NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

The Clinical Effectiveness and Cost Effectiveness of Rosiglitazone for Type 2 Diabetes Mellitus

SmithKline Beecham Pharmaceuticals requested that some of the information that they submitted in confidence to the National Insititute for Clinical Excellence should be removed from this report. The relevant text has been removed. The Institute's Appraisals Committee had access to the full report when drawing up their guidance for the use of rosiglitazone for Type 2 diabetes.

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CONTRIBUTIONS OF AUTHORS

JL selected papers for inclusion, assessed the quality of studies, extracted and analysed data and drafted the report. SP advised on the design of the review and assisted in the literature search. RT provided advice on data extraction and synthesis. SP and RT commented on a draft of the report.

CONFLICTS OF INTEREST

None

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Professor Philip Home gave background information and advised on the clinical aspects of the review.

All responsibility for the contents of the report remains with the authors.

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AIM OF THE REVIEW

The aim of the review was to evaluate the clinical effectiveness and cost-effectiveness of rosiglitazone in the treatment of patients with Type 2 diabetes mellitus.

BACKGROUND

Type 2 diabetes is a chronic metabolic disorder that results from defects in insulin secretion and insulin action. The resulting build up of glucose in the blood can cause a range of diabetic complications, including *microvascular* and *macrovascular* damage to various organs as small blood vessels or large arteries become narrow or blocked. People with diabetes are at particularly high risk of cardiovascular disease. This appears to be related directly to hyperglycaemia, but also to hypertension and adverse lipid profiles.

Evidence from the United Kingdom Prospective Diabetes Study (UKPDS) has shown that maintaining good control of blood glucose reduces the incidence of diabetic complications. It is thought that the prevalence of Type 2 diabetes is around 800,000 for England and Wales.

Guidelines recommend a “step-up” policy of treatment for Type 2 diabetes, starting with diet and lifestyle advice, adding oral glucose-lowering agents (principally metformin and the sulphonylureas) and ultimately insulin if targets are not achieved. Type 2 diabetes tends to be progressive and the effectiveness of treatment falls over time. Rosiglitazone is one of a new class of oral glucose-lowering drugs, the PPAR-gamma agonists, which have a different mode of action to existing medications.

METHODS

A structured search was conducted to identify evidence relating to the clinical effectiveness and cost-effectiveness of rosiglitazone for the treatment of Type 2 diabetes mellitus. Randomised controlled trials that compared rosiglitazone monotherapy or combination therapy to alternative oral glucose-lowering medications were included. Searches for relevant systematic reviews and economic evaluations were also conducted. The methodological quality of the randomised controlled trials was assessed using a standard checklist. Data was extracted and entered into the Cochrane RevMan software. Where the study designs and patient populations were similar, and where statistical tests of heterogeneity were not significant, data from different studies was pooled (weighted mean difference or Peto odds ratio with fixed effects model). Where heterogeneity was suspected no quantitative meta-analysis was performed.

RESULTS

Quantity and quality of evidence

Six RCTs were judged to have met the inclusion criteria. The methodological quality and standard of reporting of the trials was very high. Data from two studies, with very similar study design and patient populations, related to the metformin combination comparison. Three, rather less homogeneous, studies included data on the sulphonylurea combination. . Information was

obtained for one monotherapy trial. An assessment of the results of this trial are not included in this report, since rosiglitazone has not been licensed for use in monotherapy. Supplementary data on safety was also available from two other randomised studies and from cumulative data on the incidence of adverse events in the clinical trial programme and open label extension studies [16;64].

Clinical effectiveness

Blood glucose levels (HbA1c) at six months were significantly lower for the patients who were randomised to the rosiglitazone/metformin combination than for those randomised to metformin: weighted mean difference (WMD) 0.8% (95% confidence interval (CI): 0.6-1.1%). Mean HbA1c was also significantly lower for the rosiglitazone/sulphonylurea patients than for the sulphonylurea patients: WMD 0.5%(95% CI: 0.2-0.7%) for 2mg/d and 1.1%(95% CI: 0.9-1.3%) for 4mg/d.

There is no direct evidence that adding rosiglitazone to oral monotherapies will reduce the incidence of diabetic complications, and hence mortality or quality of life adjusted mortality. However, the results of the UKPDS trial suggest that improved glycaemic control reduces the incidence of diabetic complications. Thus, it is likely that, by lowering blood glucose levels, rosiglitazone combination therapy for patients who fail to meet glycaemic targets on oral monotherapy will reduce the risk of diabetic complications.

Evidence from the clinical trial programme shows that rosiglitazone combination therapy has various effects on other cardiovascular risk factors. On the positive side, the results of the meta-analysis show:

For rosiglitazone/metformin compared to metformin alone:

- a greater increase in HDL cholesterol over six months;
- lower diastolic blood pressure at six months, though this reduction was not statistically significant after adjusting for baseline differences between the groups.

For rosiglitazone/sulphonylurea compared to sulphonylurea alone:

- a greater increase in HDL cholesterol over six months with 4mg rosiglitazone per day.

However, on the negative side there was:

For rosiglitazone/metformin compared to metformin alone:

- a greater increase in LDL cholesterol over six months;
- a greater weight gain over the six month period.

For rosiglitazone/sulphonylurea compared to sulphonylurea alone:

- a greater increase in LDL cholesterol over six months;
- a greater increase in weight over six months.

Rosiglitazone reduces insulin resistance and improves beta-cell function.

There is no direct evidence of the impact of rosiglitazone on quality of life. However, in the clinical trials rosiglitazone/metformin and

rosiglitazone/sulphonylurea combination therapies were at least as well tolerated as metformin or sulphonylurea alone and the incidence of adverse events was comparable. A lower proportion of the 4mg rosiglitazone/sulphonylurea patients, compared to the sulphonylurea monotherapy patients, withdrew from the studies because of an adverse event, odds ratio 0.57(95% CI: 0.38-0.87). The profile of adverse events was rather different for the rosiglitazone/metformin, rosiglitazone/sulphonylurea, metformin and sulphonylurea groups.

There is no direct evidence that the addition of rosiglitazone to metformin or sulphonylurea for this group of patients is any more (or less) effective at improving glycaemic control than moving to a metformin/sulphonylurea combination or starting insulin therapy.

Cost effectiveness

There is evidence from an economic evaluation of the UKPDS study that 'intensive' blood glucose control in patients with Type 2 is relatively cost-effective: additional cost per additional year free of diabetes-related end points (death or the onset of serious diabetic complications) £563 (95% CI: –£344 to £5,632).

This finding is supported by the results of other economic models [38;78].

No published evidence on the relative cost-effectiveness of alternative treatment strategies to achieve good glycaemic control was identified.

[SmithKline Beecham submitted data from a confidential economic model. Information about this study was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document.]

CONCLUSION

The evidence shows that rosiglitazone is clinically effective at reducing blood glucose when added to oral monotherapy (metformin or sulphonylurea) for patients who have insufficient glycaemic control on oral monotherapy alone. This is suggestive of a reduction in the risk of diabetic complications. However, uncertainty remains over the extent to which improved glycaemic control is maintained over time, the overall effect of rosiglitazone on cardiovascular risk, and hence the likely impact on quality of life, mortality, and cost-effectiveness. There is no direct trial evidence regarding the relative effectiveness of alternative add-on therapies.

ABBREVIATIONS

CI	Confidence interval
DBP	Diastolic blood pressure
DDD	Defined Daily Dose
EMEA	The European Agency for the Evaluation of Medicinal products
FFA	Free Fatty Acids (Non-Esterified Fatty Acids)
FPG	Fasting plasma glucose
FBG	Fasting blood glucose
GPRD	General Practice Research Database
$HbA1_c$	Glycated (glycosylated) haemoglobin
HDL	High Density Lipoprotein
HOMA	Homeostasis model assessment (mathematical estimation of insulin resistance and beta-cell function)
HTA	Health technology assessment
IDDM	Insulin-dependent diabetes mellitus
IGT	Impaired glucose tolerance
IFG	Impaired fasting glycaemia
LDL	Low density lipoprotein
M	Metformin
NIDDM	Non-insulin-dependent diabetes mellitus
PPA	Prescription Pricing Authority
R	Rosiglitazone
RCT	Randomised controlled trial
QALY	Quality adjusted life year
S	Sulphonylureas
SB	SmithKline Beecham
SBP	Systolic blood pressure
SPC	Summary of Product Characteristics
UKPDS	United Kingdom Prospective Diabetes Study
VLDL	Very Low Density Lipoprotein
WHO	World Health Organisation
WMD	Weighted mean difference

1. AIMS

The aim of this review is to evaluate the clinical effectiveness and cost-effectiveness of rosiglitazone in the treatment of patients with Type 2 diabetes mellitus.

2. BACKGROUND

2.1 Description of underlying health problem

2.1.1 Definition of Type 2 diabetes mellitus

Diabetes mellitus is a group of chronic disorders characterised by elevated glucose levels in the blood (*hyperglycaemia*). Glucose is the main source of energy for human cells. It is derived from carbohydrates in the diet, and passes by the blood stream to the tissues, or for storage in muscle and the liver. Stored glucose, together with glucose made from other foods, can also be recycled through the liver, and released into the blood for use by the tissues between meals and when fasting (e.g. at night).

Diabetes is usually diagnosed by a single high random plasma or blood glucose level together with typical symptoms, or by repeated high random plasma/blood glucose measurements. Marginally raised glucose levels require the diagnosis to be made fasting (plasma glucose >=7.0 mmol/l), or after a glucose tolerance test (2-hour plasma glucose >=11.1 mmol/l).

Hyperglycaemia is related to the production and use of a hormone called insulin, which is produced by islet B-cells in the pancreas. Insulin helps cells to take up glucose. Diabetes occurs when the pancreas produces too little insulin for the body's needs. Two main ***aetiological types*** of diabetes have been identified [95]:

- **Type 1 diabetes** – is a condition in which the pancreas makes little or no insulin because the islet B-cells have been destroyed through an autoimmune mechanism. The body is then less able to use glucose for energy and there is a build up of glucose in the blood.
- **Type 2 diabetes** – is a condition in which the pancreas is unable to produce enough insulin (for reasons unknown) to enable the insulin-dependent tissues to take up glucose. Often, usually in association with excess body weight, the tissues are very insensitive to insulin in people with Type 2 diabetes, but the pancreas is unable to produce enough insulin to overcome with insensitivity.

In addition to Type 1 and Type 2 diabetes, the current WHO classification system includes a number of other aetiological types:

- Other specific types
  - Genetic defects of islet B-cell function
  - Genetic defects in insulin action
  - Diseases of the exocrine pancreas
  - Endocrinopathies
  - Drug- or chemical-induced
  - Infections
  - Uncommon forms of immune-mediated diabetes
  - Other genetic syndromes sometimes associated with diabetes
- Gestational diabetes

Those with diabetes mellitus may be further sub-divided according to treatment:

1. patients not requiring insulin;
2. patients who use insulin in order to control blood glucose levels;
3. and patients who require insulin for survival.

The labels 'insulin-dependent diabetes mellitus' (IDDM) and 'non-insulin-dependent diabetes mellitus' (NIDDM) were previously used for Type 1 and Type 2 disease respectively. However, since patients with Type 2 disease may take injected insulin, these terms are no longer recommended.

Similarly, the terms 'juvenile onset' and 'adult onset' diabetes - corresponding to Type 1 and Type 2 disease respectively - may be misleading. Although Type 1 diabetes usually appears before the age of forty, it may occur at any age. The incidence of Type 2 diabetes increases with age, but is increasingly found under the age of 35 in people from non-European ethnic groups.

This review relates exclusively to the use of the drug rosiglitazone in Type 2 diabetes.

2.1.2 Symptoms and complications

Type 2 diabetes sometimes presents with the classical symptoms of hyperglycaemia (frequent urination, thirst, weight loss, recurrent infections). More usually it is diagnosed 5-10 years after onset as a result of a complication (such as a heart attack), or by testing in high-risk individuals (such as those with high blood pressure). Occasionally severe hyperglycaemia, often in conjunction with an infection, can lead to an emergency admission with vomiting or lowered consciousness.

Hyperglycaemia can cause a range of chronic diabetic complications. These include *microvascular* and *macrovascular* damage to various organs as small blood vessels or large arteries become narrow or blocked. Though largely preventable, these diabetic complications can cause severe morbidity, including visual handicap, kidney failure, angina, myocardial infarction, stroke, foot ulceration and erectile dysfunction. People with diabetes are at particularly high risk of cardiovascular disease, which is the main cause of their excess mortality. This appears to be related directly to hyperglycaemia, but also to hypertension and adverse lipid profiles.

The onset of diabetic complications may often precede the appearance of symptoms - by the time they present clinically, over 50% of people with Type 2 diabetes already have significant complications [83]. Thus early diagnosis is very important.

Evidence suggests that maintaining good control of blood glucose levels has beneficial long-term effects. The United Kingdom Prospective Diabetes Study (UKPDS) found that the risk of microvascular complications was reduced by 25% in patients with type 2 diabetes randomised to 'intensive' treatment with sulphonylureas or injected insulin compared to 'conventional' treatment with diet alone (p=0.0099) [87]. Overweight patients randomised to 'intensive' treatment with metformin rather than 'conventional' treatment had a reduced risk of any diabetes-related endpoint (p=0.0034) [85]. Reductions in macrovascular risk were only observed for obese patients treated with metformin. Recent debate has questioned the interpretation of the UKPDS results [49]. In particular, it has been pointed out that there was no clear correlation between blood glucose and treatment outcomes.

The UKPDS study has demonstrated that tighter control of blood pressure by the use of beta-blockers or angiotensin converting enzyme (ACE) inhibitors reduced diabetes-related mortality and the incidence of microvascular and macrovascular complications [86;88]. An economic evaluation based on the UKPDS data has shown that antihypertensive therapy for patients with Type 2 diabetes mellitus is highly cost - effective [84].

Symptoms of low blood glucose levels (hypoglycaemia), including shaking, sweating and disorientation, are not due to diabetes, but to the action of some glucose-lowering drugs or injected insulin when too little glucose is entering the blood due to a missed or late meal, or too much is being removed from it during or after exercise.

2.1.3 Epidemiology

2.1.3.1 Prevalence and incidence

Some estimates of the prevalence of diabetes are shown in Table 1. It is thought that around 2.4% of the adult population have been diagnosed with diabetes mellitus, about one million people in England and Wales [20]. The proportion of people with diabetes who have Type 2 disease is estimated at around 80% [92], suggesting that the prevalence of Type 2 diabetes is around 800,000 for England and Wales.

Table 1. Estimates of incidence and prevalence 1999

	thousands of people		
	England	Wales	E&W
Population[56]	49,300	2,900	52,200
Adult population[56]	39,200	2,300	41,500
Incidence of Type 2 diabetes mellitus			
1.73 cases per 1,000 pa age/sex adjusted (95% CI 1.55-1.91)[19]	85 (76-94)	5 (4-6)	90 (81-100)
Prevalence of diabetes mellitus			
Diagnosed: 2.4% of adults [20]	940	60	1,000
Prevalence of Type 2 diabetes mellitus			
80% [92] of diagnosed cases	750	50	800

Self-reported prevalence is rather higher than the above estimates. In the 1994 Health Survey for England, 3% of respondents reported that they suffered from diabetes mellitus [24]. Amongst those who did not report a history of diabetes, blood tests showed that 3% of men and 2% of women had raised glycated haemoglobin levels (HbA_{1c}>=8%). This evidence is consistent with other data [37] suggesting that approximately half of the population with Type 2 diabetes remain undiagnosed.

Extrapolating from the Poole Diabetes Study [19] the incidence of Type 2 diabetes mellitus in England and Wales may be estimated at 90,000 (95% CI 81,000 to 100,000) new cases per year. However, this estimate is not adjusted to allow for the ethnic mix of the population.

2.1.3.2 Morbidity and mortality

Diabetic complications are a major cause of morbidity [13;54]:

- Diabetes is associated with a two to threefold increase in the risk of coronary heart disease and stroke.
- Diabetic retinopathy is the commonest cause of blindness in people of working age.
- About 30% of people with Type 2 diabetes have kidney disease and about 16% of new renal replacement therapy patients have diabetes.
- 15% of people with diabetes develop foot ulcers and 5-15% of people with diabetic foot ulcers need amputations.

Estimates of diabetes-related mortality from death certificate data are seriously misleading, because diabetes will have been a contributory factor in many deaths attributed to other underlying causes [76].

It is clear that age and sex-adjusted mortality rates are higher for people with Type 2 diabetes than for non-diabetic individuals [52;57;91]. Precise estimates of

the scale of this excess mortality are not available because of the following reasons:

- difficulties in classifying Type 1/Type 2 disease,
- the lack of reliability and validity of death certification,
- selection bias (people with diabetes are also likely to have adverse risk profiles for other diseases).

Estimates of the all-cause excess mortality associated with Type 2 diabetes range from 1.07 to 3.01 [57]. The greatest cause of excess mortality in people with Type 2 diabetes is cardiovascular and cerebrovascular disease [27;52;57;91].

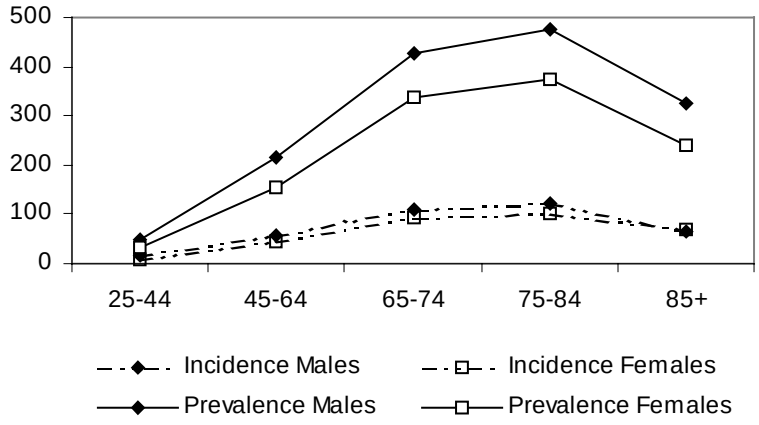
2.1.3.3 Risk factors

The incidence and prevalence of diabetes mellitus are positively related to age, at least up to the age of 85 (Figure 1). A large majority of cases that occur in adulthood are due to Type 2 disease.

Type 2 disease is now more prevalent in men than in women (Figure 1).

Figure 1. Incidence and prevalence by age and sex

Rates per 10,000 person years at risk [50]
Diabetes Mellitus



The prevalence of Type 2 diabetes varies by ethnic group. It is estimated to be 3-5 times more prevalent in South Asia people [46], and twice as prevalent in people of African-Caribbean origin [67], than in white Europeans.

Weight is a major risk factor for Type 2 diabetes. It is estimated that 75% of people who develop Type 2 diabetes are obese [92]. This association may be causative, with excess weight being related to the onset of Type 2 diabetes, possibly through the mechanism of increased insulin resistance. However, it is also possible that overeating and low physical activity are common causative factors for obesity and Type 2 diabetes.

2.2 Current treatment options and service provision

2.2.1 Lifestyle modification

Type 2 diabetes can be managed through diet and exercise alone, at least in the early stages. Data from five general practice or community studies shows that 16-24% of people with known diabetes are not prescribed any oral glucose-lowering medication [89]. However, Type 2 diabetes is a progressive disease. Nearly all patients require oral glucose-lowering drugs after some time and now most patients eventually need insulin in order to maintain satisfactory blood glucose levels.

Current guidelines recommend a diet that is similar to the healthy diet advised for the general population, with controlled intake of fat and a focus on whole grains, fruit and vegetables [18]. Regular exercise is important to control weight and to use up blood sugar, increase cell sensitivity to insulin, and improve circulation.

Modification of other cardiovascular risk factors (such as smoking, alcohol and salt intake) is also important, since diabetes is associated with a particularly high risk of cardiovascular disease.

2.2.2 Medication

Patients with Type 2 diabetes whose glucose levels are inadequately controlled by diet and exercise alone may need to take an oral glucose-lowering drug (whilst maintaining efforts to control diet and to exercise). There are four main groups of oral glucose-lowering drugs currently in the British National Formulary [6]:

- **Sulphonylureas** (chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, tolazamide and tolbutamide).
  These drugs work by augmenting insulin secretion, and are thus only suitable for Type 2 diabetes, where some pancreatic islet B-cell activity is present. In the long-term sulphonylureas appear to have other modes of action, since the levels of insulin in the blood return to pre-medication levels whilst blood glucose remains reduced. Sulphonylureas are associated with weight gain, and should be avoided in obese patients. They may also lead to hypoglycaemia, which, though rare and less common than with insulin, may be a hazard for elderly patients. Chlorpropamide is no longer recommended because it has more side effects than other sulphonylureas. Glibenclamide should be avoided in patients who are elderly, or who have renal impairment.
- **Biguanides** (Metformin)
  Metformin reduces the release of glucose stored in the liver and increases peripheral utilisation of glucose. It only works if endogenous insulin is present, and so is only suitable for Type 2 diabetes. Unlike sulphonylureas, metformin does not lead to problems of hypoglycaemia or weight gain. However, it can cause the rare, but potentially very serious, problem of lactic acidosis. Because of this,

metformin is contraindicated if there is renal or hepatic impairment. Gastrointestinal symptoms, such as heartburn or diarrhoea, are a common problem with metformin, and mean that many patients cannot tolerate this drug.

- **Alpha-glucosidase inhibitors** (acarbose)
  Acarbose slows the digestion and absorption of carbohydrates (by blocking the action of alpha-glucosidase enzymes), reducing the postprandial spike in blood glucose. Thus, glycosylated haemoglobin levels are kept closer to normal. Acarbose has a small but significant effect on blood glucose. It does not cause hypoglycaemia or weight gain, though it can lead to gastrointestinal side effects (flatulence, diarrhoea and bloating). This drug is little used in the UK because it is less efficacious than the sulphonylureas or metformin, and the GI side effects are troublesome and common.
- **Meglitinides** (repaglinide)
  Oral repaglinide has a similar action to the sulphonylureas; it lowers blood glucose levels by stimulating the production of insulin by the pancreas. However, it binds to different sites on the islet B-cells and is relatively short acting. Repaglinide can cause hypoglycaemia.

If diet, exercise and oral medication do not give adequate glycaemic control, then people with Type 2 diabetes may need to commence insulin therapy.

The UKPDS study was not powered to show differences in effectiveness between the various agents [87]. However, it did show that 'intensive' sulphonylurea or insulin therapy was associated with weight gain. Amongst the overweight patients allocated to 'intensive' treatment, there was a greater effect for those treated with metformin than for those treated with a sulphonylurea or insulin on any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032) [85].

