDs alone or in combination with other anti-diabetic agents, can cause or exacerbate fluid retention and, in susceptible subjects, edema and symptoms of heart failure. Mild to moderate plasma volume expansion is believed to contribute to decreases in hematocrit (Hct) observed with this class of drugs.

Fluid retention can be caused by direct or indirect effects on the kidney or vasculature. Primary sodium retention by the kidney can lead to expanded plasma volume, decreased Hct, and increased blood pressure. Vasodilation can also result in plasma volume expansion.

GSK have conducted a number of preclinical and clinical studies to investigate fluid-retention, fluid-related events and how best to manage them. These mechanistic and fluid balance studies with RSG have produced data that support the involvement of both renal and vascular mechanisms in TZD-related fluid retention. Spironolactone or hydrochlorothiazide has been shown to be effective at reversing RSG-associated hemodilution, while furosemide was less effective. The efficacy of spironolactone as a diuretic in RSG-treated diabetics argues for a significant renal epithelial sodium transporter ENaC component in TZD-induced fluid overload.

RSG has been shown to improve endothelial function and insulin sensitivity, but has no effect on NO-dependent vasodilation in the forearm or vascular permeability in obese, insulin-resistant, non-diabetic subjects. These data in combination with the observed reductions in blood pressure suggest a vasodilatory effect of RSG.

If patients manifest peripheral edema, it can be managed with diuretics or, if necessary, by withdrawal of RSG.

4.6.2. Effects on Weight and Visceral Fat

Dose-related weight gain occurs with RSG treatment. Weight gain is also seen with SU and insulin. The mechanism of weight gain with RSG is unclear but probably involves a combination of fluid retention and increased fat mass.

Treatment of subjects with T2DM with RSG results in an increase in subcutaneous fat volume, predominantly in non-abdominal sites, but no increase in intra-abdominal (visceral) fat and a large reduction in hepatic fat [Carey, 2002; Tiikkainen, 2004; Virtanen, 2003]. The increase in fat mass corresponded with the increase in weight.

Although insulin resistance and other obesity-related metabolic abnormalities are frequently associated with overall accumulation of fat, there is growing evidence that abdominal fat has a stronger relationship with insulin resistance than peripheral, non-abdominal fat [Lefebvre, 1998]. Another difference between abdominal and peripheral fat accumulation is the association between intra-abdominal fat accumulation and a significant increase in overall morbidity and mortality [Bjorntorp, 1991; Emery, 1993]. This suggests that the pattern of body fat accumulation with RSG should not lead to a worsening of CV profile or insulin resistance. In ADOPT, RSG was associated with a stable waist:hip ratio and a progressive improvement in insulin sensitivity over the median 4 year treatment period despite continued increase in body weight.

4.6.3. Cardiac Structure and Function

Pre-clinical studies with RSG have demonstrated cardiac hypertrophy in rats and dogs that were partially reversible on withdrawal of treatment. Investigations indicated that hypertrophy was the result of a volume-driven increase in preload arising from plasma volume expansion that also resulted in reduced erythrocyte parameters. These hemodynamic effects were fully reversible upon cessation of treatment.

To assess the impact of RSG on cardiac structure and function, GSK conducted five clinical trials with echocardiography evaluation. These included 2 studies in combination with insulin therapy, two 3-year open-label studies versus glyburide, and one in subjects with NYHA I/II heart failure. These studies included a wide range of patient ages (up to 80 years of age). Echocardiography is considered to be the gold standard non-invasive method for assessment of cardiac structure and function. In all of these studies, variability of result reporting was minimized by blinded centralized review.

Overall, there were no deleterious changes in cardiac structure or function during treatment with RSG up to 3 years of treatment. In the studies in which RSG was added to insulin, left ventricular ejection fraction, left ventricular mass and other echocardiographic parameters were not significantly different from insulin monotherapy. In one of the studies, however, there was a significant reduction in left ventricular end systolic diameter with RSG compared to insulin.

In a study in T2DM subjects with pre-existing treated heart failure (NYHA class I/II), there were no deleterious effects overall on cardiac structure and function as determined by echocardiography. This was despite more fluid-related adjudicated events such as edema or dyspnea in the RSG group compared with control. These events were generally not associated with worsening heart failure or hospitalization and were managed by investigators using standard medications used to treat heart failure.

4.6.4. Heart Failure

Fluid retention which can lead to or exacerbate heart failure is a known effect of the TZD class of antidiabetic agents. The potential for the development or exacerbation of heart failure during RSG therapy is highlighted under WARNINGS, Cardiac Failure and Other Cardiac Effects. At the request of the FDA, GSK have submitted a labeling supplement to add a boxed Warning to address patients with heart failure.

In the clinical trial program, the incidence of events of heart failure was low ranging from 0.12% to 2.42% in the RSG group and 0.25% to 1.36% in the control group. The dual combination therapies with the highest incidence is RSG added to established SU and RSG added to established insulin therapy. In the insulin combination studies, patients had a longer duration of diabetes (mean duration ranged from 12 to 15 years) were older (mean age ranged from 53 to 66 years) and most had pre-existing cardiovascular disease. The fluid adverse event profile observed in the trials when RSG was added to insulin may have been influenced by the clinical trial design and the advanced patient population. In a study where insulin was added to RSG + MET therapy, there were no reports of heart failure. The study demonstrates that when current treatment guidelines regarding the use of oral agents and insulin therapy are followed (i.e. optimize oral agents before INS is started and then continued oral agents in conjunction with INS), the risk of fluid-related events such as edema and heart failure may be minimized.

4.6.5. Hepatic Effects

In light of the hepatic safety profile of the first entrant in the TZD class, troglitazone, GSK have closely monitored hepatic adverse events reported in association with RSG since launch. In addition, an independent external board of hepatologists was established to provide expert review of any reports of hepatic events. Since the launch of RSG, there continues to be no excess reporting of hepatic events; the requirement for bimonthly liver monitoring, instituted at time of launch, was removed in May 2004. The long term study ADOPT has provided further confirmation of the hepatic safety of RSG.

In ADOPT, mean ALT levels were reduced (within the normal range) and maintained over 4-6 years at a statistically significantly lower level in RSG-treated subjects compared to either MET or GLY. This improvement most likely reflects a reduction in intra-hepatic fat accumulation associated with improved insulin sensitivity due to RSG treatment, as previously described [Carey, 2002]. This observation of a long term reduction in ALT suggests RSG-induced insulin sensitization may be associated with further benefit, namely a reduced risk of a relatively common and potentially serious comorbidity, nonalcoholic steatohepatitis (NASH). Insulin sensitization may therefore be important in treating this liver disease which currently has no single effective remedy.

NASH is a metabolic liver disorder that is seen in 2-6% of the general Western population and is commonly associated with insulin resistance [Angulo, 2002], obesity and T2DM and other cardiovascular risk factors. It may be significantly more common in other ethnic populations for example black and Hispanic [Browning, 2004]. Progression to fibrosis and cirrhosis occurs in 8-26% of NASH cases and is more common in individuals with diabetes mellitus. In its earliest stages, the only findings in NASH may be elevation in transaminases. A study was conducted to determine whether

treatment with RSG would improve the characteristic histological features (steatosis, inflammation, fibrosis and cirrhosis) that define NASH. Thirty adults with NASH diagnosed by liver biopsy and increased alanine aminotransferase (ALT) levels were treated with RSG for 48 weeks. Treatment with RSG resulted in an improvement in histologic markers of NASH and liver enzyme levels decreased significantly [Neuschwander-Tetri, 2003]. This study clearly demonstrates that RSG has a beneficial effect in subjects with pre-existing NASH

4.6.6. Fractures

In view of publications of TZD effects on bone in animals and observational studies in humans, GSK evaluated the rates of bone fractures in a post hoc analysis of serious and non-serious AEs in the ADOPT study. This analysis revealed that significantly more women receiving RSG experienced fractures than did those who received either MET or GLY (Table 2). There was no observed difference among the treatment groups in the number of fractures reported in men. The majority of fractures observed in female patients who received RSG were predominantly in the upper arm (humerus), hand, or foot, sites of fracture different from those typically associated with post-menopausal osteoporosis (e.g., hip or spine).

Table 2 Patients with Fractures in ADOPT

	Rosiglitazone		**Metformin**		**Glyburide**	
MALE PATIENTS	811 Males 2766.7 PY		864 Males 2957.6 PY		836 Males 2612.8 PY	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture	32 (3.95)	1.16	29 (3.36)	0.98	28 (3.35)	1.07
FEMALE PATIENTS	645 Females 2187.2 PY		590 Females 1948.0 PY		605 Females 1630.8 PY	
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	n (%)	Rate/100 PY
Experienced a fracture*	60 (9.30)	2.74	30 (5.09)	1.54	21 (3.47)	1.29
Lower limb **	36 (5.58)	1.65	18 (3.05)	0.92	8 (1.32)	0.49
Hip	2 (0.31)	0.09	2 (0.34)	0.10	0	0
Foot	22 (3.41)	1.01	7 (1.19)	0.36	4 (0.66)	0.25
Upper limb ***	22 (3.41)	1.01	10 (1.70)	0.51	9 (1.49)	0.55
Hand	8 (1.24)	0.37	4 (0.68)	0.21	1 (0.17)	0.06
Humerus	5 (0.78)	0.23	0	0	0	0
Spine	1 (0.16)	0.05	1 (0.17)	0.05	1 (0.17)	0.06
Other	5 (0.78)	0.23	4 (0.68)	0.21	4 (0.66)	0.25

Rate/100 PY = Patients with Events per 100 Patient Years, n = number of patients
* Some patients experienced fractures in more than one category.
** Other sites of fracture included: ankle, femur, fibula, lower limb (general), patella, and tibia.
*** Other sites of fracture included: clavicle, forearm, radius, upper limb (general), and wrist.

In an effort to ascertain the significance of the findings from ADOPT, GSK requested that the DSMB from RECORD review an interim analysis of fractures. This analyses showed more female patients who received a RSG-containing regimen experienced fractures than did female patients who received a combination therapy of comparators (MET and SU). The magnitude and sites of fractures observed in the RECORD were reported as being similar to those seen in ADOPT. An increase in fractures in female patients receiving long-term treatment with pioglitazone has also been reported.

Healthcare professionals were informed of these findings via a Dear Healthcare Professional letter in February 2007 and revised prescribing information. Further investigations are ongoing to gain a better comprehension of the underlying mechanisms, clinical risks, and potential preventative measures including pre-clinical studies, assessment of bone turnover markers, and assessment of bone mineral density.

4.6.7. Carcinogenicity

In the premarketing development of RSG, lifetime studies in rats and mice did not indicate a cancer risk with RSG. With the exception of an increase in benign adipose tissue tumors in rats, there were no treatment-related effects on the incidence, degree of malignancy or multiplicity of spontaneous/background tumors in 2 year rodent carcinogenicity studies in which systemic exposure to RSG was at least 10-fold higher than maximal clinical exposure with RSG.

However, owing to findings with other PPAR agonists, including those which activate γ, δ, α+γ, and α+γ+δ PPAR isoforms, an analysis of all reports of neoplasms in the RSG clinical trials database was undertaken. Across the integrated clinical trials, the incidence for any malignant, benign or unspecified neoplasm was similar for RSG and non-RSG treatment regimens. Two epidemiologic studies in managed care databases did not reveal an increased risk of cancer in diabetic subjects on TZD compared to diabetic subjects on non-TZDs [Koro, 2006; Koro, 2007].

ADOPT provides long-term controlled data to supplement the information summarized above, with 4954 patient-years experience on RSG, 4244 on GLY and 4906 on MET and a median follow-up of 4.0 years. The percentage of subjects with malignant neoplasms or cancers on therapy was low and similar between the RSG group (68 subjects, 4.7%, 1.4/100 PY) and the other two groups (79 subjects, 5.5% for GLY/GLIB, 1.9/100 PY and 84 subjects, 5.8%, 1.7/100 PY for MET), respectively (Table 3). These long term data substantially add to the weight of evidence indicating that RSG does not pose a carcinogenic risk in humans.

Table 3 Summary of ADOPT On-Therapy Malignant Neoplasm or Cancer AEs (All Randomized Population)

High Level Group Term	Number of subjects with malignant neoplasms or cancers, n (%)					
	RSG N=1456 PY=4953.8		MET N=1454 PY=4905.6\		GLY/GLIB N=1441 PY=4243.6	
	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY	n (%)	Rate / 100 PY
Subjects with AEs	68 (4.7)	1.4	84 (5.8)	1.7	79 (5.5)	1.9
Gastrointestinal neoplasms	17 (1.2)	0.3	12 (0.8)	0.2	16 (1.1)	0.4
Skin neoplasms	13 (0.9)	0.3	22 (1.5)	0.5	19 (1.3)	0.5
Reproductive neoplasms – male[1]	10/811 (1.2)	0.4	12/864 (1.4)	0.4	10/836 (1.2)	0.4
Breast neoplasms	6 (0.4)	0.1	7 (0.5)	0.1	3 (0.2)	0.1
Respiratory and mediastinal neoplasms	5 (0.3)	0.1	12 (0.8)	0.2	10 (0.7)	0.2
Leukemia, lymphoma, and plasma cell neoplasms	4 (0.3)	0.1	3 (0.2)	0.1	4 (0.3)	0.1
Renal and urinary tract neoplasms	4 (0.3)	0.1	5 (0.3)	0.1	6 (0.4)	0.1
Reproductive neoplasms – female[2]	4/645 (0.6)	0.2	1/590 (0.1)	0.1	3/605 (0.5)	0.2
Miscellaneous and site unspecified	3 (0.2)	0.1	3 (0.2)	0.1	2 (0.1)	<0.1
Endocrine neoplasms	2 (0.1)	<0.1	7 (0.5)	0.1	8 (0.6)	0.2
Metastases unknown origin	2 (0.1)	<0.1	1 (0.1)	<0.1	2 (0.1)	<0.1
Soft tissue sarcomas	1 (0.1)	<0.1	0	0	0	0
Nervous system neoplasms	0	0	2 (0.1)	<0.1	1 (0.1)	<0.1

1. Male subjects only (PY=2766.7, PY=2612.8, and PY=2957.6 for RSG, GLY/GLIB, and MET groups, respectively).
2. Female subjects only (PY=2187.2, PY=1630.8, and PY=1948.0 for RSG, GLY/GLIB, and MET groups, respectively).

Note: Sorted by frequency of adverse events in RSG group.

5. MYOCARDIAL ISCHEMIC EVENTS DURING TREATMENT WITH ROSIGLITAZONE

Throughout the development program, GSK evaluated investigator reported CV events in clinical studies with RSG. Typically, events rates were very low in individual studies. These events were also summarized across studies supporting specific indicated uses for RSG. Although low in numbers, more CV events were seen in insulin add-on studies. These studies demonstrated a higher incidence of edema and heart failure with the addition of RSG compared to continuation of insulin monotherapy. In addition, in a study of patients with established heart failure (NYHA class 1 or 2 at entry with treatment) and type 2 diabetes, there were numerically more events of myocardial ischemia (as reported by investigators) for RSG compared to control as well as more events of edema and dyspnea. These observations have previously been incorporated into "WARNINGS, Cardiac Failure and Other Cardiac Effects" of the US prescribing information for RSG.

As part of GSK's ongoing pharmacovigilance program, a patient-level retrospective analysis of the integrated clinical trial (ICT) database was undertaken to evaluate the association, if any, between RSG and heart failure and separately events of myocardial ischemia. Broadly inclusive adverse event terms captured from investigator reports were used to minimize the possibility of missing events. The ICT database included 42 double-blind, randomized controlled trials of varied design and patient populations and used modeling techniques to account explicitly for important patient characteristics. This analysis first evaluated RSG-containing regimens vs. comparator regimens in seven separate strata. Subsequently a single comparison across all strata was performed. Although the well-recognized limitations of this methodology were outlined in the ICT analysis plan, GSK deemed it important to undertake this exploratory analysis to gain additional perspective on the current database ahead of receiving results from longer-term trials.

In order to evaluate whether observations in the ICT with respect to myocardial ischemic events would be replicated in a real-world setting, a balanced cohort observational study was commissioned. The balanced cohort study was conducted in a US managed care database of 33,363 patients on oral anti-diabetic treatment between 2000 and 2004. This study assessed a composite cardiovascular endpoint of hospitalizations for myocardial infarction and/or coronary revascularization and compared RSG, MET, or SU as monotherapy, dual-therapy combinations, and insulin combinations. Details of the ICT and the balanced cohort study were formally submitted in August 2006 to the FDA (Supplement 022).

Subsequent to the completion of the ICT and the balanced cohort study analyses, two large prospective, multi-year, controlled trials, ADOPT and DREAM, were completed. These trials provide additional information on the long term cardiovascular safety of RSG.

In May 2007, a report published in NEJM sparked public debate on the cardiovascular safety of RSG. This study-level meta-analysis was conducted on a set of trials which largely overlapped the ICT and reported results comparing RSG to non-RSG groups for

myocardial infarction and CV death. Subsequently, an interim safety analysis on the ongoing CV outcome study, RECORD, was published in response to public debate. Recently, 2 more epidemiology studies were completed which examined cardiovascular endpoints in other managed care settings. These trials also included pioglitazone.

The ICT originally focused on a broad assessment of events related to myocardial ischemia. In subsequent analyses, 'harder' CV endpoints; MACE (CV death, MI or stroke) and its individual components; were evaluated in both the ICT and ADOPT. In RECORD and DREAM, MACE endpoint and its components were determined through a pre-planned blinded adjudication process. In contrast, for ADOPT and ICT, programmatic algorithms were used to identify events based on the standardized medical dictionary coding (MedDRA) of verbatim serious adverse event (SAE) terms provided by investigators.

PPAR, a study in high-risk patients undergoing PCI, provides additional relevant CV safety information. A number of CV outcome studies are ongoing, each with an independent Steering Committee and DSMB. A description of these ongoing studies is provided in this section.

The data presented in this section come from a wide variety of sources with endpoints ranging from broadly defined myocardial ischemic events to the more specific MACE and its components. Some of the events were adjudicated, others were defined through post study review or programmatic algorithms based on medical dictionary coding of investigator reports of adverse events. The data sources include a patient-level meta-analysis, 3 observational trials, 2 long-terms trials designed primarily to assess glycemic control or prevention of diabetes and the interim report of an ongoing CV outcomes trial.

Key criteria to consider in evaluating the relative weight of evidence conferred in each data source include:

- *Possible bias in ascertainment of the endpoints:* Trials designed with in-stream adjudication and full follow of patients offer the most complete and reliable assessment of the endpoints of interest. In contrast, when unadjudicated adverse events are used for endpoint assessment, there will remain uncertainty regarding the accuracy of the assignment of the event. The uncertainty is compounded when computer algorithms solely are used to assign events from medical dictionary coded terms from investigator reports of adverse events.
- *Nature of the endpoint:* Endpoints of death, CV death, myocardial infarction and stroke are generally accepted as the most serious and irreversible of CV outcomes. These are commonly assessed both as a composite and as individual components.
- *Possible sources of bias in patient selection:* Randomized clinical trials are generally viewed as more robust than observational trials despite propensity score matching techniques which attempt to eliminate confounding factors.
- *Number of events* : Numerical reliability and robustness of the results are compromised by small numbers of events
- *Length of exposure* : Short –term trials may not reliably provide predict long-term outcomes

- *Choice of control group*: Given the potential impact of confounding factors on the assessment of CV safety, the control group should aim to be matched for glycemic, blood pressure and lipid control.

Of the available data sources for the assessment of the CV profile of RSG, RECORD best meets these criteria. While the event rate is low and the results available are from an interim analysis, it offers the most definitive source of knowledge on CV outcomes at this time. ADOPT, while not a CV outcome trial, provides an assessment of both efficacy and safety over 4 to 6 year of exposure relative to other active treatments in the same population of drug naïve diabetics. DREAM was also not a CV outcome study but provides 3 year safety data in a pre-diabetic population. In DREAM, CV events were adjudicated but were low in number. Meta-analyses (whether patient-level or study-level) are generally used to generate hypotheses. Observational studies are used to evaluate real-world experience.

5.1. Retrospective, Integrated Analysis of Data from 42 Controlled Clinical Trials

This patient level analysis included 42 double-blind, randomized controlled trials of 14,237 patients with T2DM (including those with pre-existing heart failure (NYHA class 1 or 2) and those on background INS therapy) which evaluated RSG-containing vs. comparator regimens. Separate comparisons were performed within the following seven treatment comparison strata, representing the different combinations of RSG treatment regimens and control groups:

- RSG monotherapy vs. Placebo
- RSG monotherapy vs. SU monotherapy / MET monotherapy
- SU+RSG vs. SU monotherapy
- MET+RSG vs. MET monotherapy
- MET+RSG vs. MET+SU
- SU+ MET+RSG vs. SU+MET
- INS +RSG vs. INS monotherapy

An overall pooled estimate was calculated across all treatment comparisons for myocardial ischemic events in the ICT dataset.

5.1.1. Studies Included in the Analysis

Studies considered for inclusion in this statistical analysis were all GSK sponsored RSG studies in patients or studies included in regulatory submissions for RSG. Specific requirements for inclusion in the statistical analysis were:

- The study must have included a control regimen (placebo or active). This was required so that possible inter-study differences could be accounted for in the statistical analysis and to minimize bias.

- The study population must have been adults who have T2DM. This is the population for which RSG is currently indicated.

- The study must have included data on either 4mg or 8mg RSG doses. These are the total daily doses of RSG approved for use in the treatment of T2DM.

- The study must have been double-blind. This minimizes potential differential reporting bias between RSG and control groups.

- Studies for inclusion must have analysis completed prior to August 2005.

Forty-two clinical studies met this criteria. The complete list of studies included is provided in Appendix C.

5.1.2. Methodology

In the ICT, an analysis of events of heart failure, and separately, events related to myocardial ischemia were conducted. Since the potential for fluid retention which can lead to or exacerbate of heart failure is a known effect of the TZD class, the following discussion will concentrate on events related to myocardial ischemia.

The analysis was conducted primarily on myocardial ischemic events that were defined as "serious" adverse events or SAEs. Serious adverse events, as defined in FDA's regulations, are those events resulting in hospitalization or those events considered to be life-threatening or permanently disabling. An analysis was also conducted on ALL myocardial ischemic adverse events; this analysis included both SAEs and events that did not meet the definition of a serious event, i.e. non-serious adverse event.

SAEs identified from the ICT dataset included cardiac failure, angina pectoris, acute pulmonary edema, all cases of chest pain without a clear non-cardiac etiology, myocardial infarction/myocardial ischemia, and all SAEs with a fatal outcome. A broad definition of myocardial ischemic events was used for this analysis, without an attempt to categorize cause. This approach minimized the potential of missing events. The determination of heart failure or myocardial ischemia events was based on a retrospective blinded patient level review of narrative summaries for SAEs and a blinded review of the individual investigator-provided verbatim terms/descriptions for non-serious AEs by three GSK physicians (2 endocrinologists and a cardiologist). Since the review was conducted retrospectively on completed clinical trials, there was no opportunity to obtain additional or clarifying information about the reported events. For SAEs, the narrative summaries were also reviewed by an independent, external cardiologist. Any difference in opinion between the three GSK physicians was independently arbitrated by the external cardiologist.

Following identification, these events were categorized as heart failure or myocardial ischemia following a blinded physician review. For an SAE to be classified as myocardial ischemia, an indication of new or worsening symptoms or evidence of progression of underlying disease (e.g. cardiac enzymes, electrocardiogram or coronary angiogram), subsequent to drug administration, was required. If there was insufficient

evidence to exclude myocardial ischemia, the event category defaulted to the original investigator diagnosis. Planned coronary interventions, such as percutaneous coronary intervention or coronary artery bypass graft, where there was no evidence of worsening clinical status nor objective evidence of increasing ischemia were classified as 'neither' myocardial ischemia nor heart failure. Sudden deaths of unknown causes were classified as myocardial ischemia. Where heart failure and myocardial ischemia occurred concomitantly, the primary clinical event was identified by the independent external cardiologist and the secondary event was excluded from the evaluation.

For non-serious AEs, events were classified as myocardial ischemia or heart failure based on a blinded review of the information provided by the investigator in the case report form. In contrast to SAEs, in cases where heart failure and myocardial ischemia AEs occurred concomitantly, both events were included within the individual heart failure and myocardial ischemia counts as these data were insufficient to determine which event occurred first.

The primary data analysis for each treatment regimen was based on SAEs reported for RSG 4mg and 8mg combined. In the secondary analysis, comparisons were performed for all AE data (serious and non-serious events combined). The primary methodology employed was an exact logistic regression analysis, performed separately for data from each treatment comparison, and adjusted for the number of major CV risk factors for each patient (0, 1, ≥2). Major CV risk factors included pre-existing CHD, cerebrovascular disease, peripheral vascular disease and heart failure. Duration of exposure was accounted for within the analysis.

5.1.3. Results

Overall, the incidence of myocardial ischemia SAEs was low in the ICT dataset ranging from 0.68% to 1.40% in the RSG group and 0.21% to 2.04% in the control group (Table 4). In some comparisons, very few events were observed making interpretation difficult. The odds ratios (OR) for each of the seven strata in the ICT dataset were greater than unity for SAEs and for AEs (SAEs + non-serious AEs combined), although each had broad 95% CIs whose lower bound crossed unity. The exception was the AEs in the MET+RSG vs MET monotherapy stratum where the 95% CI ranged from 1.17–7.03 (Table 5). This result may be related to 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 in the ICT dataset.

When data on AEs (SAEs + non-serious AEs combined) from all treatment strata were pooled into a single data set, the incidence of myocardial ischemic events in the RSG group was 1.99% (171/8604) and in the control group was 1.51% (85/5633), with a corresponding hazard ratio of 1.31 (95% CI 1.01-1.70) (Table 5).

The incidence of deaths related to myocardial ischemia was similar between the all RSG group (0.14%, n=12/8604) and the all control group (0.11%, n=6/5633).

Table 4 Myocardial Ischemia SAEs – Results from the Integrated Clinical Trials Dataset

RSG Treatment Regimen	Control Group	Odds Ratio Point Estimate (95% CI)	Events / Patients (%)	
			RSG	Control
RSG Mono	Placebo	2.03 (0.67, 8.24)	19 / 1737 (1.09%)	4 / 792 (0.51%)
RSG Mono	SU or Met Mono	1.20 (0.46, 3.21)	11 / 1127 (0.98%)	10 / 1001 (1.00%)
MET+RSG	MET Mono	3.33 (0.88, 18.63)	11 / 1608 (0.68%)	3 / 1419 (0.21%)
MET+RSG	MET + SU	1.03 (0.21, 4.48)	4 / 285 (1.40%)	6 / 294 (2.04%)
SU+RSG	SU Mono	1.08 (0.57, 2.07)	25 / 2505 (1.00%)	19 / 1926 (0.99%)
SU+MET+RSG	MET + SU	1.26 (0.29, 7.61)	7 / 597 (1.17%)	3 / 310 (0.97%)
INS+RSG	INS Mono	2.29 (0.69, 9.77)	12 / 867 (1.38%)	4 / 663 (0.60%)

Calculated using exact logistic regression analysis performed separately for data from each treatment comparison, and adjusted for number of major CV risk factors and duration of exposure

Table 5 All Myocardial Ischemia AEs (Serious and Non-Serious AEs combined) – Results from the Integrated Clinical Trials Dataset

RSG Treatment Regimen	Control Group	Odds Ratio Point Estimate (95% CI)	Events / Patients (%)	
			RSG	Control
RSG Mono	Placebo	1.15 (0.58, 2.46)	32 / 1737 (1.84%)	12 / 792 (1.52%)
RSG Mono	SU or MET Mono	1.13 (0.60, 2.11)	25 / 1127 (2.22%)	22 / 1001 (2.20%)
MET+RSG	MET Mono	2.72 (1.17, 7.03)	23 / 1608 (1.43%)	8 / 1419 (0.56%)
MET+RSG	MET + SU	1.25 (0.34, 4.47)	6 / 285 (2.11%)	7 / 294 (2.38%)
SU+RSG	SU Mono	1.09 (0.72, 1.65)	53 / 2505 (2.12%)	39 / 1926 (2.02%)
SU+MET+RSG	MET + SU	1.80 (0.55, 7.63)	13 / 597 (2.18%)	4 / 310 (1.29%)
INS+RSG	INS Mono	2.07 (0.93, 5.07)	24 / 867 (2.77%)	9 / 663 (1.36%)

Calculated using exact logistic regression analysis, performed separately for data from each treatment comparison and adjusted for number of major CV risk factors and duration of exposure

5.2. Epidemiological Studies

To explore cardiovascular safety in a real world setting, GSK have conducted 1 epidemiology study and commissioned 2 epidemiology studies.

5.2.1. A Nested Case-Control Study of the Effect of Thiazolidinedione Exposure on the Risk of Myocardial Infarction in Type 2 Diabetic Patients

We updated a previously conducted nested case-control study (Koro et al. 2004) of the odds of myocardial infarction in type 2 diabetic subjects exposed to the TZDs (RSG and pioglitazone, separately) compared to subjects exposed to other anti-diabetic therapies. The previous study calculated the risk of myocardial infarction in TZD users compared to users of other types of anti-diabetic therapies during 1997-2002. The current study includes more recent data and an additional four years of observation through 2006. The study report was completed in June 2006 and submitted to FDA.

This study uses data from the Integrated Healthcare Information Services (IHCIS) healthcare claims database, a US managed care claims database. The study design is a case-control analysis nested within the cohort of eligible type 2 diabetic subjects captured in IHCIS from 1999-2006. Incident cases of hospitalization for myocardial infarction among type 2 diabetic patients were identified. Three controls were matched to each case on age (+/- 5 years), gender, calendar year of first diabetes diagnosis and year of MI diagnosis (index year). The odds of myocardial infarction were modeled using conditional logistic regression, adjusting for age, gender, ACE inhibitor use, beta-blocker use, diuretic use, nitrate use, hyperlipidemia diagnosis, and hypertension diagnosis.

The incidence rate of myocardial infarction in the diabetic cohort was 5.25 per 1,000 person-years [95% CI: 5.14, 5.35]. During an average follow-up of 2.1 years, 9,870 MI cases (1.1%) were identified and matched to 29,610 controls. In the 3 months prior to the index date (recent exposure), 1,149 (11.6%) cases and 2,690 (9.1%) controls were exposed to RSG; 910 (9.2%) cases and 2,433 (8.2%) controls were exposed to pioglitazone; and 5,644 (57.2%) cases and 13,702 (46.3%) controls were treated with other anti-diabetic therapies excluding TZDs.

The results of this study suggest that the risk of myocardial infarction in subjects exposed to rosiglitazone is not different from those exposed to other anti-diabetic agents (OR 1.02 [95% CI: 0.94–1.11]). Among subjects treated with pioglitazone, the point estimate for the risk of myocardial infarction is 10% lower than those treated with other anti-diabetic therapy (Adjusted OR 0.90 [95% CI: 0.82–0.98]). Considering that this study utilized a nested case-control design, the results of the two cohort studies utilizing propensity scores that are described in sections 5.2.2 and 5.2.3 represent a higher level of study design and evidence.

5.2.2. Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents

The objective of this study was to compare the risk of myocardial infarction and coronary revascularization (CR) in type 2 diabetic patients treated with RSG, MET, or SU, in monotherapy, dual therapy and in combinations with insulin.

The source population was derived from the Ingenix Research Database, a proprietary research database of commercial enrollees who have both medical and prescription

benefit coverage in one of the largest US managed care organizations. This study reflects real-world clinical management of subjects with type 2 diabetes. Three study groups of monotherapy, dual-therapy, and combination with insulin were formed and matched using propensity score matching. The cohorts were followed for the occurrence of hospitalizations for myocardial infarction or coronary revascularization (CR). Myocardial infarction and CR were selected because they are hard endpoints related to myocardial ischemia and were previously validated; the claims definition of CR agreed with clinical review for 95% of the cases, and there was good agreement between the claims clinical assessment of myocardial infarction and medical record confirmation (Johannes 2007). Incidence rates and 95% confidence intervals for the outcomes were calculated and the relative risks comparing RSG to other anti-diabetic agents were estimated using Cox proportional hazards models.

A total of 26,931 initiators of monotherapy, 4,086 initiators of dual-therapy, and 2,346 initiators of combination with insulin therapy are included in this analysis. Table 6 shows the incidence rates and 95% confidence intervals for the composite outcome of myocardial infarction and/or CR in the follow-up period for each of the therapy groups indicating a similar effect of RSG to both MET and to SU. Overall, there was little difference in the risk of the composite outcome or of each of the individual outcomes of myocardial infarction (Figure 5) and CR comparing RSG therapies to non-RSG therapies. The overall HR for the composite outcome comparing RSG to non-RSG regimens was 0.93 with corresponding 95% CI: 0.80, 1.10.

The investigators of this study reported the following the conclusions. “The results from the monotherapy and the dual-therapy comparisons, though not individually significant, are consistent in suggesting that the risk of cardiovascular outcome events in patients using RSG may lie between the risks associated with SUs (higher incidence) and MET (lower incidence) [McAfee, 2007].

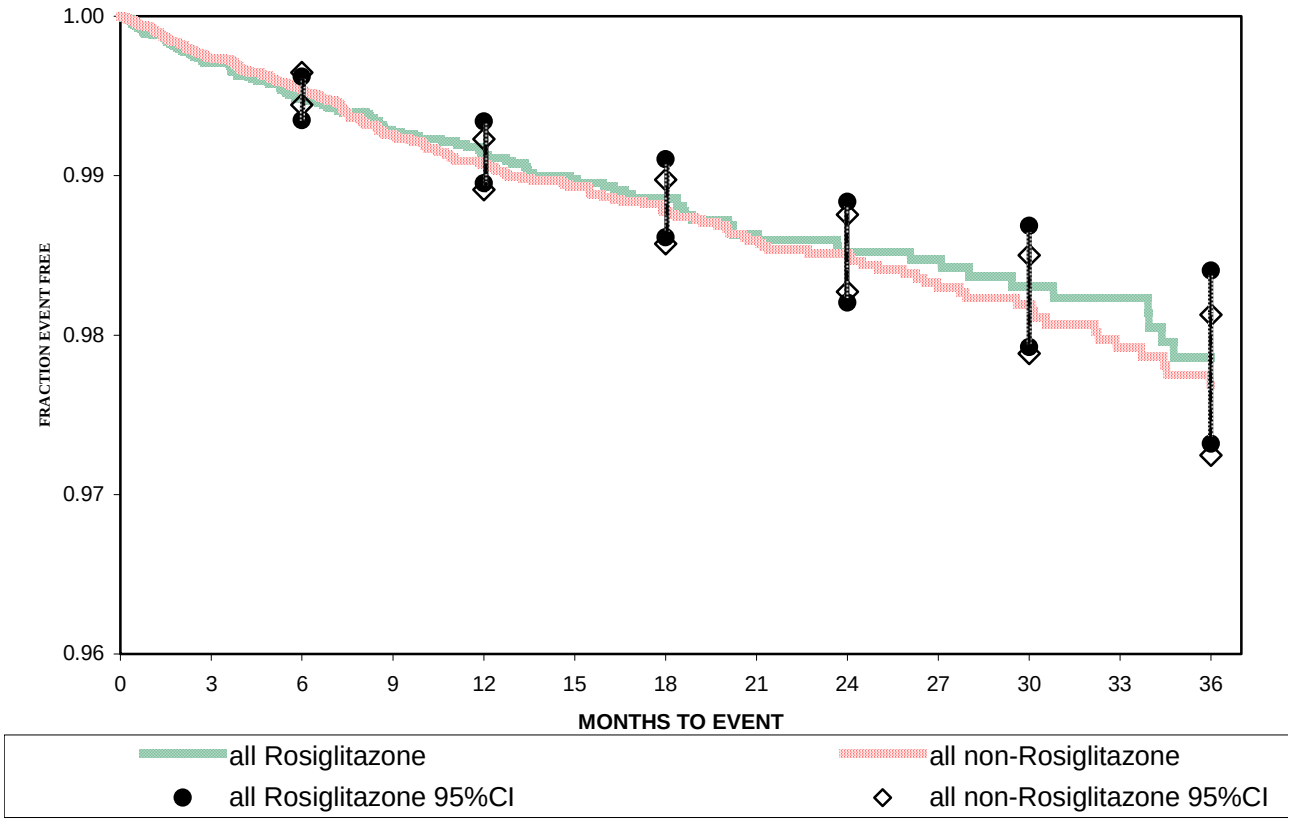
Table 6 Crude Incidence Rates of the Composite Outcome (Myocardial Infarction and/or CR) for Monotherapy, Dual Therapy, Insulin Therapy and All Therapies Combined.

	N	Events	Person-Years	IR[1]	95% C.I.[1]	
Monotherapy						
Rosiglitazone	8,977	152	9,676	15.71	13.36	18.36
Metformin	8,977	149	10,722	13.90	11.80	16.27
Sulfonylurea	8,977	191	9,772	19.55	16.92	22.47
Dual therapy						
Rosiglitazone + Metformin	1,362	24	1,683	14.26	9.37	20.86
Rosiglitazone + Sulfonylurea	1,362	39	1,474	26.46	19.10	35.78
Metformin + Sulfonylurea	1,362	36	1,852	19.44	13.84	26.60
Insulin Therapy						
Rosiglitazone	1,173	44	1,997	22.03	16.22	29.29
Other[2]	1,173	51	1,957	26.06	19.62	33.97
Combined Therapies						
Rosiglitazone	12,874	259	14,830	17.46	15.43	19.69
Non-Rosiglitazone	20,489	427	24,303	17.57	15.96	19.30

[1] Incidence rates and 95% confidence intervals per 1,000 person-years.

[2] Other antidiabetic agents, excluding TZD's

Figure 5 Kaplan-Meier curves for Myocardial Infarction for All therapy Cohorts containing RSG compared to the remaining non-RSG therapy cohorts



Number of people at risk for myocardial infarction

	0 Months	6 Months	12 Months	18 Months	24 Months	36 Months
RSG	12,874	8,475	5,671	3,717	2,482	931
non-RSG	20,489	14,150	9,393	6,121	4,064	1,523

5.2.3. Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents in the PharMetrics Data Base

Ingenix conducted a second cohort study of myocardial infarction and CR among diabetic subjects who have used a TZD compared with diabetics who used SU and MET, as monotherapy and in combination with oral anti-diabetic agents and insulin. This study tests the reproducibility of the results of the balanced cohort study described above using an independent data source, PharMetrics. In contrast to the previous study, it includes both TZDs, rosiglitazone and pioglitazone, analyzed separately. The number of patients

is nearly four-fold larger than the previously conducted balanced cohort study [McAfee et al. 2007] and includes current data up to March, 2007.

The PharMetrics Patient-Centric database used to conduct the study consists of automated claims patient data that have been aggregated over some 80 managed care databases from the United States. New users of specific anti-diabetic regimens from June 2000 through March 2007 were identified and classified into monotherapy with rosiglitazone, pioglitazone, MET and SU; dual therapy with any two of these agents; use of any of these agents or other oral anti-diabetic drugs in conjunction with insulin. During follow-up, new cases of myocardial infarction or CR were captured using hospital discharge diagnosis from insurance claims. The primary endpoint was the first occurrence of myocardial infarction or CR. Relative risks for pair wise head-to-head comparisons within monotherapy, dual therapy and combination with insulin cohorts were calculated using a stratified Cox proportional hazards model, with ten strata created from the central 90 percent of the propensity scores appropriate to each pair.