Sulphonylureas, metformin, adjunctive oral glucose-lowering drugs and insulin may be used in various combinations, as double, or even triple, combination therapy, if adequate glycaemic control can not be achieved with a single agent alone.

Other medications may be required to reduce the risk of complications, including antihypertensive therapy [54].

2.2.3 Management guidelines

Several clinical practice guidelines for the treatment of Type 2 diabetes have been developed recently [1;2;11;25;27;28;92]. These all recommend a “step-up” policy of treatment, starting with diet and lifestyle advice alone, adding various oral glucose-lowering agents and ultimately insulin if targets are not achieved. Type 2 diabetes tends to be progressive. So, although patients may be adequately managed initially on diet alone, within three years of onset 50% of patients require multiple therapy, and after nine years this figure has increased to 75% [79].

The guidelines recommend that individual treatment targets should be set, based on the need to achieve good control of blood glucose and

cardiovascular risk factors, whilst avoiding the risk of hypoglycaemia and maintaining an acceptable quality of life. The WHO blood glucose cut-offs (Appendix 1) are designed for diagnosis, and should not be used as therapeutic targets. Current European guidelines [28] suggest that targets should be based upon an assessment of risk using the levels shown in Table 3.

Table 2. Vascular risk assessment guidelines

From European Diabetes Policy Group guidelines [28]

	Low risk	*At risk*	*High risk*
Blood glucose			
Glycated haemoglobin, HbA_{1C} (%)	<=6.5	>6.5	>7.5
Venous fasting plasma glucose (mmol/l)	<=6.0	>6.0	>=7.0
Self-monitored fasting blood glucose (mmol/l)	<=5.5	>5.5	>6.0
Blood lipids			
Total serum cholesterol (mmol/l)	<4.8	<=6.0	>6.0
Serum LDL cholesterol (mmol/l)	<3.0	<=4.0	>4.0
Serum HDL cholesterol (mmol/l)	>1.2	>=1.0	<1.0
Serum triglycerides (mmol/l)	<1.7	<=2.2	>2.2
Blood pressure			
Low risk (mmHg)	<140/85		

The commencement of an oral glucose-lowering drug is advocated if blood glucose levels remain high after an adequate trial of life-style education. The European guidelines suggest initiation of an oral agent when HbA_{1c}>6.5% (FPG>6.0mmol/l), or occasionally (if other risk factors are low) when HbA_{1c}>7.5% (FPGΔ7.0mmol/l) [28]. Attempts to modify lifestyle factors should continue alongside medical treatment.

The choice of initial oral glucose-lowering drug depends upon the patient's weight (metformin is advocated for obese patients) and upon their expected susceptibility to the various side effects. Dose titration is recommended, starting with a low dose and gradually increasing towards the ceiling dose if targets are not met. Dosages should be reviewed and reduced if adverse effects are observed or if blood glucose is well within the target range.

The guidelines differ with respect to the recommended sequence and timing of the next step, after failure with a single oral glucose-lowering agent. Some recommend a trial of another single oral agent, before moving to combination therapy [92]. Other guidelines recommend adding another oral agent to current medication [2;28]. The European guidelines suggest that triple therapy may be tried if targets cannot be achieved on the maximum tolerated doses of two drugs.

If blood glucose levels remain high after an adequate trial of oral glucose-lowering drugs then insulin therapy is recommended (unless the patient has a poor life expectancy and is asymptomatic). The European guidelines suggest that, for most patients, insulin should be added to oral medication if HbA_{1c}>7.5% after "maximum attention" to diet and oral medication [28].

The guidelines also make a range of other recommendations relating to:

1. antihypertensive therapy;
2. the location and organisation of services (primary/secondary/shared care);
3. the professional skills that should be included in diabetes team (general practitioner and practice nurse, consultant physician, diabetes specialist nurse, dietician, chiropodist and other specialists as necessary);
4. the need for structured patient education and self-care programmes;
5. the need for self-monitoring and regular professional checks to ensure that blood glucose levels are maintained as close to optimal levels as is possible;
6. and the need for a range of screening tests to monitor other risk factors, side effects and complications (e.g. blood pressure monitoring, an annual test for urinary protein and microalbuminuria, regular eye and foot checks).

2.2.4 The burden of disease

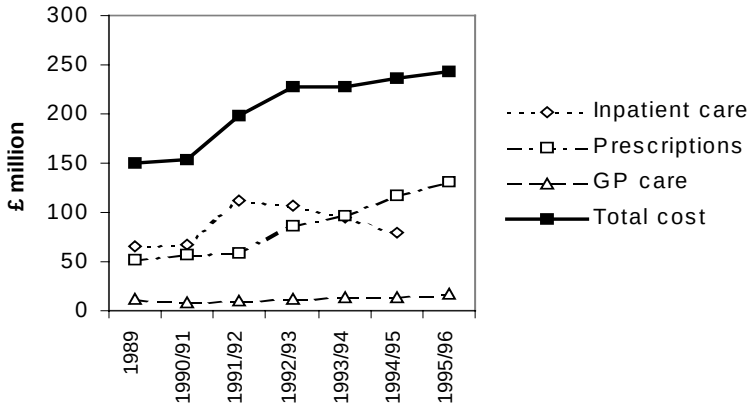
Estimates of the financial cost of diabetes vary enormously, depending on whether they include all costs or only health care costs and on whether they include costs of disease associated with or caused by diabetes [34;42-44;93].

The cost of treating diabetes mellitus (all types) has been estimated at £243m for the UK in 1995/96 [97]. This represents a real terms (i.e. inflation adjusted) increase of around 25% since 1989. Prescriptions represent the largest component of this cost estimate, closely followed by inpatient care (Figure 3). However, this figure only includes the cost of treating disease directly attributed to diabetes. It does not include the cost of treatments where diabetes was a contributory factor.

Another estimate, based on a survey of one district in South Wales [22], found that the additional hospital costs for people with diabetes was £1,800 per person. This represents 9% of UK hospital costs, around £1.9 billion each year [13].

[Information on the health service and other costs of Type 2 diabetes from two studies – the T^2ARDIS study[7;35;74] and the CODE-2 survey[4] – was included in the SmithKline Beecham submission. However, this information is currently confidential and has been removed from this document.]

Figure 2. Estimated health care costs: 1989 to 1995/96
Directly attributed to diabetes mellitus[97]
England and Wales



2.2.5 Use of oral glucose-lowering medication

The Prescription Pricing Authority (PPA) estimated that about 135,000 people in England were taking oral glucose-lowering drugs (BNF section 6.1.2) in 1996/7 [59]. This estimate is derived from the number of Defined Daily Doses (DDDs) [96] prescribed over a given time period. There was a 42% increase in the use of oral glucose-lowering drugs between June 1992 and March 1996, mainly due to increasing use of glicazide and metformin [59]. Over this period there was a 60% increase in the cost of the sulphonylureas, which account for 80% of total expenditure on oral glucose-lowering drugs.

Data from the General Practice Research Database (GPRD) [55], which includes 288 practices in England and Wales, suggests that almost one percent of patients were prescribed an oral glucose-lowering drug at least once in 1996. This implies that around 480,000 people in England and 30,000 in Wales would have been prescribed an oral glucose-lowering drug.

The GPRD figure is more consistent with estimates of prevalence (Table 1) and of the proportion of patients with Type 2 diabetes taking oral glucose-lowering drugs [79]. The large discrepancy between the PPA and GPRD data suggests that many patients may take oral glucose-lowering drugs intermittently or at doses lower than the DDDs.

2.3 Description of new intervention

The thiazolidinediones (thiazoles or glitazones) are a recently developed class of oral glucose-lowering drugs [12;75]. They are thought to work through the activation of peroxisome proliferator-activated receptor gamma (PPARγ) receptors, so reducing insulin resistance[58]. Glitazones are not intended for Type 1 diabetes.

There are now three thiazolidinedione drugs licensed by the United States' Food and Drug Administration (FDA):

- Troglitazone: Rezulin (Warner-Lambert), Romozin (Glaxo Wellcome), Sensulin (Sankyo)

- Rosiglitazone: Avandia (SmithKline Beecham)
- Pioglitazone: Actos (Takeda & Eli Lily)

Troglitazone was the first of this class of drugs to become available in the US. Following concerns over liver failure associated with troglitazone, the manufacturer advised that patients should have regular monitoring. They recommended that liver function should be checked before starting treatment, monthly during the first year, and quarterly from then on. In response to these concerns troglitazone is not being marketed in the European market.

There have also been isolated reports of hepatic problems associated with rosiglitazone in the States [9;29;32], although these have been contested by SmithKline Beecham [33]. The FDA is reported to be monitoring and evaluating such reports, and is conducting a comparative analysis of hepatic failure associated with the three glitazones to establish whether there could be a class effect. The FDA has also recommended that patients should have liver enzyme tests before starting any of the glitazones and periodically thereafter.

The European Committee for Proprietary Medicinal Products (CPMP) recommended the granting of marketing authorisation for rosiglitazone in March 2000. Pioglitazone is currently being considered by the CPMP, which is expected to give an opinion soon. This current review relates only to rosiglitazone. Pioglitazone will be subject to a separate NICE appraisal (to be considered by the NICE Appraisals Committee at its November meeting).

2.3.1 Summary of Product Characteristics

The wording of the licensed indication is:

> "Rosiglitazone is indicated only in oral combination treatment of Type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:
> – in combination with metformin only in obese patients
> – in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated"

Rosiglitazone is not licensed or marketed for use as monotherapy or in triple combination with other oral glucose-lowering drugs (metformin and a sulphonylurea). The SPC states that rosiglitazone is contraindicated for use with insulin. Other contraindications include:

- known hypersensitivity;
- cardiac failure or history of cardiac failure;
- hepatic impairment.

Caution is advised in the use of the product for patients with severe renal insufficiency.

2.4 Outcome measures

The principal goals of treatment for Type 2 diabetes are to prevent acute and chronic complications and thus to improve quality of life and to avoid excess mortality. These goals may be achieved through better control of blood glucose levels and through reductions in other cardiovascular risk factors.

For some patients there may be a trade-off between short- and long-term quality of life, due to treatment related adverse effects.

There is a wide range of possible measures that could be used to evaluate the clinical effects of rosiglitazone therapy.

2.4.1 Glycaemic control

Treatments may be compared in terms of mean blood glucose levels. The UKPDS demonstrated that good control of blood glucose, measured in terms of glycated haemoglobin (HbA_{1c}), reduces the risk of microvascular complications[87], and is thus a reasonable indicator of long-term morbidity and mortality. HbA_{1c} measures the level of blood glucose retrospectively over a two to three month period [48]. Other measures, such as fasting blood glucose (FBG) or fasting plasma glucose (FPG), may also be used to evaluate treatments in the absence of HbA_{1c}.

Treatments may also be assessed by comparison of the proportions of patients whose blood glucose is reduced by more than a given amount (responders), or who successfully achieve target blood glucose levels. Individual patient targets will vary, but indicative targets may be taken from the European guidelines (Table 3).

In addition to direct measures of glycaemic control, measures of insulin resistance and islet B-cell function may be indicative of the ability to maintain good control in the longer term. These factors may be estimated for large samples of patients using mathematical models that combine FPG, insulin and C-peptide levels: the HOMA-S model for insulin resistance and the HOMA-B model for B-cell function [47].

2.4.2 Cardiovascular risk factors

People with type 2 diabetes are subject to a particularly high excess risk of cardiovascular disease. So, it is important that evaluations of oral glucose-lowering drugs should include an assessment of cardiovascular risk factors in addition to measures of blood glucose. Risk factors that may be effected by oral glucose-lowering drugs include:

Lipids

Low-density lipoprotein (LDL) is the best-evidenced indicator of cardiovascular risk. High-density lipoprotein (HDL) is also important, and is independent from LDL cholesterol. A number of other cholesterol measures are often presented. Triglycerides are closely related to HDL cholesterol (though moving in opposite directions). Total cholesterol is really only a valid measure where triglycerides/HDL are in the normal range, thus not in Type 2 diabetes.

Blood pressure

Body weight and the distribution of fat.

2.4.3 Adverse events and tolerability

As with any medication, oral glucose-lowering drugs should be evaluated in terms of the incidence of adverse events and tolerability. Useful indicators

are: the proportion of patients who experience at least one adverse event; the proportion of patients who withdraw from studies because of adverse events; and the overall proportion of patients who withdraw,

The major adverse events associated with glucose-lowering drugs are:

- hypoglycaemia (sulphonylureas and insulin);
- gastrointestinal side effects (metformin and acarbose);
- fluid retention.

2.4.4 Incidence of diabetic complications

A good intermediate measure of health outcome is given by the rates of incidence of various diabetic complications. Given the short time that rosiglitazone has been available, there will not be follow-up of sufficient length to assess the incidence of long-term diabetic complications.

2.4.5 Quality of life, mortality and cost-effectiveness

It is essential to consider the patient's perspective in order to balance short-term clinical effects, the risk of acute and chronic diabetic complications, adverse clinical effects of treatment, and the effect on treatment on lifestyle [80]. A number of diabetes-specific instruments for measuring quality of life or health status have been developed, although no generally recommended battery of well tested quality of life measures is currently available [17]. Alternatively, generic measures, such as the SF-36 or EuroQol, could be used.

Ultimately, this medication should be evaluated in terms of its overall effect on quality of life, mortality and the use of scarce resources. However, because of the newness of the drug, direct measurement of life years gained or quality adjusted life years gained (QALYs) is not possible. Modelling may be used to estimate the overall impact of the introduction of rosiglitazone, but care is needed to ensure that the data and modelling assumptions reflect the likely costs and effects for the population of people with Type 2 diabetes in England and Wales.

3. METHODS

3.1 Identification of studies

A structured search was conducted to identify evidence relating to the clinical effectiveness and cost-effectiveness of rosiglitazone for the treatment of Type 2 diabetes mellitus. This included an electronic search of the following databases:

- MEDLINE
- EMBASE
- Science Citation Index
- Cochrane Database of Systematic Reviews
- Cochrane Controlled Trials Register
- CRD DARE
- CRD NHS EED
- CRD HTA
- OHE HEED

A series of MEDLINE search strategies is listed in Appendix 3. These are designed to identify:

A. Papers relating to rosiglitazone
B. Papers relating to any thiazolidinedione for diabetes
C. Randomised controlled trials
D. Systematic reviews
E. Guidelines
F. Quality of life studies
G. Economic evaluations

Strategy A was run on its own. Strategy B was combined with each of the methodological filters (C to G), which are standard strategies developed by information specialists for use in systematic reviews.

In addition to the electronic search, information was sought from the following sources:

- A search of current research registers (NRR, MRC Clinical Trials, US NIH clinical trials register);
- A search of websites of HTA organisations;
- The reference lists of papers identified were checked;
- Citation searches were run for the included publications.

Data was obtained from the SmithKline Beecham (SB) submission to NICE [74].

3.2 Inclusion criteria

Papers identified through the above search process were first screened for relevance to the study question on the basis of their titles and abstracts. Non-English language review papers were also excluded at this stage.

Full copies of all papers that passed this initial screen were retrieved. Papers were retrieved if their relevance was not obvious from the title and abstract.

Studies referred to in the non-excluded papers were then assessed against the following criteria:

1. *Intervention*
   Rosiglitazone alone or in combination with other oral glucose-lowering medications.
2. *Comparator(s)*
   Any oral glucose-lowering medication or insulin, as mono or combination therapy (but not placebo alone).
3. *Subjects*
   Patients with Type 2 diabetes mellitus.
4. *Outcome measure*
   Main effectiveness/cost-effectiveness data set, at least one of:
   - glycaemic control: HbA_{1c}, FPG
   - cardiovascular risk factors: lipids, blood pressure, weight
   - incidence of diabetic complications
   - quality of life
   - survival
   - QALYs
   - Cost

   Supplementary safety and tolerability data set:
   - incidence of adverse events and tolerability
5. *Study methodology*
   At least one of:
   - systematic review
   - randomised controlled trial
   - economic evaluation

3.3 Quality assessment of included studies

Standard checklists were used to assess the methodological quality of the included randomised controlled trials (Appendix 4) and economic evaluations (Appendix 5).

Since rosiglitazone was a recently developed drug, the number of reported studies was expected to be low. Consequently, studies were not excluded on the basis of publication status or methodological quality.

3.4 Data extraction and synthesis

Continuous data

The following data was extracted from study reports:

(1) Means and standard deviations for continuous outcome variables (***HbA1c, FPG, HDL, LDL, SBP, DBP and weight***) at baseline and at the end of the study period.

(2) Means and standard deviations of the changes in the continuous outcome variables over the study period.

(3) Means, confidence intervals and p-values for differences between the mean changes for each treatment group (rosiglitazone mono or combination therapy) compared to the relevant control group (metformin or sulphonylurea alone).

Where (3) was not reported, it was calculated for (2) using a t-test with the assumption of uniform variance.

Data for the final outcome assessment was entered into the Cochrane RevMan software[3].

Where the study designs and patient populations were similar, and where statistical tests of heterogeneity (chi-squared tests reported by RevMan software) were not significant, data from different studies was pooled (weighted mean difference using fixed effects model).If significant heterogeneity was found, no quantitative meta-analysis was performed.

The main meta-analysis results that are presented below compare outcome measurements at the study endpoint (six months) for the study groups. The weighted mean difference (WMD) and 95% confidence interval (CI) are calculated from the sample means and standard deviations extracted from the study reports. A second analysis was also conducted in which the changes in the outcome variables over the study period were compared. This latter analysis was conducted using the reported means and standard deviations for the change in the variables. Provided the study groups are well matched, these two types of analysis should give similar results. Where this is the case, forest plots showing the results of the former, endpoint analysis are presented. However, where the results of the two meta-analyses differ, the results of both are presented.

Dichotomous data

Data was also extracted on the number of patients who:

- ***responded to treatment*** (HbA1c reduced by at least 0.7%)***,***
- ***achieved glycaemic targets*** (FPG target of 7.8mmol/l or less met by study endpoint),
- ***experienced at least one adverse event,***
- ***withdrew from the study due to adverse events,***
- ***withdrew from the study for any reason***.

The definitions of treatment ‘response’ and ‘success’ were determined by the definitions used in study reports.

The dichotomous data was entered into RevMan. Peto odds ratios and risk differences, with confidence intervals, were calculated.

Where the study designs and patient populations were similar, and where statistical tests of heterogeneity were not significant, data from different studies was pooled.

4. RESULTS

4.1 Evidence of clinical effectiveness

4.1.1 Quantity and quality of research available

Thirteen published literature reviews were identified [5;10;14;15;23;40;53;60;61;63;65;75;82]. A total of 483 references were identified through the various search strategies. The SmithKline Beecham submission [74] included six unpublished study reports [8;39;45;51;62;90]. It also included six protocol synopses [68-73].

Thirteen studies that appeared to be relevant were identified following the initial screen of titles and abstracts. Full references were retrieved for these studies and they were assessed against the inclusion criteria (Table 4). Six RCTs were judged to have met the inclusion criteria.

Supplementary information on safety was available from two other randomised studies:

- SB080, which evaluated the effects of rosiglitazone on cardiovascular function using echocardiography [69;77];
- SB083, which assessed the effects on regional adiposity, intrahepatic fat and muscle insulin sensitivity using magnetic resonance, dual energy X-ray absorptiometry, biopsy and euglycaemic hyperinsulinaemic clamp methods[70].

The overall incidence of adverse events in the phase III clinical trial programme and open label (non-blinded) extension studies was reported in the SmithKline Beecham submission [74] and three abstracts [16;41;64].

Table 3. Assessment of identified studies against inclusion criteria

Study	*Intervention*	*Comparator(s)*	*Subjects*	*Outcome measures*	*Study method*	*Include? (relevant comparisons)*
SB015[36;90;94]	Y (R+S)	Y (S+P)	Y	Y	Y(RCT)	Y (R+S vs. S)
SB020[8;21;68]	Y (R+P)	Y (S+P)	Y	Y	Y(RCT)	Y (R vs. S)
SB079[51]	Y (R+P, R+S)	Y (S+P)	Y	Y	Y(RCT)	Y (R+S vs. S, R vs. S)
SB093[45]	Y (R+P, R+M)	Y (M+P)	Y	Y	Y(RCT)	Y (R+M vs. M, R vs. M)
SB094[30;31;62]	Y (R+M)	Y (M+P)	Y	Y	Y(RCT)	Y (R+M vs. M)
SB096[39]	Y (R+S)	Y (S+P)	Y	Y	Y(RCT)	Y (R+S vs. S)
SB080[69]	Y (R)	Y (S)	Y	Y*	Y (RCT open label)	Supplementary (cardiac safety)
SB083[70]	Y (R)	N (P)	Y	Y*	Y (RCT)	Supplementary (fat distribution)
SB011	Y (R)	N (P)	?	?	Y(RCT)	N (dose-finding, placebo control)
SB024	Y (R)	N (P)	?	?	Y(RCT)	N (dose-finding, placebo control)
SB090	Y (R)	N (P)	?	?	Y(RCT)	N (dose-finding, placebo control)
SB098	Y (R)	N (P)	?	?	Y(RCT)	N (dose-finding, placebo control)

Intervention and comparator: R (rosiglitazone), M (metformin), P (placebo)
* Efficacy data collected, but not reported.

Methodological quality of included trials

The results of the assessment of methodological quality for the included randomised-controlled trials are shown in Table 5. The methodological quality and standard of reporting of the trials was very high. The studies all had a maximum Jadad score of five.

The main analyses presented (and reported below) were based on an "intention to treat" population. This included all patients who had received at least one dose of double-blind medication and who had at least one post-treatment measurement of efficacy. Where patients were lost to follow-up efficacy measurements were extrapolated forward from the last available measurement. Statistical analysis was conducted using analysis of covariance (ANCOVA) models, where parametric analysis was appropriate, or non-parametric Wilcoxon Rank Sum tests. In each case power calculations were used to determine the appropriate sample sizes, and the target number of patients were achieved.

Table 4. Methodological quality of included trials

See Appendix 4 for definition of criteria and meaning of responses.

Study	Randomisation procedure		Allocation concealment	Methods of blinding				Completeness of trial			Jadad score	Power calculations/ target achieved?
	A1	A2	B1	C1	C2	C3	C4	D1	D2	% withdrawn by study group		
SB015[36;90;94]	Y	A	A	Y	Y	Y	Y	Y	Y *	A 36% B 28% C 24%	5	Y/Y
SB020[8;21;68]	Y	A	A	Y	Y	Y	Y	Y	Y *	A 16% B 24% C 17%	5	Y/Y
SB079[51]	Y	A	A	Y	Y	Y	Y	Y	Y *	A 33% B 56% C 21%	5	Y/Y
SB093[45]	Y	A	A	Y	Y	Y	Y	Y	Y *	A 26% B 38% C 15%	5	Y/Y
SB094[30;31;62]	Y	A	A	Y	Y	Y	Y	Y	Y *	A 19% B 15% C 16%	5	Y/Y
SB096[39]	Y	A	A	Y	Y	Y	Y	Y	Y *	A 18% B 18% C 12%	5	Y/Y

* Intention to treat (ITT) analysis included all randomised patients who had at least one dose of double-blind medication and at least one post-treatment efficacy measurement.

Study design

Aspects of study design are described in Table 6. The criteria for inclusion and exclusion of patients varied between studies. All were restricted to patients with Type 2 diabetes mellitus, with endogenous insulin production indicated by a C-peptide level of at least 0.27nmol/l. Patients with satisfactory blood glucose levels (less than 7.5% HbA1c or less than 7.0 or 7.8 mmol/l FPG) were not included. Patients with very high levels of blood glucose (FPG greater than 15 or 16.7) were excluded, along with women of childbearing potential, patients with clinically significant diabetic complications, renal, hepatic or haematological impairment or heart disease.

After initial assessment and run-in periods (during which patients were withdrawn from other medications and the dose of comparator medications was titrated if necessary), patients were randomised to one of three treatment arms. Patients then received double-blind medication for six months (one year for SB020). Patients who wished to continue were then entered on to open label extension studies.

For all of the studies, the primary measure of efficacy was the between-group difference in mean change in HbA1c between baseline and study endpoint. A range of secondary outcome measures was used, including: indicators of blood glucose (FPG and fructosamine), endogenous insulin (plasma insulin and C-peptide), and lipids (total cholesterol, HDL, LDL and other fractions). The study groups were also compared in terms of the proportions of patients who responded to treatment (HbA1c reduced by 0.7% or more or FPG reduced by 30mg/dl or more) and the proportions of patients who achieved target blood glucose levels (<140mg/dl). Three studies reported HOMA estimates of insulin resistance and beta-cell function [8;31;94]. Assessments also included weight and waist-to-hip ratio, vital signs (blood pressure and heart rate), clinical laboratory tests to ensure safety (including urinary albumin) and the incidence of adverse events.

Table 5. Study design of included trials

Study	*Treatment dates*	*Countries (centres)*	*Subjects*	*Treatment groups (n randomised)*	*Measurements*	*Study procedure*
SB015[36;90;94]	8/96 to 3/98	Europe (60) (54)* UK (n=213)	Type 2, on S therapy (glibenclamide, glicazide or glipizide) for at least 6 months, constant dose for at least 2 months, HbA1c>=7.5%, FPG<=15mmol/l, C-peptide>=0.27nmol/l.	A) S (prior dose) + P (n=198) B) S (prior dose) + R (1mg bd) (n=205) C) S (prior dose) + R (2mg bd) (n=190)	HbA1c, FPG, fructosamine, insulin, C-peptide, HOMA, albumin excretion rate and concentration, lipids, weight, waist-to-hip ratio, vital signs, adverse events, safety tests and pharmacokinetics.	2/4 week run-in on S + P, 26-week study period, 2 week follow-up or open label extension study.
SB020[8;21;68]	10/96 to 5/98	Europe (71) UK (7)	Type 2, who could be withdrawn from oral antidiabetic therapy during run-in period, FPG>=7.0mmol/l FPG<=15mmol/l C-peptide>=0.27nmol/l	A) S (titrated glibenclamide) (n=207) B) R (2mg bd) (n=200) C) R (4mg bd) (n=191)	HbA1c, FPG, fructosamine, C-peptide, insulin, HOMA, urinary albumin, lipids, weight, vital signs, adverse events and safety tests, and pharmacokinetics.	6 week run-in during which other oral treatments withdrawn and glibenclamide optimally titrated, study period one year, 2 week follow-up visit or open label extension study.
SB079[51]	4/97 to 3/98	US (41)	Type 2, on maximum dose of glibenclamide for >=30 days, FPG>=7.8mmol/l FPG<=16.7mmol/l C-peptide>=0.27nmol/l	A) S (10mg bd glibenclamide) + P (n=106) B) R (2mg bd) + P (n=104) C) S (10mg bd glibenclamide) + R (2mg bd) (n=99)	HbA1c, FPG, fructosamine, insulin, C-peptide, leptin, and lipids, weight, waist-to-hip ratio, vital signs, adverse events and safety tests.	4 week run-in on S + P, 26 week study period, 7-10 day follow-up or open label extension study.

Study	*Treatment dates*	*Countries (centres)*	*Subjects*	*Treatment groups (n randomised)*	*Measurements*	*Study procedure*
SB093[45]	6/97 to 4/98	US (34)	Type 2, on maximum dose of M during run-in period, FPG>=7.8mmol/l FPG<=16.7mmol/l C-peptide>=0.27nmol/l	A) M (2.5g/day) + P (n=109) B) R (4mg bd) + P (n=107) C) M(2.5g/day) + R (4mg bd) (n=106)	HbA1c, FPG, fructosamine, insulin, C-peptide, leptin, lipids, weight, waist-to-hip ratio, vital signs, adverse events and safety tests.	0-6 weeks M titration to bring up to maximal dose, 4 week run-in on M + P, 26-week study period, 7-10 day follow-up or open label extension study.
SB094[30; 31;62]	4/97 to 3/98	US (36)	Type 2, on maximum dose of M during run-in period, FPG>=7.8mmol/l FPG<=16.7mmol/l C-peptide>=0.27nmol/l	A) M (2.5g) + P (n=116) B) M (2.5g) + R (4mg od) (n=119) C) M (2.5g) + R (8mg od) (n=113)	HbA1c, FPG, fructosamine, insulin, c-peptide, HOMA-S, HOMA-B, lipids, weight, waist-to-hip ratio, vital signs, adverse events and safety tests.	0-3 weeks M titration to bring up to maximal dose, 4 week run-in on M + P, 26 week study period, 7-10 day follow-up or open label extension study.
SB096[39]	4/97 to 3/98	US (33)	Type 2, on at least half dose of glibenclamide, FPG>=7.8mmol/l FPG<=16.7mmol/l C-peptide>=0.27nmol/l	A) S (>=10mg/d glibenclamide) + P (n=115) B) S (>=10mg/d glibenclamide) + R(2mg od) (n=115) C) S (>=10mg/d glibenclamide) + R(4mg od) (n=116)	HbA1c, FPG, fructosamine, insulin, c-peptide, HOMA-S, HOMA-B, lipids, weight, waist-to-hip ratio, vital signs, adverse events and safety tests.	4 week run-in on S + P, 26 week study period, 1 week follow-up or open label extension study.

* Centres randomising patients

Characteristics of study populations

The characteristics of the patients in the included trials are described in Table 7. The average age of patients was around sixty years. The majority of patients (around 60-70%) were male. Ethnicity varied between the studies, with less than 5% of patients in the two European studies (SB015 and SB020) and around 30-20% of patients in the US studies from non-white ethnic groups.

The study populations differed according to prior therapy, mean duration of diabetes and mean baseline blood glucose levels. Study SB015 was (largely) restricted to patients on oral monotherapy. Studies SB079 and SB096 included only patients who had had prior oral monotherapy or combination therapy. SB093 and SB094 included patients with prior oral monotherapy and combination therapy, but also included a small number of patients (around 5%) who had not previously taken oral glucose-lowering drugs. Study SB020 included a much higher proportion of patients (around 40%) who had only had lifestyle advice before.

Table 6. Characteristics of patients in included trials

Study and treatment groups	*Age, mean (sd) years*	*Sex %F*	*Ethnicity % white*	*BMI mean (sd) kg/m²*	*Years with diabetes mean (sd)*	*Prior therapy (%)*				HbA1c mean(sd) %
						Lifestyle only	Oral monotherapy	Oral combination	Insulin	
SB015[36;90;94]										
A) S+P	61.9 (9.1)	42.7	96.9	28.1 (4.1)	9.0 (6.5)		99.5	0.5		9.21 (1.3)
B) S+R(2mg)	61.0 (9.4)	37.2	95.5	28.0 (3.9)	8.7 (6.3)		100	0		9.20 (1.2)
C) S+R(4mg)	60.6 (8.7)	44.8	98.4	28.3 (3.9)	9.1 (7.1)		100	0		9.23 (1.2)
SB020[8]										
A) S	60.1 (8.34)	29.6	99.5	28.7 (3.9)	6.4 (6.9)	37.9	53.2	8.9		8.2 (1.3)
B) R(4mg)	60.4 (8.23)	31.8	98.5	28.7 (3.7)	5.9 6.0)	42.1	48.2	9.7		8.1 (1.3)
C) R(8mg)	60.6 (9.27)	42.3	96.8	28.8 (3.7)	6.0 (7.0)	38.1	50.3	11.6		8.2 (1.4)
SB079[51]										
A) S+P	58.5 (9.1)	33.3	68.7	30.4 (4.9)	8.8 (7.0)		59.6	40.4		9.3 (1.4)
B) R(4mg) +P	59.1 (9.8)	36.4	69.7	29.8 (4.5)	9.4 (8.6)		60.6	39.4		9.1 (1.1)
C) S+R(4mg)	57.7 (9.6)	30.6	70.4	30.6 (4.7)	8.7 (6.0)		65.3	34.7		9.2 (1.3)
SB093[45]										
A) M+P	59.5 (9.6)	33.0	73.6	31.1 (4.4)	7.4 (5.9)	3.8	49.1	47.2		8.8 (1.4)
B) R(8mg)+P	58.8 (10.3)	46.3	82.1	30.7 (4.3)	7.1 (6.5)	6.3	50.5	43.2		8.7 (1.3)
C) M+R(8mg)	57.8 (9.7)	40.0	82.9	30.3 (4.5)	7.7 (8.4)	3.8	36.2	60.0		8.7 (1.4)
SB094[30;31;62]										
A) M+P	58.8 (9.2)	25.7	81.4	30.3 (4.4)	7.3 (5.7)	4.4	48.7	46.9		8.6 (1.3)
B) R(4mg)+M	57.5 (10.5)	37.9	80.2	30.2 (4.2)	7.5 (6.3)	6.0	39.7	54.3		8.9 (1.3)
C) R(8mg)+M	58.3 (8.8)	31.8	77.3	29.8 (3.9)	8.3 (6.3)	4.5	43.6	51.8		8.9 (1.5)
SB096[39]										
A) S+P	60.3 (9.1)	33.0	78.3	30.2 (4.1)	9.4 (9.1)		73.9	26.1		8.9 (1.4)
B) S+R(2mg)	59.3 (8.8)	30.4	73.9	30.1 (4.3)	8.3 (6.8)		65.2	34.8		9.3 (1.5)
C) S+R(4mg)	60.2 (9.7)	34.5	80.2	30.7 (4.3)	7.9 (6.5)		67.2	32.8		9.1 (1.5)

Available comparisons and study homogeneity

The included studies relate to four relevant comparisons.

Licensed Indications

I) Rosiglitazone in combination with metformin compared to metformin alone (**R+M vs. M**) - SB093, SB094.

II) Rosiglitazone in combination with a sulphonylurea compared to a sulphonylurea alone (**R+S vs. S**) - SB015, SB079 and SB096.

Unlicensed Indications

III) Rosiglitazone alone compared to metformin alone (**R vs. M**) - SB093.

IV) Rosiglitazone alone compared to a sulphonylurea alone (**R vs. S**) - SB020 and SB079.

The two, metformin combination studies (SB093 and SB094) had very similar study design and patient populations. In both cases all patients were on maximum dose of metformin (2.5g per day). The combination arm in SB093 (C) also received 8mg per day of rosiglitazone. The two combination arms in SB094 received 4mg (B) and 8mg (C) of rosiglitazone per day. Patients received double-blind medication for six months and similar outcome measurements were taken. Only about 5% of patients had not previously received oral-glucose lowering drugs. Roughly equal numbers of the remaining patients had previously had only monotherapy or combination therapy.

The sulphonylurea combination studies (SB015, SB079 and SB096) were less homogeneous. In SB015 patients had been on a sulphonylurea (glibenclamide, glicazide or glipizide) for at least six months, with constant dose for at least two months. This constant dose was maintained throughout the study period. SB079 and SB096 only included patients on glibenclamide: on maximum dose (20mg per day) in SB079; and on at least half of the maximum dose in SB096. The three studies used a similar range of outcome measurements over a six-month study period. The patient populations were similar in terms of demographics, except that SB015 had a much lower proportion of patients from non-white ethnic populations. Despite rather different inclusion criteria, the study populations were also similar in length of diabetes and baseline blood glucose levels. None of the three studies included patients previously managed by diet and exercise alone, but they differed in the proportion of patients who had previously had oral combination therapy (virtually none in SB015, about 40% in SB079 and about 30% in SB096).

The studies SB079 and SB093 were designed to assess the efficacy of rosiglitazone combination therapy in comparison to a sulphonylurea and metformin, respectively. Though they each had a rosiglitazone monotherapy arm, they can not be used to compare the efficacy of rosiglitazone monotherapy against conventional oral monotherapy. This is because of inherent biases against rosiglitazone monotherapy in these trials. First, the patients were pre-selected to tolerate metformin/glibenclamide, but not rosiglitazone. Second, patients randomised to rosiglitazone had reduced glycaemic control over the first 6-8 weeks of the study period, when they were withdrawn from prior metformin/glibenclamide before the onset of action of rosiglitazone.Thus, valid information was only available from one RCT (SB020) on the relative efficacy of rosiglitazone monotherapy compared directly with conventional oral monotherapy. One other head-to-head randomised

comparison of rosiglitazone monotherapy against a sulphonylurea has been conducted (SB080), however no information was available on the blood glucose results of this trial.

The current license indication does not include rosiglitazone monotherapy. Because of this, we have decided not to present the results of the SB020 trial. The results reported below thus relate purely to the licensed use of rosiglitazone in combination with metformin or a sulphonylurea.

4.1.2 Effect on blood glucose levels

The primary outcome variable in all of the included studies was mean change in HbA1c between baseline and study endpoint. Sample sizes were based upon calculations for this variable. The effects of rosiglitazone on blood glucose levels, as measured by $HbA1_c$ and FPG, are shown in Table 8 and Table 9. The proportions of patients who responded to therapy (reduction of at least 0.7% in HbA1c) and who successfully achieved target blood glucose levels (140mg/dl or less) are shown in Table 10.

Addition of rosiglitazone to metformin

The addition of rosiglitazone to metformin leads to significantly greater reductions in blood glucose over six months (Table 8 and Table 9) and to significantly lower blood glucose levels at six months (Figure 3 and Figure 4).

Figure 3. R+M vs. M comparison: HbA1c at six months

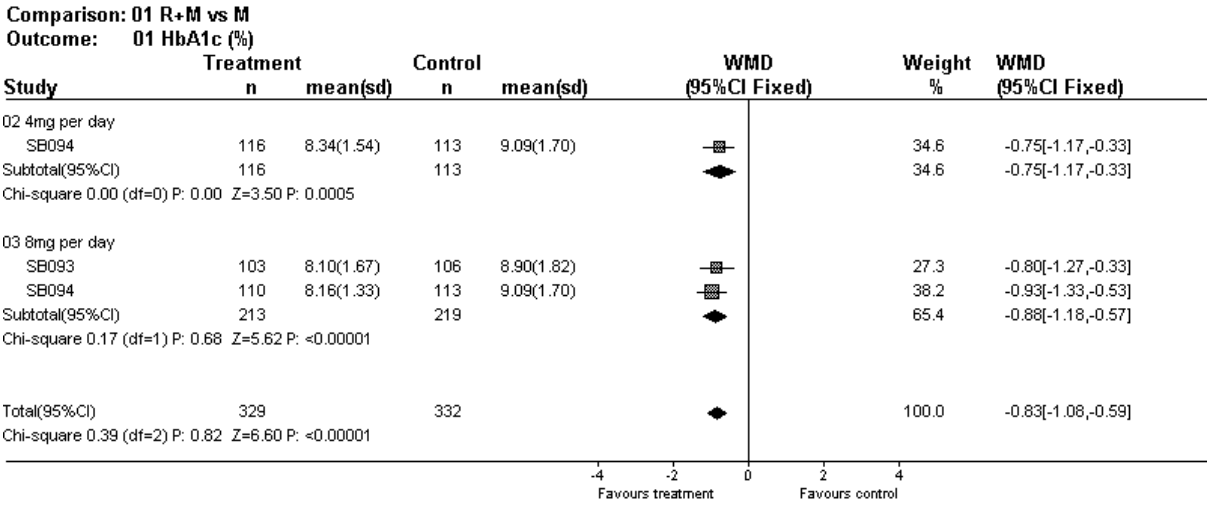
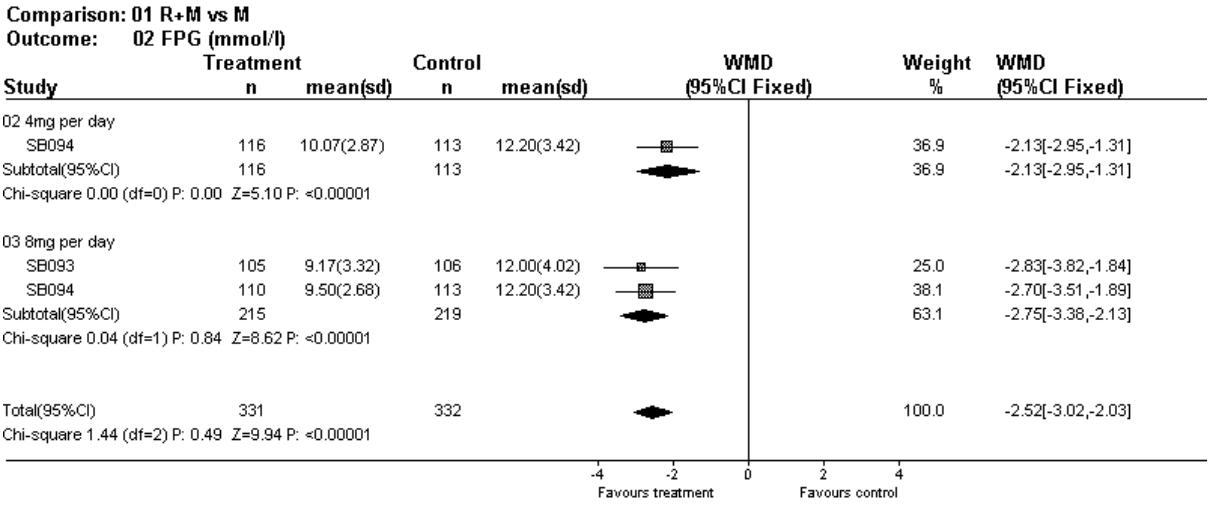


Figure 4. R+M vs. M comparison: FPG at six months

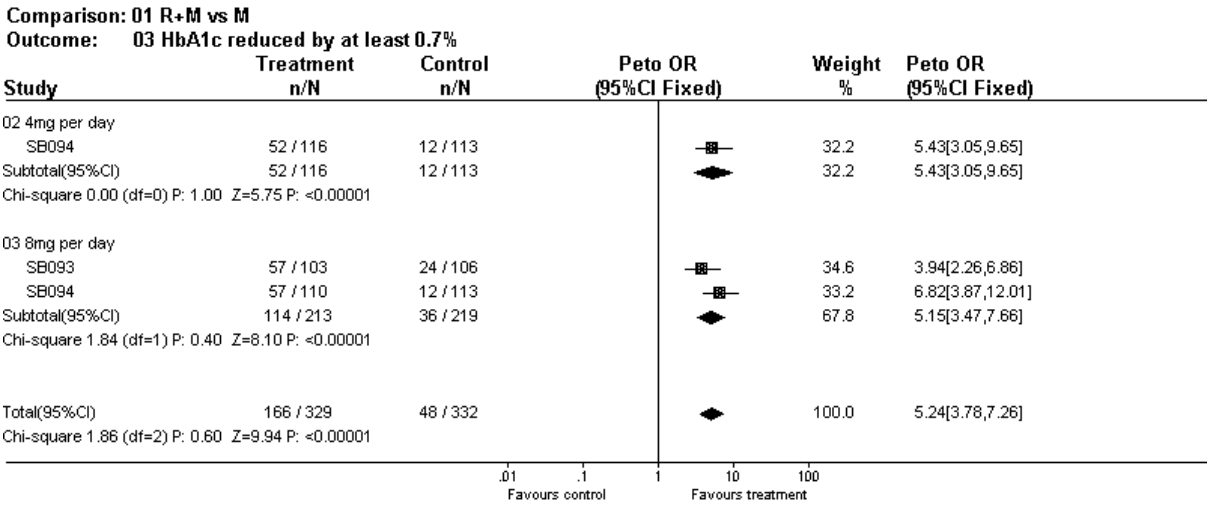


The studies SB093 and SB094 were homogeneous in design and population and there was no statistical evidence of heterogeneity. There was no evidence of a significant difference in outcome by rosiglitazone dose (4mg or 8mg per day). Thus data was pooled within and between the dose sub-groups.

Overall the meta-analysis shows a significant reduction of 0.8% (0.6-1.1%) in HbA1c and of 2.5mmol/l (2.0 -3.0 mmol/l) in FPG.

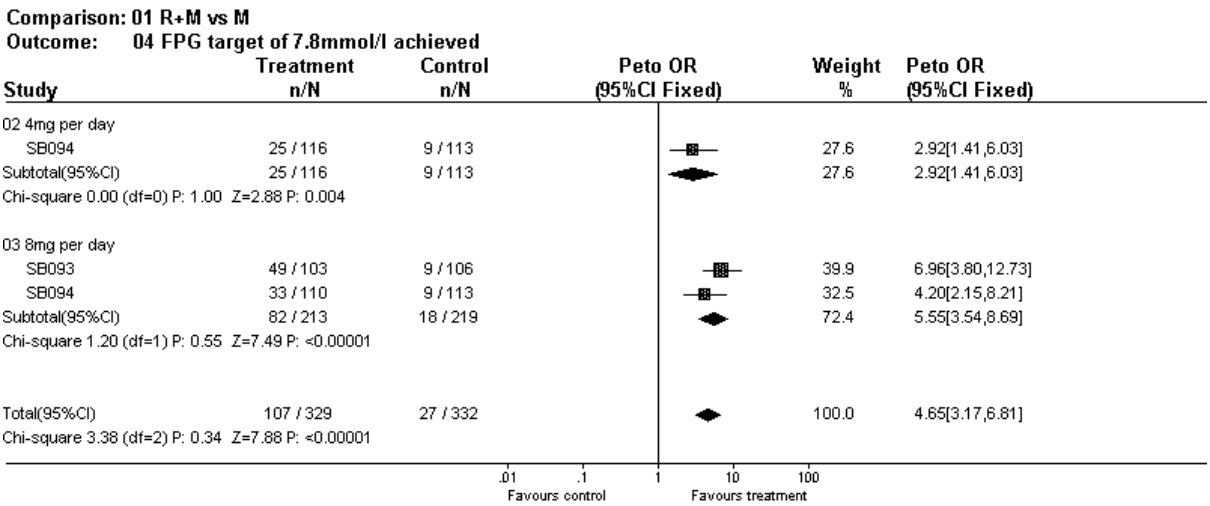
A significantly higher proportion of patients who received rosiglitazone/metformin combination therapy responded to treatment compared to those who received metformin alone (Table 9): odds ratio 5.2 (3.8-7.3) (Figure 5). The proportion of patients who responded increased by 36% (30-43%) with the addition of rosiglitazone to metformin.