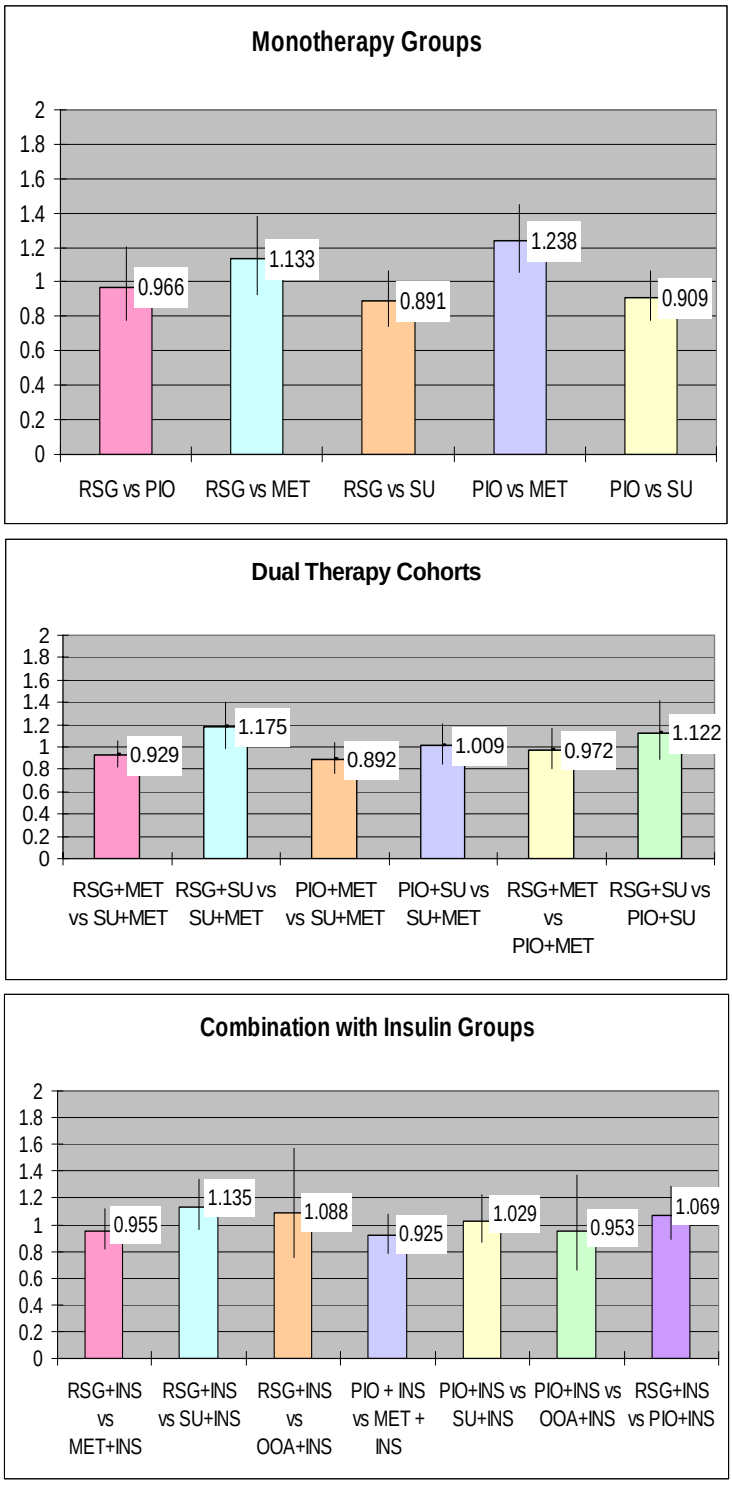
Table 7 provides the number of subjects included in the various cohorts, the number of events of myocardial infarction and the composite outcome as well as the crude incidence rate of myocardial infarction and the composite outcome. In considering these crude incidence rates, it is important to note that SU initiators were generally older compared to MET initiators (Tables 1, 2 and 3 of Draft report in Appendix D) which included a relative preponderance of subjects under the age of 35. These younger patients also had fewer comorbid conditions and baseline CV risk factors. Initiators of rosiglitazone and pioglitazone were more similar to one another in patient characteristics than were patients on other regimens. Pioglitazone initiators had a higher prevalence of baseline hyperlipidemia than did rosiglitazone initiators (48.3% for pioglitazone monotherapy compared to 42.5% for rosiglitazone monotherapy). However, this difference was adjusted by including hyperlipidemia in the propensity score.

Table 7 Incidence Rates of the Myocardial Infarction and the Composite Outcome (MI and/or CR) for Monotherapy, Dual Therapy, and Combination with insulin Cohorts

	Number of Subjects	Number of subjects with MI	Number of subjects with Composite outcome (MI &/or CR)	Rate of MI per 1000 pt-years	Rate of Composite per 1000 pt-yrs	Average Follow-up in Months
Monotherapy Cohorts						
RSG	**12,440**	44	**166**	3.13	**11.81**	**14**
PIO	**16,302**	66	**227**	3.65	**12.57**	**13**
MET	**131,075**	375	**1064**	2.42	**6.85**	**14**
SU	**48,376**	338	**821**	5.97	**14.50**	**14**
Dual therapy cohorts						
RSG+MET	**26,885**	100	**347**	3.12	**10.84**	**14**
RSG+SU	**10,021**	81	**183**	7.59	**17.15**	**13**
PIO+MET	**17,282**	49	**199**	2.79	**11.33**	**12**
PIO+SU	**10,133**	57	**171**	5.07	**15.20**	**13**
MET+SU	**79,004**	437	**1304**	4.32	**12.88**	**15**
Combination with Insulin cohorts						
RSG+INS	**8,035**	92	**264**	7.63	**21.89**	**18**
MET+INS	**21,841**	198	**663**	5.91	**19.77**	**18**
SU+INS	**12,147**	160	**397**	8.78	**21.79**	**18**
OTHER+INS	**1,380**	9	**37**	5.01	**20.60**	**16**
PIO+INS	**7,924**	89	**249**	7.31	**20.44**	**18**

Figure 6 provides the hazard rates and 95% CI for the composite outcome for monotherapy, dual therapy and combination with insulin cohorts in three panels. The hazard ratios are based on the propensity-score stratified analysis described above. The 95% confidence intervals are not adjusted for multiplicity. Unlike the crude rates of outcomes provided in Table 7, these hazard rates are adjusted for baseline differences between pair-wise compared groups that may have influenced physician's prescribing. They should not be linked to the crude rates. For the combined endpoint of myocardial infarction plus coronary revascularization, the hazard ratio for rosiglitazone versus pioglitazone was 0.97 (95% CI 0.78 – 1.20), indicating no statistically significant difference between these TZDs. Both agents had somewhat less favorable outcomes than MET, and both had somewhat better outcomes than SU.

Figure 6 Hazard rates and 95% CI* for the composite outcome for monotherapy, dual therapy and combination with insulin cohorts



*not adjusted for multiplicity

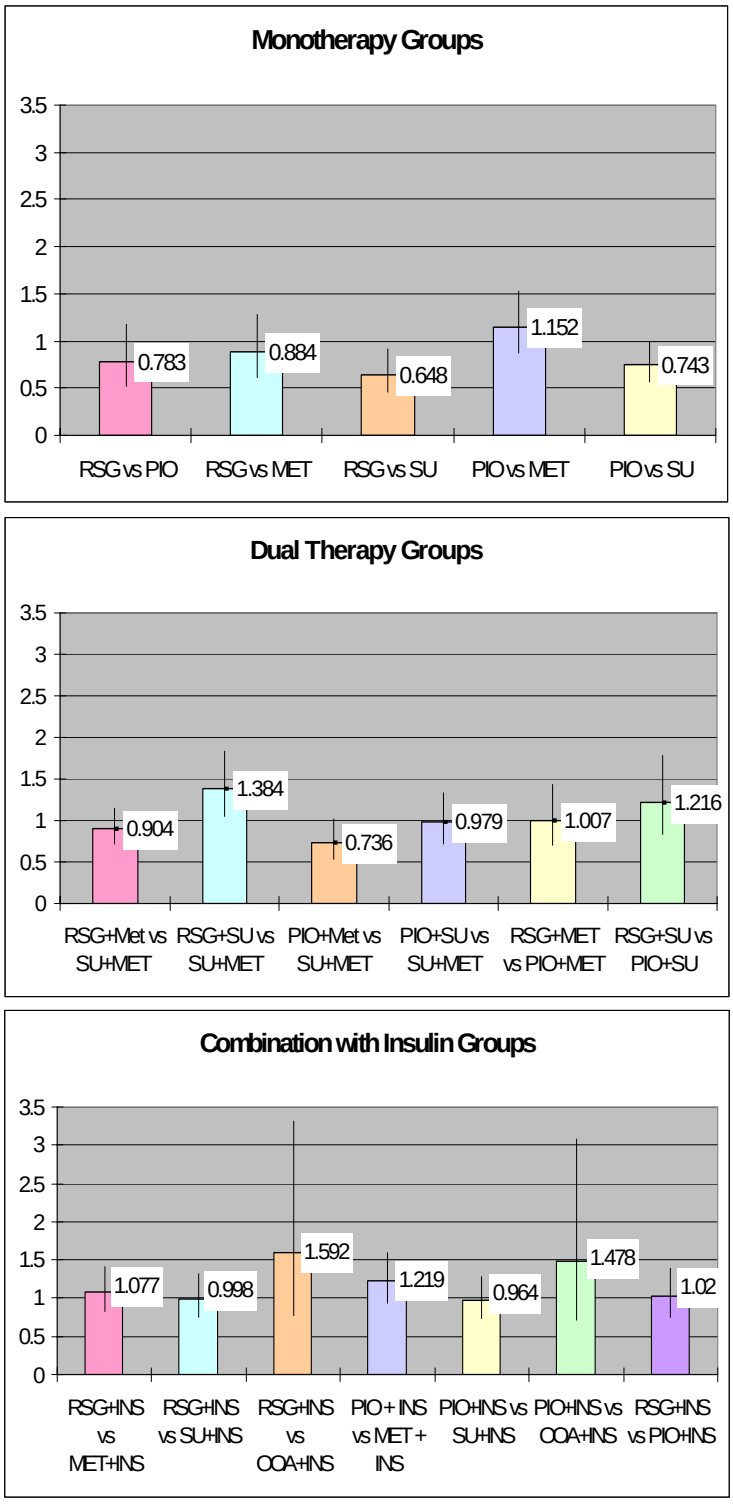
RSG = rosiglitazone PIO = pioglitazone MET = metformin SU = sulfonylureas OOA = other oral agents

In the dual therapy cohorts, outcome rates in the rosiglitazone users versus the pioglitazone users were similar in combination with both MET (HR 0.97, 95% CI 0.81 – 1.17) and SU (HR 1.12, 95% CI 0.89 – 1.41). No combination with rosiglitazone or pioglitazone was meaningfully different in terms of outcome rates from a metformin-sulfonylurea combination. In the combination-with-insulin cohorts, the risk of the combined endpoint was essentially the same in rosiglitazone and pioglitazone (HR 1.07, 95% CI, 0.89 – 1.29), and the combination of either of these with insulin had similar risks to combinations of either SU or MET with insulin. Users of other anti-diabetic drugs in combination with insulin were too few to interpret the hazard ratios as stable estimates.

The individual components of the composite outcome showed similar patterns to the composite outcome, though with more variation and wider confidence intervals. The hazard ratios for myocardial infarction are shown in Figure 7 which includes 3 panels, monotherapy, dual therapy and combinations with insulin.

In conclusion, the incidence rate of a combined endpoint of myocardial infarction and coronary revascularization and its individual components in users of rosiglitazone appears the same as in users of pioglitazone, MET and SU. Further details of the study are included in the preliminary study report (Appendix D). Ingenix is in the process of completing sensitivity analyses to confirm the robustness of the findings. An indication of the sensitivity and estimates of the hazard ratios for 100% of the study population are provided in an Appendix to the report. The conclusions stated above hold.

Figure 7 Hazard ratios and 95% CI* for Myocardial Infarction



*not adjusted for multiplicity

RSG = rosiglitazone PIO = pioglitazone MET = metformin SU = sulfonylureas OOA = other oral agents

5.3. ADOPT (A Diabetes Outcome Progression Trial)

ADOPT is the only study since UKPDS to directly compare the clinical profile of 3 commonly used oral anti-diabetic agents in long-term therapy. It was a double-blind, randomized, international, parallel group study with treatment duration ≥4 years to ≤6 years. ADOPT was conducted to fulfill a Phase 4 commitment to the FDA for a long-term safety and efficacy study for RSG. Drug naïve subjects with type 2 diabetes $\underline{<}$ 3 years since diagnosis were randomized in a 1:1:1 ratio to RSG, glyburide/glibenclamide (GLY/GLIB) or MET. The primary endpoint was time to monotherapy failure. In addition to assessing pancreatic beta-cell function, ADOPT also included the monitoring of ALT, cardiovascular events, hematologic events, serum lipids and body weight.

5.3.1. Methodology for assessment of CV reporting

Investigator-reported verbatim terms/descriptions of all adverse events were coded using a standard computerized medical coding system (MedDRA). There was no separate adjudication of CV events and subjects were followed until they met the primary endpoint event of monotherapy failure, withdrew from the study for non-monotherapy failure reasons or reached the study end. The analysis plan for the trial included statistical evaluation of cardiovascular AEs. Additional post-hoc analyses of major adverse cardiovascular events (MACE) SAEs and its components were conducted subsequently (section 5.6). Time to cardiovascular AEs was compared between treatment groups via proportional hazards regression with terms for treatment and number of major cardiovascular risk factors at baseline. Major cardiovascular risk factors included pre-existing myocardial ischemia, heart failure/pulmonary edema, peripheral vascular disease and cerebrovascular disease. Analysis was conducted separately for serious AEs and all AEs (serious and non-serious).

5.3.2. Results

Myocardial ischemic events included reported events of angina pectoris, coronary artery disease and myocardial infarction.

Events of myocardial ischemia expressed in rates per 100-PY were similar among the three treatment groups for both AEs and SAEs (Table 8). Additionally, the hazard ratios were comparable across the 3 treatment groups (Figure 8 and Figure 9). Importantly, the incidence of each component of myocardial ischemia including myocardial infarction was comparable in the three treatment groups (Table 8).

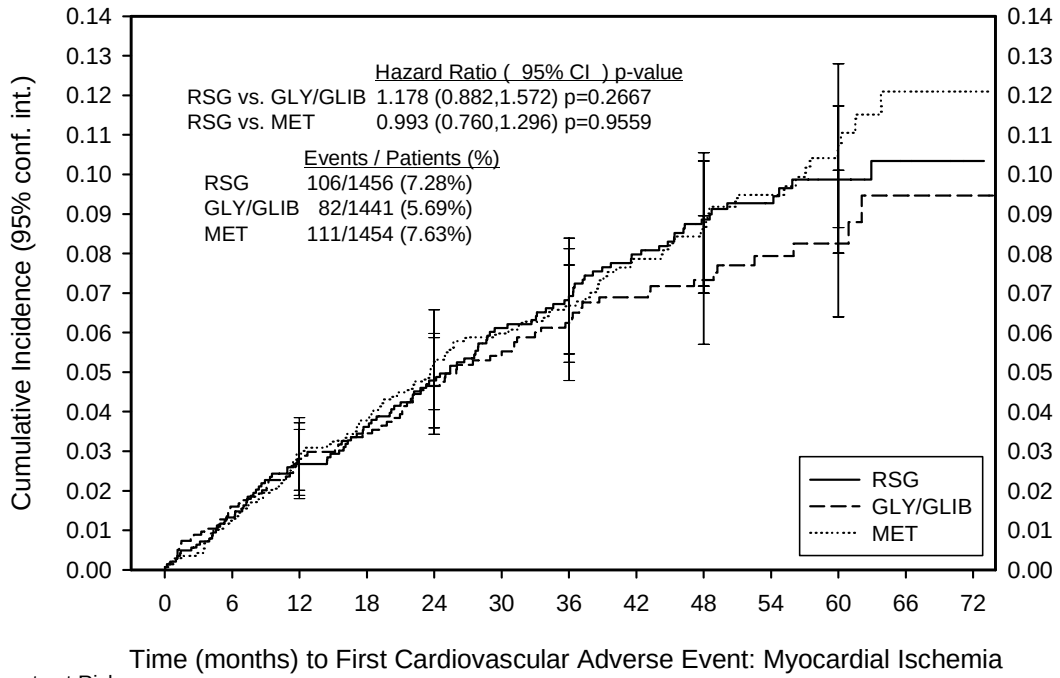
As shown in Figure 8, the incidence of myocardial ischemia with RSG was comparable to MET. In comparison to both RSG and MET, there was a slightly lower overall incidence of myocardial ischemia in the GLY/GLIB. There was a higher withdrawal rate early in the study due to hypoglycemia, and starting at 12 months, higher withdrawal due to therapy failure in subjects treated with GLY/GLIB compared to other treatments. Withdrawals in the GLY/GLIB group owing to non-random events of monotherapy failure and adverse events could create a bias in the risk estimate for myocardial ischemia AEs.

Table 8 On-therapy Cardiovascular Ischemic Adverse Events (serious plus and non-serious) and SAEs in ADOPT (All randomized population)

Preferred Term / Sub-categories	Number of Subjects, n (%)					
	RSG N=1456 PY=4953.8		MET N=1454 PY=4905.6		GLY/GLIB N=1441 PY=4243.6	
	n (%)	Rate /100 PY	n (%)	Rate /100 PY	n (%)	Rate /100 PY
Subjects with On-Therapy AEs of Myocardial Ischemia (SAE and non-serious AEs combined)	106 (7.3)	2.1	111 (7.6)	2.3	82 (5.7)	1.9
RSG vs comparator HR (95% CI)	-		0.99 (0.76, 1.29)		1.17 (0.88, 1.57)	
Angina	64 (4.4)	1.3	69 (4.7)	1.4	45 (3.1)	1.1
Coronary artery disease	39 (2.7)	0.8	48 (3.3)	1.0	33 (2.3)	0.8
Myocardial infarction	27 (1.9)	0.6	23 (1.6)	0.5	18 (1.3)	0.4
Subjects with On-therapy SAEs of Myocardial Ischemia	55 (3.8)	1.1	60 (4.1)	1.2	43 (3.0)	1.0
RSG vs comparator HR (95% CI)	-		0.95 (0.66, 1.37)		1.16 (0.77, 1.73)	
Angina	16 (1.1)	0.3	26 (1.8)	0.5	15 (1.0)	0.4
Coronary artery disease	18 (1.2)	0.4	21 (1.4)	0.4	17 (1.2)	0.4
Myocardial infarction	24 (1.6)	0.5	20 (1.4)	0.4	14 (1.0)	0.3

On-therapy non-serious AEs and SAEs were events reported from the first day of study medication through 1 day after the last dose of study medication.

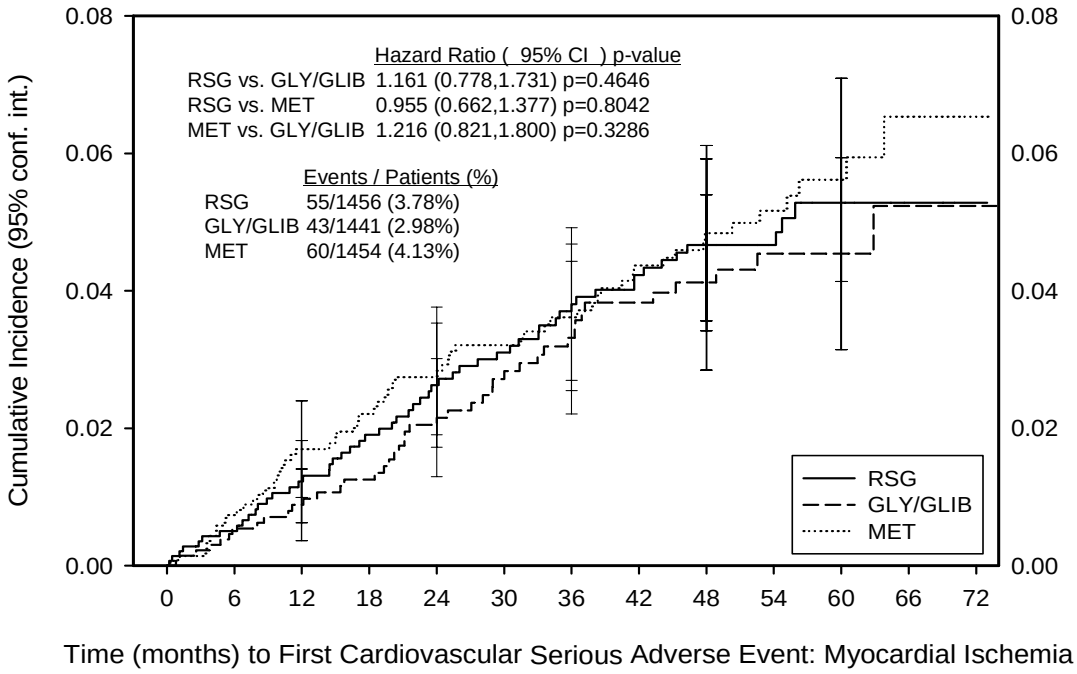
Figure 8 On-therapy Cumulative Incidence of First Cardiovascular Ischemic Adverse Events (serious plus non-serious) in ADOPT (All randomized population)



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

Figure 9 On-therapy Cumulative Incidence of First Cardiovascular Ischemic SAE (All randomized population)



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

5.3.3. Summary

ADOPT studied patients over a 4-6 year period exposed to either RSG, MET or GLY in a clinical setting where physicians were encouraged to manage the patients' lipids and blood pressure to ADA guidelines. The overall incidence of myocardial ischemia was low in all treatment groups and comparable over the duration of the trial. Glycemic control was least favorable with GLY, consistent with the higher number of patients who discontinued treatment with GLY. With respect to RSG and MET, similar proportions of patients in these two treatment groups were retained through various time points in the study. The time course of myocardial ischemic SAEs and AEs over the duration of the trial was similar for RSG and MET.

In conclusion, the ADOPT study does not suggest that RSG was associated with an increased risk of myocardial ischemia relative to the other two commonly used anti-diabetic agents.

5.4. DREAM (Diabetes Reduction Assessment with Ramipril and rosiglitazone Medication) Trial

DREAM was a large, international, multicenter, randomized double-blind placebo-controlled study designed to test if RSG and or the ACE-inhibitor, ramipril reduced the development of type 2 diabetes in non-diabetic subjects with Impaired Glucose Tolerance

(IGT) and or Impaired Fasting Glucose (IFG). DREAM was independently conducted by McMaster University, Ontario, Canada under the direction of an international steering committee chaired by Dr. H Gerstein, Dr. S Yusef and Professor Rury Holman. DREAM was funded by a peer-reviewed grant from the Canadian Institute of Health research as well as funds supplied by GSK, Sanofi-Aventis, and King Pharmaceuticals Research and Development. Population Health Research Institute at McMaster University coordinated the study and processed all the data.

Between July 2001 and August 2003, a total of 5269 subjects were recruited in 21 countries. They were randomized to either ramipril (15 mg/day) (RAM) or placebo and RSG (8mg/day) or placebo using a 2×2 factorial design and followed for a median of 3.0 years. The primary outcome of the study was a composite endpoint including the development of diabetes or death. A secondary objective of the study was the assessment of a composite cardiorenal endpoint defined as either cardiovascular events of myocardial infarction, any stroke, CV death, revascularization, heart failure, new angina (with objective evidence of ischemia) or ventricular arrhythmia requiring resuscitation or renal events looking at albuminuria progression and effects on creatinine clearance. The study was powered based on the primary outcome and was not designed as a cardiovascular outcomes trial. An independent Trial Monitoring Committee was responsible for the oversight of the safety of the trial. An Events Adjudication Committee was responsible for the adjudication of all primary and secondary endpoints.

PHRI provided the final DREAM clinical trial data to the co-sponsors in February of 2007. The data presented in this section are based on analyses performed by GSK. GSK continues to process the PHRI files into reporting data sets for a full review of all study data points. The primary objective and cardiovascular endpoint results for RSG were published in Lancet [DREAM, 2006a] and in the New England Journal of Medicine for ramipril [DREAM, 2006b]. The published results were based on an earlier dataset and therefore the numbers differ slightly from those in this final dataset.

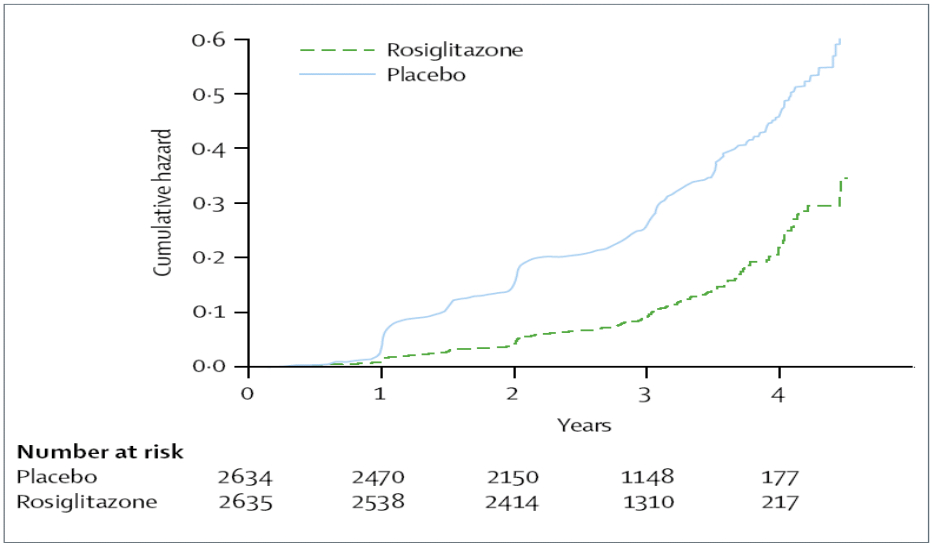
Study Population: Overall the treatment groups were well matched for all baseline characteristics (Table 9). The mean age was 54.7 yrs, 59% were female and approximately 49% were white. Subjects with known cardiovascular disease including low ejection fraction, congestive heart failure, MI and stroke were not eligible. Although, subjects with uncontrolled hypertension requiring ACE inhibitors or angiotension 2 receptor blockers were excluded, at entry approximately 44% of the subjects reported a history of hypertension and 35% were taking anti-hypertensive medication.

Table 9 DREAM Baseline Characteristics

Baseline Characteristics	Treatment Group Placebo (N=2634)	 RSG (N=2635)
Weight (kg) Mean±SD	85.0 (18.88)	84.8 (18.99)
BMI (kg/m^2) Mean±SD	31.3 (6.13)	31.2 (6.26)
Waist circumference (cm) Mean±SD	98.5 (13.99)	98.2 (14.4)
Systolic BP (mmHg) Mean±SD	136.3 (18.81)	135.9 (17.89)
Diastolic BP (mmHg) Mean±SD	83.5 (10.91)	83.3 (10.63)

Results: The primary outcome of diabetes or death was reported in significantly fewer individuals in the RSG group (313 [11.9%]) than in those randomized to placebo (687 [26.1%]), with a HR of 0.41; 95% CI 0.36 to 0.47; p<0.0001 (Figure 10). As expected, the rate of death was low and the incidence was similar in the RSG (30 [1.1%]) compared to placebo (33 [1.3%]).

Figure 10 Cumulative Hazard Plot for Time to Type 2 Diabetes Mellitus or Death by Factorial Margins



A key secondary object was a composite cardiovascular endpoint and each of the individual components (Table 10). Both treatment arms had a similar incidence in the overall composite as well as the individual components except for congestive heart failure (0.5% RSG versus <0.1% for placebo; p=0.003). There was no significant difference in the number of events of myocardial infarction or angina (adjudicated events of either new or unstable angina). There was no change in the risk when considering the additional adjudicated events of worsening angina.

Table 10 Analysis of Time to First Occurrence of Cardiovascular Events by Factorial Margin in DREAM (Intent-to-Treat Population)

Number with Events (%)	Placebo (N=2634)	RSG (N=2635)	Hazard Ratio (95% CI)	Log Rank P value
Composite CV	57 (2.2)	78 (3.0)	1.37 (0.975,1.930)	0.068
MI, Stroke, and CV Death	23 (0.9)	33 (1.3)	1.43 (0.842, 2.441)	0.182
Myocardial Infarction	9 (0.3)	16 (0.6)	1.78 (0.784,4.017)	0.162
Stroke	5 (0.2)	7 (0.3)	1.40 (0.444, 4.403)	0.567
CV Death	10 (0.4)	12 (0.5)	1.20 (0.517, 2.769)	0.673
Congestive Heart Failure	2 (<0.1)	14 (0.5)	7.00 (1.591, 30.797)	0.003
Angina*	24 (0.9)	26 (1.0)	1.08 (0.622,1.885)	0.780
CV Revascularization	28 (1.1)	37 (1.4)	1.32 (0.809, 2.159)	0.265

*definition of angina includes new angina, with or without evidence of ischemia, unstable angina and worsening angina based on adjudication.
Patients were followed for all endpoints up to study end, regardless of whether one or both study medication were discontinued
All events were adjudicated by the Events Adjudication Committee

To further understand the events in DREAM, GSK have reviewed the incidence of cardiovascular events in the randomized treatments or the factorial cells (Table 11). This factorial cell summary of the events showed similar number of subjects with events in the placebo and RSG cells, with numerically fewer in the RAM cell and with numerically more in RSG+RAM cell for myocardial infarction and congestive heart failure.

Table 11 Summary of Cardiovascular Events by the Factorial Treatment Cells in DREAM (Intent-to-Treat)

Event n(%)	Treatment Group			
	Placebo (N=1321)	RSG (N=1325)	RAM (N=1313)	RSG+ RAM (N=1310)
Cardiovascular Event	33 (2.5)	33 (2.5)	24 (1.8)	45 (3.4)
MI, Stroke and CV Death	14 (1.1)	15 (1.1)	9 (0.7)	18 (1.4)
Myocardial Infarction	6 (0.5)	5 (0.4)	3 (0.2)	11 (0.8)
Stroke	3 (0.2)	5 (0.4)	2 (0.2)	2 (0.2)
CV Death	5 (0.4)	5 (0.4)	5 (0.4)	7 (0.5)
Congestive Heart Failure	1 (<0.1)	3 (0.2)	1 (<0.1)	11 (0.8)
Angina*	14 (1.1)	10 (0.8)	10 (0.8)	16 (1.2)
CV Revascularization	18 (1.4)	19 (1.4)	10 (0.8)	18 (1.4)

*definition of angina includes new angina, with or without evidence of ischemia , unstable angina and worsening angina based on adjudication.
Patients were followed for all endpoints up to study end, regardless of whether one or both study medication were discontinued
All events were adjudicated by the Events Adjudication Committee

Summary: The incidence of cardiovascular events in DREAM was small and lower than those reported in the literature from pre-diabetic populations [Qureshi, 1998]. There was no statistical difference between the RSG and placebo in the incidence of the composite endpoint, myocardial infarction or any of the individual components except heart failure.

Numerically more subjects treated with RSG + RAM had adjudicated events of myocardial infarction and heart failure than in the other treatment cells.

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

RECORD is an ongoing cardiovascular outcomes study for which the primary endpoint is the composite of adjudicated events of CV death or CV hospitalization. This trial was designed to establish that combination of RSG with either MET or SU was non-inferior to the combination of MET and SU using a non-inferiority margin of 20% (i.e. upper bound of the 95% CI for the Hazard ratio is < 1.2). The study enrolled patients who failed to attain glycemic control on MET or SU monotherapy. The trial is run under the auspices of an external Steering Committee, an independent DSMB is responsible for the safety of patients enrolled in the trial, and a blinded adjudication committee reviews all events reported by the investigators to assess whether they meet the established definitions for endpoints of the trials.

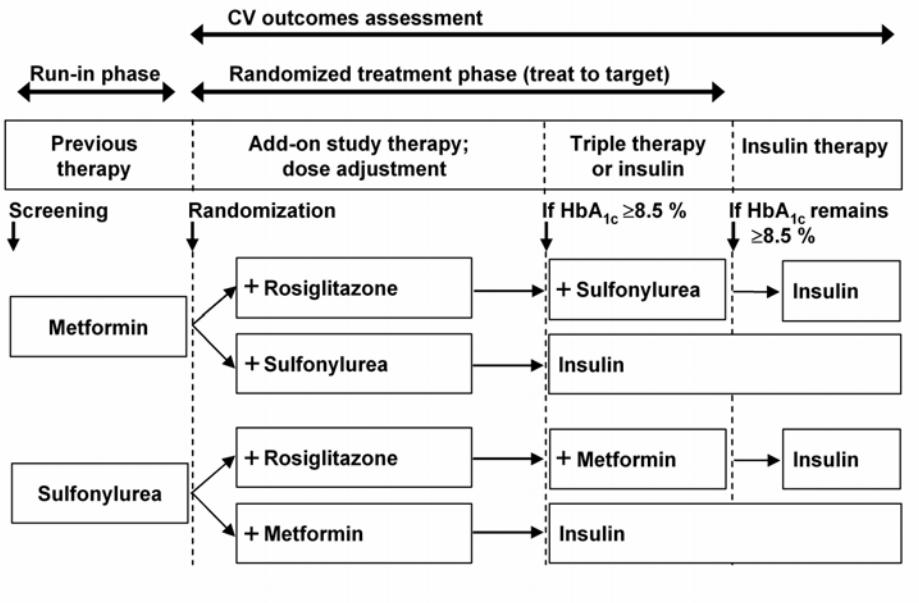
Following the publication of a meta-analysis concerning the cardiovascular safety of RSG [Nissen, 2007], the RECORD Steering Committee with agreement from the DSMB agreed to have a safety interim analysis of the trial conducted and published [Home 2007b]. Given the open label nature of the study, it was felt that the integrity of the study would be best maintained by transparency through publishing the results of this interim analysis.

The published results of the safety interim analysis have been restricted to a limited amount of information including the primary endpoint, all-cause death, heart failure, MACE and two of its components, CV death and MI. The statistical plan for this interim analysis was prospectively defined and the intent was primarily estimation based, with no planned action regarding study continuation. As such, the final analysis significance level is not affected by this interim safety evaluation and the study is not further compromised. At the time of writing, discussions are ongoing with the Steering Committee and regulatory authorities regarding additional analyses of this interim data.

5.5.1. Methodology

Study design: This randomized, multi-center, open-label, comparative study is being conducted in 23 countries in Europe, Australia and New Zealand. Enrollment began in April 2001 with the first patient being randomized in May 2001. The last patient was randomized in May 2003. The last patient, last visit will be in December 2008 and final study results will be available in 2009. The study design is summarized in Figure 11; detailed information is provided in the methodology publication [Home, 2005] (see Appendix A). Importantly, this study was designed to achieve similar glycemic control between RSG and the control group in order to assess cardiovascular safety independent of glycemia. In an 18 month interim analysis, RSG in combination with MET or SU was as effective as MET + SU [Home, 2007a].

Figure 11 Summary of RECORD Study Design



The primary outcome of RECORD is occurrence of cardiovascular death or cardiovascular hospitalization. The primary analysis is the time to the first occurrence of one of these outcomes.

The interim report evaluates RECORD study outcome data available as of 30 March 2007. A number of events were pending adjudication at the time of data cut-off. Analyses were conducted based on both adjudicated events only, and also adding in events pending adjudication – showing comparable results [Home 2007b]. Cumulative incidence for each endpoint was estimated using the Kaplan-Meier method. The relative risk comparing the RSG group to the control group was estimated as the hazard ratio and its 95% CI. These were derived from a Cox proportional hazards regression analysis stratified for background medication type (SU or MET). Two-sided p-values were obtained using the log-rank test, and were not adjusted for multiple testing.

5.5.2. Results and Summary

For each endpoint (other than heart failure) included in safety interim analysis of the RECORD trial (including CV death or CV hospitalization, acute myocardial infarction, cardiovascular death, all cause death and the composite of cardiovascular death, myocardial infarction and stroke), there is no evidence of a difference between RSG and control groups, both for adjudicated and adjudicated plus pending events (Table 12). A subgroup analysis for patients classified according to prior monotherapy stratum, MET or SU, revealed no evidence of a treatment-by-stratum interaction for the adjudicated primary endpoint (interaction test p = 0.41).

Table 12 Patients Experiencing Cardiovascular Hospitalizations and Deaths by Treatment Group

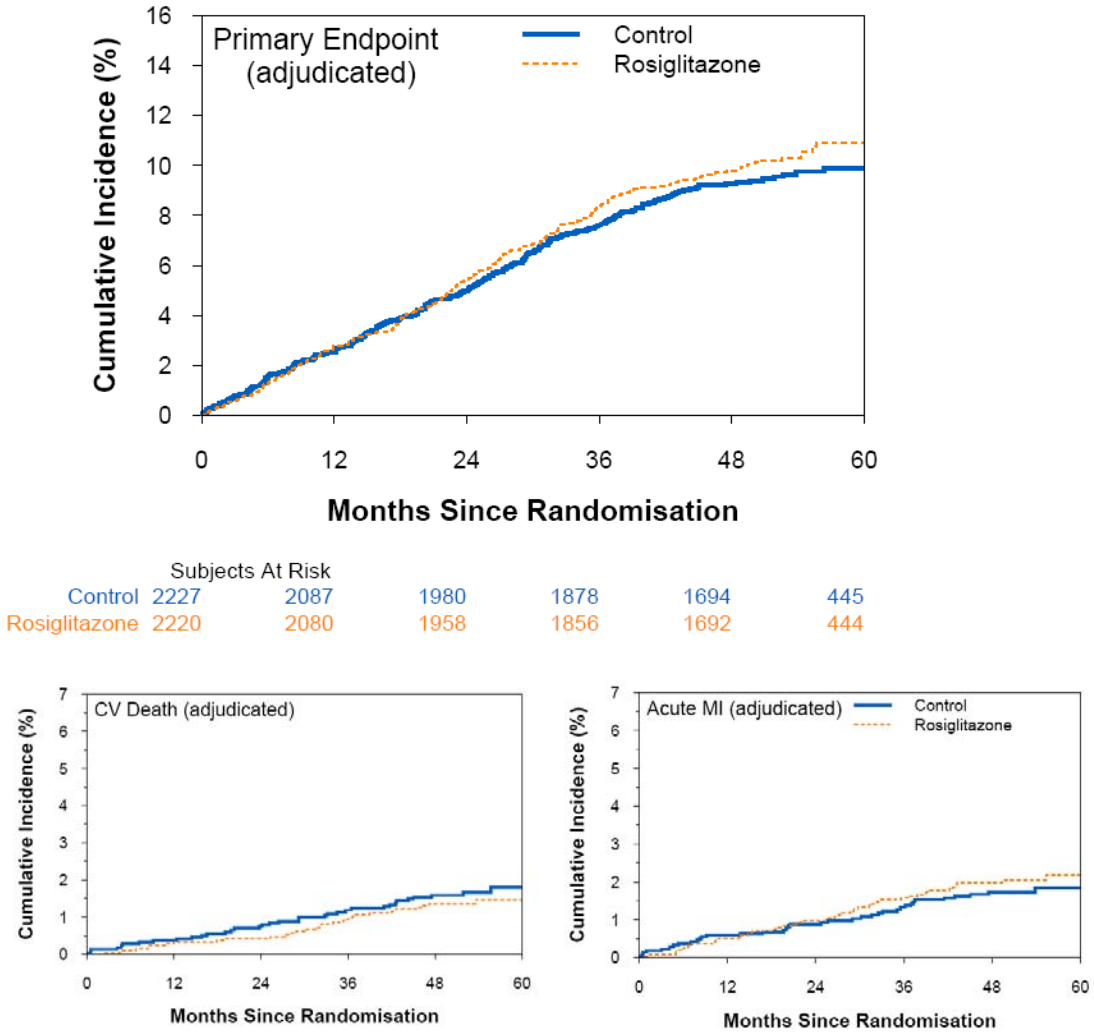
	RSG (N = 2220)	Control (N = 2227)	Hazard Ratio (95% CI)	P-value
a) Adjudicated events				
Primary Endpoint*	217	202	1.08 (0.89, 1.31)	0.43
CV death**	29	35	0.83 (0.51, 1.36)	0.46
All-cause death	74	80	0.93 (0.67, 1.27)	0.63
Acute myocardial infarction†	43	37	1.16 (0.75, 1.81)	0.50
Congestive heart failure†	38	17	2.24 (1.27, 3.97)	0.006
CV death, MI or stroke	93	96	0.97 (0.73, 1.29)	0.83
b) 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
Acute myocardial infarction†	49	40	1.23 (0.81, 1.86)	0.34
Congestive heart failure†	47	22	2.15 (1.30, 3.57)	0.003
CV death, MI or stroke	109	114	0.96 (0.74, 1.24)	0.74

**The primary endpoint is the first occurrence of a cardiovascular hospitalization or cardiovascular death*
† Including both hospitalizations and deaths. Some of the 19 CV deaths (8 RSG, 11 control) that are pending adjudication may be due to acute myocardial infarction or congestive heart failure, but these data are not available at this point.
***38 of these adjudicated CV deaths (16 RSG, 22 control) were primary endpoints. The remainder occurred after the patient had already had a CV hospitalization. For adjudicated plus pending CV deaths, 47 (20 RSG, 27 control) were primary endpoints.*

The publication also includes an assessment of heart failure as follows. "There is a significant excess of patients experiencing congestive heart failure requiring hospitalization: for adjudicated events, 38 RSG versus 17 control, hazard ratio 2.24 (95% CI 1.27, 3.97) (also see Appendix B). Including events pending adjudication increases the numbers to 47 RSG versus 22 control, hazard ratio 2.15 (95% CI 1.30, 3.57). This leads to an estimated excess of 3.0 (95% CI 1.0 to 5.0) patients with heart failure per 1000 patient years of follow-up on RSG compared to control" [Home 2007b].