Figure 5. R+M vs. M comparison: proportion of responders at six months



The proportion of patients who met the FPG target of 7.8mmol/l was also significantly higher with rosiglitazone/metformin combination therapy than with metformin alone (Figure 6). The overall risk difference was 24% (19-30%).

Figure 6. R+M vs. M comparison: proportion of successes at six months



Most of the glucose-lowering effect of adding rosiglitazone to metformin therapy was observed within the first 8 weeks of treatment (84 - 89% of maximal effect within the first 8 weeks of treatment) [74]. Evidence from the ongoing open label extension studies suggests that the six-month improvements in glycaemic control reported above are maintained for up to two years [74].

Addition of rosiglitazone to sulphonylureas

The addition of rosiglitazone to sulphonylureas also leads to significantly greater improvements in blood glucose levels at six months (Figure 7 and Figure 8). Although there are some differences in study design and patient population between the studies SB015, SB079 and SB096, statistical tests of heterogeneity suggest that it is appropriate to pool study results within (but not between) the rosiglitazone dose levels (2mg and 4mg per day). A significant improvement in HbA1c was seen with both dosages: 0.5% (0.2-0.7%) with 2mg and 1.1% (0.9-1.3%) with 4mg (Figure 7). Similarly, FPG was significantly lower with both rosiglitazone doses: 1.4mmol/l (0.9-1.8mmol/l) with 2mg and 2.6mmol/l (2.1-3.0mmol/l) with 4mg (Figure 8). Thus there is evidence of a clear dose-related response.

Figure 7. R+S vs. S comparison: HbA1c at six months

Comparison: 02 R+S vs S
Outcome: 01 HbA1c (%)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 2mg per day							
SB015	199	8.80(1.41)	192	9.40(1.63)		65.8	-0.60[-0.90,-0.30]
SB096	115	9.33(1.73)	115	9.55(1.51)		34.2	-0.22[-0.64,0.20]
Subtotal(95%CI)	314		307			100.0	-0.47[-0.72,-0.22]
Chi-square 2.07 (df=1) P: 0.15 Z=3.75 P: 0.0002							
02 4mg per day							
SB015	183	8.30(1.39)	192	9.40(1.63)		51.7	-1.10[-1.41,-0.79]
SB079	98	8.70(1.60)	99	10.10(1.76)		22.0	-1.40[-1.87,-0.93]
SB096	116	8.79(1.81)	115	9.55(1.51)		26.3	-0.76[-1.19,-0.33]
Subtotal(95%CI)	397		406			100.0	-1.08[-1.30,-0.86]
Chi-square 3.93 (df=2) P: 0.14 Z=9.58 P: <0.00001							

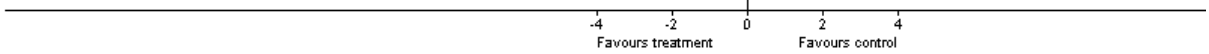
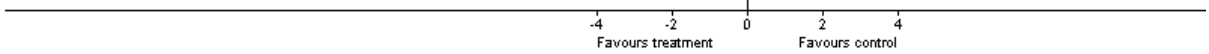


Figure 8. R+S vs. S comparison: FPG at six months

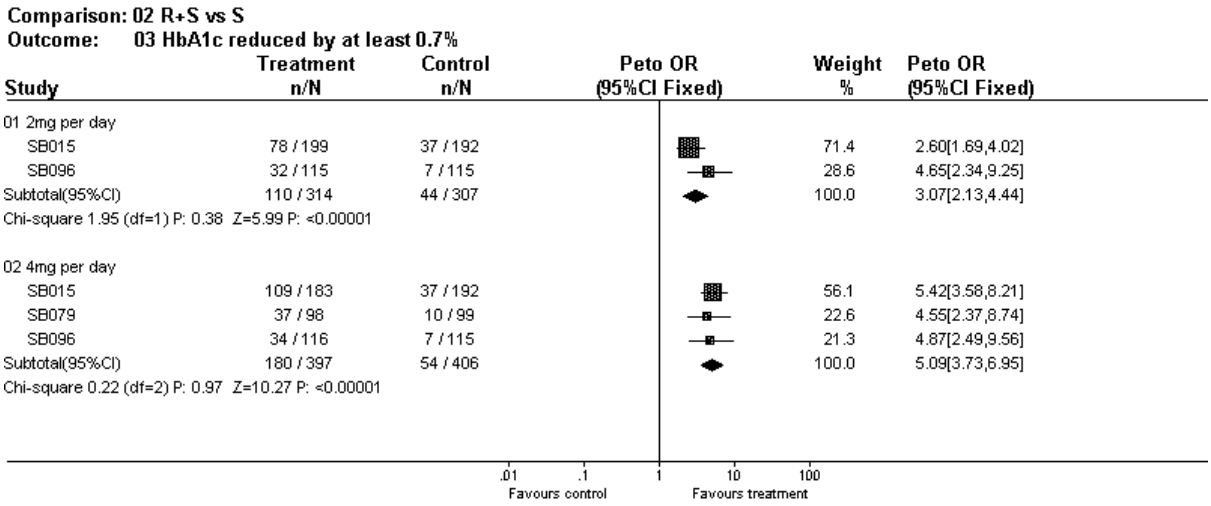
Comparison: 02 R+S vs S
Outcome: 02 FPG (mmol/l)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 2mg per day							
SB015	199	10.36(2.74)	192	11.83(3.06)		67.1	-1.47[-2.05,-0.89]
SB096	114	11.75(3.21)	115	12.88(3.15)		32.9	-1.13[-1.95,-0.31]
Subtotal(95%CI)	313		307			100.0	-1.36[-1.83,-0.89]
Chi-square 0.44 (df=1) P: 0.51 Z=5.64 P: <0.00001							
02 4mg per day							
SB015	183	9.31(2.89)	192	11.83(3.06)		54.5	-2.52[-3.12,-1.92]
SB079	98	10.58(3.55)	99	13.53(3.42)		20.8	-2.95[-3.92,-1.98]
SB096	116	10.46(3.76)	115	12.88(3.15)		24.7	-2.42[-3.31,-1.53]
Subtotal(95%CI)	397		406			100.0	-2.58[-3.03,-2.14]
Chi-square 0.72 (df=2) P: 0.70 Z=11.40 P: <0.00001							



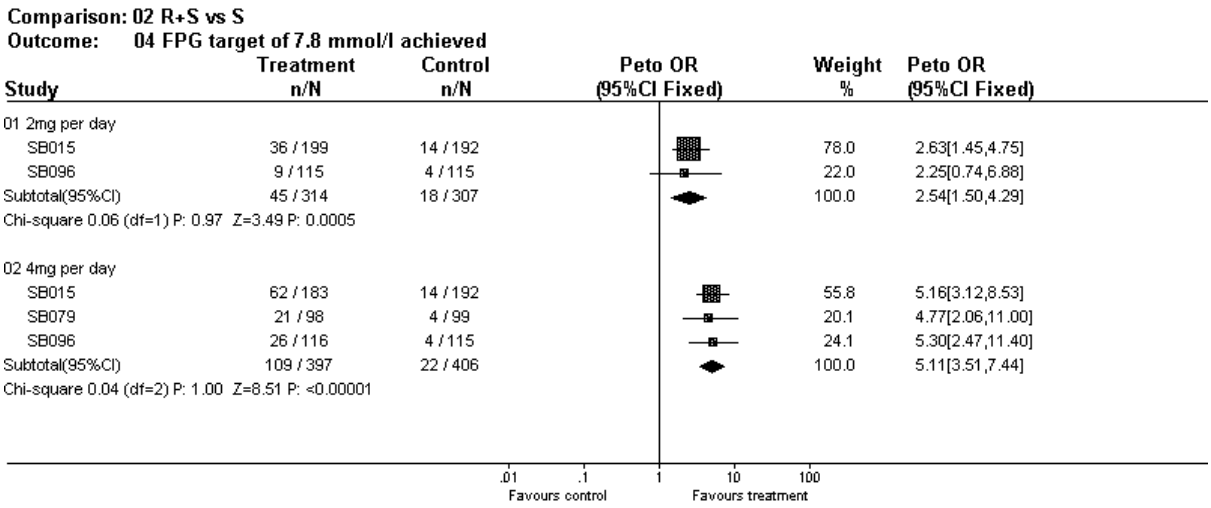
The addition of rosiglitazone (2mg or 4mg) to sulphonylureas increased the proportion of patients who responded to treatment (Figure 9). The estimated size of the risk difference was 21% (14-27%) for 2mg rosiglitazone and 32% (27-38%) for 4mg rosiglitazone.

Figure 9. R+S vs. S comparison: proportion of responders at six months



Meta-analysis suggests that an additional 8% (4-13%) of patients reached the target blood glucose level with 2mg rosiglitazone, and that an additional 22% (17-27%) reached this target with 4mg rosiglitazone (Figure 10).

Figure 10. R+S vs. S comparison: proportion of successes at six months



The majority of the glucose-lowering effect of rosiglitazone/sulphonylurea combination therapy was observed within the first 4 weeks of treatment (71 - 92% of the maximal effect was obtained within first 4 weeks) [74]. Evidence from the ongoing open label extension studies suggests that the six-month improvements in glycaemic control are maintained for up to two years [74].

Table 7. Effect on glycated haemoglobin

		HbA1c (%)								
		Baseline		Final*		Change &		Difference ~		
Study	n	mean	sd	mean	sd	mean	sd	mean	95% CI	p value
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN										
SB093										
A) M	106	8.80	1.39	8.90	1.82	0.10	1.18	-	- -	-
C) M+R(8mg)	103	8.70	1.41	8.10	1.67	-0.70	1.30	-0.8	-1.2 -0.5	<0.0001 §
SB094										
A) M	113	8.64	1.28	9.09	1.70	0.45	1.16	-	- -	-
B) M+R(4mg)	116	8.89	1.31	8.34	1.54	-0.56	1.29	-0.97	-1.32 -0.63	<0.0001 †
C) M+R(8mg)	110	8.94	1.45	8.16	1.33	-0.78	1.22	-1.18	-1.53 -0.83	<0.0001 †
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA										
SB015										
A) S	192	9.21	1.30	9.40	1.63	0.20	1.11	-	- -	-
B) S+R(2mg)	199	9.20	1.19	8.80	1.41	-0.50	1.05	-0.59	-0.8 -0.4	<0.0001 †
C) S+R(4mg)	183	9.23	1.18	8.30	1.39	-0.90	1.10	-1.03	-1.3 -0.8	<0.0001 †
SB079										
A) S	99	9.30	1.43	10.10	1.76	0.90	1.17	-	- -	-
C) S+R(4mg)	98	9.20	1.34	8.70	1.60	-0.50	1.14	-1.4	-1.7 -1.1	<0.0001 §
SB096										
A) S	115	8.94	1.40	9.55	1.51	0.55$	-	-	- -	-
B) S+R(2mg)	115	9.33	1.54	9.33	1.73	0.00$	-	-0.6	-0.9 -0.3	<0.0001 #
C) S+R(4mg)	116	9.10	1.48	8.79	1.81	-0.30$	-	-0.8	-1.1 -0.6	<0.0001 #

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
§ Analysis of covariance procedure with heterogeneous variance across treatments.
† Analysis of covariance procedure with homogeneous variance across treatments.
# Wilcoxon rank sum test.
$ Median

Table 8. Effect on fasting plasma glucose

		FPG (mmol/l)									
		Baseline		Final*		Change &		Difference ~			
Study	n	mean	sd	mean	sd	mean	sd	mean	95% CI		p value
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN											
SB093											
A) M	106	11.64	3.22	12.00	4.02	0.36	2.99	-	-	-	-
C) M+R(8mg)	105	12.05	2.99	9.17	3.32	-2.88	3.05	-3.1	-3.9	-2.3	<0.0001 †
SB094											
A) M	113	11.87	2.91	12.20	3.42	0.33	2.55	-	-	-	-
B) M+R(4mg)	116	11.90	3.17	10.07	2.87	-1.83	2.65	-2.2	-2.9	-1.5	<0.0001 †
C) M+R(8mg)	110	12.19	3.05	9.50	2.68	-2.69	2.93	-2.9	-3.7	-2.2	<0.0001 †
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA											
SB015											
A) S	192	11.51	2.40	11.83	3.06	0.32	2.74	-	-	-	-
B) S+R(2mg)	199	11.31	2.51	10.36	2.74	-0.95	2.69	-1.3	-1.9	-0.8	<0.0001 †
C) S+R(4mg)	183	11.40	2.73	9.31	2.89	-2.09	2.62	-2.4	-3.0	-1.9	<0.0001 †
SB079											
A) S	99	12.20	3.10	13.53	3.42	1.33	2.82	-	-	-	-
C) S+R(4mg)	98	12.30	3.05	10.58	3.55	-1.72	3.36	-3.1	-4.0	-2.2	<0.001 †
SB096											
A) S	115	11.61	3.15	12.88	3.15	1.28	2.67	-	-	-	-
B) S+R(2mg)	114	12.33	2.98	11.75	3.21	-0.58	2.85	-1.6	-2.4	-0.7	<0.0001 †
C) S+R(4mg)	116	11.85	2.80	10.46	3.76	-1.40	3.45	-2.6	-3.4	-1.8	<0.0001 †

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
† Analysis of covariance procedure with homogeneous variance across treatments.

To convert from md/dl units to mmol/l reported figures were multiplied by 0.0555.

Table 9. Number of treatment 'responders' and 'successes'

Study	n	HbA1c reduced by at least 0.7% N	HbA1c reduced by at least 0.7% %	FPG<140mg/dl target met N	FPG<140mg/dl target met %
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN					
SB093					
A) M	106	24	23%	9	8%
C) M+R(8mg)	103	57	55%	49	48%
SB094					
A) M	113	12	11%	9	8%
B) M+R(4mg)	116	52	45%	25	22%
C) M+R(8mg)	110	57	52%	33	30%
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA					
SB015					
A) S	192	37	19%	14	7%
B) S+R(2mg)	199	78	39%	36	18%
C) S+R(4mg)	183	109	60%	62	34%
SB079					
A) S	99	10	10%	4	4%
C) S+R(4mg)	98	37	38%	21	21%
SB096					
A) S	115	7	6%	4	3%
B) S+R(2mg)	115	32	28%	9	8%
C) S+R(4mg)	116	34	29%	26	22%

4.1.3 Effect on insulin resistance and Beta-cell function

The effect of rosiglitazone/metformin combination therapy on insulin sensitivity (HOMA-S) and beta-cell function (HOMA-B) has been reported for study SB094 [31]. The median baseline HOMA-S values ranged from 47 to 49 for the study arms. They increased significantly by 1.7 units in the 4mg group and by 3.8 units in the 8mg rosiglitazone group. A significant increase in HOMA-B was also observed: from median baseline values of 33 to 36, they increased by 10.3 and 13.7 units.

Insulin sensitivity and beta-cell function for the rosiglitazone/sulphonylurea combination has been reported for SB015 [94]. For the sulphonylurea control group mean insulin resistance increased by 15% ($p<0.05$) over the six month study period. However, mean insulin resistance fell by 2.6% (not significant) for the 2mg rosiglitazone group, and by 17.4% ($p<0.00001$) for the 4mg group. Mean beta-cell function increased by 8.6% ($p<0.05$) for the sulphonylurea group, but fell by 22.8% ($p<0.00001$) and 72% ($p<0.001$), respectively, for the 2mg and 4mg rosiglitazone groups.

A significant reduction in insulin resistance has also been reported [74] for rosiglitazone monotherapy compared to placebo) from study (SB083) [70].

4.1.4 Effect on lipids

Addition of rosiglitazone to metformin

The addition of rosiglitazone to metformin leads to significantly higher increases in HDL and LDL cholesterol over six months compared to metformin alone (Table 10 and Table 11). HDL cholesterol was 0.13mmol/l (0.08-0.18mmol/l) higher at six months for the patients who received rosiglitazone/metformin than for the control group (Figure 11). A rather larger difference in LDL cholesterol at six months, 0.31mmol/l (0.16-0.45mmol/l), was observed (Figure 12).

Figure 11. R+M vs. M comparison: HDL cholesterol at six months

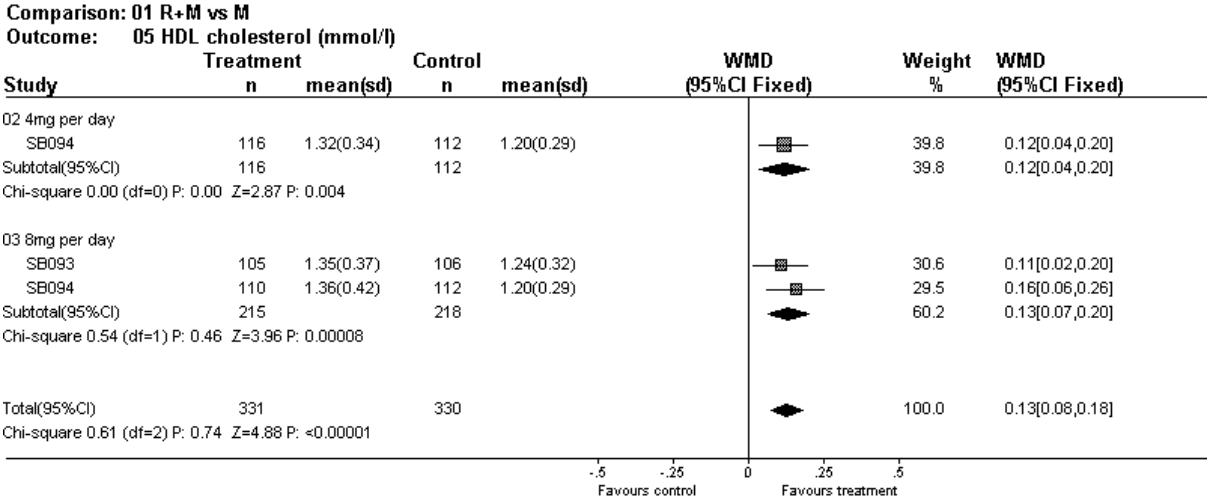
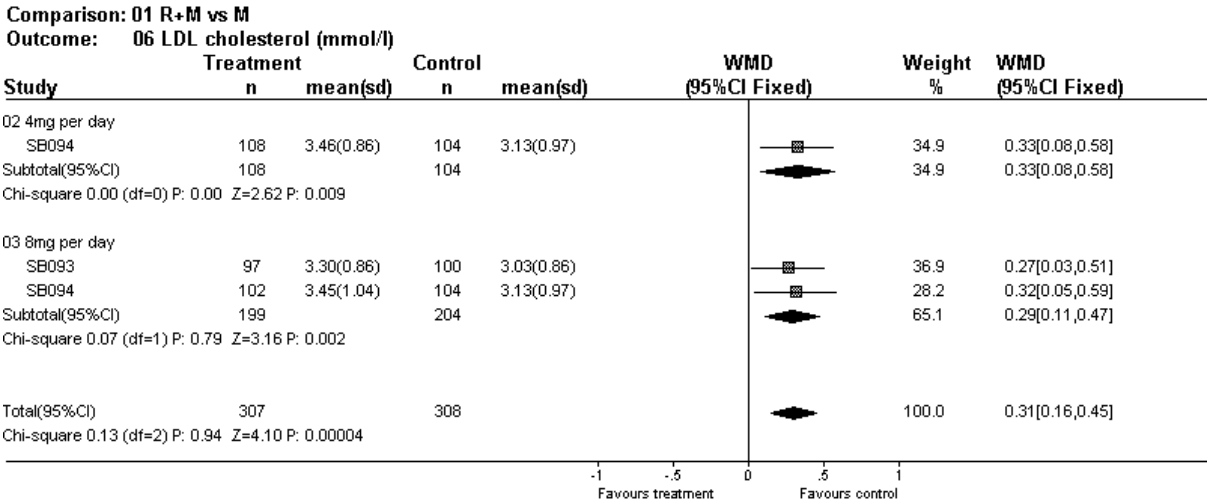


Figure 12. R+M vs. M comparison: LDL cholesterol at six months



Addition of rosiglitazone to sulphonylureas

The addition of rosiglitazone to sulphonylureas led to a significantly greater increase in HDL cholesterol for the 4mg group (Table 10 and Figure 13). However, changes in HDL levels were not significantly different for the 2mg group. Significantly greater increases in LDL cholesterol were observed for both rosiglitazone groups (Table 11 and Figure 14).