These findings represent a substantial treatment experience with which to characterize cardiovascular outcomes in diabetic patients treated with RSG compared to conventional glucose-lowering medications, and amount to around two-thirds of the intended patient years' follow-up expected by study completion.

Figure 12 Kaplan Meier Plots for RECORD



5.6. Analyses of MACE (CV Death, MI or stroke) and Components

The MACE endpoint (first events of CV death, MI SAE or stroke SAE) provides a generally accepted composite measure of overall CV mortality in terms of serious and irreversible events. Therefore, additional post-hoc analyses of MACE were conducted for the ICT and ADOPT. MACE and its components were pre-specified for DREAM and in the interim analysis of RECORD.

5.6.1. Methods

Determination of MACE and components in the ICT: Unlike the original ICT analysis where the individual SAE events were reviewed, MACE components were identified programmatically solely from standardized, computerized coding of adverse

events terms corresponding to investigator's entries on a case report form. The events did not undergo an independent review and they were not adjudicated. An overall assessment of RSG containing regimens relative to non-RSG regimens was performed, allowing the calculation of an overall hazard ratio accounting for comparison strata and for baseline assessment of major CV risk factors using a Cox Proportional Hazard model.

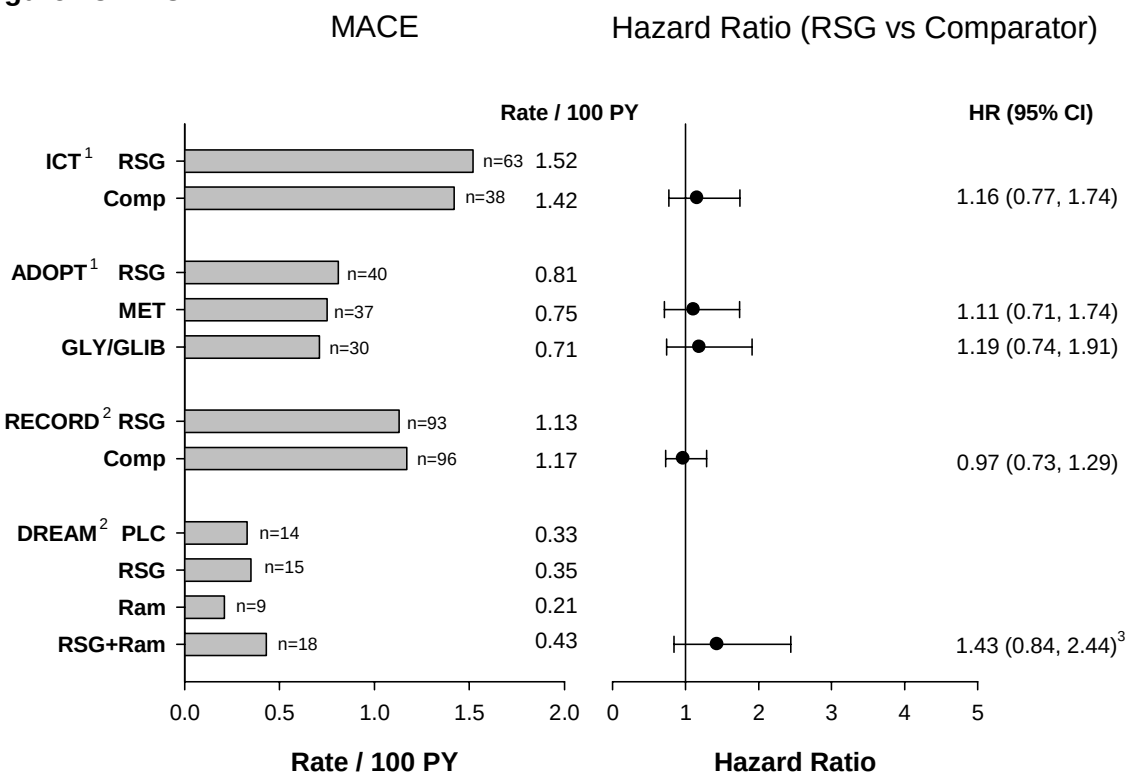
Determination of MACE and components in ADOPT: As with the ICT, MACE components were identified programmatically solely from the standardized coded terms of SAEs corresponding to investigators reports. The events did not undergo an independent review and they were not adjudicated. Treatments were compared to each other using the same methods as in the predefined analysis plan for the other CV endpoints presented in section 5.3.

Determination of MACE and components in DREAM and RECORD: MACE and its components were pre-specified and were adjudicated.

5.6.2. Results

MACE: Overall, across all data sources, the observed incidence of MACE events is comparable in the RSG and non-RSG groups Figure 13 and Table 13. This is reflected in the point estimates for the hazard ratios with associated 95% CIs which overlap unity. The cumulative incidence of MACE for RECORD is shown in Figure 14 and for ADOPT in Figure 15. The DREAM study results included few events making interpretation difficult (Note HR and 95% CI are for the all RSG [RSG, RSG + RAM] vs all non-RSG [PLA, RAM] comparison).

Figure 13 MACE



1. All events were non-adjudicated SAEs
2. All events were pre-specified and adjudicated
3. Hazard ratio for All RSG (RSG and RSG+Ram) vs. All Comparator (Placebo and Ram)

Figure 14 Cumulative Incidence of Major Adverse Cardiovascular Events (MACE) in RECORD

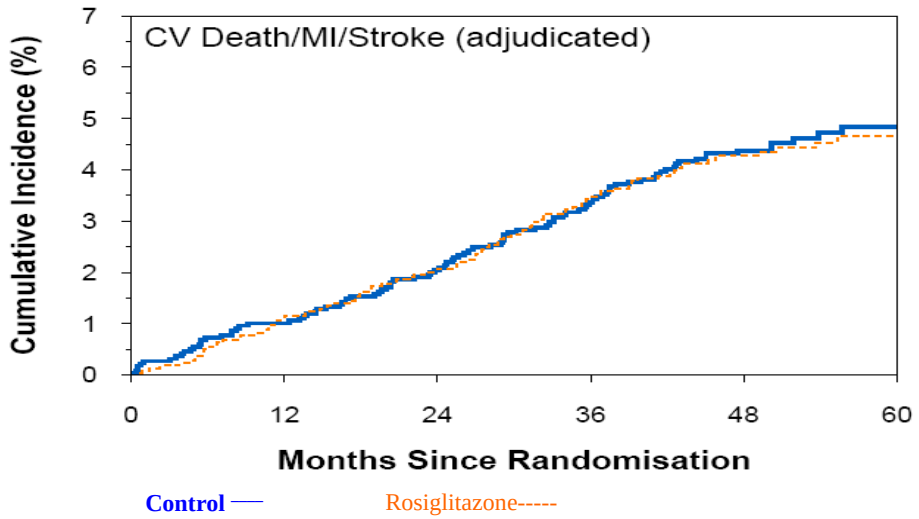
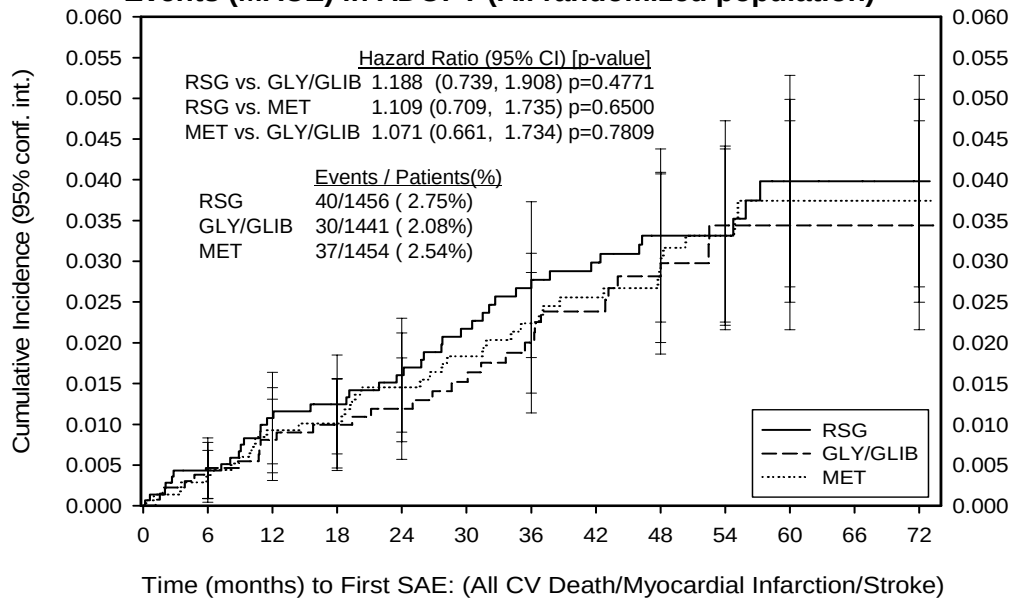


Figure 15 On-therapy Cumulative Incidence of Major Adverse Cardiovascular Events (MACE) in ADOPT (All randomized population)



Participants at Risk

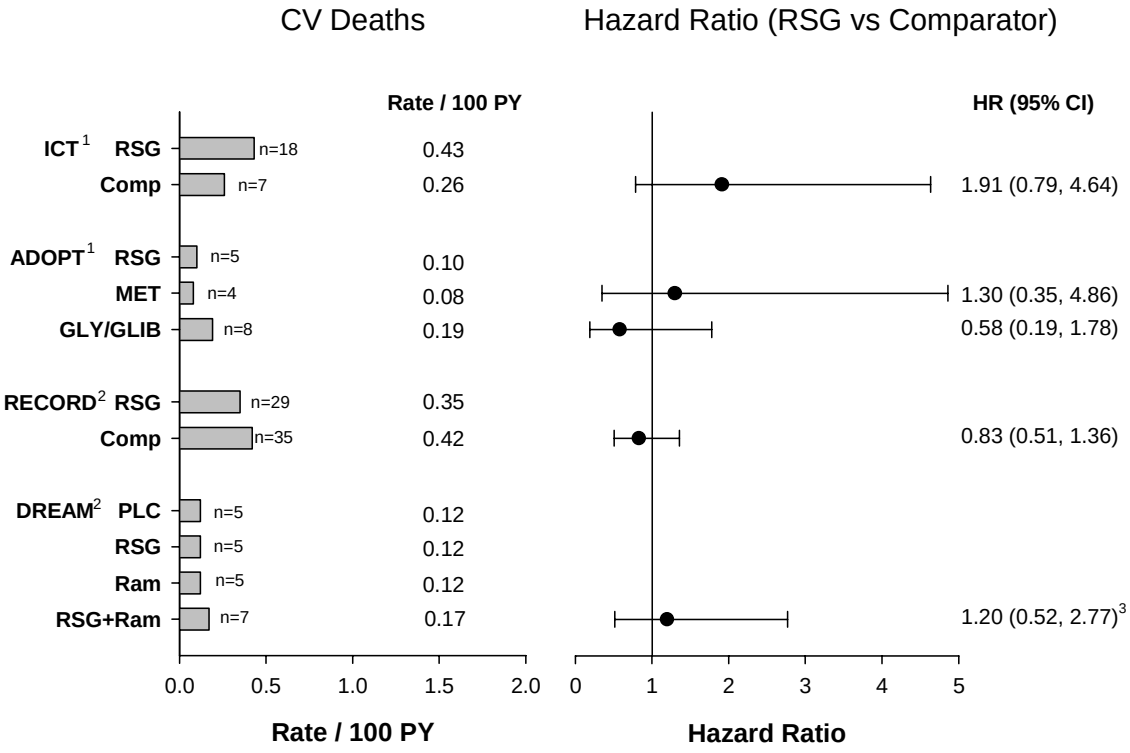
RSG	1456	1197	1067	945	799	310	8
GLY/GLIB	1441	1108	956	779	600	214	7
MET	1454	1199	1069	941	779	306	8

Table 13 Major Adverse Cardiovascular Events (MACE)

Study	Treatment	Subjects w Events/ Randomized Subjects	Rate/ 100 PY	Treatment Comparison	Hazard Ratio (95% CI)
ADOPT	RSG	40/1456	0.81		
	GLY	30/1441	0.71	RSG vs. GLY	1.19 (0.74, 1.91)
	MET	37/1454	0.75	RSG vs. MET	1.11 (0.71, 1.74)
ICT	RSG	63/8604	1.52		
	Comparator	38/5633	1.42	RSG vs. Comparator	1.161 (0.773, 1.744)
RECORD	RSG	93/2220	1.13		
	Comparator	96/2227	1.17	RSG vs. Comparator	0.97 (0.73, 1.29)
DREAM	Placebo	14/1321	0.33		
	RSG	15/1325	0.35	RSG vs. Placebo	1.065 (0.514,2.206)
	Ramipril	9/1313	0.21	Ramipril vs. Placebo	0.645 (0.279,1.491)
	Ram + RSG	18/1310	0.43	Ram+RSG vs. Placebo	1.296 (0.645,2.606)
	RSG (All)	33/2635	0.39		
	Comparator (All)	23/2634	0.27	RSG vs. Comparator	1.434 (0.842,2.441)

CV Death: Across all of the data sources, there were few CV deaths reported (Figure 16 and Table 14). Based on 23 total events in the ICT (N=14,237), a hazard ratio of 1.91 was computed. Since this observation is based on such small numbers of events, external validation is important. In ADOPT, there were 5 CV deaths on RSG, 4 on MET and 8 on GLY. In RECORD, there were a total of 64 adjudicated CV deaths, giving a HR of 0.83, 95% CI: 0.51 to 1.36.

Figure 16 CV Death



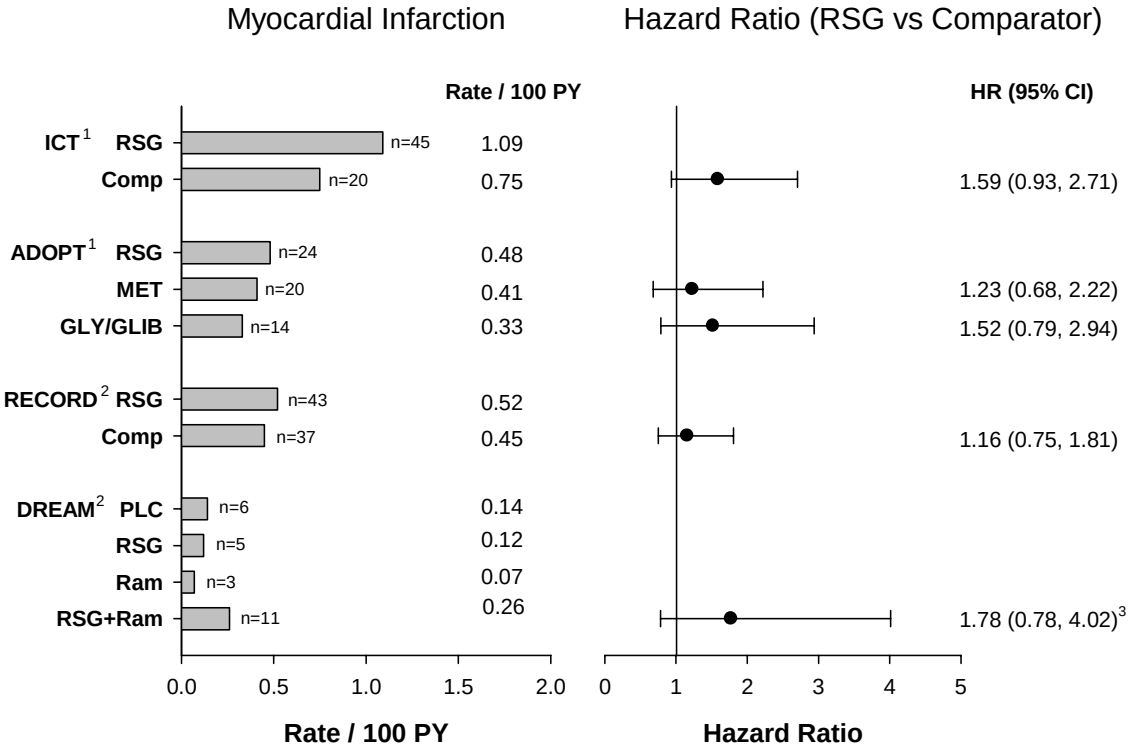
1. All events were non-adjudicated SAEs
2. All events were pre-specified and adjudicated
3. Hazard ratio for All RSG (RSG and RSG+Ram) vs. All Comparator (Placebo and Ram)

Table 14 CV Death

Study	Treatment	Subjects w Events / Randomized Subjects	Rate / 100 PY	Treatment Comparison	Hazard Ratio (95% CI)
ADOPT	RSG	5/1456	0.10		
	GLY	8/1441	0.19	RSG vs. GLY	0.58 (0.19, 1.78)
	MET	4/1454	0.08	RSG vs. MET	1.30 (0.35, 4.86)
ICT	RSG	18/8604	0.43		
	Comparator	7/5633	0.26	RSG vs. Comparator	1.914 (0.790, 4.635)
RECORD	RSG	29/2220	0.35		
	Comparator	35/2227	0.42	RSG vs. Comparator	0.83 (0.51, 1.36)
DREAM	Placebo	5/1321	0.12		
	RSG	5/1325	0.12	RSG vs. Placebo	0.994 (0.288,3.434)
	Ramipril	5/1313	0.12	Ramipril vs. Placebo	1.005 (0.291,3.471)
	Ram + RSG	7/1310	0.17	Ram+RSG vs. Placebo	1.410 (0.448,4.444)
	RSG (All)	12/2635	0.14		
	Comparator (All)	10/2634	0.12	RSG vs. Comparator	1.196 (0.517,2.769)

Myocardial Infarction: Point estimates for the hazard ratio of RSG groups relative to non-RSG groups ranged from 1.16 to 1.78 with all 95% CIs overlapping unity (Figure 17 and Table 15). The most reliable estimate of the hazard ratio comes from RECORD, where there were a total of 80 adjudicated myocardial infarctions, giving a HR of 1.16, 95% CI: 0.75 to 1.81. This data suggests that the risk of MI is comparable for RSG groups relative to other anti-hyperglycemic agents.

Figure 17 Myocardial Infarction



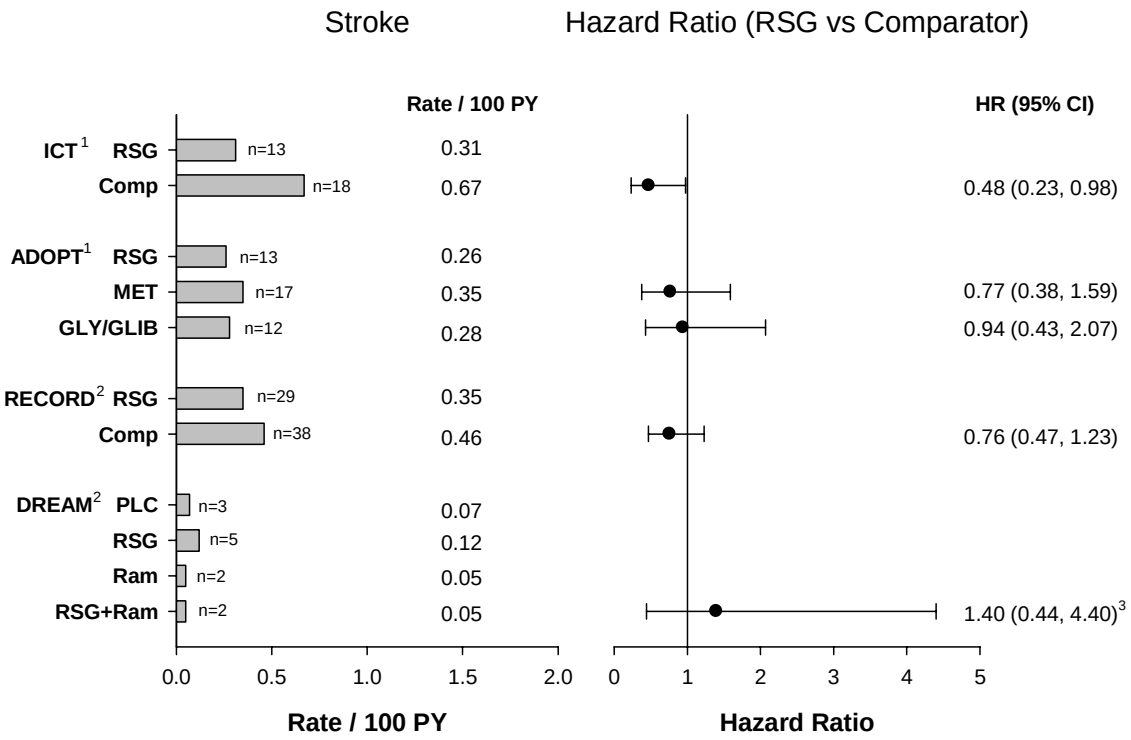
1. All events were non-adjudicated SAEs
2. All events were pre-specified and adjudicated
3. Hazard ratio for All RSG (RSG and RSG+Ram) vs. All Comparator (Placebo and Ram)

Table 15 Myocardial Infarction

Study	Treatment	Subjects with Events / Randomized Subjects	Rate/100 PY	Treatment Comparison	Hazard Ratio (95% CI)
ADOPT	RSG	24/1456	0.48		
	GLY	14/1441	0.33	RSG vs. GLY	1.52 (0.79, 2.94)
	MET	20/1454	0.41	RSG vs. MET	1.23 (0.68, 2.22)
ICT	RSG	45/8604	1.09		
	Comparator	20/5633	0.75	RSG vs. Comparator	1.590 (0.934, 2.706)
RECORD	RSG	43/2220	0.52		
	Comparator	37/2227	0.45	RSG vs. Comparator	1.16 (0.75, 1.81)
DREAM	Placebo	6/1321	0.14		
	RSG	5/1325	0.12	RSG vs. Placebo	0.828 (0.253,2.713)
	Ramipril	3/1313	0.07	Ramipril vs. Placebo	0.503 (0.126,2.011)
	Ram + RSG	11/1310	0.26	Ram+RSG vs. Placebo	1.847 (0.683,4.994)
	RSG (All)	16/2635	0.19		
	Comparator (All)	9/2634	0.11	RSG vs. Comparator	1.775 (0.784,4.017)

Stroke: The incidence of stroke for RSG groups is similar to that of non-RSG groups (Figure 18 and Table 16). This is also reflected in the point estimates for the hazard ratios and the associated confidence intervals which generally overlap unity.

Figure 18 Stroke



1. All events were non-adjudicated SAEs
2. All events were pre-specified and adjudicated
3. Hazard ratio for All RSG (RSG and RSG+Ram) vs. All Comparator (Placebo and Ram)

Table 16 Stroke

Study	Treatment	Subjects w Events / Randomized Subjects	Rate/100 PY	Treatment Comparison	Hazard Ratio (95% CI)
ADOPT	RSG	13/1456	0.26		
	GLY	12/1441	0.28	RSG vs. GLY	0.94 (0.43, 2.07)
	MET	17/1454	0.35	RSG vs. MET	0.77 (0.38, 1.59)
ICT	RSG	13/8604	0.31		
	Comparator	18/5633	0.67	RSG vs. Comparator	0.475 (0.231, 0.976)
RECORD	RSG	29/2220	0.35		
	Comparator	38/2227	0.46	RSG vs. Comparator	0.76 (0.47, 1.23)
DREAM	Placebo	3/1321	0.07		
	RSG	5/1325	0.12	RSG vs. Placebo	1.655 (0.396,6.925)
	Ramipril	2/1313	0.05	Ramipril vs. Placebo	0.666 (0.111,3.989)
	Ram + RSG	2/1310	0.05	Ram+RSG vs. Placebo	0.671 (0.112,4.016)
	RSG (All)	7/2635	0.08		
	Comparator (All)	5/2634	0.06	RSG vs. Comparator	1.397 (0.444,4.403)

5.7. Post hoc Review of Cardiovascular Events in Subpopulations of Interest

During review of various sources of data, there were suggestions of different effects in subgroups, e.g. use of nitrates from the ICT analysis, potential interaction with ACE inhibitors in the DREAM trial. Several specific factors are presented below.

5.7.1. Patients on ACE Inhibitors (ACE-I)

The cell-by-cell tabulation of CV events in the DREAM trial suggests a potential for a differential drug effect for RSG treated pre-diabetic subjects with and without background ramipril at high doses (15mg). In order to assess the potential for such an effect, post hoc analyses of the ICT and ADOPT data sources were conducted in subgroups of patients reporting taking any ACE-I prior to study start, ACE-I started during the trial but 7 days prior to an event, and those not reported to take an ACE-I.

Unlike the apparent increase in CV events in the RSG + RAM treatment group compared to other treatment arms in the DREAM trial, there was no relationship observed between exposure to ACE-I and CV events on RSG in ADOPT (Table 18). In the ICT, for most endpoints, there was no relationship between ACE-I use and RSG (Table 17).

Table 17 Summary of CV Events by ACE Inhibitor Use - ICT Analysis

	RSG N=8604	**Comparators** N=5633
Ace Inhibitor Use	Subjects with event/N (%)	Subjects with event/N (%)
MACE		
At Screening	23/2423 (0.95%)	16/1661 (0.96%)
Initiated after Screening[a]	1/264 (0.38%)	0/163 (0%)
Not initiating ACE Inhibitor[b]	39/5917 (0.66%)	22/3809 (0.58%)
CV Death		
At Screening	8/2423 (0.33%)	4/1661 (0.24%)
Initiated after Screening[a]	0/271 (0%)	1/167 (0.60%)
Not initiating ACE Inhibitor[b]	10/5910 (0.17%)	2/3805 (0.05%)
MI SAEs		
At Screening	13/2423 (0.54%)	9/1661 (0.54%)
Initiated after Screening[a]	1/264 (0.38%)	0/163 (0%)
No initiating ACE Inhibitor[b]	31/5917 (0.52%)	11/3809 (0.29%)
Stroke SAEs		
At Screening	6/2423 (0.25%)	7/1661 (0.42%)
Initiated after Screening[a]	0/271 (0%)	0/167 (0%)
Not initiating ACE inhibitor[b]	7/5910 (0.12%)	11/3805 (0.29%)
Myocardial Ischemia SAEs		
At Screening	33/2423 (1.36%)	14/1661 (0.84%)
Initiated after Screening[a]	1/260 (0.38%)	0/160 (0%)
Not initiating ACE Inhibitor[b]	52/5921 (0.88%)	26/3812 (0.68%)
Heart failure SAEs		
At Screening	21/2423 (0.87%)	11/1661 (0.66%)
Initiated after Screening[a]	0/267 (0%)	1/166 (0.60%)
Not initiating ACE Inhibitor[b]	9/5914 (0.15%)	7/3806 (0.18%)

a. At least 7 days before the event of interest for subjects with the event of interest.
b. Including subjects initiating ACE inhibitor after 7 days prior to the event of interest.

Table 18 Summary of CV Events by ACE Inhibitor Use –ADOPT

Medication Status	**RSG** N=1456	**MET** N=1454	**GLY/GLIB** N=1441
Ace Inhibitor Use	Subjects with event /N (%)	Subjects with event /N (%)	Subjects with event /N (%)
MACE			
Prior ACE Inhibitor	8/346 (2.3%)	10/350 (2.9%)	8/345 (2.3%)
Any on-therapy ACE Inhibitor[a]	1/203 (0.5%)	2/254 (0.8%)	4/196 (2.0%)
No ACE Inhibitor[b]	31/907 (3.4%)	25/850 (2.9%)	17/900 (1.9%)
CV Death			
Prior ACE Inhibitor	1/346 (0.3%)	2/350 (0.6%)	5/345 (1.4%)
Any on-therapy ACE Inhibitor pre-event[a]	0/219 (0.0%)	0/262 (0.0%)	0/200 (0.0%)
No ACE Inhibitor[b]	4/891 (0.4%)	2/842 (0.2%)	3/896 (0.3%)
MI SAEs			
Prior ACE Inhibitor	4/346 (1.2%)	5/350 (1.4%)	2/345 (0.6%)
Any on-therapy ACE Inhibitor pre-event[a]	1/207 (0.5%)	2/257 (0.8%)	3/197 (1.5%)
No ACE Inhibitor[b]	19/903 (2.1%)	13/847 (1.5%)	9/899 (1.0%)
Stroke SAEs			
Prior ACE Inhibitor	3/346 (0.9%)	4/350 (1.1%)	3/345 (0.9%)
Any on-therapy ACE Inhibitor pre-event[a]	0/215 (0.0%)	1/259 (0.4%)	1/199 (0.5%)
No ACE inhibitor[b]	10/895 (1.1%)	12/845 (1.4%)	8/897 (0.9%)
Myocardial Ischemia SAEs			
Prior ACE Inhibitor	13/346 (3.8%)	16/350 (4.6%)	5/345 (1.4%)
Any on-therapy ACE Inhibitor pre-event[a]	3/196 (1.5%)	7/249 (2.8%)	12/194 (6.2%)
No ACE Inhibitor[b]	39/914 (4.3%)	37/855 (4.3%)	26/902 (2.9%)
Heart failure SAEs			
Prior ACE Inhibitor	0/346 (0.0%)	8/350 (2.3%)	0/345 (0.0%)
Any on-therapy ACE Inhibitor pre-event[a]	1/213 (0.5%)	1/260 (0.4%)	2/200 (1.0%)
No ACE Inhibitor[b]	11/897 (1.2%)	3/844 (0.4%)	1/896 (0.1%)

a Subjects with an event of interest, restricted to cases where ACE inhibitor initiation date was at least 7 days before the event.
b Subjects with an event of interest, includes cases where ACE inhibitor initiation was not initiated at least 7 days before the event.

5.7.2. Patients on Nitrates

As expected, the use of nitrates was more common in patients with myocardial ischemia. The original ICT noted that in patients receiving nitrates and RSG there was a potential for an increased risk of myocardial ischemic events. The balanced cohort observational study specifically evaluated and did not confirm this observation. For completeness, a similar subgroup analysis was conducted for nitrate users for ADOPT which again did not confirm the ICT observation (Table 19 and Table 20). A limitation of this subgroup analysis is the small number of patients receiving nitrates in ADOPT.

Table 19 Summary of CV Events by Nitrate Use – ICT Analysis

	RSG N=8604	**Comparators** N=5633
Nitrate Use	Subjects with event /N (%)	Subjects with event /N (%)
MACE		
At Screening	13/361 (3.60%)	7/244 (2.87%)
Initiated after Screening[a]	3/108 (2.78%)	0/65 (0%)
Not initiating Nitrates[b]	47/8135 (0.58%)	31/5324 (0.58%)
CV Death		
At Screening	4/361 (1.11%)	4/244 (1.64%)
Initiated after Screening[a]	0/119 (0%)	1/76 (1.32%)
Not initiating Nitrates[b]	14/8124 (0.17%)	2/5313 (0.04%)
MI SAEs		
At Screening	10/361 (2.77%)	5/244 (2.05%)
Initiated after Screening[a]	3/108 (2.78%)	0/67 (0%)
No initiating Nitrates[b]	32/8135 (0.39%)	15/5322 (0.28%)
Stroke SAEs		
At Screening	1/361 (0.28%)	2/244 (0.82%)
Initiated after Screening[a]	0/120 (0%)	0/74 (0%)
Not initiating Nitrates[b]	12/8123 (0.15%)	16/5315 (0.30%)
Myocardial Ischemia SAEs		
At Screening	20/361 (5.54%)	9/244 (3.69%)
Initiated after Screening[a]	8/90 (8.89%)	1/57 (1.75%)
Not initiating Nitrates[b]	58/8153 (0.71%)	30/5332 (0.56%)
Heart failure SAEs		
At Screening	8/361 (2.22%)	4/244 (1.64%)
Initiated after Screening[a]	1/119 (0.84%)	0/73 (0%)
Not initiating Nitrates[b]	21/8124 (0.26%)	15/5316 (0.28%)

a At least 7 days before the event of interest for subjects with the event of interest.
b Including subjects initiating nitrate after 7 days prior to the event of interest.

Table 20 Summary of CV Events by Nitrate Use – ADOPT

Medication Status	**RSG** N=1456	**MET** N=1454	**GLY/GLIB** N=1441
Nitrate Use	Subjects with event /N (%)	Subjects with event /N (%)	Subjects with event /N (%)
MACE			
Prior Nitrates	2/35 (5.7%)	3/44 (6.8%)	2/42 (4.8%)
Any on-therapy Nitrates pre-event[a]	1/52 (1.9%)	3/54 (5.6%)	3/44 (6.8%)
No Nitrates[b]	37/1369 (2.7%)	31/1356 (2.3%)	24/1355 (1.8%)
CV Death			
Prior Nitrates	1/35 (2.9%)	1/44 (2.3%)	2/42 (4.8%)
Any on-therapy Nitrates pre-event[a]	0/62 (0%)	0/61 (0%)	1/49 (2.0%)
No Nitrates[b]	4/1359 (0.3%)	3/1349 (0.2%)	5/1350 (0.4%)
MI SAEs			
Prior Nitrates	1/35 (2.9%)	1/44 (2.3%)	0/42 (0%)
Any on-therapy Nitrates pre-event[a]	0/52 (0%)	3/55 (5.5%)	2/45 (4.4%)
No Nitrates[b]	23/1369 (1.7%)	16/1355 (1.2%)	12/1354 (0.9%)
Stroke SAEs			
Prior Nitrates	0/35 (0%)	2/44 (4.5%)	0/42 (0%)
Any on-therapy Nitrates pre-event[a]	1/62 (1.6%)	0/60 (0%)	1/49 (2.0%)
No Nitrates[b]	12/1359 (0.9%)	15/1350 (1.1%)	11/1350 (0.8%)
Myocardial Ischemia SAEs			
Prior Nitrates	5/35 (14.3%)	6/44 (13.6%)	4/42 (9.5%)
Any on-therapy Nitrates pre-event[a]	3/39 (7.7%)	6/45 (13.3%)	5/34 (14.7%)
No Nitrates[b]	47/1382 (3.4%)	48/1365 (3.5%)	34/1365 (2.5%)
Heart failure SAEs			
Prior Nitrates	2/35 (5.7%)	5/44 (11.4%)	1/42 (2.4%)
Any on-therapy Nitrates pre-event[a]	1/61 (1.6%)	0/60 (0%)	1/50 (2.0%)
No Nitrates[b]	9/1360 (0.7%)	7/1350 (0.5%)	1/1349 (0.1%)

a Subjects with an event of interest, restricted to cases where nitrate initiation date was at least 7 days before the event.
b Subjects with an event of interest, includes cases where nitrate was not initiated at least 7 days before the event.

5.7.3. Changes in LDL

LDL is known risk factor for CV disease. RSG therapy is associated with a modest increase in LDLc. Therefore, the association of changes in LDL-c following the initiation of drug therapy and myocardial infarction was evaluated. Patients were categorized into tertiles based on their changes from baseline in LDL-c at 8 weeks (for ICT) and 6 months (for ADOPT). In each tertile, those patients who had an investigator assessed SAE of myocardial infarction were tabulated. As the distribution of myocardial infarction is broadly similar in each tertile for RSG therapy in both ICT and ADOPT, it is unlikely that the early change in LDL-c is associated with the myocardial infarction (Table 21 and Table 22).

Table 21 Summary of Myocardial Infarction SAE Occurrence by Change in LDL-c by Tertile, ICT Analysis All Randomized Patients

	Comparators N=5633 Total w/ MI=20*			**RSG N=8604 Total w/ MI=45***		
	Change from baseline to Week 8 LDL (Tertiles)					
	1	2	3	1	2	3
	n=1100	n=1165	n=1159	n=1778	n=1814	n=1828
Tertile Range (mg/dL)	-159-<-8.0	-8.0-<8.0	8.0-172.0	-136- <1.0	1.0-<23.0	23.0-315.0
Subjects w/ MI SAE n(%)	2 (0.2)	6 (0.5)	5 (0.4)	6 (0.3)	7 (0.4)	9 (0.5)

*23/3184 (RSG) and 7/2209 (COMP) had an MI and are missing an LDL value or the MI occurred prior to week 8

Table 22 Summary of Myocardial Infarction SAEs Occurrence by Change in LDL-c by Tertile - ADOPT, All Randomized Patients

	RSG N=1456 Total w/ MI=24*			**Metformin N=1454 Total w/ MI=20***			**GLY/GLIB N=1441 Total w/ MI=14***		
	Change from baseline to Month 6 LDL (Tertiles)								
	1	2	3	1	2	3	1	2	3
	n=359	n=366	n=373	n=370	n=396	n=383	n=370	n=371	n=371
Tertile Range (mg/dL)	-119-<1.0	1.0-<21.0	21.0-212.0	-124-<-15.4	-15.4-<1.9	1.9-95.0	-200-<-11.5	-11.5-<4.0	4.0-114.0
Subjects w/ MI SAE n(%)	7(2.0)	6(1.6)	8(2.1)	9(2.4)	4(1.0)	2(0.5)	4(1.1)	2(0.5)	3(0.8)

* 3(RSG), 5 (Met) and 5(GLY) had an MI and are missing an LDL value or the MI occurred prior to month 6

5.7.4. Patients with a Prior Myocardial Infarction

Prior myocardial infarction increases the risk for a subsequent myocardial infarction, therefore, a subgroup analysis, specifically examining the incidence of myocardial infarction SAEs for patients reporting a history of myocardial infarction prior to randomization was performed in both the ICT and in ADOPT. In the ICT, patients with a prior myocardial infarction had a higher rate of non-adjudicated myocardial infarction SAEs on RSG therapy vs comparators (Table 23). The numbers of events were low. This observation was not replicated in ADOPT (Table 24).

Table 23 Summary of Myocardial Infarction SAEs by Prior Myocardial Infarction status - ICT

	RSG N=8604				Comparators N=5633			
MI Status	N with events/ Total Patients	%	Patient Years (PY)	Rate per 100 PY	N with events/ Total Patients	Patient Years (PY)	%	Rate per 100 PY
Prior MI	12/492	2.44	265.39	4.52	4/368	208.80	1.09	1.92
No prior MI	33/8112	0.41	3877.94	0.85	16/5265	2466.48	0.30	0.65
All Patients	45/8604	0.52	4143.33	1.09	20/5633	2675.28	0.36	0.75

Table 24 Summary of Myocardial Infarction SAEs by Prior Myocardial Infarction Status - ADOPT

	RSG		MET		GLY/GLIB	
Pts with MI SAE	Prior MI	No Prior MI	Prior MI	No Prior MI	Prior MI	No Prior MI
	N= 47 PY=142.7	N=1409 PY=4811.1	N=60 PY 216.1	N=1394 PY=4689.5	N=51 PY=148.2	N=1390 PY=4095.
N (%)	1 (2.13%)	23 (1.63%)	2 (3.33%)	18 (1.29%)	0	14 (1.01%)
Rate/100PY	0.70	0.48	0.93	0.38	0	0.40

Data on patient history of myocardial infarction are not yet available for assessment of RECORD or DREAM studies. However, a study in high CV risk patients was conducted and is described in the following section.

5.8. Study in High CV Risk Population

The PPAR (Peroxisome proliferators activated receptor gamma agonist for the Prevention of adverse events following percutaneous coronary revascularization) study was a randomized, double-blind, clinical trial in high risk patients with metabolic syndrome undergoing elective or urgent PCI. Patients initiated RSG (4 mg BID, n=102) or placebo (n=98) within one hour prior to PCI and continued for 12 months. The study was conducted by the Cleveland Clinic and was recently published [Bhatt, 2007].

The primary endpoint was progression rate in Doppler ultrasound–determined cIMT recorded bilaterally on carotid bulb, common carotid and internal carotid segments during the 12-month follow-up. The secondary endpoints included the net change in cIMT from baseline to 6 and 12 months; the composite of death, MI (adjudicated), or stroke

(adjudicated); the composite of all-cause mortality, myocardial infarction, stroke, or any coronary vessel revascularization.

Eligible subjects included obese patients undergoing elective or urgent PCI with angiographic evidence of coronary artery disease with a diagnosis of hypertension, dyslipidemia, or dysglycemia. Baseline characteristics were comparable between the two treatment arms. The study population was a high cardiovascular risk group with a high prevalence of prior cardiovascular events including angina, unstable angina, myocardial infarction or cardiac interventions (Table 25).

Table 25 Baseline Characteristics in PPAR Study

Baseline Characteristics	RSG (n=102)	Placebo (n=98)	P value
Age	59.4 ± 9.8	59.4 ± 9.6	0.97
Gender (% male)	80.4	79.6	0.89
History of diabetes (%)	3.9	4.1	1.00
Body Mass Index (kg/m^2)	33.1 ± 5.3	32.3 ± 4.7	0.32
Hypertension (%)	76.5	75.5	0.87
Hypercholesterolemia (%)	85.1	87.8	0.59
Current smoking (%)	18.8	20.4	0.78
CHF (%)	2.0	3.1	0.68
Stable Angina (%)	50.5	49.0	0.83
History of Unstable Angina (%)	44.0	53.1	0.20
Prior MI (%)	35.3	39.2	0.57
Prior PCI (%)	34.3	39.8	0.42
Prior CABG (%)	20.6	20.4	0.98
Prior Stroke (%)	4.9	1.0	0.21

There was no significant difference in CIMT progression rates or maximum/mean CIMT in the RSG group compared with the placebo group at study end. The composite endpoint of death, MI, or stroke at 12 months was lower in the RSG group compared with the placebo group (Table 26). New-onset congestive heart failure occurred in 1 patient in the RSG group versus none in the placebo group (P = 0 .31).

Table 26 CV Endpoints in PPAR Study

Endpoints	RSG (n = 102)	Placebo (n = 98)	P values
Death/ MI/ Stroke	6 (6.4)	11 (11.9)	0.19
Death	1 (1.2)	2 (2.3)	0.57
MI	5 (5.2)	8 (8.4)	0.36
Stroke	1 (1.2)	2 (2.3)	0.57
New CHF	1 (1.2)	0 (0.0)	0.31

Events of MI and stroke were adjudicated

In summary, in this group of patients at high risk for cardiovascular complications, the cardiovascular safety profile was not significantly different between RSG and placebo, although the major adverse cardiovascular events were numerically lower in the RSG group.

5.9. Combination with Metformin

As presented in section 5.1, in the ICT analysis, events of myocardial ischemia were generally low. The ORs for all seven of the treatment comparisons were greater than 1, although most had wide 95% CIs which included unity (Table 4). The exception occurred in the MET+RSG vs MET monotherapy comparison, where the 95% CI did not cross unity (OR 2.72, 95% CI 1.17–7.03). This observation may be due to the unusually low incidence of events in the MET monotherapy group (0.56%) which was not only lower than the other control groups in the ICT (1.29% - 2.38%) but also lower than the rate and/or incidence of CV events reported in the literature with MET. Importantly, in those studies where MET+RSG was compared to active comparator, MET+SU, there was no apparent difference in events of myocardial ischemia.

In the ICT analysis, the rate and incidence of all myocardial ischemic events (which includes 12 separate terms) in the MET monotherapy control group is approximately two times lower than that observed in the MET group of ADOPT at 6 months. The event rate for myocardial ischemia in MET monotherapy in ICT was similar to the event rate for myocardial infarction *alone* in the UKPDS study. This finding is noteworthy as patients in both the UKPDS and ADOPT were newly diagnosed, drug-naïve T2DM patients. They would be expected to have lower CV risk than the majority of patients who entered the RSG+MET studies, where the average duration of diabetes was approximately 5.5 years and approximately 75% of patients used prior oral monotherapy or dual combination therapies prior to entry into the studies. In addition, the incidence of all myocardial ischemic events in the MET monotherapy control arm of the ICT analysis was also lower than the incidence of AEs related to coronary artery disease reported in the original MET SBA.

The myocardial ischemia event rate in the MET monotherapy control group in the relatively short-term RSG clinical trials was therefore much lower than expected and inconsistent with 2 much longer duration studies in lower risk, drug-naïve patients or the pre-registration clinical trials. Therefore, the reliability of the hazard ratios for this comparison in the ICT is questionable.

5.10. Combination with Insulin

The highest incidence of heart failure has been reported from the clinical trials when fixed dose RSG was added to established insulin therapy. In the integrated clinical trials safety data for RSG used in combination with insulin, events typically associated with myocardial ischemia were also higher in patients treated with a combination of RSG plus insulin than with insulin alone. In these studies, patients had a longer duration of diabetes (mean duration ranged from 12 to 15 years), were older (mean age ranged from 53 to 66 years), and most had pre-existing cardiovascular disease.

The clinical trial design in which RSG was added to a fixed dose of insulin may have influenced the adverse event profile. This does not reflect the usual clinical practice of adding insulin when patients are no longer adequately controlled on oral agents. In a study in which insulin was added to RSG + MET therapy and titrated as necessary, there were no reports of heart failure and only 1 patient with an event of angina for RSG + MET + INS and none for patients switched to insulin monotherapy arm. The study demonstrated that when current treatment guidelines regarding the use of oral agents and insulin therapy are followed (i.e. optimize oral agents before INS is started and then continue oral agents in conjunction with INS), the risk of fluid-related events such as edema and heart failure may be reduced.

5.11. Post-marketing Experience

The GSK safety database (OCEANS) contains reports of adverse experiences (AEs) worldwide from all sources: spontaneous (unsolicited) reports, including medically unverified consumer reports and those identified in the literature or received from regulatory authorities as well as serious adverse event reports from clinical trials and post-marketing surveillance studies.

Evaluation of individual spontaneous reports of cardiac events received with RSG and its fixed-dose products is significantly confounded by underlying diabetes and other cardiovascular risk factors, as well as reporting bias.

GSK have established an online signal detection system based on disproportionality analysis which is used to assess spontaneous adverse event data. Disproportionality Analysis involves comparing the proportion of all spontaneous cases for a drug which have the event of interest, with the proportion which would be expected if there was no association between the drug and event. This routine signal detection is conducted on a monthly basis for all drug-event pairs.

The FDA Adverse Events Database, AERS, was interrogated for AEs of interest (heart failure and myocardial ischemia associated terms). In AERs, disproportionate reporting was noted for heart failure and rosiglitazone. In contrast, there was no disproportionate reporting for the adverse events related to myocardial ischemia in association with rosiglitazone. A similar reporting pattern of cardiovascular AEs of interest (heart failure and myocardial ischemia) was also noted for pioglitazone.

5.12. Additional Ongoing Trials with Cardiovascular Outcomes

Several on-going long-term clinical trials in diabetes subjects with cardiovascular endpoints will provide additional clinical trial data on RSG. These studies include two large NHLBI-sponsored CV outcomes trials (BARI 2D and ACCORD), a Veteran Administration-sponsored diabetes trial on CV outcomes (VA DT), and a GSK-sponsored IVUS study (APPROACH). The study design, patient population, sample size, primary endpoint and key dates for each study are summarized in Table 27.

Independent Data Safety Monitoring Boards that meet regularly safeguard the patients participating in these studies, within the bounds of their charter. Although use of RSG is not randomly assigned in BARI 2D, ACCORD, and VA DT, the large number of patients receiving RSG (estimated to be a total of approximately 4500 patients) in these trials will provide data on the cardiovascular effects and further inform the benefit and risk considerations for use of RSG in patients with diabetes.

The NHLBI posted a public statement on June 15, 2007 on the use of RSG in the 2 NHLBI- funded clinical trials, BARI-2D and ACCORD.

> "Recently published studies on the effect of RSG in cardiovascular disease and death prompted the Institute to ask the ACCORD and BARI 2D Data and Safety Monitoring Boards (DSMBs) to conduct a thorough review of the safety of participants enrolled in each trial, including study interim data, and to consider the implications of the recent reports for the conduct of the trials. The DSMBs of both ACCORD and BARI 2D found no evidence to require discontinuing the use of rosiglitazone in the trials or to revise the study protocols…. The NHLBI has thoroughly reviewed the recent findings and accepts the recommendations of both DSMBs."

Recently, the APPROACH Data Monitoring Committee has met and recommended the trial continue as planned. Similarly, the study co-chairs of VA DT recommended to the study investigators that VA DT be continued without altering trial therapy.

Table 27 Additional Ongoing Outcome Trials

Study	Study Pop., No. of Subj.,	Study Design	Primary Endpoints	Anticipated Completion Date & Reporting Status
VADT (VA Diabetes Trial – VACSP #465, Glycemic Control and complications in T2DM)	Type 2 patients inadequately controlled on standard therapy 1792 Subjects	Multicenter, randomized, open-labeled, Dose Comparison, Parallel Assignment, Safety/Efficacy Study	Primary Endpoint Acute MI, Death from CV Disease Stroke, CHF, Amputation from peripheral vascular Disease (PVD, Surgical intervention for surgical coronary or PVD, Critical Limb ischemia	LPLV May 2008 No longer Recruiting Patients
ACCORD (Action to Control Cardiovascular Risk in Diabetes)	Adults with type 2 Diabetes 10,251 Subjects	Randomized, active control, parallel assignment, efficacy study	Primary Endpoint First Occurrence of a major CVD event, specifically non-fatal heart attack, non-fatal stroke, or cardiovascular death (measured throughout the study)	LPLV June 2009 No longer recruiting patients
BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)	Type 2 diabetes with stable coronary artery disease – actively managed for glycemia, lipids and BP 2368 subjects	Randomized, open-labelled, 2x2 factorial design	Primary Endpoint 5 year mortality Secondary Endpoints Death, Q-wave MI, Stroke	LPLV November 2009
APPROACH (Assessment on the Prevention of Progression by Rosiglitazone On Atherosclerosis in Diabetes Patients with Cardiovascular History	T2DM who are undergoing coronary angiography Approximately 672 patients	Multi-center, Double-blind, active-controlled, parallel group	Primary Endpoint Assess the reduction of CV Risk To compare the effects of rosiglitazone vs. glipizide on the progression of atherosclerosis, as assessed by intravascular ultrasound (IVUS)	LPLV July 2008

5.12.1.1. BARI 2D Trial

The primary aim of the BARI 2D trial is to determine the optimal treatment strategies for patients with type 2 diabetes mellitus and documented stable coronary artery disease

(CAD) in the setting of uniform glycemic control and intensive management of other risk factors, including dyslipidemia, hypertension, tobacco smoking, and obesity. BARI 2D simultaneously tests the following two treatment efficacy hypotheses with a 2x2 factorial design:

- Coronary revascularization hypothesis: The null hypothesis states that there is no difference between a strategy of initial elective revascularization of choice combined with aggressive medical therapy versus a strategy of intensive medical therapy alone.

- Method of glycemic control hypothesis: The null hypothesis states that there is no difference between a strategy of hyperglycemia management directed at insulin sensitization versus a strategy of insulin provision.

The target study population for the BARI 2D trial is patients with a diagnosis of type 2 diabetes and angiographically documented coronary artery disease for which revascularization is not required for prompt control of severe or unstable angina. Major exclusion criteria include need for immediate revascularization or revascularization (PCI and CABG) within the 12 months prior to randomization, NYHA functional class III and IV heart failure, left main coronary artery stenosis of ≥50%, and serum creatinine >2.0mg/dL. Randomization was stratified by clinical site and by intended revascularization treatment.

The primary endpoint of BARI 2D is all-cause mortality, and the stated principal secondary endpoint is the composite of death, myocardial infarction (MI), or stroke. The glycemic control goal is a target of HbA1c ≤7.0% for all patients. Patients assigned to an insulin-providing strategy of glycemic control may be treated with SU drugs, repaglinide, nateglinide, or insulin itself. Patients assigned to an insulin-sensitizing strategy may be treated with TZDs or MET. The α-glucosidase inhibitors are considered neutral drugs and can be used with either treatment group.

A total of 2368 patients were randomized from United States, Canada, Brazil, Mexico, Czech Republic and Austria when enrollment ended in March 2005. The currently planned follow-up period is through November 2008. At study entry, fewer than 20% of the BARI 2D patients were receiving a TZD drug. Throughout the BARI 2D treatment and follow-up phase, a TZD has been used in approximately two-thirds of the Insulin Sensitizing strategy patients and less than 5% of the Insulin Providing Strategy patients. Over 85% of the TZD used during the treatment and follow-up phase of BARI 2D is RSG; therefore, approximately 1420 patients on RSG are participating in this study. Given the large number of subjects treated with RSG even though use of RSG was not randomly assigned, BARI 2D is likely able to estimate the effect of RSG on survival, freedom from death due to cardiovascular causes, and survival free of myocardial infarction and/or stroke.

BARI 2D is organized by the University of Pittsburgh in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), and is governed by an operations committee of study sponsors and organizers, a steering committee of principle investigators, an NHLBI-appointed data safety monitoring board, and a mortality and morbidity

classification committee, and its study activity is directed from the coordinating center at the University of Pittsburgh. The BARI 2D study receives funding from NHLBI, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with additional funding provided by GlaxoSmithKline and other pharmaceutical companies. GlaxoSmithKline and other pharmaceutical companies also contributed study drugs for the BARI 2D trial.

5.12.1.2. ACCORD Trial

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial is a randomized, open-label, multi-center study with a double 2 X 2 factorial design in approximately 10,000 patients with type 2 diabetes mellitus. In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event because of existing clinical or subclinical CVD or CVD risk factors three primary hypotheses are being tested:

(1) Does a therapeutic strategy that targets a HbA1c of < 6.0% reduce the rate of CVD events more than a strategy that targets a HbA1c of 7.0% to 7.9%?

(2) In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to raise HDL-C and lower triglyceride levels, and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin?

(3) In the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduce the rate of CVD events compared to a strategy that targets a SBP of < 140 mm Hg?

The primary outcome measure is the first occurrence of a major cardiovascular disease event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Secondary hypotheses include treatment differences in other cardiovascular outcomes, total mortality, microvascular outcomes, health-related quality of life, and cost-effectiveness.

Study enrollment was completed in July 2006 after 10,251 patients were randomized. These participants will be treated and followed for about 4 to 8 years (approximate mean of 5.6 years) in clinical sites within 7 Clinical Center Networks in the United States and Canada. Follow-up is scheduled to end in 2009, with the primary results available in early 2010. RSG is the predominant TZD in the ACCORD trial and is used in both the intensive and the standard glycemic control arms. Among the 10,251 patients enrolled in ACCORD, approximately 2,000 patients are receiving treatment with RSG.

ACCORD trial is organized and funded by the NHLBI in collaboration with NIDDK, National Eye Institute, Centers for Disease Control and Prevention, and the National Institute of Aging. A Data Safety Monitoring Board appointed by NHLBI convenes regularly to monitor the conduct of the trial. GlaxoSmithKline is one of the pharmaceutical company contributors that provide clinical trial drugs.

5.12.1.3. VA DT

The Veterans Affairs Diabetes Trial (VA DT) is a large prospective, randomized, open-label controlled study in approximately 1700 veterans with diabetes. The primary objective of the trial is to determine whether intensive glycemic control, compared to conventional treatment with a ≥1.5% HbA1c separation between groups, can lead to a reduction in CV outcomes. The primary endpoints include myocardial infarction, stroke, new or worsening congestive heart failure (CHF), amputation for ischemic diabetic gangrene, invasive intervention for coronary artery disease (CAD) or peripheral vascular disease (PVD), and CV death.

The glycemic goal in the intensive arm is as near to normal glycemia as possible in each patient, aiming for HbA1c at or below 6%. The glycemic control goal in the conventional arm is avoidance of deterioration of HbA1c, keeping levels at 8–9% and preventing symptoms of glycosuria, hypoglycemia, and ketonuria. Both arms receive step therapy: glimepiride or MET plus RSG and addition of insulin or other oral agents to achieve goals.

Veterans with type 2 diabetes and failing at least one oral anti-diabetic agent or insulin were eligible. Major exclusion criteria include class III or IV heart failure or class III or IV angina, stroke, myocardial infarction or invasive revascularization within 6 months of randomization, or impaired renal function (serum creatinine >1.6 mg/dL).

This study is supported by the Cooperative Studies Program of the Department of Veterans Affairs Research and Development Service and by the American Diabetes Association, National Eye Institute, and a number of pharmaceutical contributors including GlaxoSmithKline. This study is administered by study co-chairs offices, the Hines VA Cooperative Studies Program Coordinating Center, and an executive committee. CV endpoints are independently determined by an Endpoints committee and a DSMB provides safety oversight. As of May 2003 when enrollment completed, a total of 1792 patients were randomized. Approximately 1,160 patients are receiving RSG. End of study follow-up period is planned for November 2008.

5.12.1.4. APPROACH Trial

APPROACH is a GSK sponsored, 18-month, global, multi-center, randomized, double-blind, active-controlled, parallel-group clinical trial. The primary objective of the study is to compare RSG versus glipizide on the progression of atherosclerosis as measured by IVUS-derived change in percent atheroma volume from baseline to 18 months in non-intervened coronary arteries. Secondary objectives include assessments of other IVUS-derived and angiographic atherosclerotic endpoints; glycemic parameters; CV biomarkers and lipids; medical care utilization questionnaires; time to first occurrence and incidence of adjudicated MACE plus the safety and tolerability of RSG in subjects with T2DM and CVD.

The patient population is aged 30 to 80 years with T2DM, currently treated with diet and exercise, monotherapy or low dose dual combination OADs who are undergoing coronary angiography or PCI with angiographic 10-50% luminal narrowing of target

vessel. Patients with previous exposure to TZDs or insulin; post-procedural myocardial infarction or other major complications, left ventricular ejection fraction <40%, clinically significant renal or hepatic disease, recent myocardial infarction or heart failure were excluded. In total, 672 subjects were randomized into the study. Approximately 336 patients are treated with RSG. The study is fully enrolled and will complete in August 2008, with initial results available in early 2009.

The APPROACH study is governed by an International Steering Committee, an Independent Data Monitoring Committee and a Clinical Endpoint Adjudication Committee.

5.13. Summary

The question raised by the meta-analyses suggesting the potential for an increased risk of myocardial ischemia or myocardial infarction with RSG relative to control has not been confirmed across more robust and definitive data sources including prospectively designed clinical trials of longer exposure and in epidemiologic studies. There is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial infarction or cardiovascular death in comparison to other anti-diabetic agents.

6. SUMMARY OF SAFETY AND EFFICACY OF OTHER ANTI-DIABETIC AGENTS:

6.1. Use in Clinical Practice

Six classes of oral anti-diabetic medications (OADs) with varying modes of action are currently available for patients with type 2 diabetes mellitus (T2DM) for reducing blood glucose. No single agent addresses the full range of pathophysiological defects characteristic of T2DM. This, coupled with the inexorable deterioration of glycemic control over time, and increasingly stringent target goals makes the availability and combination use of a range of OADs essential. Patient variability heightens the need for different treatment options.

The classes of oral anti-diabetic agents (OADs) include insulin secretagogues (SUs and the meglitinides), biguandies (MET), alpha glucosidase inhibitors, insulin sensitizers/TZDs, incretins, and DPP-4 inhibitors (Table 28).

Table 28 Approved Oral Antidiabetic Agents (OADs) in the US

Class	Mechanism	Year of Introduction
Sulfonylureas	Insulin secretion	1946
Biguanides -metformin	Inhibition of hepatic glucose production	1995
α-glucosidase inhibitors -acarbose -miglitol	Inhibition of glucose absorption	1995
Meglitinides -nateglinide -repaglinide	Insulin secretion	1997
Thiazolidinediones -rosiglitazone -pioglitazone	Insulin sensitizing	1999
Incretins -exentatide	Insulin secretion via GLP-1	2005
DPP-4 inhibitors -sitagliptin	Inhibition of GLP-1 breakdown	2006

SUs and meglitinides stimulate insulin secretion from pancreatic beta-cells. The effect of MET is predominantly associated with insulin mediated suppression of hepatic glucose production and enhanced insulin stimulated glucose disposal in skeletal muscle [Inzucchi, 2002]. TZDs exert their insulin-sensitizing effects by binding to and activating the nuclear peroxisome proliferators activated receptor-gamma (PPARγ). This results in a modification of transcription factors involved in metabolism of fat and glucose, thus decreasing levels of blood glucose, circulating insulin and free fatty acids within liver, muscle, and adipose tissue. DPP-4 inhibitors and GLP-1 analogs, augment endogenous glucose-dependent insulin secretion and have additional effects that impact glycemic control including inhibition of glucagon release, and slowing of gastric emptying [Drucker, 2006].

The glucose lowering effect of the key OAD classes is generally comparable (0.7-1.5%). Published data demonstrates that SU therapy leads to a mean decrease in HbA1c of approximately 1% to 2% and fasting plasma glucose (FPG) levels by 60 to 70 mg/dL. In general, the HbA1c-lowering efficacy of SUs has been shown to be very similar to that of MET over a 6-12 month period [reviewed in Davidson 1997; Cusi 1998]. SU have a rapid onset of action and may be particularly appropriate if there is marked hyperglycemia [Home 2007a]. SUs are often used in lean patients who tend to be relatively insulin deficient, whereas MET is considered most appropriate for overweight individuals since it is associated with modest weight reduction or neutrality.

TZDs are reported to decrease glycosylated hemoglobin values on average by 1 to 1.5 percent [Nathan 2006, Yiki-Jarvinen 2004]. While no anti-diabetic agent, oral or insulin, has been shown to abolish the progressive rise in HbA1c, in 4 to 6 year, head to head comparison of RSG, glyburide and MET in the ADOPT trial, it was clear that RSG was superior in achieving and maintaining target glycemic control to the comparators [Kahn 2006]. To our knowledge, there are no similar data for pioglitazone.

Sitagliptin is currently the only marketed DPP-4 inhibitor in the US (approved October 2006). Sitagliptin demonstrated a mean absolute 0.5% – 1.0% decrease in hemoglobin HbA1c, both for monotherapy and add-on therapy to MET.

Each class of OADs has a particular safety profile, characterized over decades in the case of established agents. The main risk associated with SU therapy is hypoglycemia. Although SU-induced hypoglycemia is common, it is frequently unrecognized in clinical use and like insulin-induced hypoglycemia, and can limit the ability to achieve therapeutic goals by reducing treatment adherence and encouraging snacking with resulting weight gain. Quality of life may also be adversely impacted since hypoglycemia is more common in individuals with variable eating habits, those who consume alcohol and those with good glycemic control (i.e., an HbA1c at or just above the non-diabetic range). In the case of more potent and longer-acting SUs, hypoglycemia may be severe and prolonged, particularly in the elderly. Mild symptomatic hypoglycemia was reported by 20% of SU-treated patients in the UKPDS annually. The annual incidence of severe hypoglycemia (requiring assistance from another person), which may result in significant morbidity as well as death, has been recorded in 1% of SU-treated patients annually [Krentz, 2005].

Sulfonylureas cause weight gain which is most pronounced over the first couple of years of treatment [UKPDS 33, 1998; Kahn, 2006]. SU-associated weight gain includes increases in both subcutaneous and intra-abdominal (visceral) fat [Katoh, 1997]. Another limiting factor for SUs, noted in the Precautions section of all SU labeling, is secondary failure or diminished response over time. Secondary failure often necessitates the addition of insulin or another anti-diabetic agents with a different mechanism of action. This acknowledged shortcoming of SU therapy was reinforced in ADOPT.

The principal treatment limiting adverse effects associated with use of MET are gastrointestinal effects and lactic acidosis. The latter is a rare (0.03 per 1000 patient years) though life-threatening event. The risk of lactic acidosis is increased in conditions associated with acidosis – renal, hepatic and cardiac impairment, and chronic hypoxemia,

relatively common clinical situations. Gastrointestinal adverse effects (e.g., nausea, diarrhea, vomiting, abdominal pain) occur in 5-30% of MET-treated subjects, preclude rapid dose escalation, and require discontinuation of treatment in about 3-4% of subjects [Davidson, 1997; Kahn, 2006]. Additionally, about 10% of subjects cannot tolerate MET at any dose due to GI side effects [Krentz, 2005]. According to The National Health and Nutrition Examination Surveys (1988- 1994 and 1999-2000), which are representative of the non-institutionalized US population, at least 4.8 to 10.6% of subjects with T2DM had creatinine = 1.5 mg/dL, a value that would contraindicate the use of MET (GSK internal analysis, 2004).

TZD therapy is associated with weight gain and fluid retention, which may manifest as a reduction in hematocrit and mild anemia, peripheral edema or, in susceptible individuals, may lead to or exacerbate congestive heart failure. Another more recently identified class effect is an increased risk of peripheral bone fractures in females, which was first observed in ADOPT [Khan, 2006]. Concerns have been raised about the carcinogenic potential of PPARs. Long- term data from ADOPT substantially add to the weight of evidence indicating that RSG does not pose a carcinogenic risk in humans (Section 4.6.7.).

Safety data relating to incretins and DPP-4 inhibitors are much more limited. The most common adverse event with exenatide was mild to moderate nausea (44% vs 18% for placebo), which was dose related. Few adverse events are reported in the prescribing information for sitagliptin. The combination of sitaglitpin with SUs has not been adequately studied so the potential for hypoglycemia in this combination has not been characterized. A potential for skin necrosis (not observed with sitagliptin) was identified in preclinical studies with DPP-4 inhibitors. Because the drug target is identical to the T lymphocyte cell surface antigen CD26, concerns of infections and carcinogenity due to the potential for reduced cellular immunity. There was a slight excess of neoplasms in pre-approval studies with sitagliptin (0.7 – 0.9% vs. 0.5% in placebo treated patients).

A summary of the labeling for anti-diabetic medications is provided in Appendix E.

6.2. Short-term Safety vs. Long-term CV Outcomes

Therapeutic goals in T2DM include reduction in symptoms associated with poor glucose control, and minimization of the risk of micro and macrovascular complications. Different types of clinical studies are necessary to characterize these effects, with shorter term studies being focused on glycemic control. In short-term glycemic studies, a number of the commonly used agents have been associated with apparent increases in CV events or deaths that have not been confirmed in long-term studies. In the Veterans Affairs Diabetes Feasibility trial, a numerical excess of cardiovascular events was observed with intensification of glucose control vs standard control in the short-term (Abriara, 1997). Regardless of class, there is a tendency for short term clinical trials of OADs to suggest poorer CV outcomes than longer, more appropriately designed and substantial studies (Table 29).

Table 29 Short-term versus Long-term CV data

	Short term (<1yr)*	Long term Data
Metformin	CV events increased vs. control in short term studies – 128 vs. 80 per 1000PY	In obese subjects CV benefit demonstrated at 10yrs
SU	Increased deaths for glimepiride vs. placebo – 5/1523 (0.3%) vs. 0	UKPDS demonstrated no excess risk for glyburide at 10yrs
Rosiglitazone	Higher incidence in myocardial ischemic events 1.99% vs. 1.51% (RSG vs. control)	ADOPT - no apparent difference to Met or SU 4-6 yrs RECORD - no apparent difference to Met+ SU , 3.75 yrs
Nateglinide	CV deaths compared to placebo (4/1448 vs. 0/459)	NAVIGATOR trial ongoing
Sitagliptin	CV events: SIT 26/3179 (0.8%) PBO 3/1014 (0.3%)	No long term data available
*Sources are Summary Basis of Approval or FDA reviews available through Freedom of Information for all medication except rosiglitazone		

Although the underlying reason for the discrepancy between short and long term findings is not established, the shorter studies were not designed to specifically evaluate cardiovascular events. Most of the studies have small numbers of reported cardiovascular adverse events and these events are not pre- specified or adjudicated. The small numbers of events make it difficult to draw firm conclusions as a minor change in numbers in either direction can lead to dramatically different conclusions.

Elements of clinical trial design may confound assessment of cardiovascular events. Examples include withdrawal of prior therapy before randomization with resulting metabolic decompensation, earlier withdrawal of placebo treated patients due to poor glycemic control, and imbalances in baseline cardiovascular risk. Larger, longer term clinical trials, particularly those specifically designed to evaluate cardiovascular endpoints, should be relied upon for assessing the cardiovascular effects of anti-diabetic agents.

6.3. Glycemic Control and Macrovascular Outcomes in Type 2 Diabetes

UKPDS demonstrated the benefits of improved glycemic control on microvascular outcomes. However, benefits on macrovascular endpoints, though trending in a positive direction, did not reach statistical significance. Cardiovascular benefit was demonstrated after 10 years in a small metformin-treated subgroup of overweight patients.

In comparing cardiovascular safety of different classes of anti-diabetic agents, it is important that glycemic control be similar between treatment groups. RECORD is an active-controlled study, comparing RSG + MET or SU to MET + SU. The study design calls for targeting similar glycemic between groups. An 18 month glycemic efficacy analysis demonstrated that the reduction in HbA1c was similar between the RSG and comparator groups. As would be expected, the recently published interim analysis of

RECORD showed that, with the exception of heart failure, cardiovascular events were similar between RSG and comparator groups.

PROactive compared pioglitazone to placebo with the pioglitazone group having ~0.5% lower HbA1c. Results showed a statistically non-significant 10% reduction in the primary composite endpoint. There was a statistically significant 16% relative risk reduction (HR 0.84, 95% CI 0.72 – 0.98, p=0.027) on a principle secondary endpoint, suggestive of potential cardiovascular benefits at study end. Re-analysis of these data using UKPDS risk engine concluded that the CV benefit could be accounted for by the improvement in metabolic control [Holman, 2006].

7. CARDIOVASCULAR RISK MANAGEMENT PLAN FOR ROSIGLITAZONE-CONTAINING PRODUCTS

This targeted Risk Management Plan (RMP) provides a summary of the known cardiovascular risks associated with rosiglitazone and GSK's planned expansion in efforts to manage these risks with use of the product. For purposes of this Briefing Document, please note that GSK have focused on the known cardiovascular risks associated with rosiglitazone, i.e., the risk of edema and congestive heart failure. GSK understands that FDA is seeking advice from its Advisory Committees, and medical-scientific information and dialogue with GSK, regarding the association, if any, between rosiglitazone and the risk of myocardial ischemic adverse events. GSK welcomes this dialogue as an essential precursor to FDA deciding whether additional risk management activities are warranted.

This plan outlines pharmacovigilance activities to obtain outcome data that will further inform the association, if any, between myocardial ischemia and rosiglitazone. This plan describes risk management activities which comprise proposed labeling updates, communications to prescribers and patients, continuing education activities for prescribers, and updates on ongoing pharmacovigilance activities (including outcome studies).

Fluid Retention and Heart Failure

It is well-established that rosiglitazone, like other TZDs, can cause fluid retention which may lead to or exacerbate heart failure. Rosiglitazone and other thiazolidinediones can cause fluid retention when used alone or in combination with other agents for the treatment of T2DM.

To further mitigate this known risk of rosiglitazone, GSK have agreed to make additional changes in labeling by adding a boxed WARNING and CONTRAINDICATION statement regarding heart failure to the labeling for all products containing rosiglitazone. These sections of labeling will emphasize the following points:

- Patients initiating therapy with rosiglitazone, as well as patients whose dose of rosiglitazone is increased, should be observed carefully for rapid weight gain, significant edema, or other signs of heart failure.
- Rosiglitazone will not be recommended for patients with certain types of heart failure.
- Recommendations regarding the management of patients who develop symptomatic heart failure on rosiglitazone therapy will be specified.

There are other rosiglitazone-drug combinations which are noted to have an increased incidence of heart failure or fluid retention, as described below:

Addition of Rosiglitazone to Therapy with Insulin

The USPI for rosiglitazone has in the Warnings and Precautions section a caution about the higher incidence of heart failure when rosiglitazone is used in combination with insulin. Furthermore, an increased incidence of events typically associated with ischemia

is described. All of the RSG studies upon which this recommendation was based were conducted with rosiglitazone as add-on therapy to patients on pre-existing insulin. More recently in a study of approximately 300 diabetic patients, where insulin was added on to established rosiglitazone + metformin therapy compared to a continued insulin monotherapy group, there were no cases of heart failure reported and only one subject in the AVANDAMET + insulin group experienced an ischemic event of angina. GSK will recommend a change in labeling whereby rosiglitazone should not be given as add-on therapy to patients already receiving insulin. Instead, insulin can be added to patients on established rosiglitazone therapy. Add-on insulin therapy should be titrated cautiously with appropriate clinical evaluation for fluid retention and other cardiovascular 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 clinically significant adverse events.

Potential Cardiovascular Risks in Settings of Limited Data

Limited data are available at present from prospectively designed, controlled, randomized cardiovascular outcome studies. Currently, the results of an interim analysis of the RECORD study (a cardiovascular outcome study, including adjudication of cases) have been presented in this Briefing Document. The final results of RECORD, as well as other CV outcome studies, will be available in 2008-2010. The status of these studies is summarized in the following table:

Status of Studies Contributing Cardiovascular Safety Data to the Risk Assessment and Risk Management Plan (with timelines for each study).

	Status of Study		Key Dates		
Study	Completed	Ongoing	Start Enrollment	Last Patient Visit	Estimated Date for Results
Cohort study on RSG and PIO	√		June 2007	July 2007	July/Aug 2007
VA DT		√	Dec 2000	May 2008	Oct 2008
APPROACH		√	Feb 2005	July 2008	2Q 2009
RECORD		√	April 2001	Dec 2008	April 2009
ACCORD		√	Jan 2001	June 2009	2010
BARI 2D		√	April 2001	Nov 2009	2010

In addition, there is limited data on the use of rosiglitazone in patients experiencing acute coronary syndrome (ACS). In view of the acute unstable condition of patients experiencing ACS, the potential for the development of heart failure , and the lack of data on rosiglitazone in such patients, GSK will discuss with FDA, and these Committees as requested, the proposal that rosiglitazone is not recommended for use in patients experiencing an acute coronary syndrome.

7.1. Communication and Education

While the fluid related effects of rosiglitazone and other TZDs are well known, GSK will increase prescriber and patient awareness of the risk of edema and heart failure, including attention to product specific labeling for use of rosiglitazone in combination with insulin. Proactive communication and education on labeling updates will be pursued through the following routes:

- GSK's internet site will provide the revised prescribing information and revised Patient Information Leaflet, for ready access by prescribers and patients. The document will be posted to this publicly accessible web site within 48 hours of FDA approval of the updated labeling.

- A "Dear Healthcare Provider" letter with updated labeling on heart failure will be sent to all board-certified Endocrinologists, as well as all physicians who have prescribed AVANDIA, AVANDAMET, or AVANDARYL in the last 12 months. The mailing list consists of approximately 170,000 physicians. This letter will highlight the changes in labeling and the actionable recommendations to physicians, as well as provide a copy of the revised prescribing information (including revised Patient Information). GSK's objective is to begin mailing this "Dear Healthcare Provider" letter within 1 week of FDA's approval of the updated labeling. A copy of the final "Dear Healthcare Provider" letter will be provided by GSK to FDA for posting on FDA's publicly accessible MedWatch site. GSK's intent is to have copies of the "Dear Healthcare Provider" letter available to our field sales representatives to carry and hand out (with the attached prescribing information for Avandia Tablets) to the healthcare providers they visit. This effort will continue for up to 3 months after approval of proposed labeling. Sales representatives will have specific "speaking points" about this letter and will be encouraged to refer detailed queries to GSK's Medical Information Department.
- A Dear Investigator Letter will be dispatched to all investigators actively involved in ongoing GSK sponsored rosiglitazone studies worldwide.
- Informed Consents for ongoing studies will be updated and patients re-consented as appropriate; depending on the inclusion and exclusion criteria for studies and the final agreed upon label.

- Data Safety Monitoring Boards (DSMBs) for ongoing trials in patients or study subjects receiving rosiglitazone will be updated with new labeling information.

- Tear-off pads of Patient Information can be made available as a convenient means of providing the FDA-approved "Patient Information Leaflet" on AVANDIA. These tear-off pads can be provided to retail pharmacies and physicians' clinics/offices. We are still determining the number of pharmacies and clinics/offices to receive this direct mailing. Supplies of tear-off pads would be available for 6 months, on request. GSK will submit a draft version of the Dear Healthcare Provider letter and Tear-Off Pad for review and comment by FDA.

- Educational programs aligned with final approved labeling can be developed (e.g., CME conferences or publications on management of TZD-related fluid events and heart failure).

Assessment of Effectiveness of the Pharmacovigilance/Risk Management Plan

Proactive monitoring of cardiovascular safety and adverse events reported in association with AVANDIA and rosiglitazone-containing products by GSK's Safety review teams will be ongoing following approval of this labeling update. This monitoring will occur in ongoing clinical trials in type 2 diabetes, as well as in non-diabetes populations. In addition, independent DSMBs have been established for all ongoing outcome trials to ensure patient safety. GSK will initiate a dialogue with FDA and the Data Safety Monitoring Boards to explore a means of sharing information among DSMBs and FDA for these outcome studies and fostering periodic updates (e.g., every 6 months) to be shared with FDA on the status of each ongoing study.

With respect to postmarketing spontaneous reports of heart failure, prescribing patterns will be assessed to confirm appropriate use of AVANDIA and rosiglitazone-containing products. A Targeted Follow-Up Questionnaire (TFUQ) could be developed for spontaneous reports of heart failure to ascertain appropriate use of rosiglitazone in accordance with final approved labeling.

Overall, the effectiveness of the risk management plan for AVANDIA will be indicated by the demonstration of appropriate use of rosiglitazone according to the labeling. The risk management plan will be re-assessed periodically for revision, as appropriate, based on the availability of new information from ongoing pharmacovigilance activities, including recommendations from the DSMBs, and final data upon completion of outcome trials.

All activities proposed for rosiglitazone will be implemented for the approved fixed-dose combination products of Avandamet® and Avandaryl®.

8. SUMMARY AND CONCLUSIONS

Type 2 diabetes is a chronic progressive disease with short-term symptomatology and long-term devastating microvascular and macrovascular complications. Good glycemic control reduces microvascular complications. Multiple therapeutic modalities are required to achieve optimal metabolic control. This was highlighted in the UKPDS which demonstrated that monotherapy with metformin or sulfonylurea failed to maintain glycemic control as the disease progressed.

In the short-term, rosiglitazone significantly reduces HbA1c by 1-1.5% and has been shown to be effective in a wide range of patients from newly diagnosed to patients with advanced disease treated with combination therapy. Rosiglitazone has been studied in various patient types including, elderly, renally impaired, various ethnicities, those with known heart failure or with known cardiovascular disease. In the long-term, ADOPT demonstrated that rosiglitazone was superior to metformin and glyburide in newly diagnosed type 2 diabetes patients in maintaining glycemic control. Mean HbA1c was maintained at <7% for 54 months for rosiglitazone compared to 45 months for metformin and 32 months for glyburide. This durability reflects rosiglitazone's favorable impact on the underlying pathophysiological defects of type 2 diabetes, insulin resistance and beta cell dysfunction. In DREAM, rosiglitazone reduced incident type 2 diabetes in subjects at high risk of progression to diabetes.

Rosiglitazone has an established efficacy and tolerability profile with an absence of hypoglycemia and lack of gastrointestinal intolerability. Rosiglitazone can be used in a wide range of patients in whom other agents may not be suitable due to lack of tolerability or contraindication. Benefits risk consideration may favor the use of rosiglitazone in some elderly patients who are at particular risk of serious consequences of hypoglycemia with SUs. Metformin, though extremely useful, is also limited due to contraindication in renally impaired patients and, in some patients, poor gastrointestinal tolerability. In patients unable to achieve or maintain adequate glycemic control on their current therapy, due to its complementary mode of action, rosiglitazone has been shown to provide additional benefits. Current treatment guidelines (ADA, AACE, AHA/ACC, IDF) recognize the role of rosiglitazone in the treatment of type 2 diabetes.