Figure 13. R+S vs. S comparison: change in HDL cholesterol over six months

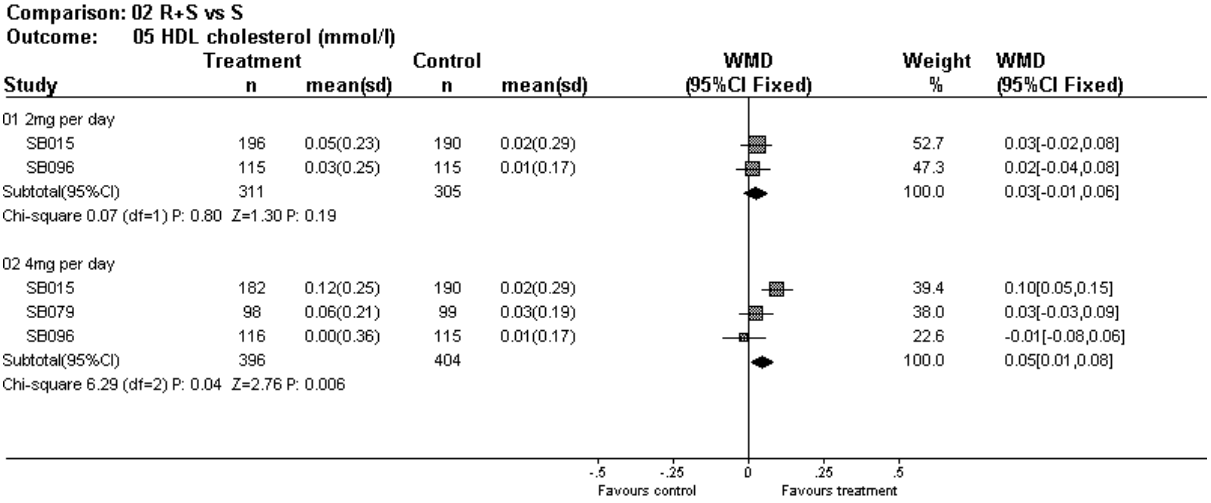
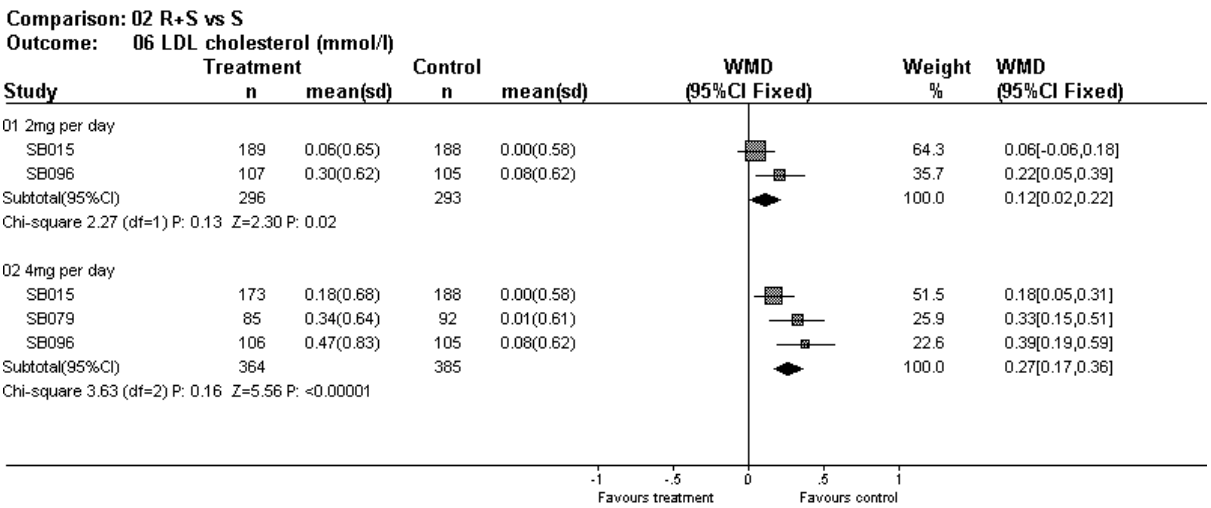


Figure 14. R+S vs. S comparison: change in LDL cholesterol over six months



There was no significant difference in HDL cholesterol levels at six months for the rosiglitazone/sulphonylurea combination groups (2mg or 4mg) compared to the groups who received sulphonylurea alone (Figure 15). There was no clear evidence of an effect on LDL cholesterol levels due to the addition of 2mg rosiglitazone to sulphonylurea therapy (Figure 16). However, with 4mg rosiglitazone, LDL cholesterol levels were significantly higher than for the controls, a difference of 0.2mmol/l (0.1-0.3mmol/l).

Figure 15. R+S vs. S comparison: HDL cholesterol at six months

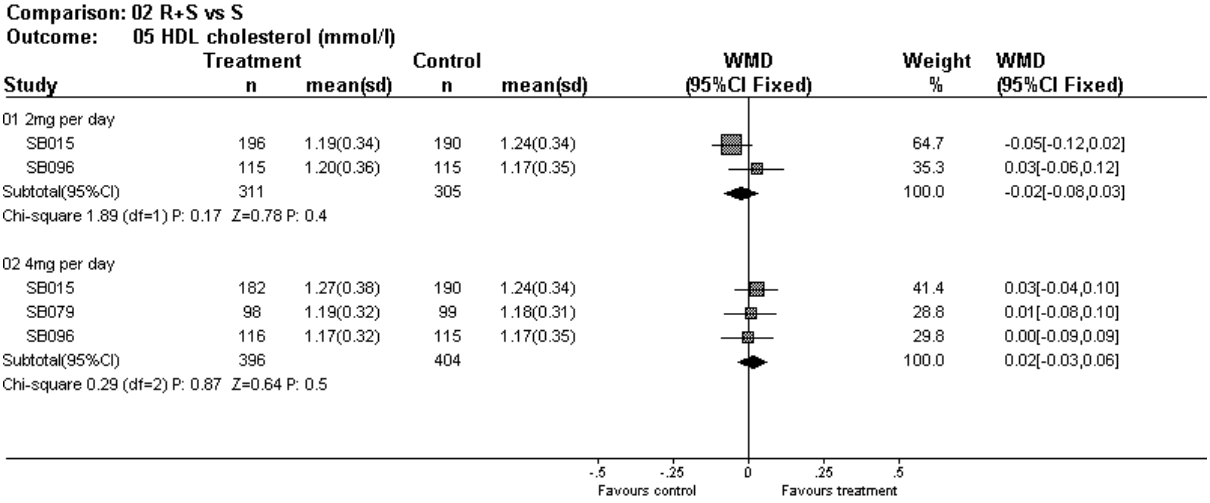
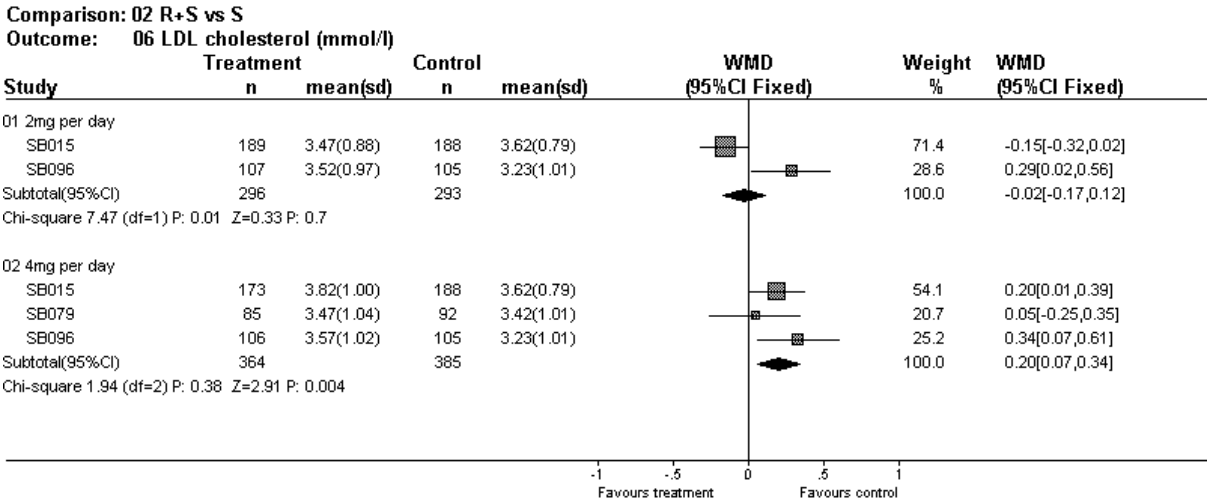


Figure 16. R+S vs. S comparison: LDL cholesterol at six months

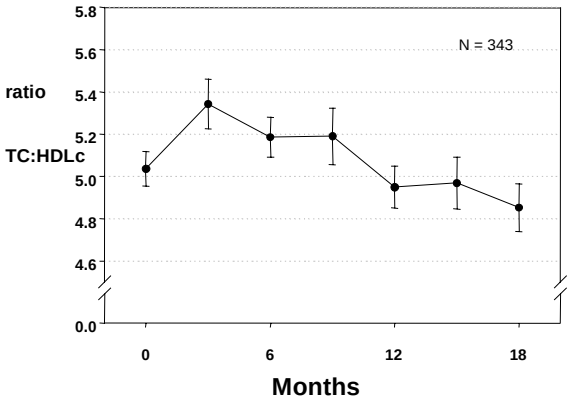


Longer term effects on lipid parameters

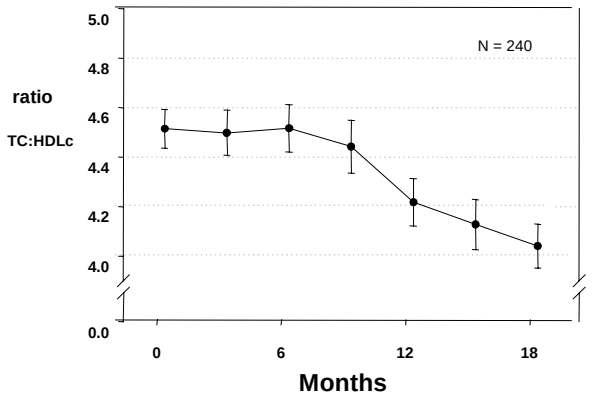
Evidence from open label extensions to studies SB015, SB020, SB079, SB096, SB093 and SB094 regarding the longer-term lipid effects of rosiglitazone combination therapy were reported in the SmithKline Beecham submission [74]. These data suggest that the initial increase in LDL cholesterol seen with rosiglitazone stabilises, whereas HDL cholesterol continues to increase over 18 months. Thus the mean total/HDL cholesterol ratio falls over 18 months (Figure 17). This reduction appears to be statistically significant for the rosiglitazone/metformin group but not for the rosiglitazone/sulphonylurea group.

Figure 17. Longer term lipid effects from open label extension studies

From SmithKline Beecham submission [74]



Rosiglitazone + sulphonylureas



Rosiglitazone + metformin

Table 10. Effect on HDL cholesterol

		HDL (mmol/l)									
		Baseline		*Final**		*Change* [&]		*Difference* [~]			
Study	*n*	*mean*	*sd*	*mean*	*sd*	*mean*	*sd*	*mean*	*95% CI*		*p value*	
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN												
SB093												
A) M	106	1.19	0.28	1.24	0.32	0.05	0.14	-	-	-	-	
C) M+R(8mg)	105	1.17	0.30	1.35	0.37	0.17	0.25	0.12	0.06	0.18	<0.0001	§
SB094												
A) M	112	1.14	0.28	1.20	0.29	0.06	0.14	-	-	-	-	
B) M+R(4mg)	116	1.18	0.29	1.32	0.34	0.14	0.19	0.08	0.03	0.13	0.0002	§
C) M+R(8mg)	110	1.20	0.37	1.36	0.42	0.16	0.24	0.10	0.04	0.16	0.0002	§
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA												
SB015												
A) S	190	1.22	0.36	1.24	0.34	0.02	0.29	-	-	-	-	
B) S+R(2mg)	196	1.14	0.31	1.19	0.34	0.05	0.23	0.01	-0.05	0.06	0.7971	†
C) S+R(4mg)	182	1.15	0.32	1.27	0.38	0.12	0.25	0.08	0.02	0.13	0.0019	†
SB079												
A) S	99	1.16	0.29	1.18	0.31	0.03	0.19	-	-	-	-	
C) S+R(4mg)	98	1.13	0.29	1.19	0.32	0.06	0.21	0.03	-0.03	0.08	0.3690	†
SB096												
A) S	115	1.17	0.33	1.17	0.35	0.01	0.17	-	-	-	-	
B) S+R(2mg)	115	1.17	0.32	1.20	0.36	0.03	0.25	0.03	-0.04	0.10	0.3773	†
C) S+R(4mg)	116	1.17	0.43	1.17	0.32	0.00	0.36	0.00	-0.07	0.07	0.9340	†

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
§ Analysis of covariance procedure with heterogeneous variance across treatments.
† Analysis of covariance procedure with homogeneous variance across treatments.

To convert from mg/dl units to mmol/l reported figures were multiplied by 0.0259.

Table 11. Effect on LDL cholesterol

		LDL (mmol/l)									
		Baseline		*Final**		*Change* [&]		*Difference* [~]			
Study	*n*	*mean*	*sd*	*mean*	*sd*	*mean*	*sd*	*mean*	*95% CI*		*p value*	
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN												
SB093												
A) M	100	2.87	0.83	3.03	0.86	0.16	0.50	-	-	-	-	
C) M+R(8mg)	97	2.67	0.67	3.30	0.89	0.63	0.69	0.45	0.28	0.62	<0.0001	§
SB094												
A) M	104	3.03	0.88	3.13	0.97	0.10	0.44	-	-	-	-	
B) M+R(4mg)	108	2.99	0.78	3.46	0.86	0.46	0.58	0.36	0.20	0.52	<0.0001	§
C) M+R(8mg)	102	2.91	0.84	3.45	1.04	0.53	0.76	0.40	0.20	0.60	<0.0001	§
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA												
SB015												
A) S	188	3.62	0.81	3.62	0.79	0.00	0.58	-	-	-	-	
B) S+R(2mg)	189	3.41	0.90	3.47	0.88	0.06	0.65	0.02	-0.12	0.15	0.7921	†
C) S+R(4mg)	173	3.64	0.82	3.82	1.00	0.18	0.68	0.19	0.05	0.33	0.0030	†
SB079												
A) S	92	3.41	0.91	3.42	1.01	0.01	0.61	-	-	-	-	
C) S+R(4mg)	85	3.13	0.97	3.47	1.04	0.34	0.64	0.27	0.08	0.46	0.0052	t
SB096												
A) S	105	3.15	0.92	3.23	1.01	0.08	0.62	-	-	-	-	
B) S+R(2mg)	107	3.22	0.87	3.52	0.97	0.30	0.62	0.24	0.02	0.45	0.0146	†
C) S+R(4mg)	106	3.10	0.78	3.57	1.02	0.47	0.83	0.38	0.17	0.60	<0.0001	†

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
§ Analysis of covariance procedure with heterogeneous variance across treatments.
† Analysis of covariance procedure with homogeneous variance across treatments.
t Confidence interval and significance test not reported, t-test calculated by authors.

To convert from mg/dl units to mmol/l reported figures were multiplied by 0.0259.

Table 12. Lipid summary (total cholesterol, HDL, LDL, total/HDL)

Study	*Baseline mean (sd)*	*Change mean (95% CI)*	*Baseline mean (sd)*	*Change mean (95% CI)*	*Baseline mean (sd)*	*Change mean (95% CI)*	*Baseline mean (sd)*	*Change mean (95% CI)*
SB015								
A) S+P	218 (37)	1.5 (-2.2, 5)	47 (14)	0.7 (-0.9, 2.3)	140 (31)	0.1 (-3.2, 3.3)	4.7 (2.1-10.0)$	-0.1 (-0.2, 0.0)
B) S+R(2mg)	209 (41)	10 (6, 15)	44 (12)	1.8 (0.6, 3.1)	132 (35)	2.5 (-1.1, 6.1)	4.9 (2.0-9.4)$	0.0 (-0.2, 0.0)
C) S+R(4mg)	218 (37)	15 (10, 20)	44 (12)	4.6 (3.1, 6.0)	140 (32)	7.0 (3, 11)	5.1 (2.1-10.1)$	-0.1 (-0.2, 0.0)
SB079								
A) S+P	219 (42)	8 (0.7, 16)	45 (11)	1.0 (-0.4, 2.5)	132 (35)	0.3 (-4.6, 5.1)	5.1 (1.4)	0.2 (-0.1, 0.5)
B) R(4mg) +P	210 (41)	44 (33, 54)	44 (13)	3.2 (1.6, 4.8)	125 (34)	22 (16, 28)	5.0 (1.4)	0.6 (0.4, 0.9)
C) S+R(4mg)	213 (44)	33 (24, 43)	44 (11)	2.2 (0.5, 3.8)	121 (37)	13 (8, 18)	5.1 (1.4)	0.7 (0.3, 1.1)
SB093								
A) M+P	193 (37)	10 (6, 15)	46 (12)	1.8 (0.7, 2.8)	111 (32)	6 (2.1, 9.8)	4.4 (1.2)	0.05 (-0.1, 0.2)
B) R(8mg)+P	201 (47)	46 (38, 55)	47 (11)	5.2 (3.5, 7)	110 (29)	32 (26, 39)	4.6 (1.6)	0.6 (0.3, 0.9)
C) M+R(8mg)	192 (33)	34 (28, 41)	45 (12)	6.7 (4.9, 9)	103 (26)	24 (19, 30)	4.5 (1.3)	0.1 (-0.0, 0.3)
SB094								
A) M+P	205 (40)	7 (2.7, 12)	44 (11)	2.2 (1.1, 3.2)	117 (34)	4 (0.7, 7.4)	4.9 (1.4)	-0.02 (-0.1, 0.1)
B) R(4mg)+M	203 (36)	28 (23, 33)	46 (11)	5.3 (4, 6.6)	116 (30)	18 (14, 22)	4.6 (1.1)	0.1 (-0.03, 0.3)
C) R(8mg)+M	200 (47)	32 (24, 40)	47 (14)	6.2 (4.5, 8)	113 (32)	21 (15, 26)	4.6 (1.4)	0.1 (-0.06, 0.3)
SB096								
A) S+P	212 (45)	5 (-0.6, 12)	45 (13)	0.3 (-0.9, 1.5)	122 (35)	3 (-1.7, 8)	5.0 (1.6)	0.1 (-0.05, 0.2)
B) S+R(2mg)	210 (41)	20 (15, 26)	45 (12)	1.1 (-0.6, 2.9)	124 (34)	11 (7, 16)	4.9 (1.4)	0.3 (0.2, 0.5)
C) S+R(4mg)	207 (43)	28 (15, 42)	45 (17)	0.0 (-2.5, 2.6)	120 (30)	18 (12, 24)	4.9 (1.4)	0.4 (0.2, 0.6)

$ Median (range)

Table 13. Lipid summary (LDL/HDL, triglycerides, FFA, VLDL)

	LDL/HDL ratio		*Triglycerides (mg/dl)*		*FFA (mg/dl)*		*VLDL (mg/dl)*	
	Baseline	*Change*	*Baseline*	*Change*	*Baseline*	*Change*	*Baseline*	*Change*
Study	*mean (sd)*	*mean (95% CI)*	*mean (sd)*	*mean (95% CI)*	*mean (sd)*	*mean (95% CI)*	*mean (sd)*	*mean (95% CI)*
SB015								
A) S+P	3 (1, -7)$	-0.1 (-0.2, 0)	160 (90)	4.3 (-6, 15)	28 (8.2)	-0.9 (-2.2, 0.4)	27 (10-93)	-0.5 (-1.5, 1)
B) S+R(2mg)	3(0.7, -7)$	-0.1 (-0.2, 0)	171 (98)	36 (21, 51)	26 (8.7)	-1.5 (-2.7, -0.2)	29 (8-118)	4 (2, 6)
C) S+R(4mg)	3 (1, -7)$	-0.1 (-0.2, 0)	176 (108)	20 (3, 37)	27 (8.8)	-4 (-5.5, -2.7)	29 (8-122)	2 (0, 4)
SB079								
A) S+P	3.1 (1.0)	-0.1 (-0.2, 0.1)	248 (187)	32 (-4, 69)	17 (6.3)	1.0 (-0.3, 2.4)	22 (14)	8 (4, 12)
B) R(4mg) +P	2.9 (0.9)	0.2 (0.1, 0.4)	264 (198)	78 (17, 138)	16 (7.1)	0.6 (-1.3, 2.6)	22 (16)	15 (7, 23)
C) S+R(4mg)	2.8 (0.9)	0.2 (-0.0, 0.3)	271 (272)	60 (4, 115)	16 (7.2)	-1.6 (-3.1, -0.2)	24 (18)	16 (10, 21)
SB093								
A) M+P	2.5 (0.9)	0.1 (-0.0, 0.2)	190 (125)	11 (-12, 35)	17.8 (6.0)	0.4 (-1.0, 1.8)	16 (9)	3 (1, 5.5)
B) R(8mg)+P	2.4 (0.8)	0.5 (0.3, 0.7)	249 (231)	38 (-4.6, 80)	18.8 (6.6)	-3.4 (-4.8, -2.0)	21 (16)	12 (8, 17)
C) M+R(8mg)	2.3 (0.7)	0.3 (0.1, 0.4)	243 (182)	-11 (-39, 17)	18.3 (7.4)	-4.5 (-6.1, -2.9)	19 (10)	7.5 (5, 10)
SB094								
A) M+P	2.7 (0.9)	-0.0 (-0.1, 0.1)	246 (194)	0.7 (-21, 22)	18.3 (7.7)	-0.1 (-1.5, 1.3)	21 (16)	5.1 (1.7, 8)
B) R(4mg)+M	2.6 (0.8)	0.1 (0.0, 0.2)	225 (138)	7 (-15, 29)	18.4 (7.6)	-2.6 (-4, -1.4)	20 (11)	9.5 (6.3, 13)
C) R(8mg)+M	2.5 (0.8)	0.1 (-0.0, 0.2)	227 (184)	-0.3 (-29, 28)	18.4 (8.0)	-4.3 (-6, -2.8)	20 (17)	9.9 (6.5, 13)
SB096								
A) S+P	2.9 (1.1)	0.0 (-0.1, 0.1)	267 (299)	13 (-23, 48)	16.4 (7.1)	2.4 (1.1, 3.7)	25 (19)	6 (2.4, 9)
B) S+R(2mg)	2.8 (0.9)	0.2 (0.1, 0.3)	214 (147)	49 (28, 69)	16.1 (6.1)	-0.9 (-2, 0.3)	19 (12)	11 (8, 14)
C) S+R(4mg)	2.8 (0.9)	0.3 (0.1, 0.5)	249 (294)	59 (-40, 159)	15.8 (6.4)	0.0 (-1.2, 1.3)	22 (20)	12 (8, 16)

$ Median (range)

4.1.5 Effect on blood pressure

Addition of rosiglitazone to metformin

No significant between-group differences were seen in changes in blood pressure over six months (Figure 18 and 19, Table 14 and 15).