Throughout the clinical development program and with post-marketing experience, GSK have evaluated, on an ongoing basis, the safety profile of rosiglitazone, including the cardiovascular safety. GSK have conducted numerous investigative/mechanistic studies with rosiglitazone and evaluated the effects on biomarkers and risk factors that may contribute to cardiovascular events.

GSK have worked consistently over the life of rosiglitazone, through regulatory submissions to the FDA, to add substantially to the safety information in the labeling, with recent updates to the labeling regarding class effects including macular edema and fractures. Fluid retention which can lead to or exacerbate heart failure is a known effect of the TZD class of anti-diabetic agents. The potential for the exacerbation of heart failure during rosiglitazone therapy is highlighted in the current product labeling. At the request of the FDA, GSK have submitted a supplement to make information with regards

to heart failure more prominent in labeling, thereby further assisting physicians in the appropriate use of TZDs.

Recently meta-analyses by GSK, FDA and others have raised the question whether rosiglitazone use results in an increased incidence of myocardial infarction in diabetic patients. Given the recognized limitations of these analyses, GSK have sought to answer this question by examining all available data, including long-term, ongoing, prospective studies specifically designed to evaluate rosiglitazone cardiovascular safety, as well as large epidemiological studies reflecting actual clinical usage in the United States.

Across these multiple sources of data, there is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial infarction or cardiovascular death in comparison to other anti-diabetic agents.

The most robust data for assessing cardiovascular effects with rosiglitazone comes from the RECORD study which was started in 2001 and was specifically designed to evaluate the cardiovascular safety of rosiglitazone, using well accepted adjudicated endpoints. An interim analysis has shown no statistically significant difference between rosiglitazone in combination with either metformin or sulfonylurea vs the active comparators of metformin plus sulfonylurea, regarding myocardial infarction and death from cardiovascular causes or any cause.

This was confirmed in ADOPT where, overall there was no meaningful difference among groups for myocardial infarction or death and in DREAM, in pre-diabetic patients, where there was no statistical difference between rosiglitazone and the placebo groups for myocardial infarction or cardiovascular death. Although not designed as CV outcomes trials, these 2 trials inform the cardiovascular safety of rosiglitazone.

Several other long-term clinical trials with cardiovascular endpoints in diabetes subjects are currently underway and fully enrolled, including two large NHLBI-sponsored CV outcomes trials (BARI 2D and ACCORD), a Veterans Administration-sponsored diabetes trial on CV outcomes (VA DT), and a GSK-sponsored IVUS study (APPROACH). The large number of patients receiving rosiglitazone in these trials (estimated to be a total of approximately 4500 patients) will provide additional data on cardiovascular effects and further inform the benefit:risk profile of rosiglitazone for use in patients with type 2 diabetes. The independent Data Safety Monitoring Boards for these studies continue to review the accruing safety data in their study and the studies are continuing unaltered.

GSK have also conducted three large epidemiological studies, encompassing over 500,000 patients with type 2 diabetes, to determine whether use of rosiglitazone in the real world setting is associated with an increase in myocardial infarction or coronary revascularization. The results of these studies show that rosiglitazone use is not associated with an increased risk of myocardial infarction vs. other standard anti-diabetic agents. Specifically in the most recently performed and largest study, there is no difference seen in the risk of myocardial infarction between rosiglitazone and pioglitazone.

The overall data on cardiovascular risk markers do not suggest that rosiglitazone would lead to progression of atherosclerosis or increased plaque rupture, and therefore do not

support a plausible biological hypothesis to link use of rosiglitazone with myocardial infarction. The totality of the available data from large long term prospectively designed studies, along with the three large epidemiological studies do not support the conclusion that rosiglitazone is associated with an increased risk of myocardial infarction.

Events in the last two months have prompted public discussion of the role of RSG in the treatment of type 2 diabetes. GSK maintains that there is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial infarction or cardiovascular death in comparison to other anti-diabetic agents. Therefore, the benefit risk profile of rosiglitazone continues to be favorable. The need for long-term pharmacologic therapy of type 2 diabetes, with most patients needing combination drug therapy, reinforces the need for multiple choices in the armamentarium. Rosiglitazone is an important therapeutic choice for physicians and their appropriate patients with type 2 diabetes mellitus.

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ARTICLE

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Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol

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Abstract *Aims/hypothesis:* Studies suggest that in addition to blood glucose concentrations, thiazolidinediones such as rosiglitazone improve some cardiovascular (CV) risk factors and surrogate markers, that are abnormal in type 2 diabetes. However, fluid retention might lead to cardiac failure in a minority of people. The aim of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study is to evaluate the long-term impact of these effects on CV outcomes, as well as on long-term glycaemic control, in people with type 2 diabetes. *Materials and methods:* RECORD is a 6-year, randomised, open-label study in type 2 diabetic patients with inadequate blood glucose control (HbA_1c 7.1–9.0%) on metformin or sulphonylurea alone. The study is being performed in 327 centres in Europe and Australasia. After a 4-week run-in, participants were randomised by current treatment stratum to add-on rosiglitazone, metformin or sulphonylurea, with dose titration to a target HbA_1c of ≤7.0%. If confirmed HbA_1c rises to ≥8.5%, either a third glucose-lowering drug is added (rosiglitazone-treated group) or insulin is started (non-rosiglitazone group). The same criterion for failure of triple oral drug therapy in the rosiglitazone-treated group is used for starting insulin in this group. The primary endpoint is the time to first CV hospitalisation or death, blindly adjudicated by a central endpoints committee. The study aim is to evaluate non-inferiority of the rosiglitazone group vs the non-rosiglitazone group with respect to CV outcomes. Safety, tolerability and study conduct are monitored by an independent board. All CV endpoint and safety data are held and analysed by a clinical trials organisation, and are not available to the study investigators while data collection is open. *Results:* Over a 2-year period a total of 7,428 people were screened in 25 countries. Of these, 4,458 were randomised; 2,228 on background metformin, 2,230 on background sulphonylurea. Approximately half of the participants are male (52%) and almost all are Caucasian (99%). *Conclusions/interpretation:* The

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RECORD study should provide robust data on the extent to which rosiglitazone, in combination with metformin or sulphonylurea therapy, affects CV outcomes and progression of diabetes in the long term.

Keywords Cardiovascular outcomes · RECORD study · Rosiglitazone · Thiazolidinediones · Type 2 diabetes

Abbreviations AER: albumin excretion rate · ALT: alanine aminotransferase · CV: cardiovascular · CRP: C-reactive protein · DSC-R: Diabetes Symptom Checklist revised version · DSMB: data safety monitoring board · FPG: fasting plasma glucose · βhCG: β-human chorionic gonadotrophin · hPI: intact human proinsulin · PAI-1: plasminogen activator inhibitor-1 · PPAR-γ: peroxisome proliferator-activated receptor-γ · RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes · UKPDS: UK Prospective Diabetes Study

Introduction

Type 2 diabetes is a progressive condition characterised by hyperglycaemia and other metabolic disorders, and their associated complications. Studies show that type 2 diabetes is significantly associated with all-cause and cardiovascular (CV) mortality [1], and that CV disease is the leading cause of death in people with type 2 diabetes [2].

Since insulin insensitivity has been identified as an important underlying or associated factor in the pathogenesis of type 2 diabetes and related CV disease [3, 4], drugs that ameliorate insulin insensitivity and the CV risk factors and markers associated with it, might be of benefit in reducing CV disease risk. This cluster of abnormalities includes insulin insensitivity itself, glucose intolerance, abdominal adiposity, dyslipidaemia (raised triglyceride and small, dense LDL particles, and decreased HDL cholesterol), raised blood pressure and microalbuminuria.

Rosiglitazone and pioglitazone are the two clinically available peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, a class of oral glucose-lowering drugs that improves glycaemic control in type 2 diabetes by improving insulin sensitivity [5–11]. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study is concerned with rosiglitazone. Consistent with its insulin-sensitising effect, this drug has shown improvements in CV risk factors associated with insulin insensitivity, such as raised blood pressure, AER [12], plasminogen activator inhibitor-1 (PAI-1) [13] and C-reactive protein (CRP) [13, 14], and low serum HDL cholesterol (notably HDL_2) [8, 15, 16]. Whilst increases in serum LDL cholesterol concentrations have been observed, these are associated with shifts towards larger, presumably less atherogenic LDL particles, making the significance of this observation unclear [15, 17].

An additional concern with this drug class, particularly the dual PPAR-αγ agonists that are under development, is fluid retention and, thus, whether this predisposes a population already at risk of cardiac failure to a higher rate of possible adverse outcomes [18, 19]. Weight gain also occurs with these drugs, but this is consistent with improved glucose control, fat redistribution to less metabolically active peripheral adipose tissue, and some fluid retention [20]. The PPAR-γ agonist troglitazone has been associated with rare cases of serious hepatic damage leading to liver failure, but there has been no evidence of this hepatotoxicity in wide clinical experience with rosiglitazone or pioglitazone [21, 22].

The glucose-lowering effects of oral glucose-lowering drugs were shown by the UK Prospective Diabetes Study (UKPDS) to translate into improved health outcomes [23]. A substudy of the UKPDS suggested that metformin had some additional advantage in cardiovascular risk protection [24]. Thiazolidinediones, as newer drugs, now need to be evaluated in the same way, which is the rationale for the current study.

In the management of type 2 diabetes, after lifestyle changes have been made in terms of diet (following dietary advice) and increased physical activity, drug therapy usually becomes necessary over time to maintain good glycaemic control. However, the ability of available drugs to maintain adequate long-term glycaemic control as a monotherapy is limited [23, 24], and the usual recourse is then to combination therapy with metformin plus a sulphonylurea. This dual therapy context appears to be the most logical in which to test the overall effectiveness of thiazolidinediones, although this complicates study design by requiring separate strata for those participants entering on metformin and those on a sulphonylurea. Furthermore, the expected continuing deterioration in glucose control during the course of the study leads to design issues over how to manage further intensification of treatment: should triple oral therapy or insulin be used? At which glycaemic thresholds should this occur?

This paper describes the RECORD study protocol, devised in an attempt to best meet these needs.

Subjects and methods

The study is being conducted according to Good Clinical (Research) Practice guidelines and the Declaration of Helsinki (1996) [25]. The conduct of each participating centre is monitored by regular visits from study staff. Two centres with suspected conduct problems were suspended from participation very early in the study. The study protocol was approved by ethics review committees or institutional review boards according to the local laws and customs of each participating country. Written informed consent was obtained from all participants before beginning protocol-specific procedures. Participants were informed of their right to withdraw from the study at any time. A steering committee meets to review progress every 6 months, and an independent data safety monitoring board (DSMB) has been established to monitor safety and outcomes throughout the course of the study (see below). The steering committee comprises six senior clinical ex-

perts, one senior expert statistician and two sponsor employees with specialism in clinical research.

Participants In total, 7,428 people with type 2 diabetes were enrolled into the study, and 4,458 were randomised in 327 centres (secondary care clinics and general practitioner surgeries, including site management organisations and private diabetes clinics) in 25 countries in Europe and Australasia. Each centre attempted to enrol 10–20 people. Recruitment began in April 2001 and was completed in April 2003. People with type 2 diabetes were screened for eligibility for study entry according to the criteria presented in Table 1. The requirement for patients to be taking the maximum tolerated dose of their background monotherapy at study entry was to ensure compliance with the product licence for rosiglitazone at the time of study design.

Study design The study is a multicentre, randomised, open-label, comparative, parallel-group trial. Eligible participants (see above) entered a 4-week run-in period that included reinforcement of lifestyle education (Fig. 1). During this period, subjects continued to take the oral glucose-lowering drug (metformin or sulphonylurea) taken prior to entry into the study. At the end of the run-in period, randomisation is followed by planned participation for a minimum of 5 years (maximum of 21 visits) and a median of 6 years. After randomisation, participants continued their pre-study glucose-lowering therapy in addition to their study medication. An open-label design was dictated by the different timings of progression to insulin therapy in the rosiglitazone and comparator groups (see below), and by the considerable number of types and doses of the sulphonylurea medications used in the comparator arms.

Randomisation and treatments The treatment allocation schedule was computer generated in blocks and stratified according to background glucose-lowering medication (metformin or sulphonylurea). Participants were randomised centrally using an interactive voice response telephone system. If already taking a sulphonylurea, participants were randomised to either additional rosiglitazone or metformin. If already taking metformin, they were randomised to additional rosiglitazone or sulphonylurea (glyburide/glibenclamide [normal or micronised], gliclazide or glimepiride; chosen according to local practice). It has been assumed that each of these three sulphonylureas is likely to have a similar effect on CV clinical outcomes. Each of these four treatment arms consists of approximately 1,100 people. Background glucose-lowering medications may be stopped or reduced at any time if intolerance develops or they become contraindicated (according to local practice).

Throughout the study, the protocol specifies that participants are to be treated using a target HbA_1c of ≤7.0%. If a person's HbA_1c rises above 7.0% at any point after 8 weeks of treatment, the dose of the randomised study medication should be increased. If the initial dose of rosiglitazone (4 mg) has been well tolerated, rosiglitazone may be increased to a maximum of 8 mg/day (taken as 4 mg twice daily). Metformin, glibenclamide, gliclazide and

Table 1 Eligibility criteria for participation in RECORD study

Inclusion criteria	Type 2 diabetes (male or female) as diagnosed according to the 1999 WHO criteria [25]
	Age 40–75 years
	BMI >25.0 kg/m^2
	HbA_1c >7.0% and ≤9.0%
	On maximum permitted/tolerated doses of background monotherapy (metformin, glyburide/glibenclamide, gliclazide or glimepiride)
	On oral glucose-lowering drugs for ≥6 months and on current drug at the maximum permitted/tolerated dose for ≥2 months
	If female, then post-menopausal, sterilised or using effective contraceptive measures
Exclusion criteria	Using other glucose-lowering therapies
	Use of a combination of two or more oral glucose-lowering agents within 6 months
	Use of insulin, except for pregnancy, intercurrent illness or stabilisation
	Previous use of any PPAR-γ agonist
	Hospitalisation for a major CV event in the last 3 months, scheduled major CV intervention, or gangrene
	Diagnosed or receiving medication specifically for heart failure (except diuretics alone)
	Systolic or diastolic blood pressure >180/105 mmHg, on therapy if used
	Fasting serum triglycerides >12.0 mmol/l
	Serum creatinine >130 μmol/l (>1.47 mg/dl)
	ALT, AST, total bilirubin or alkaline phosphatase ≥2.5 times the upper limit of normal
	Haemoglobin <11.0 g/dl for males or <10.0 g/dl for females or haemoglobinopathy interfering with valid HbA_1c assay
	Contraindication/intolerance to metformin, glyburide, gliclazide or glimepiride
	Pre-existing medical condition judged to preclude safe participation in the study
	Abuse of alcohol or drugs, or presence of any condition that may lead to poor adherence to study protocols
	Recent use of an investigational drug
	Pregnancy, breast feeding or planning pregnancy

AST aspartate aminotransferase

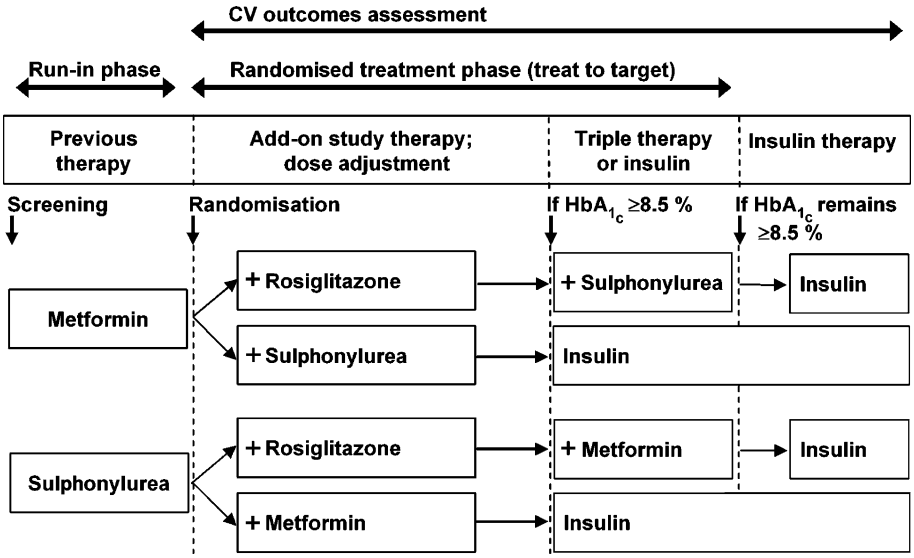

Fig. 1 A summary of the RECORD study design. After the run-in period, participants were randomised to add-on treatment with rosiglitazone or the oral glucose-lowering drug (metformin or sulphonylurea) not already being taken as background medication. If, during the study and despite titration (to a HbA_1c of 7.0%) of the study medication, HbA_1c is ≥8.5% in two consecutive measurements >1 month apart (and at least 8 weeks from titration to maximum dose of study medication), participants using rosiglitazone will start a third oral glucose-lowering drug, while non-rosiglitazone users will transfer to insulin therapy. Insulin therapy will also be started in the rosiglitazone group if the same conditions are later met on triple therapy, with the rosiglitazone then being stopped

glimepiride may be similarly increased up to maximum dosages of 2,550, 15, 240 or 4 mg, respectively.

If a participant's HbA_1c is ≥8.5% (confirmed by a second measurement at least 1 month later) despite having been on a maximum permitted or tolerated dose of add-on study medication for at least 8 weeks, additional therapy changes are made, as shown in Fig. 1. Participants in a rosiglitazone treatment arm have a third oral drug added, to make a triple oral combination treatment of rosiglitazone+sulphonylurea+metformin. Those on a metformin+sulphonylurea combination start insulin with or without continuing metformin and/or sulphonylurea, according to local practice. If participants who are receiving triple therapy including rosiglitazone later have a confirmed $HbA_1c \geq 8.5\%$, they start insulin therapy (± metformin/sulphonylurea) and cease rosiglitazone therapy. This asymmetric approach to insulin therapy was judged the most appropriate design, being clinically rational without breaching contraindications to combination insulin+rosiglitazone use. Any participants starting insulin therapy, although withdrawn from the requirement to use their randomised treatment, continue to have CV outcomes monitored and evaluated as before until the planned end of the study. Blood glucose control and safety measurements and adverse events also continue to be collected. The HbA_1c threshold for starting insulin or triple oral therapy was set at 8.5% to attempt to balance the need to avoid excessive hyperglycaemia against ensuring sufficient exposure to the randomised study medication.

Use of concomitant medications is permitted throughout the study, with the exception of glucose-lowering medications in participants taking the randomised treatments.

Visits and procedures Study visits are scheduled for the morning, after an overnight fast of ≥8 h and omission of any morning doses of glucose-lowering medications. Following screening (visit 1), a baseline (randomisation) visit (visit 2) was scheduled for 4 weeks later. While taking the randomised treatments, visits are scheduled to occur 2-monthly until month 12, then 3-monthly to month 24, then 4-monthly (all ±14 days). For those participants no longer taking randomised treatments, visits are scheduled to occur every 12 months, timed from the baseline visit.

During the screening visit (visit 1), the following procedures were performed after written informed consent was obtained: (1) completion of a checklist of inclusion/exclusion criteria; (2) recording of clinical characteristics, including smoking and alcohol; (3) recording of medical history, including current signs/symptoms, glucose-lowering medications taken within the last 6 months, and other prescription-only medications taken within the last month; (4) physical examination, including standardised measurement of blood pressure, heart rate, height, body weight and WHR; (5) laboratory measurements of blood specimens (see below), including serum β-human chorionic gonadotrophin (βhCG) in premenopausal, non-sterilised women; and (6) standard 12-lead ECG. Lifestyle education was provided.

At the baseline visit (visit 2), vital signs and blood sampling were repeated, and the following procedures were completed: (1) first-pass morning urine sample for determination of the urinary albumin:creatinine ratio; (2) measurement of body weight; (3) the Diabetes Symptom Checklist, revised version (DSC-R) [26] and the Medical Care Utilization and Restricted Activity Days question-

naires [27]; (4) a check for concomitant medications; (5) a check for any baseline signs/symptoms; and (6) a review of current diet and exercise.

Routine assessments made while patients are taking the randomised treatments include: (1) complete physical examination (yearly); (2) vital signs; (3) laboratory assessment of fasting blood specimens, including liver function monitoring; (4) first-pass morning urine sample for determination of the urinary albumin:creatinine ratio (months 6, 12, and then yearly); (5) the DSC-R (yearly); (6) the Medical Care Utilization and Restricted Activity Days questionnaires; (7) body weight; (8) smoking habits; (9) WHR; (10) standard 12-lead ECG (yearly); (11) recording of concomitant medications; (12) recording of adverse experiences; and (13) a review of current diet and exercise. Add-on study medication was dispensed following the completion of all assessments.

For those participants withdrawn from randomised treatments (see above), the following assessments are made yearly: (1) vital signs; (2) non-fasting blood specimens (HbA_1c and liver function tests only); (3) body weight; (4) DSC-R; (5) the Medical Care Utilization and Restricted Activity Days questionnaires; and (6) complete physical examination. Contact is made between these visits by telephone, following the same frequency as when on randomised treatments, for completion of the Medical Care Utilization and Restricted Activity Days questionnaires and ascertainment of cardiovascular outcomes.

Methods of evaluation A central laboratory is being used for all routine laboratory assessments (Quest Diagnostics, Heston, UK). Assessment of fasting blood specimens includes evaluation of HbA_1c (all visits), plasma glucose (all visits), insulin and proinsulin (baseline and 12, 18, 24 months, then yearly), standard lipid profile (baseline and 12, 18, 24 months, then yearly) and surrogate markers (PAI-1 antigen, apolipoprotein B, CRP and fibrinogen; baseline and 12, 24, 36 and 60 months). Other laboratory assessments include a urinary albumin:creatinine ratio, as well as safety assessments, including standard biochemistry and haematology markers, pregnancy screen, hepatitis testing and liver function tests.

HbA_1c is measured by HPLC using a DCCT-harmonised Biorad Variant HbA_1c assay (Hercules, CA, USA). Fasting plasma glucose concentration is measured using an enzymatic method and is read biochromatically. Serum immunoreactivity is determined by a two-site fluoroimmunometric assay (Perkin Elmer, Turku, Finland). The assay is specific for insulin, with negligible cross-reactivity for proinsulin and its intermediates (intact human proinsulin [hPI] 0.1%; des 32,33 hPI 0.4%; des 64,65 hPI 66%). Intact proinsulin is measured using a two-site fluoroimmunometric assay. The assay typically shows <1% cross-reaction with insulin and 32,33 split proinsulin at concentrations of 2,500 and 400 pmol/l, respectively. There is no detectable cross-reaction with C-peptide. Urinary albumin is measured by fixed-time nephelometry. Urinary creatinine is measured by a kinetic modification of the Jaffé method in which creatinine reacts with picric acid at alkaline pH to form a yellow–orange complex. PAI-1 antigen is quantified using a Biopool TintElize enzyme immunoassay kit (Ventura, CA, USA). Apolipoprotein B and CRP are measured by fixed-time nephelometry. Fibrinogen is measured using photo-optical clot detection in plasma when thrombin is added. The chemiluminometric βhCG immunoassay (Bayer Advia Centaur, Walpole, MA, USA) is used to measure βhCG.

Health status and pharmacoeconomic outcomes are assessed using the DSC-R [26] and the Medical Care Utilization and Restricted Activity Days questionnaires [27]. The DSC-R is a 34-item self-report questionnaire comprising eight subdimensions (hyperglycaemic, hypoglycaemic, neurological-pain, neurological-sensory, cardiovascular, psychological-cognitive, psychological-fatigue and ophthalmological). Each of the 34 items is scored on a dichotomous scale for the presence/absence of the symptom. If a symptom is present, the degree of discomfort is recorded on a five-point Likert scale. Medical care utilisation data, including hospitalisations, accident and emergency unit visits, and non-protocol visits to or by any doctor, are collected in the trial as events requiring the intervention of a health-care professional. In addition, days of restricted activity (during which the participant is unable to perform the normal activities of daily life) over the 7 days prior to the scheduled visit are recorded. For Medical Care Utilization and Restricted Activity Days assessments, the relationship to diabetes (direct, indirect or none) is also recorded.

The DSC-R will be analysed according to the developer's instructions. Pharmacoeconomic outcomes include the frequency of casualty department visits, number of days hospitalised, unscheduled visits to study investigators, and restricted activity days.

Primary efficacy outcome The primary efficacy variable is the combined endpoint of CV death or CV hospitalisation. Its primary analysis will be time to first CV hospitalisation or CV death. The CV death component will include death following heart failure or acute myocardial infarction, sudden death, and death caused by acute vascular events. Cardiovascular hospitalisation will include hospitalisation due to acute myocardial infarction, CHF, stroke, unstable angina pectoris, transient ischaemic attack, unplanned invasive CV therapeutic procedure, amputation of extremities, or for a definite CV reason not defined by the protocol. A clinical endpoints committee (CEC) with vascular expertise has been appointed to review and adjucate all potential CV hospitalisation and CV death endpoints. This committee is blind to study medication and independent of the steering committee and study sponsor. For the sponsor to comply with its legal obligations to regulatory authorities, endpoints that meet the definition of 'serious adverse events' are reported to its clinical safety department. This department is separated by an information firewall from the sponsor's staff who work on clinical trials.

Secondary efficacy outcomes Secondary measures of CV and diabetes-related endpoints are: (1) all-cause mortality; (2) definite heart failure; and (3) microvascular endpoints and combined CV hospitalization or CV death endpoint plus microvascular endpoints. Microvascular outcomes are assessed from diabetes-related (as determined by a local investigator) adverse events only, including foot ulceration, progression to dialysis, laser photocoagulation and blindness. Secondary endpoints will be analysed both in terms of time to first event and frequency of events.

Assessment of cardiac failure is very variable between clinicians; this poses a problem when studying drugs that cause fluid retention. Accordingly, hospitalisation (as for most other CV endpoints) and confirmation on review by the clinical endpoints committee are required for this to be included as an endpoint.

The following were defined as secondary variables for the metabolic measures: (1) changes from baseline in HbA_1c and fasting plasma glucose (FPG) and the proportion of participants achieving predefined targets of glycaemic control (FPG $\leq$7.0 mmol/l and HbA_{1c} $\leq$7.0%); (2) failure of glycaemic control (addition of a third oral glucose-lowering agent or initiation of insulin treatment); (3) serum insulin and proinsulin; (4) urinary albumin:creatinine ratio; (5) insulin sensitivity and islet beta-cell function, as estimated by homeostasis model assessment [28]; (6) serum lipids; (7) NEFA; (8) PAI-1 antigen; (9) fibrinogen; (10) apolipoprotein B; and (11) CRP.

Safety assessments Changes in findings on physical examination (including body weight), vital signs, clinical laboratory tests (including liver function tests) and ECGs, and abnormal experiences are assessed throughout the course of the study by the DSMB. If alanine aminotransferase (ALT) is more than three times the upper limit of the normal range, or the participant reports symptoms suggestive of hepatic dysfunction (unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine) at any visit after randomisation, evaluation for viral hepatitis (A, B and C) is performed and liver function tests are assessed within 1 week. If ALT remains more than three times the upper limit of the normal range, the individual is withdrawn from randomised treatment and transferred to monitoring of CV outcomes and glycaemic control only (see above) for the planned duration of the study.

The DSMB meets independently of the steering committee, and is separated from staff of the monitoring organisation and sponsor by an information firewall. Stringent statistical criteria have been set prospectively for early study termination in the event of a clear-cut difference between the treatment groups with respect to all-cause mortality. A stopping guideline is being applied to interim analyses for overwhelming evidence of benefit/harm using the Haybittle–Peto procedure [29] with a fixed nominal p value of 0.0005 (one-sided) for the comparison of the combined rosiglitazone group with the combined metformin+sulphonylurea group. For evidence of harm of the combined rosiglitazone group, the criterion is evaluated annually. For evidence of benefit, the criterion is evaluated after the end of year 3 of the study and annually thereafter. In addition, the DSMB may also recommend termination of the study for other serious safety reasons. A protocol has been established to ensure the rapid consideration and execution of such a recommendation throughout the geographical reach of the study.

Statistical analysis A sample size of 4,000 participants followed for a median of 6 years (assuming a 2-year recruitment period) was estimated to be sufficient for the primary objective of this study: to compare the time to the combined CV endpoint (CV death or CV hospitalisation) between those participants randomised to add-on treatment with rosiglitazone and those randomised to add-on treatment with sulphonylurea, pooling the data across study treatment arms. RECORD was designed as a non-inferiority trial. The rosiglitazone group is defined to be non-inferior to the non-rosiglitazone control group if the upper limit of the 95% confidence interval for the hazard ratio falls below 1.20. A total of 2,000 participants per treatment stratum was estimated to give 99.2% power to confirm non-inferiority when the control group has an 11% event rate per year (3% CV deaths and 8% CV hospitalisations) [30, 31] and 2% of participants are lost to follow-up each year.

For the primary CV endpoint, the times to event will be summarised using Kaplan–Meier survival curves and compared between treatment groups using the proportional hazards model, with background therapy (metformin or sulphonylurea) as a covariate. A sensitivity analysis will be performed to assess the influence of geographical region on the conclusions. All supporting endpoints will test the null hypothesis of no treatment difference, using two-sided tests at the 95% significance level. Participants who do not achieve the endpoint during their time in the study will have their data censored based on the date of final observed contact.

For metabolic endpoints (HbA_1c, FPG, insulin, insulin sensitivity, islet beta-cell function and lipids) treatment differences will be assessed at 3 years and study end using analysis of covariance adjusted for the values of the measure at baseline and screening. Additionally, a subgroup analysis of the metabolic endpoints of the first 1,040 or more participants to reach 18 months of therapy was planned prospectively, and has been completed [32].

For blood pressure a 6-month substudy (and extension) using ambulatory devices in a limited number of centres has been completed [33]. For the DSC-R, at each visit, the item scores for each participant will be averaged for each subdimension and for the overall 34 items, and the changes from baseline will be calculated. For the overall mean score, treatment differences over time will be assessed using a multivariate linear model analysis. Assessment of pharmacoeconomic endpoints at study end will use a Poisson regression model to estimate the event rate per 1,000 subject-days.

For efficacy analyses, the primary analysis population was defined as those participants who were randomised and received at least one dose of add-on study medication

(the intention-to-treat population). Efforts are being made to collect CV endpoint data to study termination even in those withdrawing from the study, such as those who move away from their study centre. A secondary population, for the primary CV endpoint only, will be the 'per protocol' population, defined as participants who were randomised and still on the randomly allocated treatment up to 30 days before the primary CV endpoint or the time of non-inclusion. For a non-inferiority study, a per protocol analysis carries potentially less bias in favour of the tested drug than an intention-to-treat analysis. All individuals who receive at least one dose of randomised study medication will be assessed for clinical safety and tolerability.

Data analysis is provided by the study's clinical trial contract organisation (Quintiles, Bracknell, UK). Confirmatory analyses of the data will be conducted within the institution to which the independent statistician member of the steering committee (S. Pocock) is affiliated. Data are not made available to the sponsor except as planned analyses or descriptions approved by the steering committee.

Results

Screening for the study began on 23 April 2001 and the last individual was randomised on 29 April 2003. During this period 7,428 individuals were screened in 25 countries. Of these, 4,458 were randomised; 2,228 on background metformin, 2,230 on background sulphonylurea. The numbers randomised in each country were as follows: Australia 51, Belgium 104, Bulgaria 204, Croatia 274, Czech Republic 145, Denmark 57, Estonia 220, Finland 193, France 86, Germany 178, Greece 139, Hungary 400, Italy 116, Latvia 173, Lithuania 134, the Netherlands 76, New Zealand 36, Poland 363, Romania 157, Russia 149, Slovakia 325, Spain 64, Sweden 469, Ukraine 103, UK 242.

Demographic details, baseline assessments and clinical history are summarised in Table 2. Approximately half of the participants are male (52%) and almost all (99%) are Caucasian. Patients have a mean age of 58 years and time since diagnosis of type 2 diabetes is 7 years. Compared with those in the background sulphonylurea stratum, the participants in the background metformin stratum are younger and more obese, with a shorter time since diagnosis (Table 2). They otherwise appear similar.

Discussion

While preliminary data concerning the impact of thiazolidinediones on insulin insensitivity and its associated cluster of CV risk factors appear promising [5–17], there is a need to investigate whether these effects will translate into improved CV outcomes and to assess the long-term efficacy and safety profile of this class of drugs. Such a

Table 2 Baseline characteristics of the people with type 2 diabetes who were randomised, divided according to background therapy

	Background metformin	Background sulphonylurea	All
N	2,228	2,230	4,458
Demographic details			
Age (years)	57.1±8.1	59.7±8.3	58.4±8.3
Men	1,187 (53)	1,111 (50)	2,298 (52)
Caucasian	2,198 (99)	2,212 (99)	4,410 (99)
Duration from diagnosis (years)	6.3 (4.5)	7.9 (5.5)	7.1 (5.1)
Baseline measurements			
Weight (kg)	93.5±16.5	84.8±14.4	89.2±16.1
BMI (kg/m^2)	32.8±5.1	30.3±4.1	31.5±4.8
Waist circumference (cm)	107.8±11.8	101.7±11.0	104.8±11.8
Systolic blood pressure (mmHg)	139.4±16.0	138.2±14.9	138.8±15.4
Diastolic blood pressure (mmHg)	83.7±8.6	82.3±8.0	83.0±8.3
HbA_1c (%)	7.82±0.66	7.97±0.73	7.90±0.70
LDL cholesterol (mmol/l)	3.18±0.90	3.39±0.91	3.29±0.91
HDL cholesterol (mmol/l)	1.20±0.29	1.20±0.30	1.20±0.29
Triglycerides (mmol/l)	2.32±1.39	2.25±1.67	2.28±1.54
Other clinical history			
Ischaemic heart disease	316 (14)	418 (19)	734 (16)
Cerebrovascular disease	92 (4)	103 (5)	195 (4)
Peripheral arterial disease	91 (4)	166 (7)	257 (6)
Retinopathy	182 (8)	328 (15)	510 (11)
Neuropathy	107 (5)	165 (7)	272 (6)
Diagnosed hypertension	1,476 (66)	1,447 (65)	2,923 (66)
Diagnosed lipid disorder	830 (37)	677 (30)	1,521 (34)
Current smoker	394 (18)	314 (14)	708 (16)
Former smoker	642 (29)	465 (21)	1,107 (25)

Data are means±SD, or *n* (%)

study will also address concerns over cardiac failure; confirm that the better health outcomes associated with improved glucose control, as reported by the UKPDS [23], are applicable to this group of drugs; and allay concerns based on LDL cholesterol concentrations rather than LDL particle atherogenicity. In the chosen context of people with diabetes initially inadequately controlled on metformin or sulphonylurea medication, and with comparison of rosiglitazone addition to these therapies with the standard combination of metformin and sulphonylurea over a period of up to 5–7 years, the RECORD study should provide valuable information, both on CV outcomes and long-term glycaemic control in individuals with limited treatment options other than the addition of insulin therapy.

As a result of necessary compromises of study design, the RECORD study protocol has a number of strengths and weaknesses. Although the frequency of adverse CV events is high in people with type 2 diabetes—as high as in a non-diabetic population with declared vascular disease [34]—with the assumed event rate and specified limit of non-inferiority margin, the study was designed to follow at least 4,000 people for an average of 6 years. Furthermore, the context of the current study is rosiglitazone in combination with standard oral glucose-lowering therapies, while current European International Diabetes Federation (IDF) guidelines suggest limits to the extent of hyperglycaemia that is acceptable before insulin therapy is introduced [35]. Together, these criteria limit the patient population that can be recruited into the study, implying the need for the participation of a large number of centres, each recruiting a relatively small number of participants. However, this does have the benefit of making the results more widely generalisable across the European population. In addition, a composite CV endpoint is needed to provide adequate statistical power, since the use of other preventative drug therapy (such as aspirin, ACE inhibitors and statins), which cannot of course be denied to participants, is likely to reduce the background event rate below that estimated from earlier studies.

Conducting a large multicentre study of this duration, involving two comparator drug types, the need for titration of therapies, a narrow glucose control window, and the need to capture diverse outcomes, presents its own problems in terms of recruitment, protocol compliance and subject retention. This has been addressed by substantial external monitoring of study centres to optimise protocol adherence. Investigator continuity is also an issue; this is achieved through repeated national and regional meetings and newsletters, as well as frequent contact with monitoring staff. Specific programmes address participant retention issues.

The asymmetry of the study design in terms of the initiation of insulin therapy stems from the need to address the continued deterioration of blood glucose control (resulting from the progressive loss of islet beta-cell function [23, 24]). The study needs to ensure significant exposure to the trial medications in one group, while avoiding periods of more marked hyperglycaemia arising from the absence of other oral glucose-lowering drugs of similar efficacy in the other group. In one sense this asymmetry may not matter, as the earlier (in time not glucose control) use of insulin in the non-rosiglitazone groups is clinically pragmatic and allows the putative advantages and disadvantages of rosiglitazone to continue to be compared with standard glucose-lowering medications. On the other hand, it may also bias the study against rosiglitazone if the glucose-lowering properties of insulin are used aggressively.

RECORD is an open-label study, reflecting the difficulties of providing dummy versions of the five oral add-on treatments at different doses, and of persuading participants who are often already using a variety of other therapies to take both active and dummy treatments over long periods. In any case, the study could not proceed in a blinded fashion at the time of introduction of insulin therapy, which differs in the rosiglitazone and non-rosiglitazone arms. Open-label studies carry a risk of differential assessments of outcomes because of the differential expectations of the participants and investigators. The use of hard primary endpoints (death and hospitalisation) assessed by a blinded endpoints group, together with biochemical measurements in a central laboratory, should reduce this risk, as should the tight external monitoring by a contract clinical trial organisation (Quintiles), appointed by the sponsor.

While the primary endpoint is well defined, the diversity of macrovascular and microvascular assessments and the needs of safety monitoring for a drug of a novel class all lead to a plethora of secondary endpoints, which may increase the risk of statistically significant chance findings, but may also allow for the cross-checking of consistency between measures which on a priori grounds may be associated. The deployment of a steering committee and an independent Data Safety Monitoring Board, both comprising senior clinical experts and external statisticians as full members, should help ensure the availability of appropriate expertise in trial design, execution, interim monitoring, analysis and reporting.

The study has recruited 2,160 women (48%). This can be considered a strength of the study, since women are often not proportionately represented in CV outcome trials or in intervention studies assessing the treatment of type 2 diabetes.

Long-term clinical outcome trials such as RECORD provide the opportunity to test the safety and tolerability of newer agents in relation to standard therapies; in this study, safety data for rosiglitazone in combination therapy is anticipated to comprise more than 10,000 person-years of experience. Current experience with rosiglitazone suggests that it lacks a troglitazone-like hepatotoxicity [21, 36], but liver function tests will, nevertheless, be extensively monitored. Equally, the issue of whether weight gain or fluid retention associated with thiazolidinedione therapy has any long-term cardiac sequelae should be resolved by the RECORD study.

In conclusion, results from this study will provide a clearer picture of the benefits of rosiglitazone therapy vs traditional agents with more established efficacy and safety profiles. In particular, it will investigate the premise that thiazolidinediones, which improve glycaemic control by decreasing insulin insensitivity, reduce the incidence of macrovascular complications in individuals with type 2 diabetes.

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Duality of interest

The RECORD study sponsor is GlaxoSmithKline, the manufacturer of rosiglitazone. Members of the steering committee, the DSMB and the Clinical Endpoints Committee, or their institutions, are remunerated for time and expenses and, in some cases, other activities relating to the sponsor. J. Gubb, N. Biswas and N. P. Jones are employees of GlaxoSmithKline. Local investigators and/or their institutions are paid fees per participant for study activities; some will also be remunerated for other activities relating to the sponsor.

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ORIGINAL ARTICLE

Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

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ABSTRACT

BACKGROUND

A recent meta-analysis raised concern regarding an increased risk of myocardial infarction and death from cardiovascular causes associated with rosiglitazone treatment of type 2 diabetes.

METHODS

We conducted an unplanned interim analysis of a randomized, multicenter, open-label, noninferiority trial involving 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea, in which 2220 patients were assigned to receive add-on rosiglitazone (rosiglitazone group), and 2227 to receive a combination of metformin plus sulfonylurea (control group). The primary end point was hospitalization or death from cardiovascular causes.

RESULTS

Because the mean follow-up was only 3.75 years, our interim analysis had limited statistical power to detect treatment differences. A total of 217 patients in the rosiglitazone group and 202 patients in the control group had the adjudicated primary end point (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of end points pending adjudication, the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There were no statistically significant differences between the rosiglitazone group and the control group regarding myocardial infarction and death from cardiovascular causes or any cause. There were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio, 2.15; 95% CI, 1.30 to 3.57).

CONCLUSIONS

Our interim findings from this ongoing study were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. There was no evidence of any increase in death from either cardiovascular causes or all causes. Rosiglitazone was associated with an increased risk of heart failure. The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction. (ClinicalTrials.gov number, NCT00379769.)

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For patients with type 2 diabetes, cardiovascular disease is the leading cause of death and the major cause of morbidity.[1] In such patients, cardiovascular risk is considerably elevated,[2] although recent reports have moderated this concern.[3,4] Factors that are implicated in the development of atherosclerosis include dyslipidemia, obesity, hypertension, hyperglycemia, and hyperinsulinemia.[5]

Type 2 diabetes is a progressive disease and its prevalence in the population is increasing. Since there is greater attention to glycemic targets, more patients are receiving combination therapies. Clinical trials comparing monotherapies are common, but comparisons of new dual-agent combinations with the standard of metformin plus sulfonylurea are rare. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial is a long-term, multicenter, randomized, open-label study[6] that compares cardiovascular outcomes in patients with type 2 diabetes treated with rosiglitazone (Avandia) plus metformin or sulfonylurea (rosiglitazone group) with outcomes in patients treated with metformin plus sulfonylurea (control group). The results of the United Kingdom Prospective Diabetes Study (UKPDS) suggest that the comparators metformin and sulfonylurea used in the RECORD trial reduce myocardial infarction by 39% and 16%, respectively, as compared with conventional treatment and diet.[7,8]

After a recent meta-analysis by Nissen and Wolski[9] raised concern about the cardiovascular safety of rosiglitazone, the current totality of evidence needs to be made available. Accordingly, this interim report presents the outcomes and deaths from cardiovascular causes so far in the RECORD study.

Methods

Patients

The RECORD study has been described in detail previously.[6] We recruited patients for the study from April 2001 through April 2003. Eligible patients had type 2 diabetes, as defined by criteria of the World Health Organization[10]; were between the ages of 40 and 75 years; had a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 25.0; and had a glycated hemoglobin level of more than 7.0% and less than or equal to 9.0% while receiving maximum doses of metformin or a sulfonylurea. Exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension. The study protocol was approved by ethics review committees or institutional review boards in accordance with the laws and customs of each country participating in the study.[6] Written informed consent was obtained from all patients.

Study Design

The study is being conducted at 338 centers in 23 countries in Europe and Australasia. After a 4-week run-in period, patients who were already taking a sulfonylurea were randomly assigned to receive either additional rosiglitazone or metformin; those taking metformin were assigned to receive either additional rosiglitazone or a sulfonylurea (glyburide, gliclazide, or glimepiride, according to local practice). Random allocation was performed by telephone, with random permuted blocks stratified according to background medication.

Throughout the study, the target glycated hemoglobin level was 7.0% or less. The starting dose of rosiglitazone (Avandia, GlaxoSmithKline) was 4 mg per day. The starting doses of metformin and sulfonylurea were determined according to local practice. If the glycated hemoglobin level exceeded 7.0% after 8 weeks of treatment, the doses of study drugs were increased to a maximum daily dose of 8 mg of rosiglitazone, 2550 mg of metformin, 15 mg of glyburide, 240 mg of gliclazide, and 4 mg of glimepiride. If the glycated hemoglobin level exceeded 8.5% while patients were receiving the maximum tolerated dose, a third agent was added for patients in the rosiglitazone group or insulin was initiated for patients in the control group. If patients receiving triple therapy in the rosiglitazone group had glycated hemoglobin levels of more than 8.5%, the study protocol recommended that rosiglitazone be stopped and insulin therapy started.

Outcome Measures

The primary end point was hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient

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ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke); the outcome was analyzed as the time to first occurrence. Members of an independent committee evaluating clinical end points (five cardiologists, a neurologist, and a diabetologist) were unaware of study-group assignments and used prespecified criteria to adjudicate all potential outcomes reported by investigators. Evaluators in the trial's contract organization (Quintiles) were unaware of study-group assignments in screening all serious adverse events for potential end points.

This interim report evaluated data that were available as of March 30, 2007. Secondary end points were death from cardiovascular causes and from any cause, myocardial infarction (resulting in either hospitalization or death), congestive heart failure (hospitalization or death), and the composite of death from cardiovascular causes, myocardial infarction, and stroke. Some events were pending adjudication while this report was being written. Analyses are reported both for adjudicated events only and for adjudicated events plus events pending adjudication. For 19 cardiovascular deaths pending adjudication, we cannot determine yet whether any were due to acute myocardial infarction or congestive heart failure.

STUDY OVERSIGHT

An independent data and safety monitoring board meets twice annually to review unblinded safety data for the ongoing study; the most recent meeting took place on May 24, 2007. Members of the steering committee (seven academic investigators and one representative of the sponsor) developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported. Study committees and investigators are listed in the Appendix.

STATISTICAL ANALYSIS

The RECORD study was designed as a noninferiority trial. The rosiglitazone group was defined as noninferior to the control group if the upper limit of the two-sided 95% confidence interval for the hazard ratio for the primary end point comparing the rosiglitazone group with the control group was below 1.20 on completion of the study. A total of 4000 patients to be followed for a median of 6 years would give a power of 99% to detect such noninferiority when the control group had an event rate of 11% per year (3% with deaths from cardiovascular causes and 8% with hospitalizations), allowing for a 2% annual loss to follow-up.

This interim report follows a prespecified plan for statistical analysis. All analyses were performed according to the intention-to-treat principle, with the exclusion of 11 patients who received no study medication. The time from randomization to the event was derived for each end point, with follow-up censored at the cutoff date of March 30, 2007, for patients who did not have an event. Cumulative incidence was estimated with the use of the Kaplan–Meier method. The relative risk comparing the rosiglitazone group with the control group was estimated as a hazard ratio and 95% confidence interval on the basis of Cox proportional-hazards regression stratified according to background medication. Two-sided P values were calculated with the use of log-rank tests, unadjusted for multiple testing.

RESULTS

PATIENTS

Of 7428 patients who underwent screening, 4458 were randomly assigned to study groups (Fig. 1). No study medication was received by 11 patients (6 in the rosiglitazone group and 5 in the control group), who were excluded from the analysis. At baseline, 2222 patients who were receiving metformin monotherapy were assigned to receive either rosiglitazone plus metformin (1117 patients) or metformin plus sulfonylurea (1105 patients); 2225 patients receiving sulfonylurea monotherapy were assigned to receive rosiglitazone plus sulfonylurea (1103) or metformin plus sulfonylurea (1122). Results presented here are for all patients who were randomly assigned to receive rosiglitazone combinations (2220), as compared with all patients assigned to receive metformin plus sulfonylurea (2227).

Approximately 10% of patients (218 in the rosiglitazone group and 223 in the control group) were lost to follow-up. This fact, along with the much lower overall event rate than we

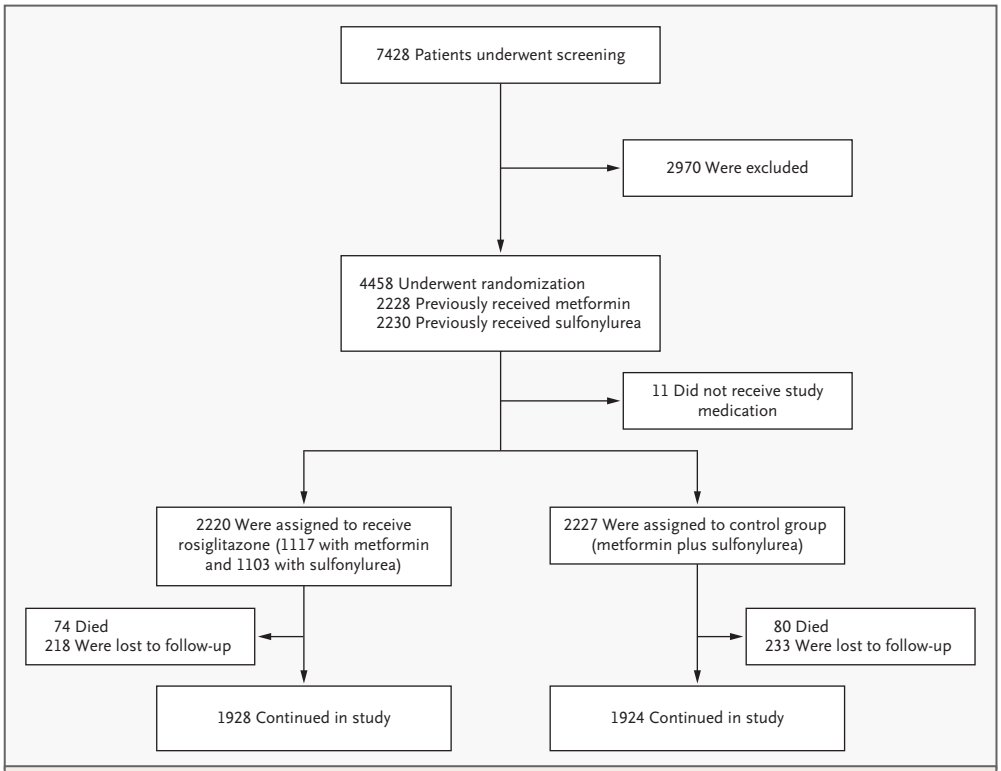

Figure 1. Enrollment and Outcomes.

The numbers of participants who were assessed for safety were 2220 in the rosiglitazone group and 2227 in the control group.

had predicted, substantially lowered the statistical power of our analysis. A total of 140 patients in the rosiglitazone group and 244 patients in the control group began to receive insulin. At the latest visit, 1626 patients in the rosiglitazone group and 1476 patients in the control group were receiving their allocated treatment. In total, 675 patients (263 in the rosiglitazone group and 412 in the control group) withdrew from receiving study drugs but were still in follow-up.

Baseline characteristics were well balanced between the groups (Table 1). Table 2 shows by group the numbers of patients with the primary end point (hospitalization or death from cardiovascular causes) and several secondary end points over a mean follow-up of 3.75 years (3.77 years for the rosiglitazone group and 3.73 years for the control group). Results are reported for adjudicated events and for events adjudicated plus those pending adjudication. Kaplan–Meier plots are shown in Figures 2 and 3.

For adjudicated primary end points (217 in the rosiglitazone group and 202 in the control group), the hazard ratio was 1.08 (95% confidence interval [CI], 0.89 to 1.31). An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. The inclusion of these events resulted in a hazard ratio of 1.11 (95% CI, 0.93 to 1.32). A subgroup analysis of patients who were classified according to previous monotherapy with metformin or sulfonylurea revealed no evidence of a treatment-by-stratum interaction (interaction test, $P=0.41$). The time-to-event curves in Figure 2 may suggest possible divergence between groups, with more events in the rosiglitazone group after 2.5 years of follow-up. However, data after 4 years involve small numbers of patients, and further follow-up will be necessary.

There was no statistically significant differ-

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ence between the rosiglitazone group and the control group for the following secondary end points: acute myocardial infarction, death from cardiovascular causes or any cause, or the composite of cardiovascular death, myocardial infarction, and stroke (both for adjudicated events and adjudicated plus pending events). However, the power to detect significant differences was low, as reflected by the wide 95% confidence intervals (Table 2). The hazard ratio for death from cardiovascular causes for adjudicated plus pending events was 0.80 (95% CI, 0.52 to 1.24). For myocardial infarction, the hazard ratio for adjudicated plus pending events was 1.23 (95% CI, 0.81 to 1.86).

Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of heart failure in the rosiglitazone group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient-years of follow-up.

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.

DISCUSSION

Since patients with type 2 diabetes have a high risk of cardiovascular disease, any hypoglycemic agent the patient receives should not worsen that risk and preferably should lower it. Although the RECORD study is ongoing, we believe the exceptional circumstances surrounding a recent safety concern regarding rosiglitazone make it important to publish interim data.

A recent meta-analysis by Nissen and Wolski raised concern that rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular causes.[9] The limitations of the meta-analysis have been pointed out by its authors and by others.[11] Many contributing studies were small-scale and short-term, were designed to evaluate glycemic control, had no event adjudication, and had an imbalance in follow-up (with more patients in the control group withdrawing owing to hyperglycemia). Trials with no myocardial infarctions and no deaths from cardiovascular causes were excluded, and rates of myocardial infarction were low.[12]

The RECORD trial is a large, randomized, long-term study involving patients with type 2 diabetes that was designed to assess the cardiovascular safety of rosiglitazone combined with metformin or sulfonylurea, as compared with the combination of metformin and sulfonylurea, medications with previous evidence of a reduction in cardiovascular risk.[7,8] All cardiovascular end points that are reported by investigators in the trial undergo independent blinded adjudica-

Table 2. Hospitalization or Death from Cardiovascular Causes.*

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)	Hazard Ratio (95% CI)	P Value
	no. of patients			
Adjudicated events				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
Events adjudicated and pending adjudication				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

* Each patient was counted only once for each category. The primary end point was the first occurrence of a hospitalization or death from cardiovascular causes.
† Of the adjudicated deaths from cardiovascular causes, 38 (16 in the rosiglitazone group and 22 in the control group) were primary end points. The remainder occurred after the patient had already been hospitalized for a cardiovascular event. For deaths from cardiovascular causes that were adjudicated or pending adjudication, 47 (20 in the rosiglitazone group and 27 in the control group) were primary end points.
‡ This category included both hospitalizations and deaths. Some of the 19 deaths from cardiovascular causes (8 patients in the rosiglitazone group and 11 in the control group) that were pending adjudication may have been due to acute myocardial infarction or congestive heart failure, but these data were not available at the time of the study cutoff.

tion to enhance the quality of the data. A wide variety of patients with type 2 diabetes, with and without previous cardiovascular disease, are included in the study.

This interim report is based on data for 4447 participants with a mean follow-up of 3.75 years, representing 16,675 patient-years of follow-up — almost two thirds of the follow-up that was intended by the end of the study. The study design calls for targeting similar glycemic control in the rosiglitazone group and the control group to assess cardiovascular safety independent of glycemia. Patients and investigators are encouraged to follow a carefully planned treatment algorithm. A recent report on the first 1122 patients showed that patients in the rosiglitazone group and the control group had similar glycemic control after 18 months of treatment.[13]

Overall, the rate of primary end points (hospitalization or death from cardiovascular causes) was low: 3.1% per year for adjudicated plus pending events. The protocol excluded some high-risk patients (e.g., those with heart failure, hospitalization for cardiovascular causes during the previous 3 months, and pending cardiovascular intervention). Targeting treatment toward current management guidelines for dyslipidemia, hypertension, and improved glucose control may also contribute to the low event rate. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD, ISRCTN number 64783481) study reported an increase from 0 to 36% in the use of lipid-lowering therapy in its control group during 1998–2005.[14] This finding reflects guidelines that patients should be actively treated to reduce cardiovascular risk, notably with glucose-lower-

ing drugs, statins, aspirin, and more intensive use of blood-pressure–lowering agents.[15] Moreover, event rates in recent similar trials involving patients with diabetes — the Collaborative Atorvastatin Diabetes Study (CARDS,[4] NCT00327418), Heart Protection Study (HPS,[3] ISRCTN 48489393), and FIELD[14] — are similar to those in the RECORD trial.

The interim results for the primary end point were inconclusive, with a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) on the basis of events adjudicated by the committee reviewing clinical end points. In any interim trial report, there are inevitably some potential primary events pending adjudication. Adding in these pending events increased the hazard ratio to 1.11 (95% CI, 0.93 to 1.32). Thus, the data for the primary end point are compatible with as much as a 7% improvement, or as much as a 32% worsening, in cardiovascular risk. The study lost statistical power because of the withdrawal of patients from their assigned treatment and losses to follow-up, although patients in the rosiglitazone group fared better in these respects than did patients in the control group. We cannot determine whether some consequent bias in end-point ascertainment occurred. All serious adverse events were screened for possible end points.

The low rate of the primary end point, along with the notable loss to follow-up, meant that the study has less statistical power than was originally planned. Assuming a continued primary-event rate of 3.1% per year, we project that 750 patients will have a primary end point by study completion. Under the hypothesis of no true treatment difference, this estimate would provide a power of 70% to claim noninferiority relative to a noninferiority margin of 1.20 for the hazard ratio. However, we already have 510 patients with a primary event (adjudicated plus pending events) and an observed hazard ratio of 1.11, which means that the conditional power to claim noninferiority on study completion is somewhat less.

As compared with the control group, the rosiglitazone group had no evidence of an increased risk of death, either from any cause (hazard ratio, 0.93; 95% CI, 0.67 to 1.27) or from cardiovascular causes (hazard ratio, 0.80, 95% CI, 0.52 to 1.24). The primary end point included all first hospitalizations or deaths from cardiovascular causes and as such included myocardial infarction and congestive heart failure. Our study showed that the risk of heart failure in the rosiglitazone group was more than twice that in the control group. This finding is consistent with previous evidence regarding heart failure and the thiazolidinediones.[16,17] Although the absolute excess risk was relatively small, this finding is of concern and reinforces advice that patients should be warned of the risk and that thiazolidinediones should not be started or continued in patients with heart failure.

For acute myocardial infarction, the difference between the rosiglitazone group and the

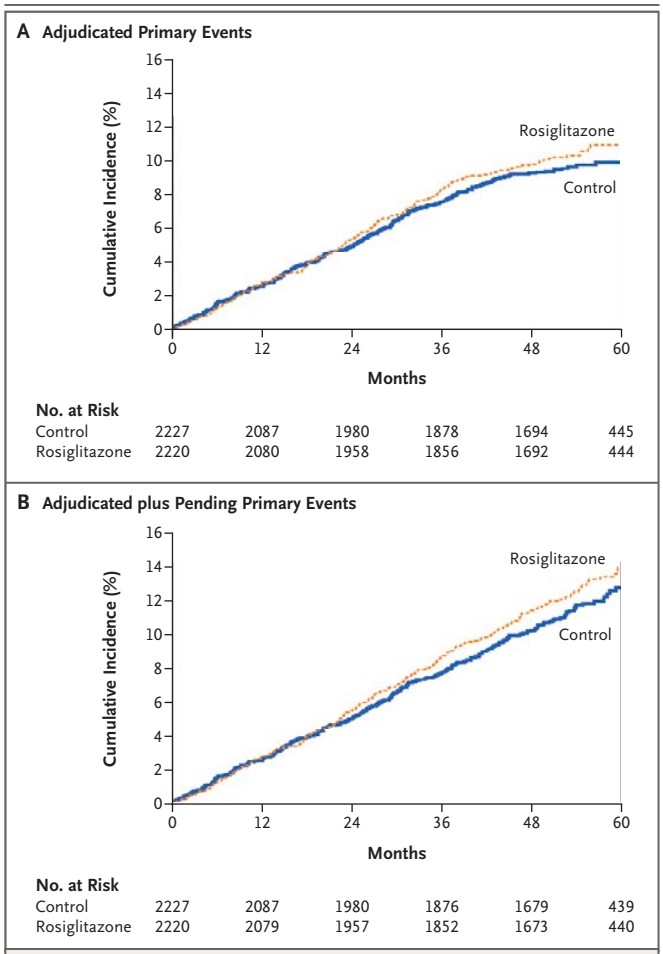

Figure 2. Kaplan–Meier Analysis of the Primary End Point of Hospitalization or Death from Cardiovascular Causes.

The graph shows the adjudicated events in the study (Panel A) and the adjudicated events plus events that were being analyzed at the time of the study cutoff (Panel B).

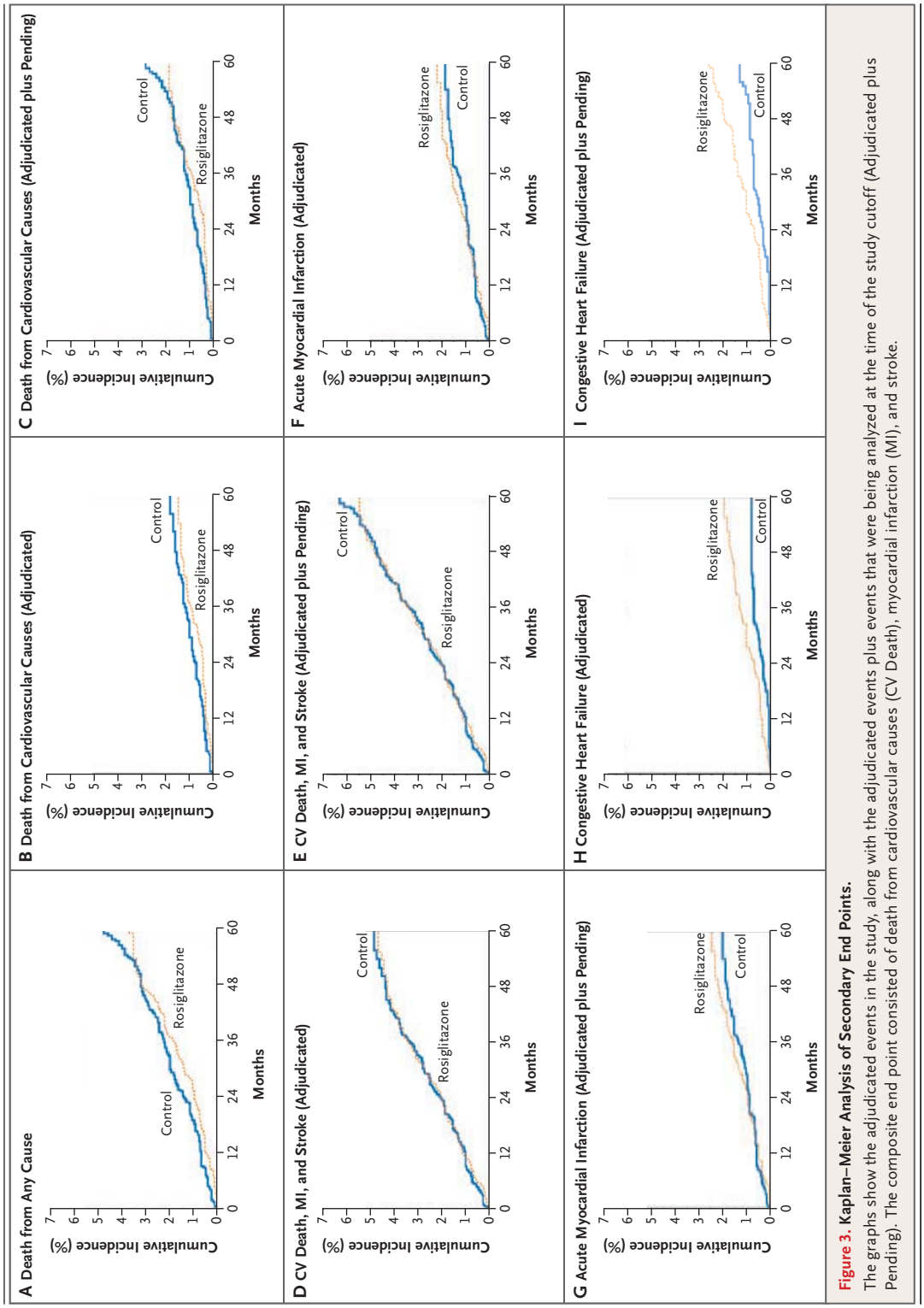

Figure 3. Kaplan–Meier Analysis of Secondary End Points.
The graphs show the adjudicated events in the study, along with the adjudicated events plus events that were being analyzed at the time of the study cutoff (Adjudicated plus Pending). The composite end point consisted of death from cardiovascular causes (CV Death), myocardial infarction (MI), and stroke.

control group was not statistically significant (hazard ratio for adjudicated events, 1.16; 95% CI, 0.75 to 1.81; hazard ratio for adjudicated plus pending events, 1.23; 95% CI, 0.81 to 1.86). These estimates are somewhat lower than those reported in the meta-analysis by Nissen and Wolski.[9] They are consistent with as much as a 19% improvement, and as much as an 86% worsening, in risk. For the composite end point of death from cardiovascular causes, myocardial infarction, and stroke, the rosiglitazone group did not differ significantly from the control group.

A significant limitation of our study was that it was an open-label trial. The allocation of drugs was nonblinded owing to the number of preparations and dosing schedules and because the time for the introduction of insulin therapy differed between groups. Monitoring staff checked site records for missing events, and all serious adverse events underwent blinded screening for potential cardiovascular end points; in addition, the adjudication of events was blinded. These procedures and the choice of end points reduce, but do not remove, the risk of ascertainment bias.

The primary composite end point reflects the study objective — an assessment of overall cardiovascular safety — but therefore includes some hospitalizations (e.g., for valvular disease) that no observer would consider potentially related to treatment. The inclusion of such events tends to favor the achievement of noninferiority. Hence, sensitivity analyses will be performed at the end of the study that include only events related to atherosclerotic arterial disease.

We made the decision to publish our interim findings because in their absence, concern raised by the meta-analysis by Nissen and Wolski could well compromise the study's integrity through an increase in the dropout rate and potential biases in reporting events. At present, every effort is being made to maintain follow-up until study completion in 2 years. Extra inquiries to investigators, to identify any end points previously missed,[18] are expected to reduce substantially the extent of loss to follow-up by the end of the study.

This interim analysis is restricted to a limited amount of information. The statistical plan was predefined. The intent was primarily to estimate treatment differences, with no planned action regarding study continuation, so the significance level of the final analysis was not affected. The final report will be more extensive, with data presented for different background medications and other subgroups and examining possible imbalances across treatment groups for concomitant medications and other possible confounders.

In conclusion, our interim findings from a large, prospective trial are inconclusive with respect to the primary end point of hospitalization or death from cardiovascular causes and are as yet insufficient to claim noninferiority. There is no evidence of any increased mortality, either from any cause or from cardiovascular causes. There is a significant increase in the risk of heart failure. The data do not allow a conclusion as to whether treatment with rosiglitazone results in a higher rate of myocardial infarction than does therapy with metformin or a sulfonylurea. The study's data and safety monitoring board, which is charged with safeguarding the study patients, has recommended continuation of the trial. Study completion will enable a clearer determination of the long-term cardiovascular effects of treatment with rosiglitazone and thus help determine the most appropriate combination therapies for patients with type 2 diabetes.

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Dr. Home reports being involved in research, consulting, health care development, and teaching activities for all major pharmaceutical companies active in diabetes research (including GlaxoSmithKline), but all consulting and lecture fees he receives are donated to the institutions with which he is associated (Newcastle University, Worldwide Initiative for Diabetes Education, and the International Diabetes Federation); Dr. Pocock, receiving consulting fees and grant support from GlaxoSmithKline; Dr. Beck-Nielsen, receiving consulting fees from GlaxoSmithKline, Merck, and Novartis and grant support and lecture fees from GlaxoSmithKline and Novo Nordisk; Dr. Gomis, receiving consulting and lecture fees from GlaxoSmithKline, Novartis, Pfizer, Merck, and Sanofi-Aventis; Dr. Hanefeld, receiving consulting fees from GlaxoSmithKline, Novo Nordisk, and Sanofi-Aventis and lecture fees from Bayer-AG, Sanofi-Aventis, Hoffmann–La Roche, Takeda, and Eli Lilly; Mr. Jones, being an employee of and holding stock in GlaxoSmithKline; Dr. Komajda, receiving consulting fees from GlaxoSmithKline and Servier and lecture fees from GlaxoSmithKline and Takeda; and Dr. McMurray, receiving consulting fees from GlaxoSmithKline and Amgen and grant support from GlaxoSmithKline, Novartis, and Amgen. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following were participants in the RECORD study: **Steering Committee:** P.D. Home (chair), H. Beck-Nielsen, R. Gomis, M. Hanefeld, N.P. Jones, M. Komajda, J.J.V. McMurray, S.J. Pocock. **Data and Safety Monitoring Board:** I. Campbell (chair), I. Ford, P. Hildebrandt, R. Landgraf, F. Verheugt. **Clinical End Point Committee:** M. Komajda (chair), M. Böhm, A. Gavazzi, K. Lees, M. Marre, P. Ponikowski, M. Syvänne. **Investigators (numbers in parentheses after country indicate number of randomized patients):** *Australia (51)* — G. Jerums, Heidelberg West; A. Lang, Malvern; R. Watts, Port Lincoln; F. De Looze, Sherwood; S. Colagiuri, Randwick; R. Moses, Wollongong; V. Heazlewood, Kippa Ring; M. McKeirnan, Carina Heights; A. Lowy, Miranda; T. Roberts, Keswick. *Belgium (104)* — E. Weber, Arlon; F. Coucke, Sint-Gillis-Waas; J. Tits, Genk; B. Keymeulen, Brussels; M. Giri, Gent; J. Mortelmans, Oostham; A. Hutsebaut, Moerkerke; W. Denier, Genk. *Bulgaria (204)* — A. Borissova, N. 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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
BRL-049653/								
006	II	Rosiglitazone (RSG) mono vs Placebo (PBO): *1) RSG 0.05mg bd (n=74)* [i] *2) RSG 0.25mg bd (n=72)* *3) RSG 1.0mg bd (n=79)* 4) RSG 2.0mg bd (n=80*) 5) PBO bd (n=75†) *74 patients (pts) included in analysis; 6 pts excluded. †69 pts included in analysis; 6 pts excluded. Patients enrolled at one of the sites were excluded from all integrated analysis due to unethical data practices at that site.	Single-blind PBO bd for 4 wks	12 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	
011	IIIa	RSG mono vs PBO: 1) RSG 2mg bd (n=175) 2) RSG 4mg bd (n=182) 3) PBO bd (n=176)	Single-blind PBO bd for 4 wks	26 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	

[1] *Throughout the document, italicized font indicates treatment arms not included in the integrated analysis since the analysis only included total daily doses of RSG of 4 mg or 8 mg.*

- Bulleted subgroups delineate the treatment group assignment for the integrated analysis which takes into account differences in the background anti-diabetic therapy

Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
015	IIIa	Sulphonylurea (SU)+RSG vs SU mono: *1) SU+RSG 1mg bd (n=205)* 2) SU+RSG 2mg bd (n=190) 3) SU+PBO (n=198)	Single-blind PBO+SU for 2-4 wks	26 wks	Add-on to background SU	Fixed dose	Prior therapy	
020	IIIa	RSG mono vs SU mono: 1) RSG 2mg bd (n=200) 2) RSG 4mg bd (n=191) 3) Glibenclamide (GLB) 2.5mg od to 7.5mg bd (n=207)	PBO for 4 wks (6 wks total run-in)	52 wks	Monotherapy	RSG fixed; GLB titrated to glycemic target for first 12 wks, then fixed dose	Combination of drug naïve and prior therapy	
024	IIIa	RSG mono vs PBO: 1) RSG 2mg bd (n=196) 2) RSG 4mg od (n=194) 3) RSG 4mg bd (n=197) 4) RSG 8mg bd (n=187) 5) PBO (n=185)	Single-blind PBO bd for 4 wks	26 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	
025	IIIa	RSG mono vs Metformin (MET) mono vs PBO: 1) RSG 4mg bd (n=30) 2) MET 500mg tid (n=32) 3) PBO (n=31)	Single-blind PBO bd for 4 wks	16 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	

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Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
044	IIIa	MET+RSG vs MET mono: 1) MET 2.5g/day+RSG 2mg bd (n=50) 2) MET 2.5g/day+RSG 4mg bd (n=51) 3) MET 2.5g/day+PBO (n=51)	MET 2.5g/day+PBO bd	26 wks	Add-on to MET	Fixed dose	Prior therapy	
079	IIIa	RSG mono vs SU mono vs SU+RSG: 1) RSG 2mg bd+PBO bd (n=104) 2) PBO bd+Glyburide (GLY) 10mg bd (n=106) 3) RSG 2mg bd+GLY 10mg bd (n=99)	Single-blind run-in GLY 10mg bd+PBO bd	26 wks	Add-on to SU	Fixed dose	Prior therapy	
082	IIIa	Insulin (INS)+RSG vs INS mono: 1) INS bd+RSG 2mg bd (n=107) 2) INS bd+RSG 4mg bd (n=105) 3) INS bd+PBO (n=107)	n/a	26 wks	Add-on to INS	Fixed dose	Prior therapy	
083	IIIb	RSG mono vs PBO: 1) RSG 4mg bd (n=16) 2) PBO (n=17)	n/a	16 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
085	IIIb	INS+RSG vs INS mono: 1) INS+RSG 4mg/8mg (n=138) 2) INS+PBO (n=139)	n/a	26 wks	Add-on INS	Titration of RSG at wk 8 from 4mg to 8mg; INS titrated down while maintaining glycemic control	Prior therapy	
090	IIIa	RSG mono vs PBO: 1) RSG 2mg bd (n=78) 2) RSG 4mg bd (n=71) *3) RSG 6mg bd (n=79)* 4) PBO (n=75)	Single-blind PBO for 2 wks	8 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	
093	IIIa	RSG mono vs MET mono vs MET+RSG: 1) RSG 4mg bd+PBO (n=107) 2) MET 2.5g+PBO bd (n=109) 3) RSG 4mg bd+MET 2.5g/day (n=106)	Single blind MET 2.5g/day tid+PBO bd	26 wks	Add-on to MET	Fixed dose	Prior therapy	
094	IIIa	MET+RSG (4/8mg) vs MET mono: 1) MET 2.5g/day+RSG 4mg od (n=119) 2) MET 2.5g/day+RSG 8mg od (n=113) 3) MET 2.5g/day+PBO (n=116)	n/a	26 wks	Add-on to MET	Fixed dose	Prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
095	IIIa	INS+RSG vs INS mono: 1) INS+RSG 4mg od (n=99) 2) INS+RSG 8mg od (n=97) 3) INS+PBO (n=96)	n/a	26 wks	Add-on to INS	Fixed dose	Prior therapy	
096	IIIa	SU+RSG vs SU mono: *1) GLY ≥10mg/day+RSG 2mg od (n=116)* 2) GLY ≥10mg/day+RSG 4mg od (n=116) 3) GLY ≥10mg/day+PBO od (n=115)	n/a	26 wks	Add-on to SU	Fixed dose	Prior therapy	
098	II	RSG mono vs PBO: 1) RSG 4mg od (n=98) 2) RSG 8mg od (n=93) *3) RSG 12 mg od (n=93)* 4) PBO od (n=96)	Single-blind PBO for 3 wks	8 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior therapy	
127	IIIb	SU+RSG vs SU mono: 1) GLY+RSG 4mg bd (n=56) 2) GLY+PBO bd (n=58)	Single-blind for 6-7 wks with PBO+GLY titrated to max dose (10mg bd)	26 wks	Add-on to SU	Fixed dose	Prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
132	II	SU+RSG vs SU: 1) SU+RSG 2mg bd (n=221*) 2) SU+RSG 4mg bd (n=221†) 3) SU+PBO (n=112‡) *217 pts included in analysis; 4 pts excluded. †220 pts included in analysis; 1 pt excluded. ‡110 pts included in analysis; 2 pts excluded. Randomized pts that did not take at least one dose of study medication were excluded from the analysis.	Single-blind PBO for 2 wks	24 wks	Add-on to SU	Fixed dose	Prior therapy	
134	IIIb	SU+MET+RSG vs SU+MET: 1) GLY 10mg bd+MET 1000mg bd+RSG 2mg bd (n=281) 2) GLY 10mg bd+MET 1000mg bd+RSG 4mg bd (n=280) 3) PBO (n=276)	Single-blind GLY 10mg bd+MET 1000mg bd+PBO for 4 wks	26 wks	Add-on to SU+MET	Fixed dose	Prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
135	IIIb	SU+RSG vs SU mono: 1) Glipizide (GLIP) 10mg/20mg bd+RSG 4mg/8mg od (n=116) 2) GLIP 10mg/20mg bd+PBO (n=111)	Single-blind GLIP 10mg bd+PBO od for 4 wks	104 wks	Add-on to SU	Titration to max doses of each therapy after 6 wks	Prior therapy	Elderly (at least 60 yrs of age) T2DM subjects
136	IIIb	INS and/or SU+RSG vs INS and/or SU: 1) INS/SU+RSG 4mg/8mg (n=148) • INS+RSG 4mg/8mg od (n=112) • SU+ RSG 4mg/8mg od (n = 36) 2) INS/SU+PBO od (n=143*) • INS+ PBO od (n=109) • SU+PBO od (n = 33) *One patient randomized to placebo is not included in the analysis; the subject was on placebo, but had no INS and/or SU background therapy.	n/a	26 wks	Add-on to INS and/or SU	RSG titrated to 4mg bd	Prior therapy	T2DM subjects with chronic renal failure (not on dialysis) defined by estimated creatinine clearance of ≤79mL/min

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
137	IIIb	MET+RSG vs. MET+SU: 1) MET ≥1g/day+RSG 4mg/8mg od (n=204) or 2) MET ≥1g/day+GLY 5mg od/10mg bd (n=185)	Single-blind PBO+max tolerated MET dose for 4 wks	32 wks	Add-on to MET	Both RSG and GLY could be titrated for optimal glycemic control	Combination of drug naïve and prior oral antidiabetic therapy	T2DM subjects with micro-albuminuria (defined by ACR ≥30mcg/mg &<300mcg/mg)
140	IIIb	RSG mono vs PBO: 1) RSG 8mg od (n=65) 2) PBO od (n=71)	Single-blind PBO for 4 wks	12 wks	Monotherapy	Fixed dose	Combination of drug naïve and prior monotherapy	
143	IV	SU+RSG vs SU mono: 1) GLY 5mg od+RSG 8mg od (n=121) 2) GLY 5mg od+PBO od (n=124)	Single-blind PBO+GLY for 4 wks	24 wks	Add-on to SU	Fixed dose	Prior therapy	African American or Hispanic T2DM subj.
145	IIIb	SU+RSG vs SU mono: 1) GLIC 160mg od+RSG 4mg bd (n=231) 2) GLIC 320mg od+PBO (n=242)	Single-blind with GLIC 160mg od+PBO for 4 wks	26 wks	Add-on to SU	RSG fixed dose; GLIC titrated to max dose within first 2 wks, then fixed.	Prior therapy	

[1] *Throughout the document, italicized font indicates treatment arms not included in the integrated analysis since the analysis only included total daily doses of RSG of 4 mg or 8 mg.*

- Bulleted subgroups delineate the treatment group assignment for the integrated analysis which takes into account differences in the background anti-diabetic therapy

Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
147	IIIb	SU+RSG vs SU mono: 1) SU+RSG 4mg bd (n=89) 2) SU+PBO bd (n=88)	Single-blind PBO for 2 wks	26 wks	Add-on to SU	Fixed dose	Prior therapy	Indo-Asian T2DM subj.
162	IIIb	SU+RSG vs SU mono: 1) GLB 7.5mg od+RSG 4mg bd (n=168) 2) GLB 7.5mg to 15mg+PBO (n=172)	Open-label with GLB for 4 wks and single-blind GLB 7.5mg+PBO for 4 wks	26 wks	Add-on to SU	RSG fixed dose, GLB titrated to max dose by week 2 then fixed	Prior therapy	
211	IV	RSG vs PBO: 1) RSG 4mg/8mg (n=110) • RSG 4mg/8mg mono (n=17) • SU+RSG 4mg/8mg (n=67) • MET+RSG 4mg/8mg (n=4) • MET+SU+RSG 4mg/8mg (n=22) 2) PBO (n=114) • PBO (n=19) • SU (n=59) • MET (n=12) • MET+SU (n=24)	Single-blind PBO for 4 wks	52 wks	Monotherapy or add-on to background anti-diabetic therapy	RSG titrated to 4mg bd	Combination of drug-naïve and prior therapy	T2DM subjects with CHF (NYHA Class I/II)

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
234	IIIb	SU+RSG vs SU mono: 1) Glimepiride (GLIM) 3mg od+RSG 4mg od (n=57) 2) GLIM 3mg od+RSG 8mg od (n=59) 3) GLIM 3mg od+PBO (n=58)	Single-blind, open-label GLIM 3mg od+PBO for 4 wks	26 wks	Add-on to SU	Fixed dose	Prior therapy	
282	IV	MET+RSG vs MET+SU: 1) MET+RSG 4mg/8mg (n=70) 2) Met+GLY 2.5mg od/7.5mg bd (n=75)	Single-blind PBO for 2 wks	24 wks	Add-on to MET	RSG titrated to 8mg od or 4mg bd after 8 wks; GLY titrated up to final dose of 7.5mg bd	Prior therapy	
284	IV	sub-max MET+RSG vs max-dose MET mono: 1) MET 1000mg/day+RSG 4mg/8mg (n=382) 2) MET 2000mg/day (n=384)	n/a	24 wks	Add-on to MET	After 8 weeks all subjects uptitrated to either RSG 8mg od or blinded MET 500mg bd (to 2000mg/day, inclusive of open-label portion)	Combination of drug-naïve and prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
311	IV	RSG 4mg, RSG 8 mg vs PBO,: 1) RSG 4mg od (n=29) • RSG 4mg od (n=7) • RSG 4mg od+MET (n=22) 2) RSG 4mg bd (n=29) • RSG 4mg bd (n=8) • RSG 4mg bd+MET (n=21) 3) PBO (n=14) • PBO (n=7) • MET (n=7)	n/a	12 wks	Monotherapy or add-on to MET	Fixed dose	Combination of drug naïve or prior therapy	
325	IIIb	SU+RSG vs SU mono: 1) GLIM 2mg/4mg od+RSG 4mg od (n=196) 2) GLIM 4mg/8mg od+PBO (n=195)	Subjects discontinued current OAD meds and commenced treatment with GLIM 2mg od+PBO for 6 wks	24 wks	Add-on to SU	RSG fixed dose; GLIM titratable after 8 wks	Prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
334	IV	RSG vs PBO: T2DM patients only*: 1) Prior therapy+RSG 4mg/8mg (n=99) • RSG Mono 8mg (n=45) • RSG 8mg+SU (n=19) • RSG 8mg+MET (n=35) 2) PBO (n=101†) • 2) Placebo (n = 38) • 4) SU (n = 30) • 6) MET (n = 27) *Patients with Insulin Resistance Syndrome not included in analysis. †95 pts included in the analysis; 6 excluded due to being on background combination therapy [MET+INS (n=2); MET+SU (n=4)]	PBO for 6 wks	52 wks	Monotherapy or add -on to MET or SU	RSG titrated at week 8; prior background therapy titrated to glycemic control	Combination of drug naïve and prior therapy	Subjects with T2DM or Insulin Resistance Syndrome
347	IV	INS+RSG vs INS: *1) INS+RSG 2mg od (n=209)* 2) INS+RSG 2mg bd (n=209) 3) INS+PBO (n=212)	Single-blind PBO for 2 wks	24 wks	Add-on to INS	Fixed dose	Prior therapy	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
352	IIIb	RSG vs PBO: 1) RSG 4mg/8mg (n=32*) • RSG 4mg/8mg mono (n=4) • SU+RSG 4mg/8mg (n=6) • MET+RSG 4mg/8mg (n=7) • MET+SU+RSG 4mg/8mg (n=14) 2) PBO (n=30) • PBO (n = 8) • SU (n = 5) • MET (n=7) • MET+SU (n = 10) *One patient missing first and last treatment date was excluded from integrated analysis.	Single-blind PBO for 4 wks	16 wks	Monotherapy or add-on to prior anti-diabetic therapy	RSG titrated to 4mg bd after 8 wks	Combination of drug naïve and prior therapy	T2DM subjects with stable Coronary Heart Disease
369	IV	RSG mono vs SU mono: 1) RSG 4mg/8mg od (n=25) 2) GLB 2.5mg od to 7.5mg bd (n=24)	n/a	26 wks	Monotherapy	Titration	Drug naïve	

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Study Descriptions for Studies Included in the Integrated Clinical Trial Analysis

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
SB-712753/								
002	III	RSG/MET Fixed Dose Combination (FDC) vs MET mono: 1) RSG/MET FDC 4mg/2000 mg to 8mg/2000mg (n=289) 2) MET 2500mg to 3000mg (n=280)	Single-blind run-in period with MET 1g bd for 4 wks	24 wks	Combination	Titration	Prior therapy	
003	III	RSG/MET FDC vs MET mono: 1) RSG/MET FDC 4mg/500mg to 8mg/2000mg (n=254) 2) MET 500mg/3000mg (n=272)	n/a	32 wks	Combination	Titration	Combination of drug naïve and prior therapy	

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Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
007	IIIb	RSG mono vs MET mono vs RSG/MET FDC: 1) RSG 4mg/8mg+PBO (n=159) 2) MET 500mg/2000mg+PBO (n=154) 3) RSG/MET 2mg/500mg to 8mg/2000mg FDC (n=155)	n/a	32 wks	Combination	Titration	Drug naïve only	

Study	Type of Trial	Treatment arms with dose and sample size	Run-in Characteristics	Duration of double blind portion of trial	Monotherapy, add-on or combination	Fixed dose or titration	Patient population	Unique quality of trial patients
SB-797620/								
004	III	RSG mono vs SU mono vs RSG/ GLIM FDC: 1) RSG 4mg/8mg+PBO (n=232*) 2) GLIM 1mg/4mg+PBO (n=225†) 3) RSG/GLIM FDC 4mg/1mg to 4mg/4mg (n=225‡) 4) RSG/GLIM FDC 4mg/1mg to 8mg/4mg (n=219§) *230 pts included in analysis; 2	n/a	28 wks	Combination	Titration	Drug naïve only	

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		pts excluded. †222 pts included in analysis; 3 pts excluded. ‡224 pts included in analysis; 1 pt excluded. §218 pts included in analysis; 1 pt excluded. All randomized subjects who received at least one dose of double-blind study medication were included in the integrated analysis.						