Figure 18. R+M vs. M comparison: change in systolic blood pressure over six months

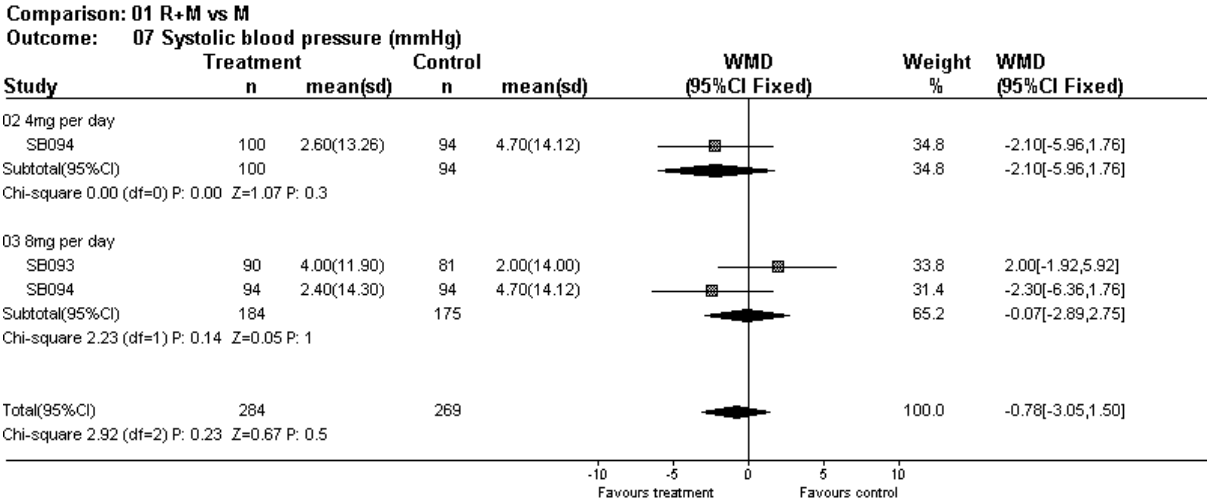
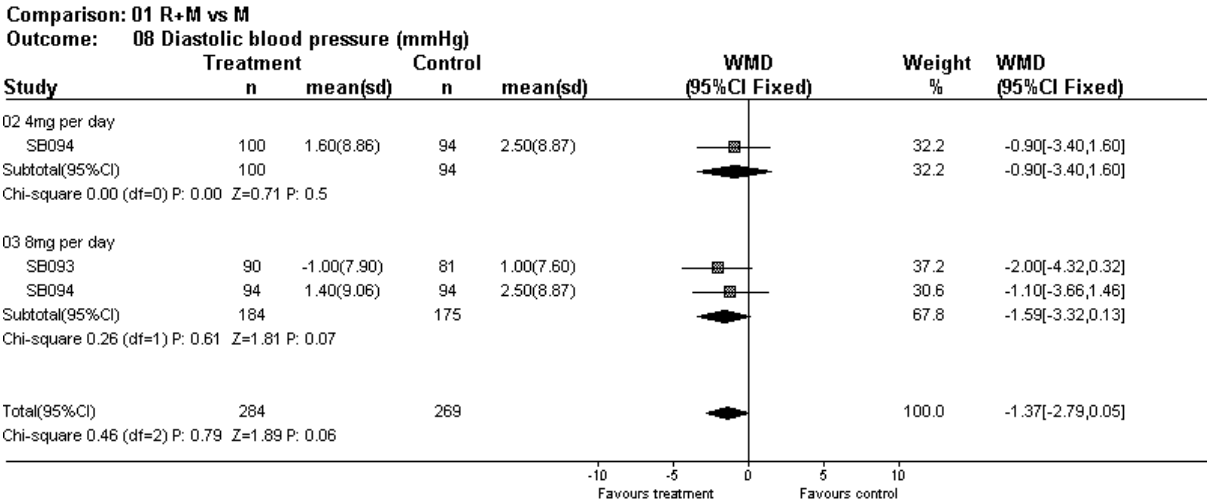


Figure 19. R+M vs. M comparison: change in diastolic blood pressure over six months



There was no significant difference in absolute systolic blood pressure at six months (Figure 20). However, there was a small statistically significant difference in diastolic blood pressure: 1.8mmHg (0.3-3.3mmHg) lower for the rosiglitazone groups compared to metformin controls.

Figure 20. R+M vs. M comparison: systolic blood pressure at six months

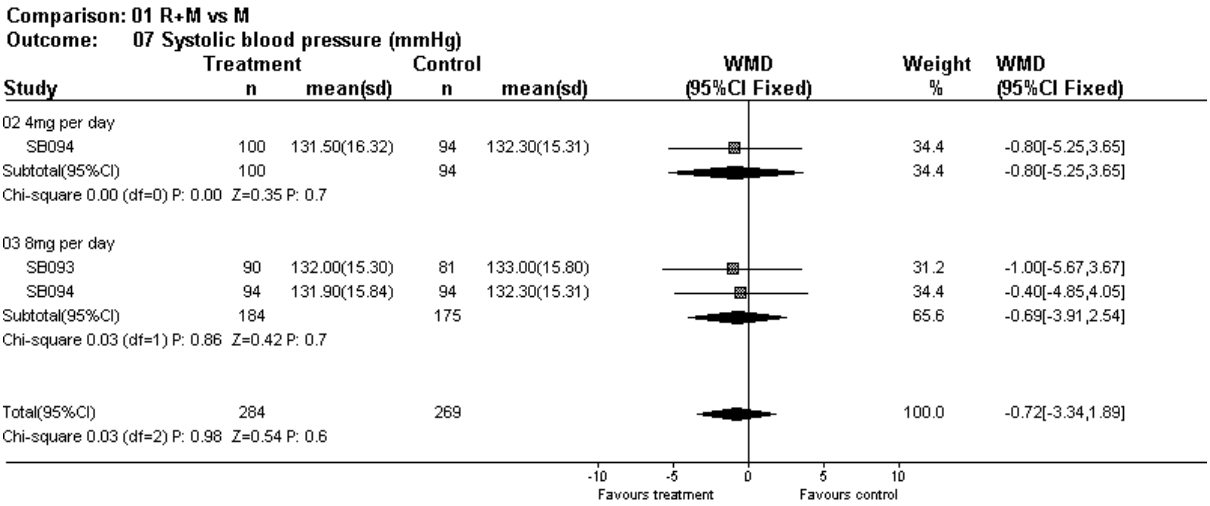
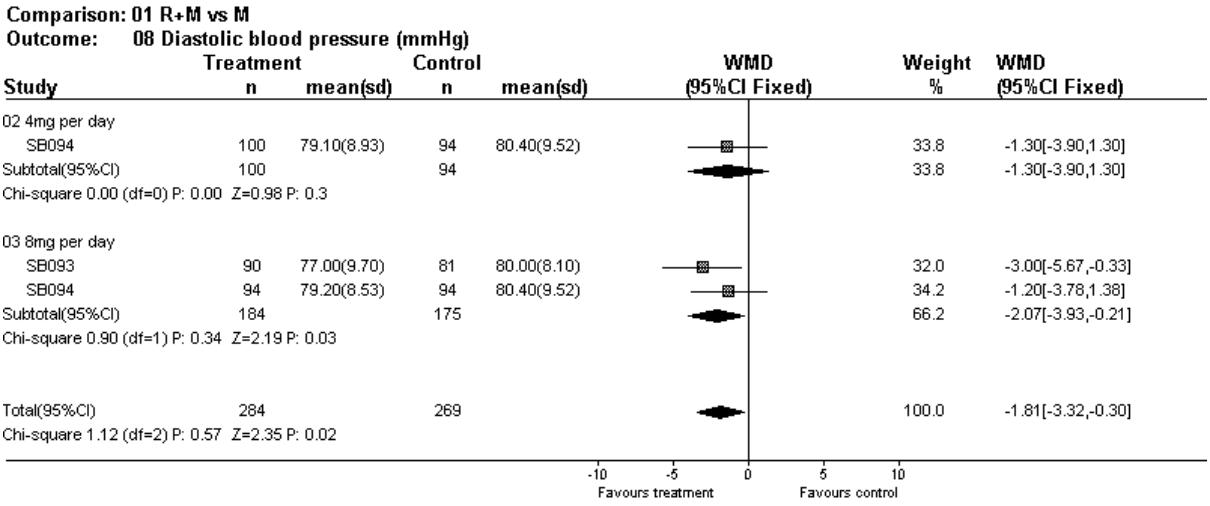


Figure 21. R+M vs. M comparison: diastolic blood pressure at six months



Addition of rosiglitazone to sulphonylureas

There were no significant differences between treatment and control groups in changes in systolic blood pressure over six months, except for the 4mg rosiglitazone group in SB015, which showed a significant reduction compared to the control group (Table 14). No differences were observed in changes in diastolic blood pressure for this comparison (Table 15). Meta-analysis of six-month blood pressure levels showed no significant difference between the groups, although the mean diastolic blood pressure was lower for the rosiglitazone groups (Figure 22 and Figure 23).

Figure 22. R+S vs. S comparison: systolic blood pressure at six months

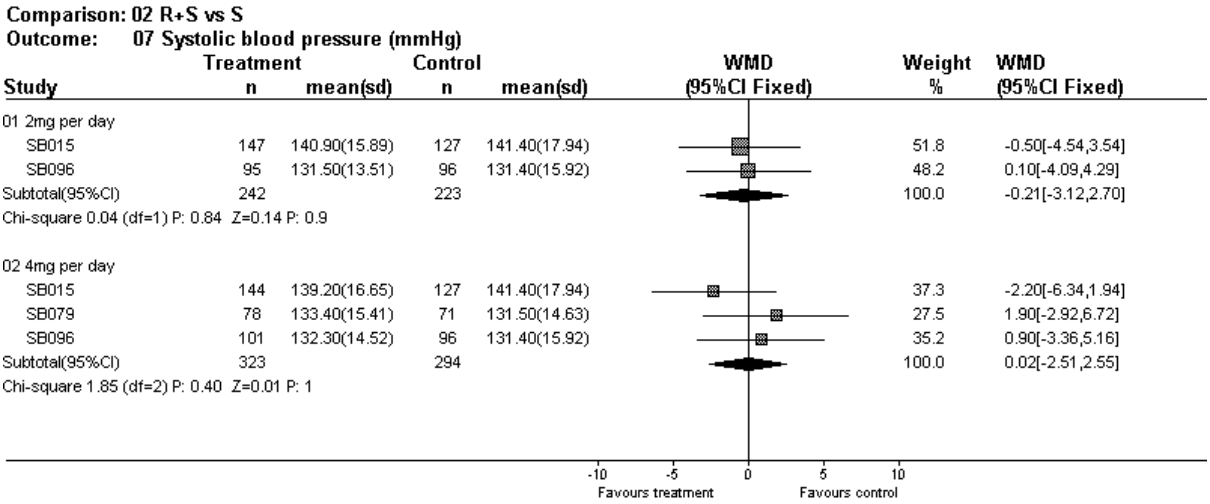


Figure 23. R+S vs. S comparison: diastolic blood pressure at six months

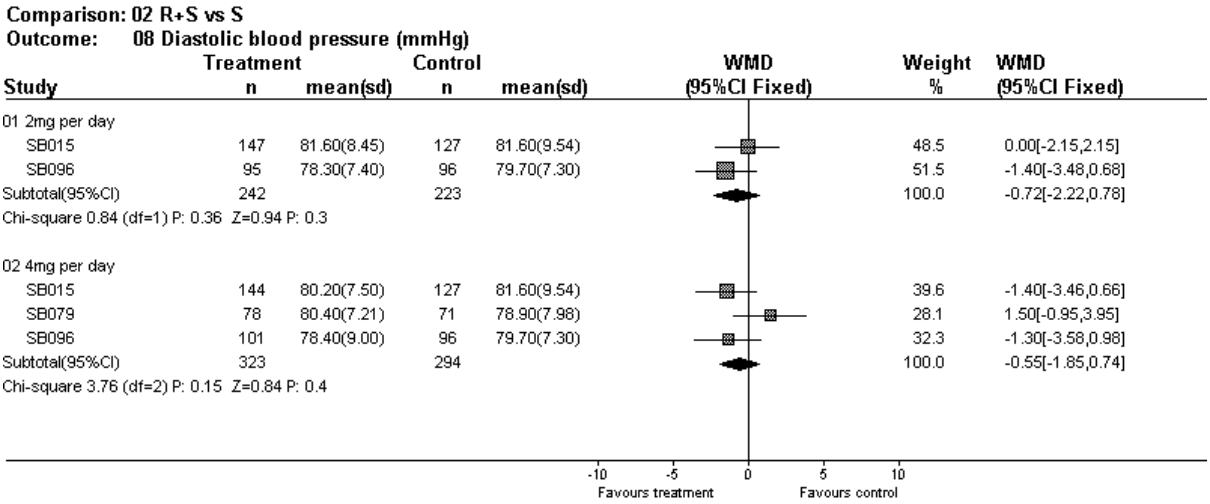


Table 14. Effect on systolic blood pressure

		SBP (mmHg)										
		Baseline		Final*		Change &		Difference ~				
Study	n	mean	sd	mean	sd	mean	sd	mean	95% CI		p value	
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN												
SB093												
A) M	81	131.0	14.2	133.0	15.8	2.00	14.00	-	-	-	-	
C) M+R(8mg)	90	128.0	14.3	132.0	15.3	4.00	11.90	2.00	-1.70	6.20	0.2665	†
SB094												
A) M	94	127.7	12.8	132.3	15.3	4.70	14.12	-	-	-	-	
B) M+R(4mg)	100	128.8	15.8	131.5	16.3	2.60	13.26	-2.00	-5.98	1.88	0.3052	†
C) M+R(8mg)	94	129.5	15.8	131.9	15.8	2.40	14.30	-2.30	-6.30	1.68	0.2554	†
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA												
SB015												
A) S	127	138.2	14.6	141.4	17.9	3.2	17.88	-	-		-	
B) S+R(2mg)	147	141.1	17.3	140.9	15.9	-0.2	15.06	-3.40	-7.12	0.31	0.0726	†
C) S+R(4mg)	144	140.5	17.2	139.2	16.7	-1.3	13.92	-4.50	-8.21	-0.74	0.0189	†
SB079												
A) S	71	128.7	15.0	131.5	14.6	2.80	-	-	-	-	-	
C) S+R(4mg)	78	128.8	14.8	133.4	15.4	4.60	-	1.80	-2.25	5.89	0.3770	†
SB096												
A) S	96	128.9	13.4	131.4	15.9	2.50	13.07	-				
B) S+R(2mg)	95	126.9	13.1	131.5	13.5	4.70	11.37	2.20	-1.70	6.00	0.2746	†
C) S+R(4mg)	101	129.2	14.3	132.3	14.5	3.10	15.87	0.60	-3.20	4.50	0.7384	†

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
† Analysis of covariance procedure (details not reported).

Table 15. Effect on diastolic blood pressure

		DBP (mmHg)										
		Baseline		Final*		Change &		Difference ~				
Study	n	mean	sd	mean	sd	mean	sd	mean	95% CI		p value	
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN												
SB093												
A) M	81	79.0	9.1	80.0	8.1	1.00	7.60	-	-	-	-	
C) M+R(8mg)	90	78.0	8.9	77.0	9.7	-1.00	7.90	-2.00	-3.80	0.80	0.1990	†
SB094												
A) M	94	77.9	8.7	80.4	9.5	2.50	8.87	-	-	-	-	
B) M+R(4mg)	100	77.5	8.4	79.1	8.9	1.60	8.86	-0.90	-3.47	1.58	0.4631	†
C) M+R(8mg)	94	77.8	8.4	79.2	8.5	1.40	9.06	-1.20	-3.73	1.39	0.3697	†
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA												
SB015												
A) S	127	82.4	8.2	81.6	9.5	-0.8	8.34	-	-	-	-	
B) S+R(2mg)	147	81.7	8.5	81.6	8.5	-0.1	10.00	0.70	-1.42	2.84	0.5103	†
C) S+R(4mg)	144	81.5	8.2	80.2	7.5	-1.3	8.28	-0.50	-2.66	1.61	0.6303	†
SB079												
A) S	71	78.8	8.1	78.9	8.0	0.10	-	-	-	-	-	
C) S+R(4mg)	78	78.9	8.2	80.4	7.2	1.60	-	1.40	-0.96	3.81	0.2399	†
SB096												
A) S	96	77.5	7.3	79.7	7.3	2.20	7.25	-	-	-		
B) S+R(2mg)	95	76.7	8.0	78.3	7.4	1.60	6.59	-0.60	-2.70	1.50	0.5753	†
C) S+R(4mg)	101	77.2	7.9	78.4	9.0	1.20	8.01	-1.10	-3.10	1.00	0.3040	†

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
† Analysis of covariance procedure (details not reported).

4.1.6 Effect on weight

The effects of rosiglitazone combination and mono therapy on body weight are summarised in Table 16.

Addition of rosiglitazone to metformin

Although increases in body weight were significantly greater for the rosiglitazone/metformin combination therapy groups compared to the metformin control groups (Figure 24 and Table 16), there were no significant absolute differences between the groups in body weight at six months (Figure 25).

Figure 24. R+M vs. M comparison: change in weight over six months

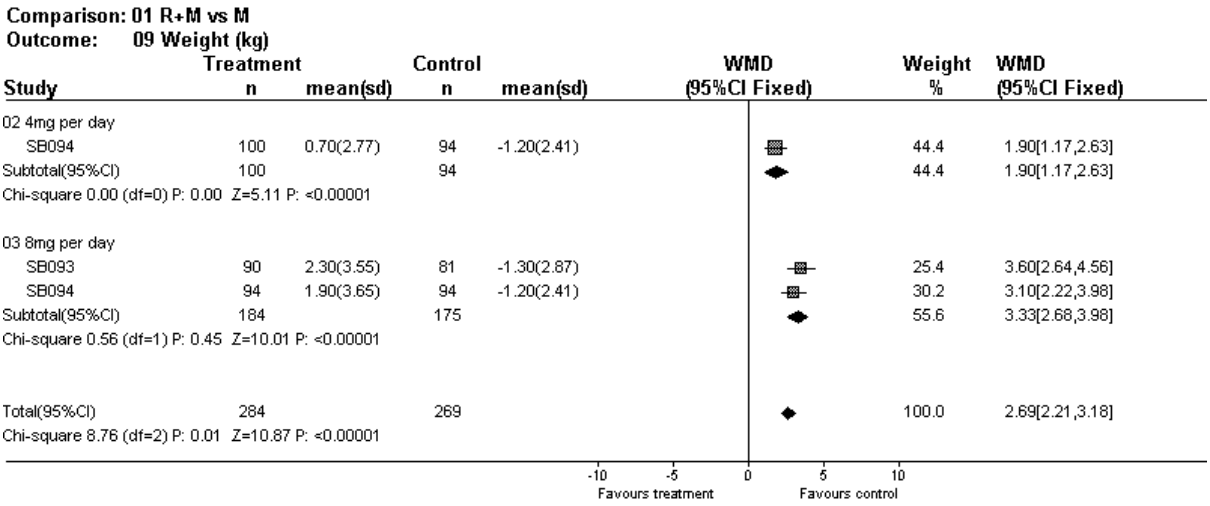
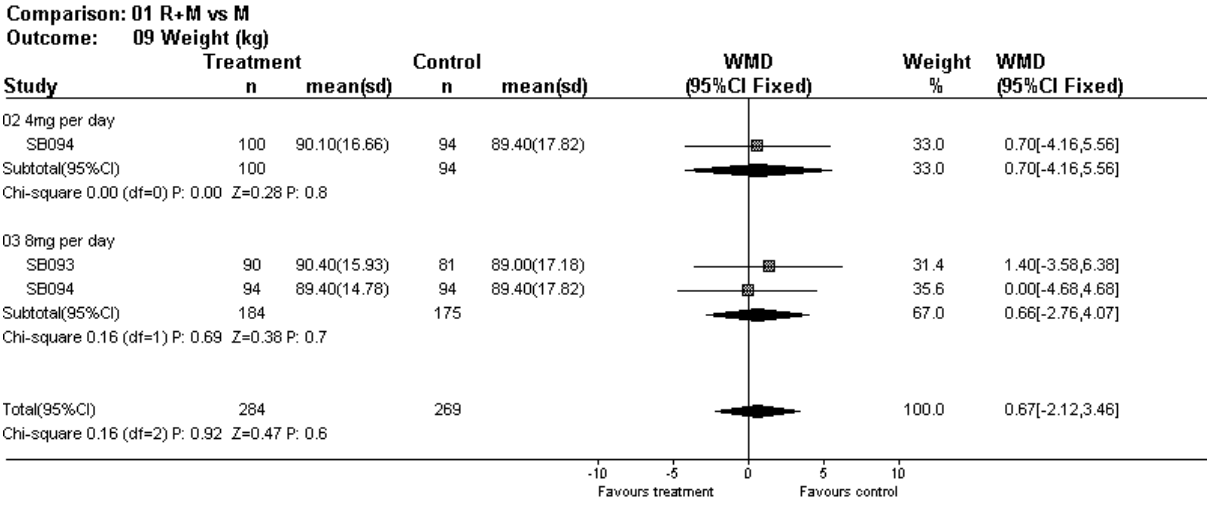


Figure 25. R+M vs. M comparison: weight at six months



Addition of rosiglitazone to sulphonylureas

The rosiglitazone/sulphonylurea combination groups showed significantly greater weight increases over six months than the sulphonylurea control groups (Figure 26 and Table 16). There was a significant difference in weight at six months for the 4mg rosiglitazone groups, but not for the 2mg groups (Figure 27).