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Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents in the Pharmetrics Data Base

Preliminary Report

June 27, 2007

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Summary

Background

In data from a large health insurance plan associated with i3 Drug Safety, for the years 2000-2004, we found in any earlier study that the rates of myocardial infarction and coronary revascularization were closely similar in groups of monotherapy recipients of rosiglitazone, metformin, and sulfonylurea; rates were also similar in groups of dual therapy users with different pairwise combinations of these agents and in users of these agents and other oral antidiabetic agents in conjunction with insulin. Metformin was significantly preferable to sulfonylureas in the sense of having lower rates of cardiovascular events. The cardiovascular outcome experience of rosiglitazone users appeared to lie between those of the other agents, and was not significantly different from either. Analyses of data from the same source for 1999 through mid-2002 had shown that users of thiazolidinediones had essentially identical cardiovascular risk to users of metformin and sulfonylurea combination therapy.

Observational studies may be subject to unmeasured biases, and inferences from them are greatly strengthened when independent data sources provide similar answers. To test the reproducibility of the earlier findings, we have conducted an analysis of US health insurance claims data that have been aggregated over some 80 health plans by Pharmetrics. The Pharmetrics data available to us extend to the beginning of 2007, permitting additional follow-up and allowing for an assessment of pioglitazone, whose use has increased in recent years.

Methods

We identified all new users of specific antidiabetic therapeutic regimens, as follows: monotherapy with rosiglitazone, pioglitazone, metformin and sulfonylureas; dual therapy with any two of these agents; use of any of these agents or other oral antidiabetic drugs in conjunction with insulin from June 2000 through March 2007. Users were permitted to change cohorts (e.g. from monotherapy to dual therapy, or to therapy with insulin), but were followed until such change without respect to degree of adherence to the initiated regimen. We identified new cases of myocardial infarction or coronary

revascularization in the follow-up of these cohorts from hospital insurance claims data. The primary endpoint was the earlier of myocardial infarction or coronary revascularization.

Within each cohort group we performed a series of pairwise head-to-head comparisons between regimens. Each comparison was carried out through a stratified Cox proportional hazards model, with ten strata created from the central 90 percent of the propensity scores appropriate to each pair.

Results

Average follow-up ranged from 12 to 18 months across the different cohorts. Overall combined endpoint incidence rates were on the order of 10 per 1,000 per year in the mono- and dual therapy cohorts, and about twice that in the cohorts of combination therapy with insulin.

In the monotherapy cohorts, there were 12,440 users of rosiglitazone, 16,302 of pioglitazone, 131,075 of metformin, and 48,376 of sulfonylureas. For the combined endpoint of myocardial infarction plus coronary revascularizations, the hazard ratio for rosiglitazone versus pioglitazone was 0.97 (95%CI 0.78 – 1.20), indicating essentially no difference between these thiazolidinediones. Both agents had somewhat less favorable outcomes than metformin, and both had somewhat better outcomes than sulfonylureas.

In the dual therapy cohorts, there were 37,906 users of rosiglitazone in conjunction with metformin or sulfonylureas and 27,415 users of pioglitazone in similar combinations. Outcome rates in the rosiglitazone users versus the pioglitazone users were similar in combination with both metformin (HR 0.97, 95%CI 0.81 – 1.17) and sulfonylureas (HR 1.12, 95%CI 0.89 – 1.41). No combination with rosiglitazone or pioglitazone was meaningfully different in terms of outcome rates from a metformin-sulfonylurea combination.

In the combination-with-insulin cohorts, there were 8,035 and 7,924 users of rosiglitazone and pioglitazone, respectively. Risk of the combined endpoint was

essentially the same in these two groups (HR 1.07, 95%CI, 0.89 – 1.29), and the combination of either of these with insulin had similar risks to combinations of either sulfonylureas or metformin with insulin. Users of other antidiabetic drugs in combination with insulin were too few to interpret the hazard ratios as stable estimates.

The upper confidence bounds of the hazard ratios for all cohort pairs comparing rosiglitazone alone or in combination to pioglitazone, metformin, sulfonylureas or insulin were at or below 1.4, essentially ruling out risk increases of 40 percent or greater.

Conclusions

The incidence of a combined endpoint of myocardial infarction and coronary revascularization in users of rosiglitazone appears to be nearly the same as in users of pioglitazone, metformin and sulfonylureas. There is strong evidence against the proposition that rosiglitazone in particular is associated with as much as a 40 percent increase in risk. As in previous analyses of observational data in the US, the results from the monotherapy and the dual-therapy comparisons, though not individually significant, are consistent in suggesting that the risk of CHD events in patients using thiazolidinediones may lie between the risks associated with sulfonylureas (higher incidence) and metformin (lower incidence).

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Background

We recently found in data covering the years 2000-2004 from a large US health insurer that the rates of myocardial infarction and coronary revascularization were similar in groups of monotherapy recipients of rosiglitazone, metformin and sulfonylurea; they were also similar in groups of dual therapy users and in users of these agents and other oral antidiabetic agents in conjunction with insulin.[1] Metformin was significantly preferable to sulfonylureas, in these comparisons. The cardiovascular outcome experience of rosiglitazone appeared to lie between those of the other agents, and was not significantly different from either. An earlier study, covering 1999 through mid-2002, had found that thiazolidinediones as a group carried cardiovascular risks very close to those of a metformin-sulfonylurea combination.[2]

Observational studies may be subject to unmeasured biases, and inferences from them are greatly strengthened when independent data sources can provide similar answers. Accordingly, we have conducted an analysis of US health insurance claims data that have been aggregated over some 80 health plans by Pharmetrics. The Pharmetrics data available to us extend to the beginning of 2007, permitting additional follow-up and allowing for the assessment of pioglitazone, whose use has increased in recent years.

Methods

Source population

The Pharmetrics database contains insurance claims information from over 80 health plans in the United States. Available data include all paid claims for medical services, drugs, and facility costs, linked by common, coded patient identifiers. The health plan in which our own previous studies were conducted is not included in Pharmetrics data.

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1. McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM. Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf. Epub ahead of print, June 12, 2007. DOI: 10.1002/pds.1443

2. Johannes CB, Koro CE, Quinn SG, Cutone JA, Seeger JD. The risk of coronary heart disease in type 2 diabetic patients exposed to thiazolidinediones compared to metformin and sulfonylurea therapy. Pharmacoepidemiol Drug Saf. 2007 May;16(5):504-12.

Pharmetrics manipulated its source data to produce study files to specifications supplied by i3 Drug Safety.

In data covering the period July 2000 through March 2007, Pharmetrics identified all initiators of rosiglitazone, pioglitazone, metformin, and sulfonylurea for whom the first recorded dispensing followed 1) at least six months membership in a participating plan; and 2) the member's 18th birthday. Patients were required to have medical and pharmacy benefits.

Using all of the available information in each patient's insurance records, Pharmetrics identified claims for dispensings for any antidiabetic therapy, including insulin. Pharmetrics also counted insulin use as present if the patient had claims for insulin syringes. See Appendix A for drug and insulin supply codes.

Cohort formation and drug exposure definition

The three study groups within which we compared the outcomes were monotherapy, dual therapy, and therapy combined with insulin. Study group eligibility required at least six months' information in the database prior to entry date (see below), and no history of use of troglitazone. Cohort exit dates were as defined below for each group, or – if earlier – the occurrence of a myocardial infarction or coronary revascularization procedure (as appropriate to the specific analysis), exit from health plan coverage, or March 31, 2007. Use of non-study oral antidiabetic medications did not affect cohort membership status, but was accounted for in the baseline covariates.

The study group definitions were very similar to those used in our previous study of Ingenix data.[1] The differences are that pioglitazone has been added within each of the study groups described below and we have removed any prior users of troglitazone.

Monotherapy study group

Patients receiving rosiglitazone, pioglitazone, metformin, or a sulfonylurea, in whom the study drug or insulin was not given in the preceding six months and in whom no other of the three study drugs or insulin was dispensed within 30 days following the initial drug dispensing were eligible for the monotherapy study group. Cohort membership

was defined by the study drug that brought the patient into the monotherapy group. Follow-up began on the day following dispensing of the study drug. Follow-up for members of the monotherapy groups ended on the dispensing of a different study drug or dispensing of insulin or insulin supplies

Dual-therapy study group

Users of rosiglitazone plus metformin, rosiglitazone plus a sulfonylurea, pioglitazone plus metformin, pioglitazone plus a sulfonylurea or metformin plus a sulfonylurea, in whom the same drug pair or insulin had not been dispensed in the six months preceding the first dispensing of the second drug dispensed in the pair, and in whom the remaining one of the three study drugs or insulin was not dispensed within 30 days following the first dispensing of the second drug dispensed in the pair, were eligible for the dual-therapy study group. Cohort membership was defined by the study drug pair that brought the patient into the group. Follow-up began on the day following the first dispensing of the second drug dispensed in the pair. Follow-up ended at the earlier of: dispensing of a third study drug (whether or not it replaced the original drugs initiated), dispensing of insulin.

The rule for forming the dual therapy group could not distinguish between persons who were switching from one monotherapy to another and those for whom the physician's intent was that they receive dual therapy. In practice, the initial therapy was dispensed again after the second therapy had been dispensed in approximately 85 percent of the dual therapy cohort entrants, a pattern that is more consistent with dual therapy than with switching. Because of the impossibility of distinguishing poor adherence with dual therapy from switching in the remaining minority of cases, these patients were retained in the dual-therapy group. A subsequent on-treatment analysis (planned, but not part of this report), will truncate follow-up in those who do not continue dual therapy.

Combination-with-insulin study group

Users of rosiglitazone, pioglitazone, metformin, sulfonylureas or other oral antidiabetic agents in combination with insulin, in whom the same drug combination had not been dispensed in the six months preceding the first dispensing of the second drug dispensed in the pair, were eligible for the combination-with-insulin study group. The

starting point of observation for this cohort was the day following the initiation of insulin if patients were already using an oral antidiabetic agent. Patients on prior insulin therapy were included as of the day following the date that an oral agent was added. Cohort membership was defined by the study drug combination that brought the patient into the group.

Outcomes

We identified new cases of myocardial infarction as hospitalizations with a primary discharge diagnosis (position 1 on the UB-92 hospitalization record) of myocardial infarction and new events of coronary revascularization as hospitalizations bearing procedure codes for coronary revascularization. The date of the outcome events was set at the date of hospitalization. We created a composite outcome variable for myocardial infarction and/or coronary revascularization, with the date of event set as the earlier of the two outcomes. See Appendix B for further definitions.

Baseline covariates

From the insurance claims histories in the 183 days preceding cohort entry through the day of first dispensing (inclusive) that defined cohort entry, we derived variables representing:

- Demographics
- Calendar time
- Use of antidiabetic drugs other than insulin and
- Medical history derived from insurance claims in the baseline period for
    - Myocardial infarction
    - Coronary revascularization
    - Angina
    - Acute coronary syndrome
    - Coronary heart disease
    - Congestive heart failure
    - Hypertension
    - Obesity

    - Smoking
- Dispensing of
    - Nitrates
    - Anti-platelet agents
    - Beta-blockers
    - Calcium channel blockers and
    - Diuretics
    - ACE inhibitoris and Angiotensin receptor blockers

See Appendix C for definitions. Diagnostic codes are assigned in conjunction with medical services. For smoking and obesity these reflect typically the use of smoking cessation or weight reduction programs, respectively, and do not capture all people who smoke or are obese.

Analysis

The pairwise comparisons were as follows:

Monotherapy

- Rosiglitazone vs. Pioglitazone
- Rosiglitazone vs. Metformin
- Rosiglitazone vs. Sulfonylurea
- Pioglitazone vs. Metformin
- Pioglitazone vs. Sulfonylurea

Dual therapy

- Rosiglitazone + Metformin vs. Sulfonylurea + Metformin
- Rosiglitazone + Sulfonylurea vs. Sulfonylurea + Metformin
- Pioglitazone + Metformin vs. Sulfonylurea + Metformin
- Pioglitazone + Sulfonylurea vs. Sulfonylurea + Metformin
- Rosiglitazone + Metformin vs. Pioglitazone + Metformin
- Rosiglitazone + Sulfonylurea vs. Pioglitazone + Sulfonylurea

Combination with insulin

- Rosiglitazone + Insulin vs. Metformin + Insulin

- Rosiglitazone + Insulin vs. Sulfonylureas + Insulin
- Rosiglitazone + Insulin vs. Other-oral-antidiabetic-agents + Insulin
- Pioglitazone + Insulin vs. Metformin + Insulin
- Pioglitazone + Insulin vs. Sulfonylureas + Insulin
- Pioglitazone + Insulin vs. Other-oral-antidiabetic-agents + Insulin
- Rosiglitazone + Insulin vs. Pioglitazone + Insulin

This list includes 11 independent pairwise comparisons. By a Bonferroni correction the p-value required to maintain an overall alpha-region size of 0.05 for the combined endpoint is $1 - 0.95^{1/11}$, which is 0.0047. If one were to consider the two outcomes separately, there would be 22 independent comparisons. A p-value of $1 - 0.95^{1/22}$, or 0.0023 would be required to maintain an overall alpha size of 0.05.

For every pairwise comparison within the monotherapy, dual therapy, and combination-with-insulin cohorts, we selected all the individuals receiving one or the other of the two regimens. We then fit a logistic regression model to discriminate between the two regimens. The predictors in the model were calendar era of therapy initiation (2000-2003, 2003-2004, 2005-2006), all of the baseline covariates, and all the two-way interactions between calendar time and the baseline covariates. For models in which other antidiabetic drugs with insulin were one of the compared treatment regimens, we omitted from the model past use of other oral antidiabetic drugs. For each individual, we calculated the fitted probability of receiving the first drug in each drug regimen pair, as a function of that individual's covariates. These fitted values are called propensity scores.

Continuing within each pairwise comparison, we sorted all individuals by propensity score, and set aside the highest and lowest five percent. The remaining 90 percent were sorted into ten equally sized strata. Within each stratum, we confirmed that the difference between the average propensity scores of the compared drug regimens differed by less than 20 percent of the stratum width, and we performed stratified proportional hazards regression models, with drug regimen as the sole predictor and the outcome taken as (1) myocardial infarction, (2) coronary revascularization and (3) the

combination of myocardial infarction or revascularization. The resulting hazards ratios, the corresponding 95 percent confidence bounds and two-sided p-values are presented as the core result. We also performed stratified proportional hazards analyses of the propensity-score outliers that had been set aside: these are categories in which the propensity stratification is least likely to have been effective in controlling confounding, but the results are given nonetheless for completeness.

Stratification by propensity score controls confounding by the all the baseline and calendar-time factors that are components of the score, except in the improbable circumstance of drug-by-covariate interaction in the persistence of patients for follow-up. Confounding is absent because within each stratum, the probabilities of receiving each of the regimens is the same for all the different variable combinations that characterize the individuals in the stratum. In statistical expectation, therefore, there will be a similar prevalence in the stratum of each covariate combination in the two compared regimen groups, which is a sufficient condition for absence of confounding.

All data manipulation and statistical analysis was performed with SAS 8.2.

Privacy and confidentiality

All analyses and reporting were carried out using de-identified data. i3 Drug Safety obtained no protected health information for this analysis.

Results

Population characteristics

Tables 1-3 provide the baseline characteristics of the drug-regimen cohorts in the three study groups, monotherapy, dual therapy and combination-with-insulin. In all, to the nearest thousand, there are some 57,000 rosiglitazone initiators, 51,000 pioglitazone users, and substantially larger numbers of initiators of both metformin (275,000) and sulfonylureas (160,000). With a general pattern of within-study group similarity a few recurring differences stand out. Regimens involving sulfonylureas had more of the oldest and fewer of the youngest patients than other regimens, and had corresponding modestly higher prevalence of many baseline diagnoses. Metformin users included a

distinct relative preponderance of patients under the age of 35 and consequently lower prevalence of many baseline diagnoses. Regimens involving rosiglitazone and pioglitazone were more similar to one another in patient characteristics than were other regimens. Pioglitazone-using groups in general had a higher prevalence of baseline hyperlipidemia than did rosiglitazone-using groups. Combination-with-insulin regimens had higher baseline prevalence of cardiovascular disease than did the other study groups.

Follow-up

Time of follow-up and the occurrence of events in the various groups are shown in Table 4-6, which also present the crude incidence rates. Mean follow-up time ranged over the cohorts from 12 to 18 months. Rosiglitazone and pioglitazone users had roughly similar crude rates for each of the outcomes, and these were consistently higher than the crude outcome rates in the (younger, less sick) users of metformin and below the crude rates in the (older, sicker) users of sulfonylureas. In the monotherapy and dual therapy study groups, the combined event rate was approximately 10 per 1,000 persons per year. In the combination-with-insulin study group, the combined event rate was approximately twice that rate.

Adjusted estimates

Tables 7-9 show the details of the pairwise comparison between different regimens in the different study groups, adjusted for covariate differences through propensity stratification. The results are largely in line with the crude analyses of Tables 4-6, except that the degree to which metformin appeared to be superior in the crude analysis is substantially attenuated, as is the degree to which sulfonylureas appeared to be worse. There are four head-to-head comparisons between rosiglitazone and pioglitazone (monotherapy, in combination with metformin, sulfonylureas, and insulin). For the combined endpoint, the most extreme finding had the incidence in the rosiglitazone users 12 percent higher than in pioglitazone users when the drugs were taken in combination with sulfonylureas. There were more extreme discrepancies in the myocardial infarction outcome, but not in a consistent direction. The myocardial infarction rate was 22 percent higher than pioglitazone for rosiglitazone use in

combination with sulfonylureas and 22 percent lower for rosiglitazone than pioglitazone in monotherapy. The most extreme confidence bounds for the combined outcome ranged from a 22 percent advantage for users of rosiglitazone (in the monotherapy comparison) to a 41 percent advantage for pioglitazone (in combination with sulfonylureas). The smallest p-value for the combined outcome was 0.009, for the comparison between pioglitazone and metformin using the combined outcome (pioglitazone worse). This fell short of the Bonferroni limit for significance, which was 0.0047 for the combined outcome. The individual components of the combined outcome, myocardial infarction and coronary revascularization, showed similar patterns to the combined outcome, though with more variation and wider confidence intervals, because of smaller numbers of events.

Analysis of the propensity score outliers, among whom the possibility of residual confounding is the greatest, typically showed higher relative risks for the rosiglitazone-pioglitazone comparison than did the corresponding analyses from the central 90 percent of the population. The monotherapy comparison was the exception to this. The difference between the outlier results and the central population results gives an indication of the possible direction of residual confounding in the main analysis, and suggests limits on the magnitude of residual confounding that might be present.

Discussion

This claims-based study of different antidiabetic regimens provides substantial evidence for the similarity between rosiglitazone and pioglitazone with respect to the risk of serious cardiovascular outcomes. Like previous studies, it suggests that the risks associated with thiazolidinediones may lie slightly above the risks associated with metformin and below the risks associated with sulfonylureas. As diabetes itself causes cardiovascular complications, the minor variations between treatment regimens seen here could be due either to direct harmful effects of the drugs, or to corresponding variations in their abilities to mitigate the harmful effects of diabetes.

The variations could also be the result of remaining, uncontrolled confounding. When differences from an adjusted analysis are in the same direction, but much smaller than

the corresponding differences in crude analyses of observational data, there remain questions of residual confounding (inaccuracy in the measures of patient characteristics) and unmeasured confounding (failure to identify confounding factors). The gradient in risk, running from metformin at the lower end through the thiazolidinediones to its highest in sulfonylureas, follows exactly this pattern of crude differences that are substantially attenuated by statistical adjustment. As such, the apparent small effects that remain may reflect uncontrolled, residual error. If so the overall impression of similarity in risks between regimens becomes even stronger.

The strengths of the present analysis are size, the recency of the data and the availability of head-to-head comparisons within the thiazolidinedione class, as well as between regimens that differ in only a single component. The study is nearly fourfold larger than our previous claims-based analysis in a separate data system through 2004. That study in turn was comparable to in size to all completed clinical trials to date.

The results of the present work are internally consistent across subgroups defined by varying complexities of therapy and are quite similar to those of our smaller, previous studies in a different data resource. The first of those analyses involved early data, combined the thiazolidinediones, and used pairwise matching of cohorts. The second analysis extended accrual time in the same database, focused on rosiglitazone rather than thiazolidinediones in general, and was based on matched cohort-triplets, using a two-dimensional propensity score matching process. Propensity-matching has the advantage of leading to transparent analyses, but becomes cumbersome as the number of compared groups rises. The alternative we employed here, pairwise comparisons stratified on pair-specific propensity scores, achieves a similar control of confounding in estimating drug effects, but at the cost of a more complex analysis.

Exposure came from pharmacy dispensing records. No documentation of actual compliance with prescribed therapy was available. The use of professional samples or other undocumented sources of medications was not available. The analyses were also based on outcomes determined from the administrative claims. We made no attempt to verify the claims diagnoses, though prior experience has shown that procedure codes are recorded with high accuracy (they are frequently audited by the insurers), and that a

principal discharge diagnosis of myocardial infarction is an excellent surrogate for the chart-confirmed endpoint. The analysis will have missed sudden deaths that did not result in hospitalization, representing as much as 15 percent of serious cardiac events.

In the interests of rapid turnaround of this report, i3 Drug Safety undertook modifications from our usual procedures. (1) i3 Drug Safety provided data file specifications to Pharmetrics, which produced analytic files. Although we performed numerous consistency and logic checks, we did not verify directly that the file production from original Pharmetrics claims data matched our specifications. (2) The present analysis contains an intent-to-treat evaluation, but does not adjust for nonadherence in the form of an as-treated analysis. To rectify these shortcomings, we have requested from Pharmetrics the original claims files as well as an augmented study file that will permit both the analytic file validation and an as-treated analysis. We intend to reproduce all study files from original claims data, and to carry out an as-treated analysis, which we will report in due course.

Tables

Table 1. Baseline: Monotherapy Study Group

	Rosiglitazone		Pioglitazone		Metformin		Sulfonylureas	
	N	%	N	%	N	%	N	%
Total	12,440	100.0	16,302	100.0	131,075	100.0	48,376	100.0
Male	6,362	51.1	8,864	54.4	50,873	38.8	25,529	52.8
Female	6,078	48.9	7,438	45.6	80,202	61.2	22,847	47.2
Age <35	691	5.6	861	5.3	22,363	17.1	2,842	5.9
35-44	1,948	15.7	2,356	14.5	25,294	19.3	7,457	15.4
45-54	4,204	33.8	5,605	34.4	40,363	30.8	15,159	31.3
55-64	4,691	37.7	6,650	40.8	38,239	29.2	16,697	34.5
65-74	492	4.0	473	2.9	2,882	2.2	2,959	6.1
75+	414	3.3	357	2.2	1,934	1.5	3,262	6.7
Hyperlipidemia	5,284	42.5	7,873	48.3	49,729	37.9	15,455	31.9
Prior Acute Coronary Syndrome	209	1.7	244	1.5	1,256	1.0	952	2.0
Prior Myocardial infarction	190	1.5	238	1.5	1,122	0.9	998	2.1
Prior Coronary revascularization	129	1.0	205	1.3	780	0.6	704	1.5
Angina	273	2.2	352	2.2	1,729	1.3	1,099	2.3
Coronary Heart Disease	1,346	10.8	1,772	10.9	8,508	6.5	5,516	11.4
Congestive Heart Failure	318	2.6	379	2.3	1,948	1.5	2,302	4.8
Hypertension	5,767	46.4	7,890	48.4	53,521	40.8	20,865	43.1
Smoking	260	2.1	358	2.2	3,025	2.3	1,208	2.5
Obesity	706	5.7	992	6.1	13,060	10.0	2,400	5.0
Other oral antidiabetic drugs	399	3.2	548	3.4	1,663	1.3	612	1.3
Nitrates	455	3.7	556	3.4	2,736	2.1	2,207	4.6
Beta-blockers	2,229	17.9	3,130	19.2	20,450	15.6	9,449	19.5
Calcium-channel blockers	1,654	13.3	2,097	12.9	12,859	9.8	7,157	14.8
Diuretics	2,203	17.7	2,874	17.6	24,093	18.4	9,894	20.5
Anti-platelet agents	486	3.9	621	3.8	2,529	1.9	1,683	3.5
Statins	3,976	32.0	5,958	36.5	33,222	25.3	11,586	23.9
Digoxin	187	1.5	238	1.5	1,170	0.9	1,403	2.9
Fibrates	823	6.6	1,290	7.9	6,208	4.7	2,097	4.3
ACE inhibitors and Angiotensin Receptor Blockers	4,684	37.7	6,568	40.3	40,990	31.3	16,332	33.8

Table 2. Baseline: Dual Therapy Study Group

	Rosiglitazone +Metformin		Rosiglitazone +Sulfonylureas		Pioglitazone +Metformin		Pioglitazone +Sulfonylureas		Metformin +Sulfonylureas	
	N	%	N	%	N	%	N	%	N	%
Total	26,885	100.0	10,021	100.0	17,282	100.0	10,133	100.0	79,004	100.0
Male	13,972	52.0	5,411	54.0	9,226	53.4	5,616	55.4	41,858	53.0
Female	12,913	48.0	4,610	46.0	8,056	46.6	4,517	44.6	37,146	47.0
Age <35	1,450	5.4	291	2.9	818	4.7	306	3.0	3,279	4.2
35-44	4,694	17.5	1,292	12.9	2,812	16.3	1,250	12.3	12,310	15.6
45-54	10,066	37.4	3,325	33.2	6,377	36.9	3,410	33.7	28,113	35.6
55-64	10,034	37.3	4,029	40.2	6,813	39.4	4,236	41.8	29,065	36.8
65-74	384	1.4	544	5.4	291	1.7	476	4.7	3,648	4.6
75+	257	1.0	540	5.4	171	1.0	455	4.5	2,589	3.3
Hyperlipidemia	12,829	47.7	3,948	39.4	8,861	51.3	4,249	41.9	31,009	39.2
Prior Acute Coronary Syndrome	350	1.3	153	1.5	210	1.2	181	1.8	1,190	1.5
Prior Myocardial infarction	271	1.0	169	1.7	180	1.0	187	1.8	1,055	1.3
Prior Coronary revascularization	192	0.7	102	1.0	130	0.8	132	1.3	807	1.0
Angina	456	1.7	197	2.0	268	1.6	227	2.2	1,480	1.9
Coronary Heart Disease	2,292	8.5	1,174	11.7	1,590	9.2	1,304	12.9	7,561	9.6
Congestive Heart Failure	429	1.6	408	4.1	245	1.4	386	3.8	2,031	2.6
Hypertension	13,207	49.1	4,876	48.7	8,789	50.9	5,019	49.5	36,611	46.3
Smoking	520	1.9	174	1.7	364	2.1	205	2.0	1,619	2.0
Obesity	1,826	6.8	521	5.2	1,235	7.1	572	5.6	4,873	6.2
Other oral antidiabetic drugs	1,306	4.9	366	3.7	1,191	6.9	348	3.4	1,711	2.2
Nitrates	700	2.6	476	4.8	535	3.1	506	5.0	3,074	3.9
Beta-blockers	4,591	17.1	2,074	20.7	3,178	18.4	2,218	21.9	14,835	18.8
Calcium-channel blockers	3,154	11.7	1,724	17.2	2,066	12.0	1,714	16.9	11,105	14.1
Diuretics	4,553	16.9	2,267	22.6	3,085	17.9	2,228	22.0	15,320	19.4
Anti-platelet agents	807	3.0	433	4.3	600	3.5	488	4.8	2,543	3.2
Statins	10,682	39.7	3,770	37.6	7,804	45.2	4,105	40.5	27,426	34.7
Digoxin	287	1.1	290	2.9	190	1.1	298	2.9	1,616	2.0
Fibrates	2,157	8.0	702	7.0	1,670	9.7	781	7.7	5,230	6.6
ACE inhibitors and Angiotensin Receptor Blockers	12,910	48.0	4,960	49.5	9,276	53.7	5,246	51.8	37,139	47.0

Table 3. Baseline; Combination-with-Insulin Study Group

	Rosiglitazone + Insulin		Metformin + Insulin		Sulfonylureas + Insulin		Other Anti-Diabetic Agents + Insulin		Pioglitazone + Insulin	
	N	%	N	%	N	%	N	%	N	%
Total	8,035	100.0	21,841	100.0	12,147	100.0	1,380	100.0	7,924	100.0
Male	4,264	53.1	10,203	46.7	6,013	49.5	668	48.4	4,282	54.0
Female	3,771	46.9	11,638	53.3	6,134	50.5	712	51.6	3,642	46.0
Age <35	442	5.5	1,795	8.2	642	5.3	43	3.1	389	4.9
35-44	1,257	15.6	3,720	17.0	1,526	12.6	164	11.9	1,124	14.2
45-54	2,842	35.4	7,486	34.3	3,995	32.9	471	34.1	2,764	34.9
55-64	3,021	37.6	7,570	34.7	4,780	39.4	619	44.9	3,174	40.1
65-74	274	3.4	795	3.6	568	4.7	42	3.0	270	3.4
75+	199	2.5	475	2.2	636	5.2	41	3.0	203	2.6
Hyperlipidemia	3,492	43.5	8,749	40.1	4,979	41.0	705	51.1	3,513	44.3
Prior Acute Coronary Syndrome	237	2.9	569	2.6	487	4.0	46	3.3	240	3.0
Prior Myocardial infarction	228	2.8	504	2.3	476	3.9	49	3.6	196	2.5
Prior Coronary revascularization	156	1.9	428	2.0	338	2.8	39	2.8	162	2.0
Angina	259	3.2	656	3.0	483	4.0	56	4.1	264	3.3
Coronary Heart Disease	1,220	15.2	2,930	13.4	2,368	19.5	276	20.0	1,260	15.9
Congestive Heart Failure	480	6.0	1,108	5.1	1,377	11.3	144	10.4	475	6.0
Hypertension	4,153	51.7	10,659	48.8	6,466	53.2	775	56.2	4,113	51.9
Smoking	183	2.3	637	2.9	409	3.4	20	1.4	196	2.5
Obesity	596	7.4	1,933	8.9	929	7.6	135	9.8	623	7.9
Other oral antidiabetic drugs	555	6.9	1,113	5.1	626	5.2	1,380	100.0	536	6.8
Nitrates	547	6.8	1,282	5.9	1,103	9.1	97	7.0	526	6.6
Beta-blockers	1,738	21.6	4,643	21.3	3,590	29.6	378	27.4	1,899	24.0
Calcium-channel blockers	1,344	16.7	3,229	14.8	2,475	20.4	264	19.1	1,455	18.4
Diuretics	2,057	25.6	5,348	24.5	4,129	34.0	467	33.8	2,159	27.2
Anti-platelet agents	510	6.3	1,191	5.5	850	7.0	111	8.0	528	6.7
Statins	3,665	45.6	8,435	38.6	4,755	39.1	652	47.2	3,625	45.7
Digoxin	255	3.2	569	2.6	665	5.5	65	4.7	277	3.5
Fibrates	705	8.8	1,773	8.1	1,016	8.4	145	10.5	750	9.5
ACE inhibitors and Angiotensin Receptor Blockers	4,662	58.0	11,859	54.3	6,780	55.8	818	59.3	4,747	59.9

Table 4. Follow-up: Monotherapy Study Group

	Rosiglitazone	Pioglitazone	Metformin	Sulfonylureas
Follow-up time				
Total Years	14,054	18,065	155,274	56,614
Mean (Months)	14	13	14	14
Median (Months)	10	10	11	10
Interquartile Range (Months)	16	14	15	15

Outcomes								
	N	Crude Rate	N	Crude Rate	N	Crude Rate	N	Crude Rate
Myocardial infarction	44	3.13	66	3.65	375	2.42	338	5.97
Coronary Revascularization	151	10.74	208	11.51	964	6.21	676	11.94
Persons with Myocardial Infarction, and/or Coronary Revascularization	166	11.81	227	12.57	1,064	6.85	821	14.50

Table 5. Follow-up: Dual Therapy Study Group

	Rosiglitazone +Metformin	Rosiglitazone +Sulfonylureas	Pioglitazone +Metformin	Pioglitazone +Sulfonylureas	Metformin +Sulfonylureas
Follow-up time					
Total Years	32,003	10,669	17,559	11,248	101,257
Mean (Months)	14	13	12	13	15
Median (Months)	12	9	9	10	12
Interquartile Range (Months)	16	14	12	14	16

Outcomes										
	N	Crude Rate	N	Crude Rate	N	Crude Rate	N	Crude Rate	N	Crude Rate
Myocardial infarction	100	3.12	81	7.59	49	2.79	57	5.07	437	4.32
Coronary Revascularization	324	10.12	153	14.34	184	10.48	147	13.07	1,189	11.74
Persons with Myocardial Infarction, and/or Coronary Revascularization	347	10.84	183	17.15	199	11.33	171	15.20	1,304	12.88

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Table 6. Follow-up: Combination-with-Insulin Study Group

	Rosiglitazone + Insulin	Metformin + Insulin	Sulfonylureas + Insulin	Other Anti-Diabetic Agents + Insulin	Pioglitazone + Insulin
Follow-up time					
Total Years	12,058	33,530	18,218	1,796	12,183
Mean (Months)	18	18	18	16	18
Median (Months)	15	15	14	12	15
Interquartile Range (Months)	18	19	19	17	19

Outcomes										
	N	Crude Rate	N	Crude Rate	N	Crude Rate	N	Crude Rate	N	Crude Rate
Myocardial infarction	92	7.63	198	5.91	160	8.78	9	5.01	89	7.31
Coronary Revascularization	229	18.99	589	17.57	324	17.78	34	18.93	225	18.47
Persons with Myocardial Infarction, and/or Coronary Revascularization	264	21.89	663	19.77	397	21.79	37	20.60	249	20.44

Table 7. Hazard Ratios for Monotherapy Comparisons

	Myocardial Infarction			Cardiac Revascularization			Combined Outcome		
Comparison	Hazard Ratio	Lower 95% CI p value	Upper 95% CI	Hazard Ratio	Lower 95% CI p value	Upper 95% CI	Hazard Ratio	Lower 95% CI p value	Upper 95% CI
Rosiglitazone *vs.* Pioglitazone	0.783	0.519 0.242	1.180	0.973	0.776 0.814	1.221	0.966	0.777 0.757	1.201
Outliers	*1.304*	*0.407*	*4.180*	*0.905*	*0.499*	*1.643*	*0.923*	*0.529*	*1.608*
Rosiglitazone *vs.* Metformin	0.884	0.606 0.521	1.288	1.130	0.918 0.249	1.390	1.133	0.929 0.219	1.382
Outliers	*1.063*	*0.593*	*1.903*	*1.252*	*0.912*	*1.718*	*1.25*	*0.927*	*1.685*
Rosiglitazone *vs.* Sulfonylureas	0.648	0.461 0.013	0.911	0.913	0.756 0.344	1.102	0.891	0.745 0.209	1.066
Outliers	*0.419*	*0.161*	*1.089*	*0.841*	*0.450*	*1.575*	*0.695*	*0.395*	*1.221*
Pioglitazone *vs.* Metformin	1.152	0.870 0.323	1.525	1.242	1.050 0.011	1.470	1.238	1.054 0.009	1.454
Outliers	*0.795*	*0.369*	*1.712*	*1.089*	*0.774*	*1.534*	*1.133*	*0.816*	*1.575*
Pioglitazone *vs.* Sulfonylureas	0.743	0.559 0.041	0.988	0.950	0.803 0.550	1.124	0.909	0.775 0.243	1.067
Outliers	*0.395*	*0.131*	*1.192*	*0.654*	*0.346*	*1.235*	*0.667*	*0.377*	*1.181*

Table 8. Hazard Ratios for Dual Therapy Comparisons

	Myocardial Infarction			Cardiac Revascularization			Combined Outcome		
	Hazard Ratio	Lower 95% CI p value	Upper 95% CI	Hazard Ratio	Lower 95% CI p value	Upper 95% CI	Hazard Ratio	Lower 95% CI p value	Upper 95% CI
Rosiglitazone+Metformin *vs.* Sulfonylureas+Metformin	0.904	0.714 0.402	1.145	0.922	0.807 0.231	1.053	0.929	0.817 0.262	1.057
Outliers	*0.673*	*0.309*	*1.465*	*1.596*	*0.623*	*1.541*	*0.970*	*0.633*	*1.486*
Rosiglitazone+Sulfonylureas *vs.* Sulfonylureas+Metformin	1.384	1.047 0.023	1.830	1.152	0.961 0.127	1.382	1.175	0.988 0.068	1.396
Outliers	*2.214*	*1.365*	*3.591*	*0.872*	*0.549*	*1.385*	*1.215*	*0.844*	*1.749*
Pioglitazone+Metformin *vs.* Sulfonylureas+Metformin	0.736	0.536 0.059	1.012	0.880	0.745 0.133	1.040	0.892	0.760 0.162	1.047
Outliers	*1.318*	*0.504*	*3.452*	*0.964*	*0.545*	*1.707*	*0.937*	*0.543*	*1.617*
Pioglitazone+Sulfonylureas *vs.* Sulfonylureas+Metformin	0.979	0.718 0.893	1.334	0.966	0.801 0.721	1.166	1.009	0.845 0.923	1.204
Outliers	*1.386*	*0.729*	*2.636*	*0.859*	*0.561*	*1.316*	*0.950*	*0.649*	*1.390*
Rosiglitazone+Metformin *vs.* Pioglitazone+Metformin	1.007	0.707 0.969	1.435	0.982	0.810 0.850	1.189	0.972	0.808 0.761	1.169
Outliers	*5.074*	*0.603*	*42.692*	*1.596*	*0.809*	*3.148*	*1.520*	*0.786*	*2.941*
Rosiglitazone+Sulfonylureas *vs.* Pioglitazone+Sulfonylureas	1.216	0.831 0.314	1.781	1.158	0.906 0.242	1.481	1.122	0.893 0.323	1.411
Outliers	2.332	0.983	5.530	1.052	0.569	1.944	1.200	0.698	2.064

Table 9. Hazard Ratios for the Combined-with-Insulin Comparisons

	Myocardial Infarction			Cardiac Revascularization			Combined Outcome		
	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio	Lower 95% CI	Upper 95% CI	Hazard Ratio	Lower 95% CI	Upper 95% CI
		p value			p value			p value	
Rosiglitazone+Insulin *vs.* Metformin+Insulin	1.077	0.820	1.414	0.934	0.791	1.103	0.955	0.818	1.116
		0.596			0.422			0.563	
Outliers	*2.642*	*1.309*	*5.334*	*1.447*	*0.940*	*2.228*	*1.491*	*1.002*	*2.220*
Rosiglitazone+Insulin *vs.* Sulfonylureas+Insulin	0.998	0.758	1.314	1.169	0.974	1.402	1.135	0.959	1.342
		0.987			0.093			0.140	
Outliers	*1.138*	*0.463*	*2.797*	*1.119*	*0.617*	*2.030*	*1.124*	*0.659*	*1.915*
Rosiglitazone+Insulin *vs.* Other oral antidiabetic drugs+Insulin	1.592	0.767	3.308	0.998	0.681	1.463	1.088	0.753	1.573
		0.212			0.993			0.653	
Outliers	*1.765*	*0.196*	*15.886*	*1.912*	*0.536*	*6.816*	*1.461*	*0.472*	*4.524*
Pioglitazone+Insulin *vs.* Metformin+Insulin	1.219	0.930	1.598	0.939	0.796	1.108	0.925	0.790	1.083
		0.152			0.458			0.332	
Outliers	*0.787*	*0.386*	*1.604*	*0.801*	*0.518*	*1.238*	*0.799*	*0.534*	*1.197*
Pioglitazone+Insulin *vs.* Sulfonylureas+Insulin	0.964	0.725	1.280	1.091	0.905	1.314	1.029	0.865	1.224
		0.799			0.361			0.749	
Outliers	*1.169*	*0.557*	*2.455*	*1.356*	*0.826*	*2.228*	*1.153*	*0.729*	*1.824*
Pioglitazone+Insulin *vs.* Other oral antidiabetic drugs+Insulin	1.478	0.710	3.078	0.905	0.622	1.316	0.953	0.663	1.368
		0.297			0.601			0.793	
Outliers	*2.739*	*0.321*	*23.384*	*5.764*	*0.751*	*44.256*	*3.247*	*0.737*	*14.304*
Rosiglitazone+Insulin *vs.* Pioglitazone+Insulin	1.020	0.747	1.393	1.034	0.848	1.261	1.069	0.887	1.289
		0.903			0.742			0.484	
Outliers	*1.619*	*0.644*	*4.075*	*1.458*	*0.857*	*2.482*	*1.540*	*0.937*	*2.529*

Appendix A: Study drugs

Note: Hierarchical Ingredient Code List (HICL) codes

Rosiglitazone

020214	ROSIGLITAZONE MALEATE

Pioglitazone

020324	PIOGLITAZONE HCL
033202	PIOGLITAZONE HCL / METFORMIN HCL

Troglitazone

012661	TROGLITAZONE

Sulfonylureas

000798	ACETOHEXAMIDE
000799	TOLBUTAMIDE
000800	CHLORPROPAMIDE
000801	TOLAZAMIDE
000802	GLYBURIDE
000803	GLIPIZIDE
010485	GLIMEPIRIDE
012257	GLYBURIDE,MICRONIZED

Metformin

004763	METFORMIN HCL

Combination therapy

Each of the following HICLs should be treated as a dispensing of each of the two drugs listed.

009690	GLYBURIDE / METFORMIN HCL
024353	ROSIGLITAZONE / METFORMIN HCL
024429	GLIPIZIDE / METFORMIN HCL
033202	PIOGLITAZONE HCL / METFORMIN HCL

Other oral antidiabetic drugs

008283	ACARBOSE
017915	REPAGLINIDE
018595	MIGLITOL
021859	NATEGLINIDE
032805	PRAMLINTIDE ACETATE
032893	EXENATIDE

Insulin therapy and supplies

000768	INSULIN REGULAR HUMAN REC
000770	INSULIN,PORK PURIFIED
000771	INSULIN,PORK

000772	INSULIN,PORK REG. CONCENTRATE
000773	INSULIN REGULAR,BEEF-PORK
000778	INSULIN ISOPHANE,BEEF
000780	INSULIN NPH HUMAN RECOM
000782	INSULIN ISOPHANE,PORK PURE
000783	INSULIN ISOPHANE NPH,BF-PK
000785	INSULIN ZINC BEEF
000787	INSULIN ZINC HUMAN REC
000789	INSULIN ZINC,PORK PURIFIED
000790	INSULIN ZINC,BEEF-PORK
000793	INSULIN ZINC EXTEND HUMAN REC
004327	SYRINGE W-NDL, DISP., INSULIN
004677	INSULIN REG,HUM REC BUFF
004678	INSUL NPH HU S-S/INS RG HU REC
006215	INSUL NPH HU REC/INS RG HU REC
008966	NEEDLES, INSULIN DISPOSABLE
009138	SYRINGE, INSULIN, REUSABLE
010177	INSULIN REG, HUM S-S BUFF
011528	INSULIN LISPRO,HUMAN REC.ANLOG
012929	INSULIN PUMP RESERVOIR
019949	INSULIN NPL/INSULIN LISPRO
020769	INSULIN ASPART
021801	SYRING W-O NEEDLE,DISP,INSULIN
021802	NEEDLELESS ACCESS. DEV,INSULIN
022025	INSULIN GLARGINE,HUM.REC.ANLOG
023037	SYRING W-NDL,DISP,INSUL,0.5ML
023038	SYRINGE W-NDL, DISP,INSUL,1ML
023039	SYRINGE W-NDL, DISP,INSUL,3ML
023040	SYRINGE W-NDL, DISP,INSUL,2ML
023041	SYRING W-NDL,DISP,INSUL,0.3ML
023042	SYRING W-NDL,DISP,INSUL,0.25ML
023043	SYRNG W-NDL,DISP,INSUL,0.333ML
023400	INSULN ASP PRT/INSULIN ASPART
024100	SYRING W-O NDL,DISP,INSUL, 1ML
025117	INSULIN PUMP SYRINGE, 1.8ML
025118	INSULIN PUMP SYRINGE, 3ML

Appendix B: Outcomes

Notes: All outcome codes must occur in conjunction with an inpatient hospitalization. All diagnostic codes must occur in the first position representing the primary diagnosis of the hospitalization.

Myocardial infarction

ICD	410.xx	Acute myocardial infarction

Coronary revascularization

ICD-P	36.xx	Operations on vessels of the heart
CPT	33500 – 33572	All coronary artery repair procedures
CPT	92980 – 92981	Transcatheter placement of intracoronary stent(s)
CPT	92982 – 92984	Percutaneous transluminal coronary balloon angioplasty or atherectomy
CPT	92995 – 92996	Percutaneous transluminal coronary balloon angioplasty or atherectomy

Appendix C: Baseline covariate definitions and codes

Note: each characteristic determined during the previous 6-month baseline period prior to cohort entry, except for age and geographic region, which were determined at the date of cohort entry.

Age

18-29
30-39
40-49
50-64
65+

Gender

Female
Male

Geographic region of the health plan

South & Southeast
Midwest
Northeast
West

Hyperlipidemia

ICD	272.xx	Disorders of lipoid metabolism
TherSpec	M4E	Lipotropics

Myocardial infarction

ICD	410.xx	Acute myocardial infarction
ICD	412.xx	Old myocardial infarction

Coronary revascularization

ICD-P	36.xx	Operations on vessels of the heart
CPT	33500 – 33572	All coronary artery repair procedures
CPT	92980 – 92981	Transcatheter placement of intracoronary stent(s)
CPT	92982 – 92984	Percutaneous transluminal coronary balloon angioplasty or atherectomy
CPT	92995 – 92996	Percutaneous transluminal coronary balloon angioplasty or atherectomy

Angina

ICD	413.xx	Angina pectoris

Unstable angina

ICD	411.1	Unstable angina

Coronary Heart Disease

ICD	410.xx	Acute myocardial infarction
ICD	411.xx	Other ischemic heart disease
ICD	412.xx	Old myocardial infarction
ICD	413.xx	Angina pectoris
ICD	414.xx	Chronic ischemic heart disease
ICD	429.2	Cardiovascular disease

Congestive Heart Failure

ICD	428.xx	Heart failure
ICD	402.x1	Hypertensive heart disease with heart failure
ICD	404.x1	Hypertensive heart and kidney disease with heart failure
ICD	404.x3	Hypertensive heart disease with heart failure and chronic kidney disease

Hypertension

ICD	401.xx	Essential hypertension
ICD	402.xx	Hypertensive heart disease
ICD	403.xx	Hypertensive renal disease
ICD	404.xx	Hypertensive heart and renal disease
ICD	405.xx	Secondary hypertension
ICD	437.2	Hypertensive encephalopathy

Smoking

ICD	305.1	Tobacco use disorder
ICD	V15.82	History of tobacco use
TherSpec	J3A	Smoking deterrent agents

Obesity

ICD	278.0x	Overweight and obesity

Nitrates

TherSpec A7B (exclude sodium and amyl nitrite)

Nitroglycerin
Isosorbide dinitrate
Isosorbide mononitrate

Beta-blockers

TherSpec J7A, J7C (exclude sotalol)

Acebutolol
Atenolol
Betaxolol
Bisoprolol
Carteolol

Carvedilol
Esmolol
Labetalol
Metoprolol
Nadolol
Penbutolol
Pindolol
Propranolol
Timolol

Calcium-channel blockers

TherSpec A9A

Amlodipine
Bepridil
Diltiazem
Felodipine
Isradipine
Mibefradil
Nicardipine
Nifedipine
Nimodipine
Nisoldipine
Verapamil

Diuretics

TherSpec R1B, R1C, R1F, R1H, R1K, R1L, R1M

Amiloride
Ammonium chloride
Bendroflumethiazide
Benzthiazide
Bumetanide
Chlorothiazide
Chlorthalidone
Eplerenone
Ethacrynic acid
Furosemide
Glycerin
Hydrochlorothiazide
Hydroflumethiazide
Indapamide
Mannitol
Methyclothiazide
Metolazone
Pamabrom
Polythiazide

Spironolactone
Torsemide
Triamterene
Trichlormethiazide
Urea

Anti-platelet agents

TherSpec M9P

Abciximab
Cilostazol
Clopidogrel
Dipyridamole
Eptifibatide
Ticlopidine
Tirofiban

Digoxin

TherSpec A1A

Digitoxin
Digoxin

ACE Inhibitors and Angiotensin Receptor Blockers

TherSpec A4D, A4F

Benazepril
Benazepril / Hydroclorothiazide
Captopril
Captopril / Hydroclorothiazide
Enalapril
Enalapril / Hydroclorothiazide
Fosinopril
Fosinopril
Fosinopril / Hydrochlorothiazide
Lisinopril
Lisinopril / Hydrochlorothiazide
Moexipril
Moexipril / Hydrochlorothiazide
Perindopril
Quinapril
Quinapril / Hydrochlorothiazide
Ramipril
Trandolapril

TherSpec A4F

Candesartan
Candesartan / Hydrochlorothiazide
Eprosartan
Eprosartan / Hydrochlorothiazide
Irbesartan
Irbesartan / Hydrochlorothiazide
Losartan
Losartan / Hydrochlorothiazide
Olmesartan
Olmesartn / Hydrochlorothiazide
Telmisartan
Telmisartan / Hydrochlorothiazide
Valsartan
Valsartan / Hydrochlorothiazide

Statins

Atorvastatin	HICL	012404
Cerivastatin	HICL	013041
Fluvastatin	HICL	008946
Lovastatin	HICL	002793
Lovastatin / Niacin	HICL	023090, 026600
Pravastatin	HICL	006227
Rosuvastatin	HICL	025009
Simvastatin	HICL	006312
Simvastatin / Ezetimibe	HICL	026505

Fibrates

Clofibrate	HICL	002774
Fenofibrate	HICL	006552, 020377, 033904
Gemfibrozil	HICL	002766

	THERAPEUTIC CLASS						
	Sulfonylureas (SU's)	**Biguanides**	**Alpha Glucosidase Inhibitors**	**Meglitinides**	**TZD's**	**Incretin**	**DPP-4**
Marketed Products (Brand name, Year of approval)	glyburide (**DiaBeta, Micronase, 1984, Glynase,1992**) glipizide (**Glucotrol 1984, Glucotrol XL**) glimepiride (**Amaryl, 1998**)	metformin (**Glucophage 1995),** extended release formulations **(Glucophage XR 2000, Fortamet 2004, Glumetza, 2006**)	acarbose (**Precose, 1995**) miglitol (**Glyset, 1996**)	repaglinide (**Prandin, 1997**) nateglinide (**Starlix, 2000**)	rosiglitazone (**Avandia, 1999**) pioglitazone (**Actos, 1999**)	exenatide (**Byetta, 2005**)	sitagliptin (**Januvia, 2006**)
Mechanism of Action	stimulates insulin release from pancreatic beta cell	decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization	decreases gastrointestinal absorption of glucose; delays digestion of ingested carbohydrates	stimulates insulin release from beta cell via ATP sensitive potassium channels	improves insulin sensitvity via activation of peroxisome proliferator-activated receptor (PPAR) - gamma	Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut	Inhibits dipeptidyl peptidase-4 (DPP-4) enzyme; slows the inactivation of incretin hormones, including GLP-1 and GIP.
PK	**SU's general:** highly protein bound, hepatic metabolism and primarily renal excretion **Amaryl:** 100% GI absorption orally, oxidative metabolism by 2C9	90% renally eliminated; does not undergo hepatic metabolism	**Precose**: <2% absorbed, metabolized within GI tract by intestinal bacteria; excretion primarily via the feces **Glyset**: absorption is saturable at high doses, not metabolized, >95% renal excretion; accumulation occurs in renal impairment	**Prandin**: metabolized by 2C8 and 3A4, rapidly eliminated with half life of ~1 hour, 90% excreted in feces, use lower dose in severe renal impt. **Starlix:** rapidly absorbed; highly protein bound, metabolized by 2C9 and 3A4, primarily renal excretion	**Avandia:** highly protein bound; hepatically metabolized by 2C8 and 2C9 and eliminated in urine/feces **Actos**: highly protein bound; hepatically metabolized by 2C8 and 3A4 and eliminated in bile/feces	Following SC administration reaches median peak plasma concentrations in 2 hours. Predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.	Rapidly absorbed; half life 12 hours; low protein binding, primarily renally eliminated, substrate for p-glycoprotein.

	THERAPEUTIC CLASS						
	Sulfonylureas (SU's)	**Biguanides**	**Alpha Glucosidase Inhibitors**	**Meglitinides**	**TZD's**	**Incretin**	**DPP-4**
Indications	**Glucotrol/Diabeta (glipizide)**: Monotherapy, consider addition of insulin or other oral therapies if still not controlled **Micronase (glyburide)**: Monotherapy, Combination w metformin; consider addition of insulin or other oral therapies if still not controlled **Amaryl (glimepiride)**: Monotherapy, Combination w metformin, insulin	Monotherapy, Combination w SU or insulin. Can be used in pediatric patients (10 yrs of age or older)	**Precose:** Monotherapy, Combination w SU, metformin, or insulin **Glyset**: Monotherapy, Combination w SU	**Prandin**: Monotherapy, Combination w metformin or TZD in pts uncontrolled on met, SU, repaglinide, or TZD **Starlix**: Monotherapy, Combination w metformin or TZD. Should not be used in pts on SU (either switch or add-on therapy)	**Avandia:** Monotherapy, Combination w metformin, SU, or insulin, Triple therapy with SU and metformin **Actos**: Monotherapy, Combination w metformin, SU, or insulin	Adjunctive therapy with metformin, SU, or TZD or combination of metformin/SU or combination metformin/TZD	Monotherapy, Combination w metformin or TZD

	THERAPEUTIC CLASS						
	Sulfonylureas (SU's)	**Biguanides**	**Alpha Glucosidase Inhibitors**	**Meglitinides**	**TZD's**	**Incretin**	**DPP-4**
Clinical Studies	No clinical studies presented in label for SU's including **Amaryl, Micronase, Glynase, Diabeta** **Glucotrol**: 4 monotherapy trials of Glucotrol XL, 1 open, 2-way X-over study (8 weeks) of Glucotrol XL vs. Glucotrol.	**Glucophage:** 1 monotherapy trial of 29 weeks in obese pts, 1 combination SU trial of 29 weeks in obese pts, 2 combination insulin trials of 16 to 24 weeks, 1 pediatric trial of 16 weeks **Glucophage XR**: 1 monotherapy trial of 24 weeks, 1 dose ranging trial of 16 weeks, 1 trial (XR vs. IR) of 24 weeks **Fortamet:** 1 trial vs. immediate release metformin of 20 weeks, 2 combo insulin trials using immediate release metformin (16, 24 weeks) **Glumetza:** 1 dose ranging trial of 24 weeks, 1 combination SU trial of 24 weeks, 2 combo insulin trials using immediate release metformin (16, 24 weeks)	**Precose**: 6 monotherapy dose ranging trials, 1 monotherapy trial of 4 months, 1 combination SU trial of 6 months, 1 combination metformin trial of 6 months, 1 combination insulin trial of 6 months, , 1 one-year study of monotherapy, combination metformin, SU, and insulin patients. **Glyset:** 5 monotherapy trials of 14 weeks to 1 year, 3 combination SU trials	**Prandin**: 3 monotherapy trials of 4 to 24 weeks, 1 year trial vs. glyburide or glipizide, 1 combination metformin study, 2 combination TZD (one pio, one rosi) studies **Starlix:** 9 DB trials of 8 to 24 weeks including 1 monotherapy study, 1 study vs metformin or combination nateglinide/metformin, 1 vs. SU, 1 vs. metformin, 2 combination metformin studies, 1 combination TZD (rosi) study, 1 combination SU study (no benefit seen)	**Avandia:** 6 monotherapy trials including 2 trials of 26 weeks, 1 one-yr study, and 3 dose ranging trials, 2 combination metformin studies of 26 weeks, 3 combination SU studies of 26 weeks, 2 combination insulin studies of 26 weeks **Actos:** 3 monotherapy studies 16 to 26 weeks, 2 combination SU studies (16, 24 weeks), 2 combination metformin studies (16, 24 weeks), 2 combination insulin studies (16, 24 weeks)	**Byetta:** 3 studies of 30 weeks including combination SU, combination metformin, and combination SU plus metformin; 1 combination TZD or combination TZD/ metformin study of 16 weeks; Small cohort completed 52 weeks treatment	**Januvia:** 2 trials (18 wks, 24 wks) as monotherapy. 1 combination metformin study of 24 weeks 1 pioglitazone combination study of 24 weeks 1 study pts with chronic renal insufficiency

	THERAPEUTIC CLASS						
	Sulfonylureas (SU's)	**Biguanides**	**Alpha Glucosidase Inhibitors**	**Meglitinides**	**TZD's**	**Incretin**	**DPP-4**
Contra-indications	Diabetic ketoacidosis w or w/o coma, Type 1 diabetes as sole therapy, Hypersensitivity to drug	Renal disease or dysfunction, acute or chronic metabolic acidosis, including diabetic ketoacidosis with or without coma; hypersensitivity to drug. Temporarily discontinue in pts undergoing radiological studies	**Precose:** Diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, chronic ulceration, partial intestinal obstruction or patients prone to obstruction, chronic intestinal disease, hypersensitivity to drug **Glyset:** same as above except cirrhosis	Type 1 diabetes, diabetic ketoacidosis, Hypersensitivity to drug	Hypersensitivity to drug	Hypersensitivity to drug	None
Warnings	Bolded warning for increased risk of cardiovascular mortality (based on UGDP study with tolbutamide)	Boxed warning for lactic acidosis	None	None	Cardiac failure and other cardiovascular AE's. Description of studies in patients with congestive heart failure	None	Use in pts w renal insufficiency (dosage adjustment recommended) Use w meds that cause hypoglycemia (not studied w SU or insulin) *note: new labeling format combines Warnings and Precautions sections
Precautions	Hypoglycemia Elderly patients and those with decreased renal function should be started on lowest doses Secondary failure; diminished response over time **Glucotrol:** metabolism and excretion may be slowed in impaired renal or hepatic function	Monitor renal function, meds or disease states affecting renal function (ie. contrast media), surgery, alcohol, should avoid in significant hepatic disease, monitor for decrease in vitamin B12	Hypoglycemia, LFT elevations, renal impairment	**Prandin:** Not indicated for use with insulin; hypoglycemia, p450 3A4 meds, use cautiously in impaired liver function; dose reduction in renal impairment **Starlix:** Hypoglycemia, hepatic Impairment, highly protein-bound meds; secondary failure - diminished response over time.	Hypoglycemia in combination with other agents, edema, macular edema, weight gain, fractures, anemia, stimulation of ovulation in anovulatory women, monitor hepatic function	Do not substitute for insulin and not for use in Type 1 diabetes or for diabetic ketoacidosis, formation of anti-exenatide antibodies; not recommended in severe renal impairment; hypoglycemia (increased with SU)	

	THERAPEUTIC CLASS						
	Sulfonylureas (SU's)	**Biguanides**	**Alpha Glucosidase Inhibitors**	**Meglitinides**	**TZD's**	**Incretin**	**DPP-4**
Drug Interactions	Drugs that cause hypo- or hyperglycemia Drugs that are highly protein bound	Cationic drugs eliminated by renal tubular secretion, drugs that cause hyperglycemia; furosemide; nifedipine	**Precose:** drugs that cause hyperglycemia, intestinal adsorbents (e.g. charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g. amylase, pancreatin), digoxin **Glyset:** Ranitidine, propranolol, intestinal adsorbents (e.g. charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g. amylase, pancreatin)	**Prandin**: p450 3A4 intx (gemfibrozil, ketoconazole, rifampin), drugs that cause hypo- or hyperglycemia **Starlix:** Highly protein bound drugs, drugs that cause hypo- or hyperglycemia	**Avandia:** p450 2C8/2C9 interaction **Actos**: p450 3A4 interaction	Slows gastric emptying; use with caution with drugs that require rapid GI absorption. Take oral contraceptives or antibiotics at least 1 hour before exenatide; warfarin	Digoxin; monitor closely
Adverse Events	**MOST COMMON AE's** Primarily hypoglycemia **AE POPULATIONS** No AE population numbers provided for **Micronase, Glynase, Diabeta**. **Amaryl:** 2013 pts in US trials and 1551 pts in foreign trials. 1650 pts treated ≥12 months	**MOST COMMON AE's** Primarily gastrointestinal AE's **AE POPULATIONS** **Glucophage/ Glucophage XR:** 141 pts for Glucophage vs. 145 pts on placebo (one monotherapy study) and 900 patients for Glucophage XR **Fortamet:** 424 pts for Fortamet vs. 430 pts for immediate release metformin **Glumetza:** over 1000 pts in US clinical trials	**MOST COMMON AE's** Primarily gastrointestinal AE's **AE POPULATIONS** **Precose**: 1255 pts, including one year safety study **Glyset:** US trials in 962 pts on miglitol vs. 603 on placebo	**MOST COMMON AE's** hypoglycemia **AE POPULATIONS** **Prandin:** 2931 pts, 1500 treated ≥3 months, 1000 treated ≥6 months, 800 treated ≥12 months. **Starlix**: 2600 pts, 1335 treated ≥6 months, 190 treated ≥12 months.	**MOST COMMON AE's** URTI, headache **AE POPULATIONS** **Avandia:** ~8400 pts, ~6000 treated ≥6 months, ~3000 treated ≥12 months. **Actos:** 8500 pts treated, 2605 high-risk pts in PROactive trial. Over 6000 pt treated ≥6 months, over 4500 treated ≥12 months. Over 3000 treated ≥24 months	**MOST COMMON AE's** Nausea, vomiting, diarrhea; hypoglycemia **AE POPULATIONS:** 963 exenatide pts vs 483 placebo in combination with metformin, SU or metformin/SU. One 16 wk study of combination TZD with or without metformin (112 exenatide vs. 112 placebo)	**MOST COMMON AE's** Nasopharyngitis, URTI, headache **AE POPULATIONS:** 443 sitagliptin and 363 placebo in monotherapy trials; 175 sitagliptin plus pio and 178 pio in combination TZD trial.

	THERAPEUTIC CLASS						
	Sulfonylureas (SU's)	**Biguanides**	**Alpha Glucosidase Inhibitors**	**Meglitinides**	**TZD's**	**Incretin**	**DPP-4**
Dosage and Administration	**Micronase/Diabeta**: 1.25 – 20 mg QD or divided BID **Glynase:** 1.5 to 12 mg QD **Glucotrol** 2.5-40 mg QD or divided BID **Glucotrol XL** 5-20 mg QD **Amaryl** 1-8 mg QD	**Glucophage**: 1000–2550 mg with meals in divided doses **Glucophage XR** 1000–2000 mg QD	**Precose** 25-100 mg TID with meals **Glyset** 25-100 mg TID with meals Take with first bite of meal	**Prandin** 0.5-4 mg TID to QID with meals to maximum of 16 mg/day **Starlix** 60-120 TID 1 to 30 minutes before meals Do not take dose if meal skipped	**Avandia** 4 to 8 mg QD or BID in divided doses; maximum of 4 mg in combination with insulin **Actos** 15-45 mg QD	**Byetta**: Initiate at 5 mcg BID at any time within 60-minute period before the morning and evening meals; should not be administered after a meal. Based on clinical response, increase dose to 10 mcg twice daily after 1 month of therapy.	**Januvia:** 100 mg once daily. In moderate and severe renal insufficiency, 50 mg and 25 mg, respectively, daily.
How Supplied	**Micronase** (Pfizer)**/Diabeta** (Aventis): 1.25, 2.5 and 5 mg tablets **Glynase (Pfizer):** 1.5, 3, and 6 mg tablets **Glucotrol** (Pfizer): 5 and 10 mg tablets **Glucotrol XL** (Pfizer): 2.5, 5 and 10 mg tablets **Amaryl** (Aventis): 1, 2, and 4 mg tablets	**Glucophage** (BMS): 500, 850, and 1000 mg tablets **Glucophage XR** (BMS): 500, 750 mg tablets **Fortamet** (Andrx) 500, 1000 mg tablets **Glumetza** (Depomed) 500 mg tablets	**Precose** (Bayer): 25, 50 and 100 mg tablets **Glyset** (Pfizer): 25, 50 and 100 mg tablets	**Prandin** (Novo Nordisk): 0.5, 1, and 2 mg tablets **Starlix** (Novartis): 60 and 120 mg tablets	**Avandia** (GSK): 4 and 8 mg tablets **Actos** (Eli Lilly): 15, 30, and 45 mg tablets	**Byetta:** 5 mcg per dose, 60 doses, 1.2 mL prefilled pen;10 mcg per dose, 60 doses, 2.4 mL prefilled pen	**Januvia:** 25, 50, and 100 mg tablets
Label version	**Diabeta** April 2004 **Micronase** March 2002 **Glucotrol/Glucotrol XL** Sept 2006 **Amaryl** Feb 2006	**Glucophage/ Glucophage XL** June 2006 **Fortamet** Apr 2006 **Glumetza** Apr 2006	**Precose** 2004 **Glyset** Oct 2004	**Prandin** June 2006 **Starlix** Nov 2006	**Avandia** June 2007 **Actos** Feb 2007	**Byetta** Feb 2007	**Januvia** April 2007

*Abbreviations: QD = once daily, BID = twice daily, TID = three times daily, SC = subcutaneous, URTI = upper respiratory tract infection

Appendix F
FDA Public Communication

Safety Alert from FDA

On May 21, 2007, FDA issued a Safety Alert for rosiglitazone maleate, which is marketed in Avandia Tablets, Avandamet Tablets, and Avandaryl Tablets. This Safety Alert included a 4-page document providing information for healthcare professionals. For the information of Committee members, a copy of this 4-page document from FDA is included here as an Appendix to this Briefing Document.

Rosiglitazone maleate
(marketed as Avandia, Avandamet, and Avandaryl)

FDA ALERT [5/2007]: FDA is aware of a potential safety issue related to rosiglitazone maleate. 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 rosiglitazone. However, other published and unpublished data from long-term clinical trials of rosiglitazone provide contradictory evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. FDA's review of all available data is ongoing. FDA has not confirmed the clinical significance of the reported increased risk of ischemic cardiovascular events in the context of other studies. Myocardial ischemic events are currently described in the WARNINGS section of the rosiglitazone label. FDA does not know whether the other approved medication in the same pharmacologic class or other oral drugs for treating type 2 diabetes have less, the same, or greater risks. Switching diabetic patients to other therapies also confers its own risks. For those reasons, FDA is providing this emerging information to prescribers so that they and their patients can make individualized treatment decisions.

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging drug safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing the product. FDA is considering, but has not reached a conclusion about, whether this information warrants any regulatory action. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this page.

FDA has received additional safety information, a pooled analysis of 42 clinical studies for the treatment of type 2 diabetes mellitus, from the manufacturer of rosiglitazone, GlaxoSmithKline. There are three products, all manufactured by GlaxoSmithKline, that contain rosiglitazone: Avandia, Avanadamet (rosiglitazone with metformin), and Avandaryl (rosiglitazone with glimepiride). The data from these 42 studies and the associated analyses are complex and are currently being reviewed by the FDA. In the meantime, FDA is providing information on the initial results of these analyses. The degree of risk of rosiglitazone related to ischemic cardiovascular events is not yet certain.

Recommendations and Considerations

The current prescribing information for rosiglitazone includes data in the WARNINGS section about cardiac adverse events (congestive heart failure and ischemic events). These warnings can be found in the current prescribing information available at this link: http://www.fda.gov/cder/foi/label/2007/021071s023lbl.pdf Healthcare professionals should consider this and other available data when making individual treatment decisions for their patients with type 2 diabetes.

Report serious adverse events to
FDA's MedWatch reporting system by completing a form on line at
http://www.fda.gov/medwatch/report/hcp.htm, by faxing (1-800-FDA-0178),
by mail using the postage-paid address form provided on line
(5600 Fishers Lane, Rockville, MD 20852-9787),
or by telephone (1-800-FDA-1088).

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Background Information and Data

FDA has received data from several different clinical studies of rosiglitazone for treatment of type 2 diabetes. These studies vary with respect to the study design (e.g., pooled analysis, individual randomized controlled clinical trial, observational epidemiological study), patient populations enrolled, treatment groups, and length of patient follow-up. The studies analyzed to date have shown different rates of ischemic cardiovascular events. Based on these data, the risk of ischemic cardiovascular events remains unclear. Following are summaries of the studies and data.

Clinical Trial Data - Pooled Analysis of 42 Studies

FDA has received the pooled data from 42 separate double-blinded, randomized controlled clinical trials to assess the efficacy of rosiglitazone for treatment of type 2 diabetes compared to a variety of alternative therapies. The combined studies included 8,604 patients on rosiglitazone and 5,633 patients randomized to a variety of alternative therapeutic regimens, including placebo. In general, these studies had differing primary efficacy endpoints; they were not designed to thoroughly investigate cardiovascular safety. Treatment groups varied and included rosiglitazone alone or in combination with insulin, sulfonylureas, and/or metformin. The comparator arms were varied and included placebo alone or as an add-on treatment to other anti-diabetic agents, and other active anti-diabetic treatment regimens. The combined patient population was diverse, including patients with average duration of diabetes ranging from 5 to 13 years as well as patients with significant risk factors for cardiovascular disease (e.g., history of myocardial infarction, bypass surgery, stroke, peripheral vascular disease, and NYHA Class 1 and 2 heart failure). All but four studies were of six months in duration. In this pooled analysis as submitted by GlaxoSmithKline, the overall incidence of myocardial ischemia in rosiglitazone-treated subjects relative to the comparators was 1.99% vs. 1.51% with a hazard ratio of 1.31 (95% CI 1.01-1.70). This risk equates to a more than 30% excess risk of myocardial ischemic events in rosiglitazone-treated patients.

Balanced Cohort Study of Coronary Heart Disease Outcomes in Patients Receiving Anti-diabetic Agents

The Balanced Cohort Study is an observational study of 33,363 patients using a managed care database. Propensity matching was used to match risk factors for cardiovascular disease and other considerations for patients initiating therapy. About 90% of the patients had no history of cardiovascular disease. The composite cardiovascular endpoint was hospitalizations for myocardial infarction and coronary revascularization. Patients included in this study began

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treatment with rosiglitazone between 2000 and 2004. The treatment groups were monotherapy with rosiglitazone, metformin, or sulfonylurea; oral dual therapy combinations, and insulin combinations. Follow-up was 1.2 years. The incidence of the composite cardiovascular endpoint was 1.75 events per 100 patient-years for the rosiglitazone-containing regimens and 1.76 events per 100 patient-years for other treatments (hazard ratio 0.93; 95% CI 0.80-1.10).

A Diabetes Outcomes Progression Trial (ADOPT)

ADOPT is a randomized, double-blind study of 4,351 patients that compared rosiglitazone, metformin, or glyburide monotherapy on the improvement of and maintenance of glycemic control in patients newly diagnosed with type 2 diabetes. Patients with underlying cardiovascular disease were excluded. Median follow-up was 4 years. The myocardial ischemic event hazard ratios for rosiglitazone vs. metformin; rosiglitazone vs. glyburide; and metformin vs. glyburide were 0.96 (95% CI 0.66, 1.38), 1.16 (95% CI 0.78, 1.73) and 1.22 (95% CI 0.082, 1.80), respectively. The results of the ADOPT trial have been published, see the *New England Journal of Medicine* 355;23 pg 2427-2443 December 7, 2006. These data do not support an ischemic risk of rosiglitazone relative to metformin (the first line therapy for type 2 diabetes and a drug that has been shown to lower long term cardiovascular risk).

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Study

The DREAM study is a placebo-controlled, randomized, double-blind clinical trial in pre-diabetic patients designed to determine if the use of early treatment with medication could forestall the development of overt type 2 diabetes. The study was conducted in nearly 5,300 patients who were randomized to either rosiglitazone or placebo and were followed-up for a mean duration of 3 years. The study also was intended to examine whether rosiglitazone and/or ramipril delayed onset of overt type 2 diabetes. Therefore the trial used a factorial design, with patients randomized to any of four treatment arms: placebo with placebo; rosiglitazone with placebo; placebo with ramipril; and rosiglitazone with ramipril. This study, as reported in the Lancet, showed an effect of rosiglitazone in delaying the development of type 2 diabetes (not found with ramipril) in these prediabetic patients. GlaxoSmithKline has shared with FDA an analysis of the data for rosiglitazone alone versus placebo which showed no increased risk of myocardial infarction, stroke or cardiovascular death with rosiglitazone. FDA has not received the DREAM study data so cannot independently evaluate these data at this time. However, GlaxoSmithKline recently received the data from McMaster University and will be submitting it soon to FDA for review.

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

The RECORD study is a large, ongoing, randomized, open-label trial evaluating cardiovascular outcomes in patients treated with rosiglitazone as add-on therapy to either metformin or sulfonylurea in comparison to metformin and a sulfonylurea. It is a post-marketing, non-inferiority safety study of rosiglitazone vs. combined controls with a primary endpoint of cardiovascular death and hospitalization (including congestive heart failure). Cardiac events are being adjudicated in a blinded fashion to treatment assignment by a Cardiovascular Endpoints Committee.

Over 300 study centers in 25 countries in Europe are involved in the conduct of this study with each center attempting to enroll 10 to 20 patients. This non-IND study (done outside the United States and without input to the protocol or study design by the FDA) started in 2001 and completed enrollment in 2003, with over 4400 patients enrolled and proposed to be followed for 5 years. This study is still ongoing with the last patient reaching the duration of follow-up targeted in late 2008. This study has regularly been monitored by a data monitoring committee aware of the apparent elevation in cardiovascular ischemic risk from the pooled analysis. The Committee has not called for study cessation. Further, FDA has been allowed to see the results of a recent interim safety analysis and these interim data will be taken into account in FDA's considerations and actions. However, to preserve the study integrity, FDA is not explicitly commenting on these analyses.

Next Steps for FDA

FDA's Office of New Drugs, Office of Surveillance and Epidemiology, and Office of Biostatistics are collaborating to evaluate the data from the pooled analysis of 42 randomized clinical trials of rosiglitazone, in the context of all other available data. As information becomes available from the continued analysis of the 42 clinical studies and from other ongoing clinical studies, FDA will communicate this information to ensure that healthcare professionals and patients have the information necessary to make appropriate therapeutic decisions. FDA will take the issue of cardiovascular risk associated with rosiglitazone and other drugs in this pharmaceutical class to a public Advisory Committee meeting as soon as one can be convened. In the interim, healthcare professionals should factor this new information into their individual treatment decisions for their patients.