Figure 26. R+S vs. S comparison: change in weight over six months

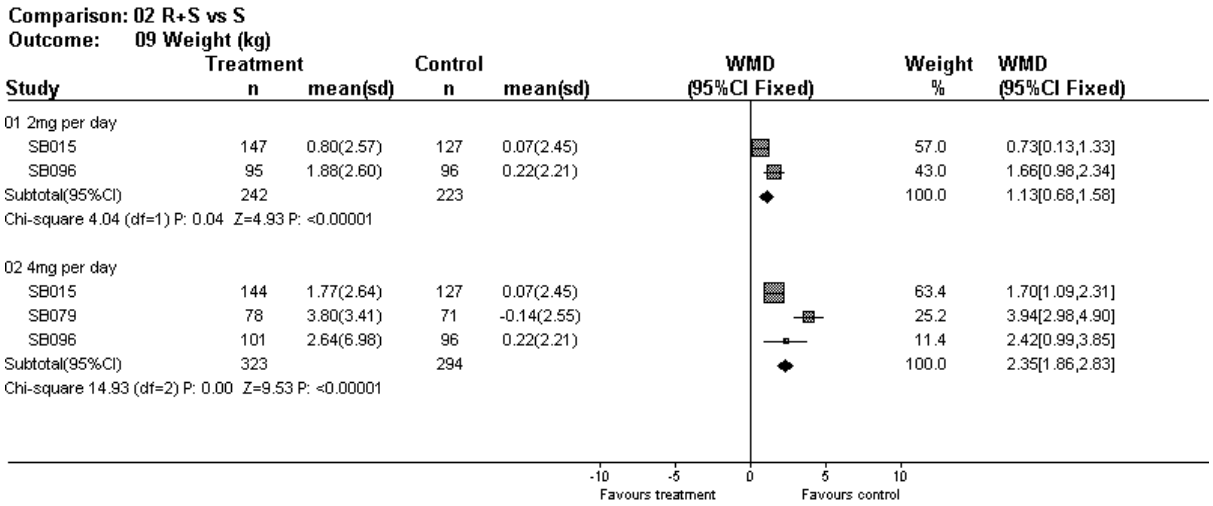
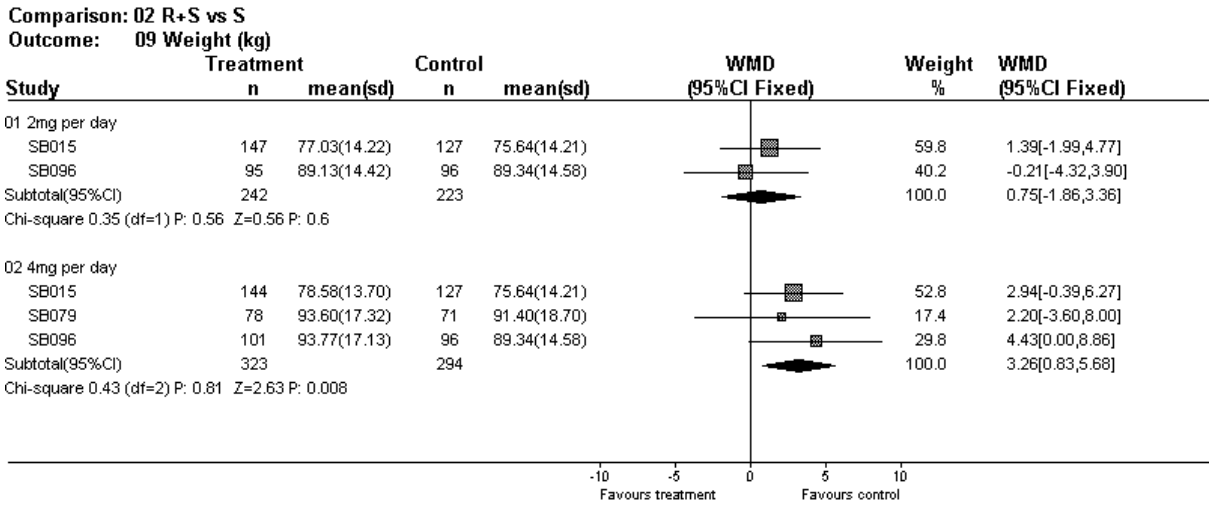


Figure 27. R+S vs. S comparison: weight at six months



Changes in fat distribution

Although, waist-to-hip ratio was measured in all of the studies, no significant changes over time or differences between the groups were found.

Intra-abdominal and visceral fat were measured by magnetic resonance imaging. in study SB083 [70] . The results of this study were reported in the SmithKline Beecham submission [74]. There was no change in intra-abdominal fat for the placebo group (n=14, p=0.652) or for the rosiglitazone (8mg) group (n=10, p=0.695). Intra-hepatic fat did not change for the placebo group (n=16, p=0.692), but reduced significantly for the rosiglitazone (8mg) group (n=12, p=0.036).

Table 16. Effect on body weight

		Weight (kg)									
		Baseline		Final*		Change &		Difference ~			
Study	n	mean	sd	mean	sd	mean	sd	mean	95% CI	p value	
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN											
SB093											
A) M	81	90.3	16.9	89.0	17.2	-1.30	2.87	-	- -	-	
C) M+R(8mg)	90	88.1	15.1	90.4	15.9	2.30	3.55	3.60	2.55 4.66	0.0001	†
SB094											
A) M	94	90.5	17.9	89.4	17.8	-1.20	2.41	-	- -	-	
B) M+R(4mg)	100	89.4	15.7	90.1	16.7	0.70	2.77	1.90	1.05 2.73	0.0001	†
C) M+R(8mg)	94	87.6	13.7	89.4	14.8	1.90	3.65	3.10	2.17 3.89	0.0001	†
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA											
SB015											
A) S	127	75.6	13.7	75.6	14.2	0.07	2.45	-	- -	-	
B) S+R(2mg)	147	76.2	14.3	77.0	14.2	0.80	2.57	0.73	0.12 1.34	0.0196	†
C) S+R(4mg)	144	76.8	13.3	78.6	13.7	1.77	2.64	1.70	1.09 2.31	0.0001	†
SB079											
A) S	71	91.5	18.9	91.4	18.7	-0.14	2.55	-	- -	-	
C) S+R(4mg)	78	89.8	16.1	93.6	17.3	3.80	3.41	3.96	2.98 4.95	0.0001	†
SB096											
A) S	96	89.1	14.7	89.3	14.6	0.22	2.21	-	- -	-	
B) S+R(2mg)	95	87.3	14.3	89.1	14.4	1.88	2.60	1.66	0.37 2.96	0.0120	†
C) S+R(4mg)	101	91.1	16.7	93.8	17.1	2.64	6.98	2.42	1.15 3.70	0.0002	†

* Final assessment at week 26.
& Mean difference in outcome between baseline and final assessment.
~ Difference in mean change for study group compared to control group (group A).
† Analysis of covariance procedure (details not reported).

4.1.7 Adverse events and withdrawals

Addition of rosiglitazone to metformin

There was no significant difference between the rosiglitazone/metformin combination groups compared to the metformin group in terms of the proportion of patients who experienced at least one adverse event (Figure 28), the proportion who withdrew from the studies because of an adverse event (Figure 29), or in the proportion who withdrew for any reason (Figure 30). There was a trend towards reduced overall withdrawals for the rosiglitazone combination arms.

Figure 28. R+M vs. M comparison: patients with at least one adverse event

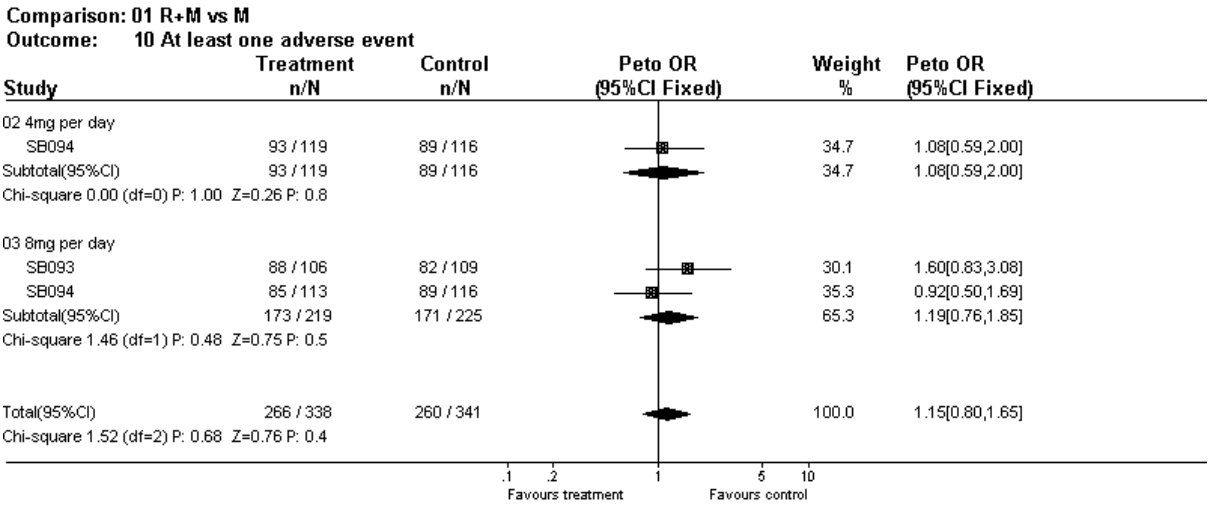


Figure 29. R+M vs. M comparison: patients withdrawing due to adverse event

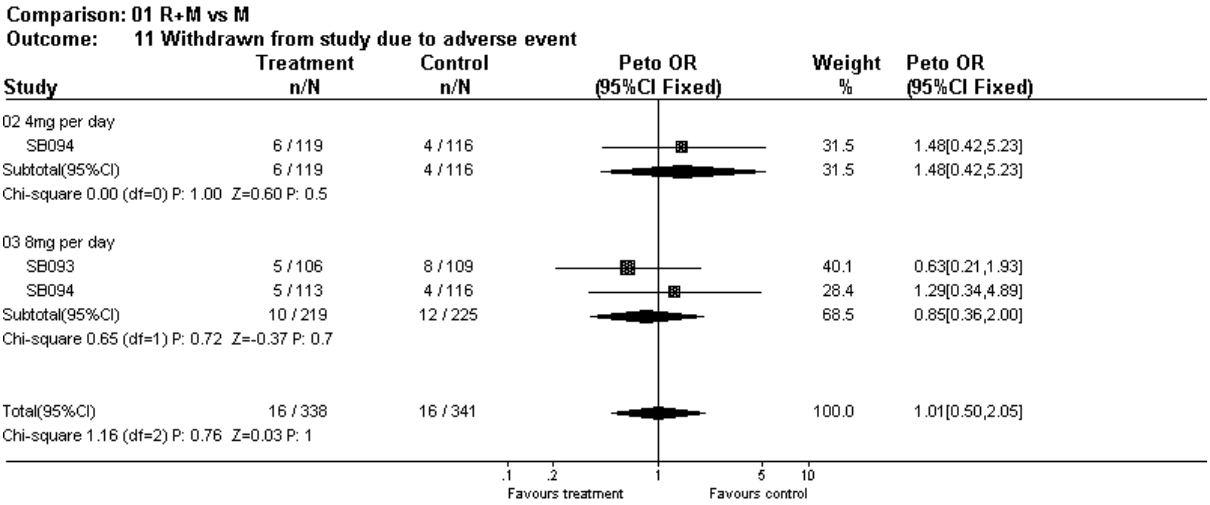
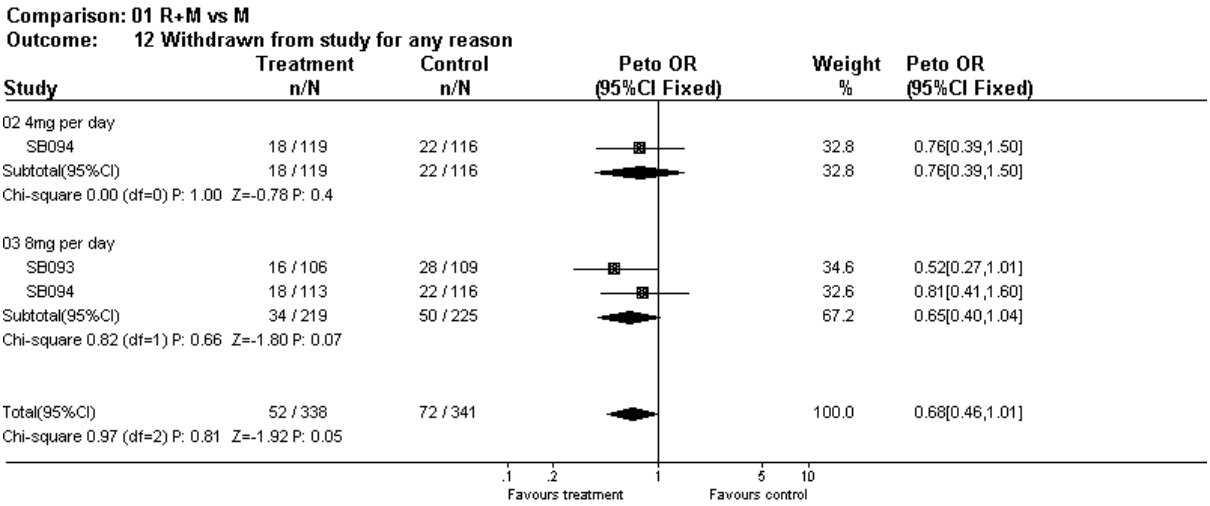


Figure 30. R+M vs. M comparison: patients withdrawing from study



Addition of rosiglitazone to sulphonylureas

There was no significant difference in the incidence of adverse events for the sulphonylurea combination arms compared to the control arms (Figure 25). Significantly lower proportions of patients withdrew in the 4mg rosiglitazone combination groups compared to the controls. There was a non-significant trend towards fewer withdrawals due to adverse events in the combination groups.

Figure 31. R+S vs. S comparison: patients with at least one adverse event

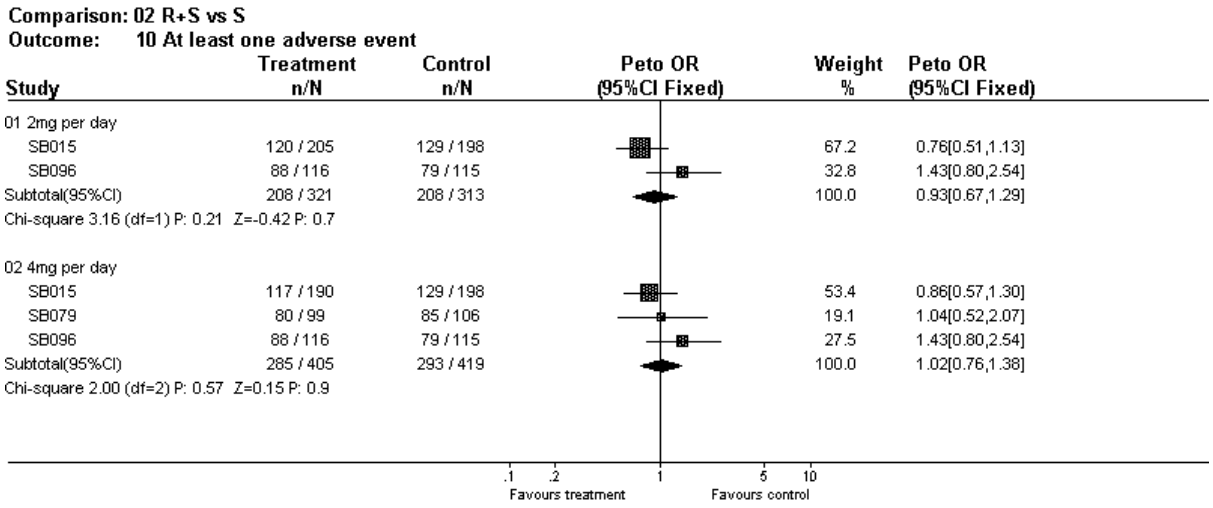


Figure 32. R+S vs. S comparison: patients withdrawing due to adverse event

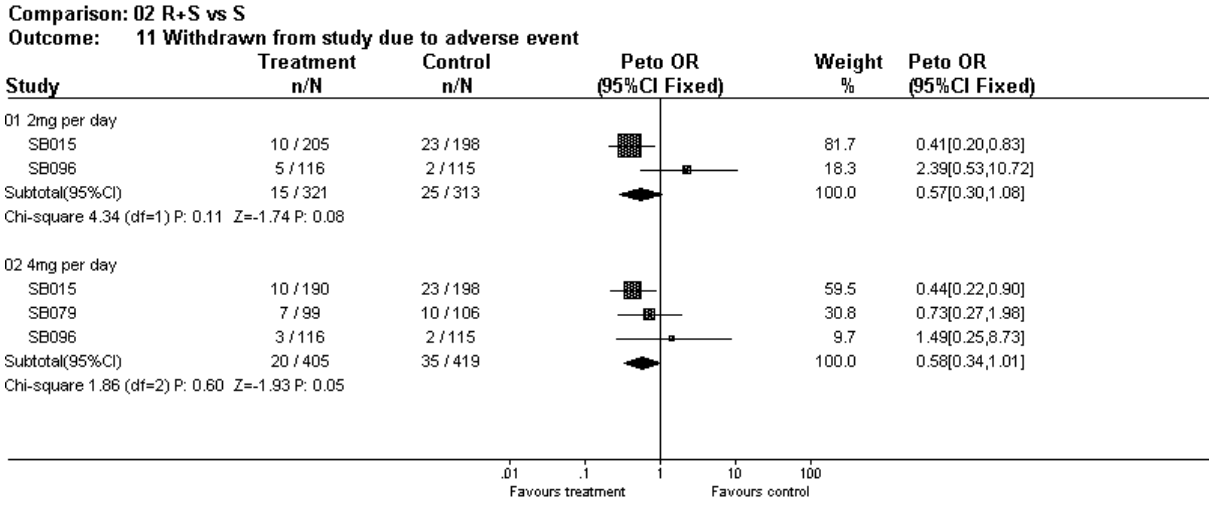
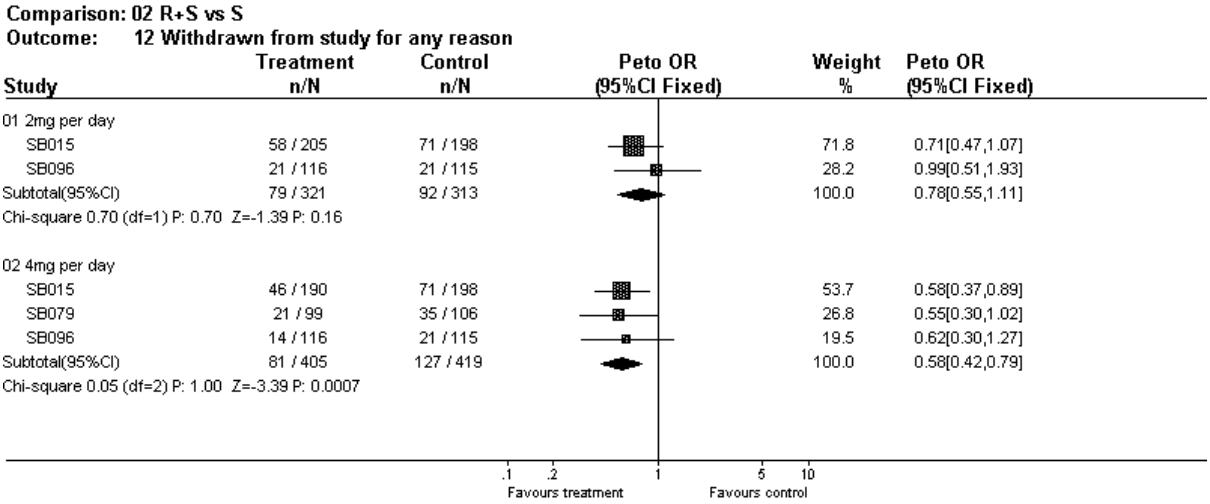


Figure 33. R+S vs. S comparison: patients withdrawing from trials



Cumulative incidence of adverse events

The SmithKline Beecham submission [74] presented data on the cumulative incidence of adverse events from the clinical trial patients. This included data on over 5,000 patient years of exposure to rosiglitazone, including over 1,000 patients treated for two years or longer (at 5 November 1999). The incidence rates (per 100 patient years) for the most common adverse events are shown in Table 18.

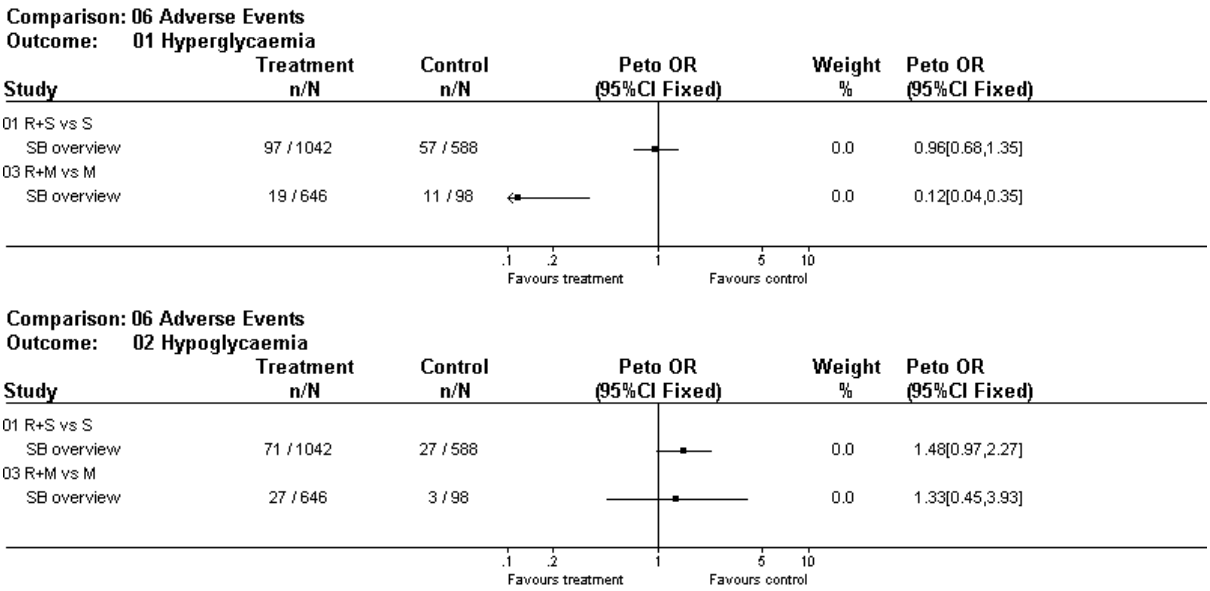
Estimated odds ratios for selected adverse events are presented below. These represent the key adverse events associated with conventional therapies (metformin and sulphonylurea) and those thought to be a potential problem for rosiglitazone from pre clinical trial data.

The addition of rosiglitazone to metformin was associated with a significant reduction in the risk of hyperglycaemia (Figure 28). No significant effect on the incidence of hyperglycaemia was seen with rosiglitazone/sulphonylurea combination therapy compared to sulphonylurea therapy. The addition of rosiglitazone to metformin or sulphonylurea did not effect the incidence of hypoglycaemia.

Over the clinical trial programme no differences in hepatic enzyme elevations were observed for the rosiglitazone intervention groups compared to the control groups [74]. No patients in the clinical trial programme showed signs of liver toxicity.

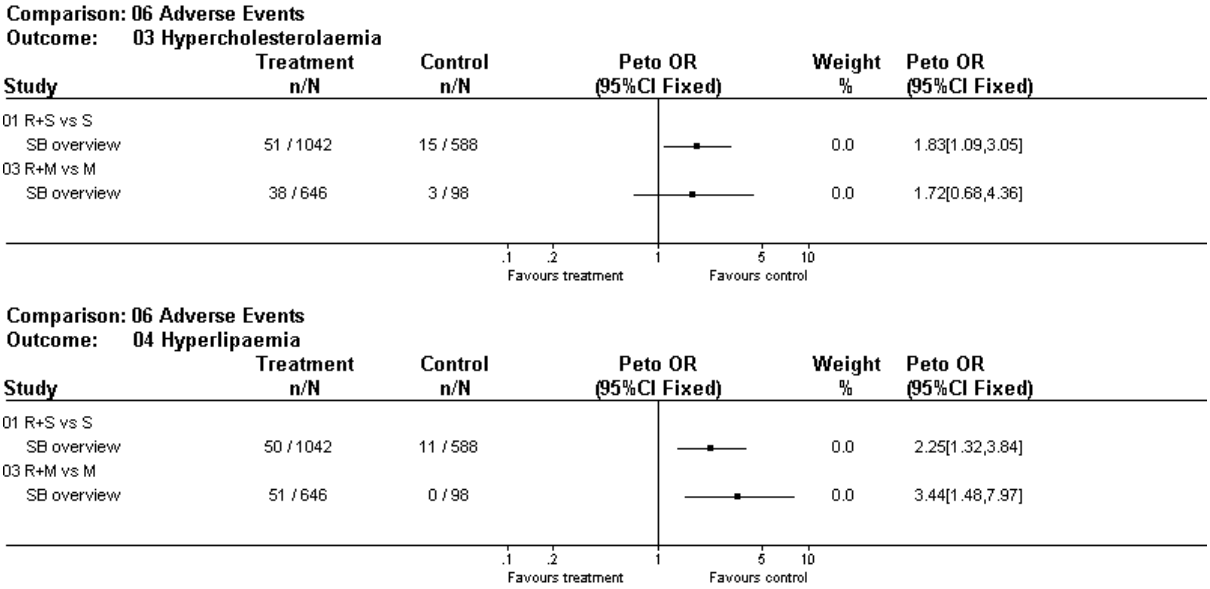
Evidence from the monotherapy study SB80 [69] suggests that rosiglitazone reduces microalbuminurea [74], which is an early indicator of renal damage.

Figure 34. Cumulative incidence of glycaemic adverse events



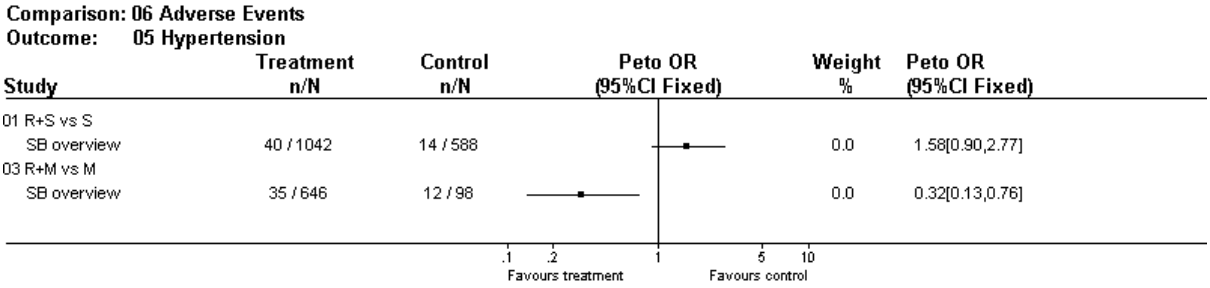
Significant increases in the incidence of hypercholesterolaemia and hyperlipaemia were observed with rosiglitazone/sulphonylurea combination therapy compared to sulphonylurea alone (Figure 29). For rosiglitazone/metformin combination therapy, a significant increase in hyperlipaemia (but not hypercholesterolaemia) was observed.

Figure 35. Cumulative incidence of hypercholesterolaemia & hyperlipaemia



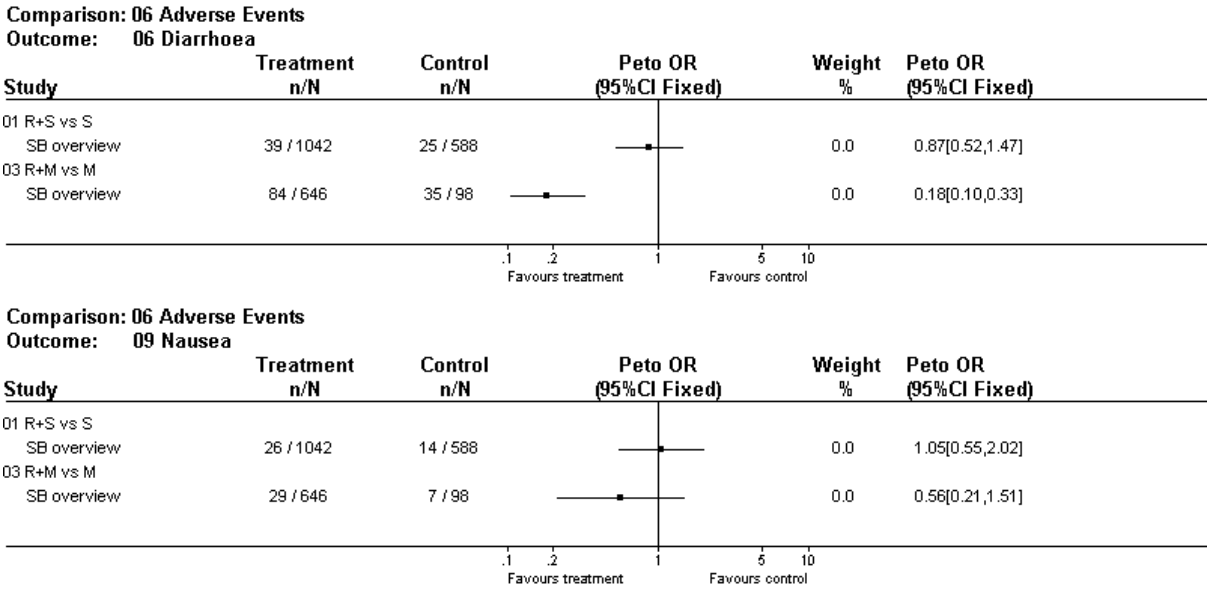
A significant reduction in the incidence of hypertension was seen with rosiglitazone/metformin compared to metformin alone (Figure 30). No significant difference in the incidence of hypertension was seen with the rosiglitazone/sulphonylurea combination compared to sulphonylurea monotherapy.

Figure 36. Cumulative incidence of hypertension



The incidence of diarrhoea was significantly lower for the rosiglitazone/metformin groups than for the metformin monotherapy groups (Figure 31). No difference was seen in the incidence of diarrhoea for the metformin/sulphonylurea groups compared to the sulphonylurea groups. The incidence of nausea was not significantly different for either of the rosiglitazone combination therapy groups than for the control groups.

Figure 37. Cumulative incidence of gastrointestinal adverse effects



The incidence of anaemia (including cases of reduced haemocrit) was significantly higher for the rosiglitazone combination therapy groups than for the controls (Figure 32). Oedema was also significantly more common for the rosiglitazone/sulphonylurea combination groups than for the control groups.

Figure 38. Cumulative incidence of anaemia and oedema

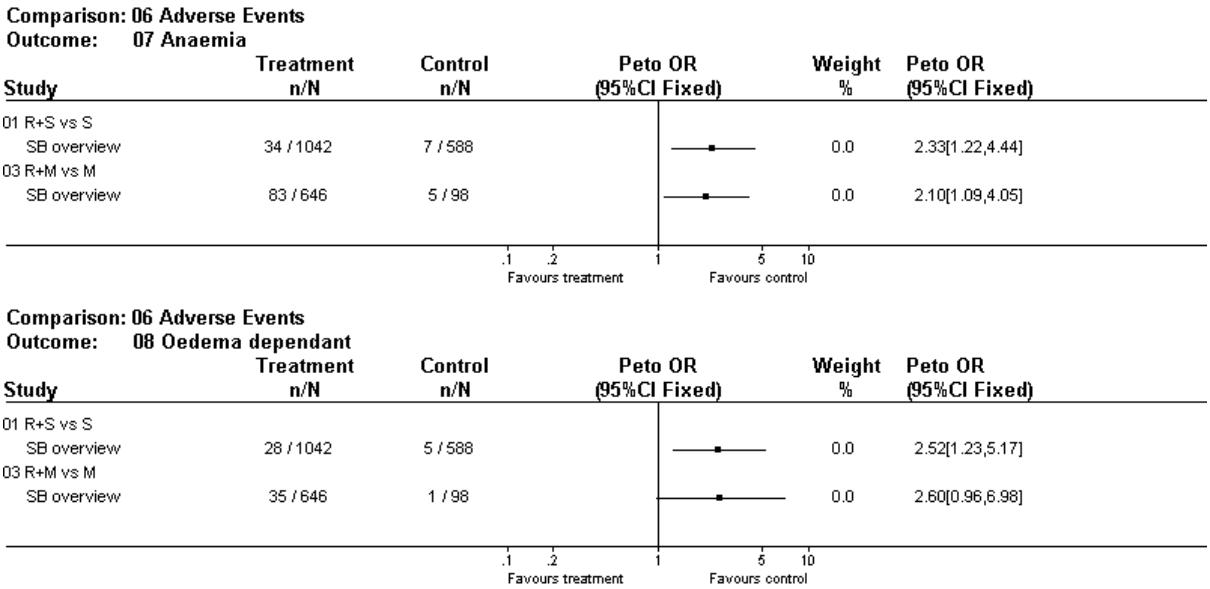


Table 17. Incidence of adverse events and withdrawals

Study	n	Total withdrawn N	Total withdrawn %	At least one adverse event N	At least one adverse event %	Withdrawn due to adverse event N	Withdrawn due to adverse event %
ROSIGLITAZONE/METFORMIN COMPARED TO METFORMIN							
SB093							
A) M	109	28	26%	82	75%	8	7%
C) M+R(8mg)	106	16	15%	88	83%	5	5%
SB094							
A) M	116	22	19%	89	77%	4	3%
B) M+R(4mg)	119	18	15%	93	78%	6	5%
C) M+R(8mg)	113	18	16%	85	75%	5	4%
ROSIGLITAZONE/SULPHONYLUREA COMPARED TO SULPHONYLUREA							
SB015							
A) S	198	71	36%	129	65%	23	12%
B) S+R(2mg)	205	58	28%	120	59%	10	5%
C) S+R(4mg)	190	46	24%	117	62%	10	5%
SB079							
A) S	106	35	33%	85	80%	10	9%
C) S+R(4mg)	99	21	21%	80	81%	7	7%
SB096							
A) S	115	21	18%	79	69%	2	2%
B) S+R(2mg)	116	21	18%	88	76%	5	4%
C) S+R(4mg)	116	14	12%	88	76%	3	3%

Table 18. Cumulative incidence of adverse events in clinical trial programme

Table from SmithKline Beecham submission[74]

Rate per 100 patient years of most frequent adverse experiences (≥ 5% patients) irrespective of relationship to medication

	Rosiglitazone + SU 1042 Pt years	SU 588 Pt Years	Rosiglitazone + MET 646 Pt Years	MET 98 Pt Years
URTI	*13.6*	*18.9*	*25.1*	*20.4*
Injury	*11.9*	*11.6*	*12.2*	*17.3*
Hyperglycaemia	*9.3*	*9.7*	*2.9*	*11.2*
Infection viral	*7.5*	*7.7*	*7.9*	*8.2*
Arthralgia	*7.4*	*6.0*	*7.0*	*5.1*
Hypoglycaemia	*6.8*	*9.9*	*4.2*	*3.1*
Headache	*6.2*	*9.5*	*8.2*	*19.4*
Urinary tract infection	*6.1*	*6.5*	*7.1*	*7.1*
Pain	*6.0*	*5.4*	*6.5*	*9.1*
Sinusitis	*6.0*	*9.0*	*8.7*	*12.2*
Back pain	*5.7*	*8.0*	*7.6*	*9.2*
Hypercholesterolaemia	4.9	2.6	5.9	3.1
Hyperlipaemia	4.8	1.9	7.9	0
Dizziness	4.7	5.6	4.5	8.2
Bronchitis	4.0	5.1	5.9	5.1
Abdominal pain	4.0	4.4	4.5	6.1
Hypertension	3.8	2.4	5.4	12.2
Diarrhoea	3.7	4.3	13.0	35.7
Fatigue	3.6	3.7	7.3	9.2
Anaemia*	3.3	1.2	12.8	5.1
Oedema dependant	2.7	0.8	5.4	1.0
Nausea	2.5	2.4	4.5	7.1
Coughing	2.4	1.2	4.3	7.1

* Cases related to reduced haematocrit have been coded above as anaemia

4.2 Evidence of cost-effectiveness

An economic evaluation of 'conventional' versus 'intensive' blood glucose control in patients with Type 2 diabetes based on the UKPDS study has been published [66]. This estimated the additional health care cost of the intensive policy at £338 (95% CI: -£207 to £882) per patient (6% discount rate for non-trial setting). The gain in "endpoint-free years" – years before subjects died or experienced the onset of a serious diabetic complication - was 0.60 (95% CI: 0.12 to 1.10) (undiscounted). The resulting incremental cost per endpoint free year gained was low at £563 (95% CI: -£344 to £5,632). The cost-effectiveness of a policy of intensive glycaemic control for people with Type 2 diabetes is further supported by the results of economic models [38;74;78].

However, there is no published evidence on the relative cost-effectiveness of alternative treatment strategies to achieve good glycaemic control. The UKPDS was not designed to detect such differences, and no statistically significant differences between metformin, sulphonylurea or insulin treatments were found, either in terms of clinical effectiveness or cost-effectiveness. No published economic evaluations of rosiglitazone were identified through the search of published literature.

[SmithKline Beecham included an economic evaluation as part of their submission to the Institute. Information about the methods and results of this study were included in the version of this report that was sent to the NICE Appraisals Committee. However, it has been removed from this current document because of confidentiality.]

5. DISCUSSION

5.1 Summary of clinical evidence

There is good evidence that rosiglitazone is effective at reducing blood glucose over six months when added to oral monotherapy for patients who have inadequate blood glucose control on oral monotherapy alone:

- The addition of rosiglitazone to metformin is effective at reducing blood glucose at a dose of 4mg/d or 8mg/d, with no evidence of a significantly greater response at the higher dose.
- When added to sulphonylurea, rosiglitazone 2mg/d and 4mg/d is effective at reducing blood glucose. There was evidence of a significantly greater response at the higher dose.

Evidence from open label extension studies suggests that these improvements in glycaemic control are maintained for at least two years. This evidence is not yet fully reported and is less robust than that from the double-blind periods of the randomised controlled trials.

There is no direct evidence that adding rosiglitazone to oral monotherapies will reduce the incidence of diabetic complications, and hence mortality or quality of life adjusted mortality. However, the results of the UKPDS trial suggest that improved glycaemic control reduces the incidence of microvascular complications [87], and that metformin therapy reduces the incidence of macrovascular complications for overweight patients [85]. Thus, it is likely that, by lowering blood glucose levels, rosiglitazone combination therapy for patients who fail to meet glycaemic targets on oral monotherapy will reduce the risk of diabetic complications.

Evidence from the clinical trial programme shows that rosiglitazone combination therapy has various effects on other cardiovascular risk factors. On the positive side, the results of the meta-analysis show:

For rosiglitazone/metformin compared to metformin alone:

- a greater increase in HDL cholesterol over six months;
- lower diastolic blood pressure at six months, though this reduction was not statistically significant after adjusting for baseline differences between the groups.

For rosiglitazone/sulphonylurea compared to sulphonylurea alone:

- a greater increase in HDL cholesterol over six months with 4mg rosiglitazone per day.

However, on the negative side there was:

For rosiglitazone/metformin compared to metformin alone:

- a greater increase in LDL cholesterol over six months;
- a greater weight gain over the six month period.

For rosiglitazone/sulphonylurea compared to sulphonylurea alone:

- a greater increase in LDL cholesterol over six months;

- a greater increase in weight over six months.

It is not clear what the long-term net effect of these changes in risk factors will be. Neither is it clear what impacts the reduced insulin resistance and improved beta-cell function that rosiglitazone provides will have on the maintenance of glycaemic control and cardiovascular risk.

There is no direct evidence of the impact of rosiglitazone combination therapy on quality of life in the short term. However, within the six-month double-blind randomised clinical trials rosiglitazone/metformin and rosiglitazone/sulphonylurea combination therapies were at least as well tolerated as metformin or sulphonylurea alone and there was no difference in the overall incidence of adverse events. A lower proportion of the 4mg rosiglitazone/sulphonylurea groups, compared to the sulphonylurea monotherapy control groups, withdrew from the studies because of an adverse event, odds ratio 0.57(95% CI: 0.38-0.87). The profile of adverse events was rather different for the rosiglitazone/metformin, rosiglitazone/sulphonylurea, metformin and sulphonylurea groups.

There is no direct evidence that the addition of rosiglitazone to metformin or sulphonylurea for this group of patients is any more (or less) effective at improving glycaemic control than moving to a metformin/sulphonylurea combination or starting insulin therapy.

5.2 Summary of economic evidence

There is evidence that 'intensive' blood glucose control for patients with Type 2 diabetes is relatively cost-effective compared to 'conventional' management [38;74;78]. However, there is no published evidence on the relative cost-effectiveness of alternative treatment strategies to achieve good glycaemic control.

[SmithKline Beecham submitted data on the cost-effectiveness of rosiglitazone from a modelling study. However, this information is currently confidential and has been removed from this document.]

5.3 Implications for equity

Sub-group analysis of the results of the clinical trials programme showed no significant differences in outcomes for people by ethnicity, sex or age [74].

5.4 Estimated impact on the NHS

It has been estimated that approximately 0.4% of the population (200,000 for England and 12,000 for Wales) could take a thiazolidinedione [81;82]. This figure is based upon the assumption that 1.6% of the population are taking drugs for diabetes mellitus, that 50% of these have inadequate metabolic control, and about 50% of these would respond to a thiazolidinedione. This represents an upper limit on the number of patients who might be prescribed rosiglitazone. In practice, many of these patients would be likely to continue on existing treatment or to progress to metformin/sulphonylurea combination therapy or insulin.

The financial impact of rosiglitazone on the NHS would depend upon the cost of the drug itself, the avoided cost of alternative add-on medications (metformin,

sulphonylureas and insulin), and the additional avoided costs of health care due to any additional reduction in the incidence of complications.

[SmithKline Beecham submitted estimates of the likely uptake and cost to the NHS of rosiglitazone combination therapy. This data has been removed because of confidentiality.]

6. CONCLUSION

The evidence reviewed in this report shows that rosiglitazone is clinically effective at reducing blood glucose when added to oral monotherapy (metformin or sulphonylurea) for patients who have insufficient glycaemic control on oral monotherapy alone. This is suggestive of a beneficial effect on the risk of diabetic complications. However, uncertainty remains over the extent to which improved glycaemic control is maintained over time. The overall effect of rosiglitazone combination therapy on cardiovascular risk is also unclear. Hence it is difficult to predict the likely impact on quality of life, mortality, and cost-effectiveness.

No direct trial evidence was identified regarding the relative effectiveness of rosiglitazone, metformin and insulin as add-on therapy for patients with inadequate glycaemic control on oral monotherapy.

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APPENDIX 1. WHO diagnostic criteria

Adapted from Table 1 [95]

	Glucose concentration, mmol l^{-1} (mg dl^{-1})			
	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes Mellitus:				
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)	≥ 7.0 (≥ 126)
or				
2-h post glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)	≥ 12.2 (≥ 220)
or both				
Impaired Glucose Tolerance (IGT):				
Fasting (if measured)	< 6.1 (< 110)	< 6.1 (< 110)	< 7.0 (< 126)	< 7.0 (< 126)
and				
2-h post glucose load	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 8.9 (≥ 160) and < 12.2 (< 220)
Impaired Fasting Glycaemia (IFG):				
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
and (if measured)				
2-h post glucose load	< 6.7 (< 120)	< 7.8 (< 140)	< 7.8 (< 140)	< 8.9 (< 160)

For epidemiological or population screening purposes, the fasting or 2-h value after 75 g oral glucose may be used alone.

For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms.

Glucose concentrations should not be determined on serum unless red cells are immediately removed, otherwise glycolysis will result in an unpredictable under-estimation of the true concentrations. It should be stressed that glucose preservatives do not totally prevent glycolysis.

If whole blood is used, the sample should be kept at 0-4 °C or centrifuged immediately, or assayed immediately.

APPENDIX 2. WHO classification of disorders of glycaemia

Reproduced from Figure 2 [95]

Aetiological types	Clinical stages				
	Normoglycaemia	Hyperglycaemia			
	Normal glucose tolerance	Impaired glucose regulation (IGT and/or IFG)	Diabetes Mellitus		
			Not insulin requiring	Insulin requiring for control	Insulin requiring for survival
Type 1 • Autoimmune • Idiopathic					
Type 2* • Predominantly insulin resistance • Predominantly insulin secretory defects					
Other specific types *					
Gestational diabetes *					

* In rare instances patients in these categories (e.g. Vacor Toxicity, Type 1 presenting in pregnancy, etc.) may require insulin for survival.

APPENDIX 3. Medline search strategies

A. Rosiglitazone

1. (rosiglitazone or avandia or BRL 49653 or BRL49653 or 122320 73 4).af.

B. Thiazolidinediones for diabetes

1. exp thiazoles/
2. (thiazoles or thiazolidinedione).af.
3. (PPAR gamma agonists or PPAR-gamma agonists).af.
4. (rosiglitazone or avandia or BRL 49653 or BRL49653 or 122320 73 4).af.
5. or/1-4
6. exp diabetes mellitus/
7. (diabetes or diabetic).af.
8. 8 or 9
9. 7 and 10

C. Randomised controlled trials

(Based on a strategy originally developed by Carol Lefebvre, UK Cochrane Centre, Oxford)

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 single blind method/
7 or/1-6
8 clinical trial.pt.
9 exp clinical trials/
10 (clin$ adj25 trial$).ti,ab.
11 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
12 placebos/
13 placebos.ti,ab.
14 random.ti,ab.
15 research design/
16 or/8-15
17 comparative study/
18 exp evaluation studies/
19 follow up studies/
20 prospective studies/
21 (control$ or prospectiv$ or volunteer$).ti,ab.
22 or/17-21
23 7 or 16 or 22
24 animal/
25 human/
26 24 and 25
27 24 not 26
28 23 not 27

D. Systematic reviews

(Developed by NHS Centre for Reviews and Dissemination at the University of York)

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw.
4 meta analysis.pt.
5 review academic.pt.
6 review literature.pt.
7 letter.pt.
8 review of reported cases.pt.
9 historical article.pt.
10 review multicase.pt.
11 or/1-6
12 or/7-10
13 11 not 12
14 animal/
15 human/
16 14 and 15
17 14 not 16
18 13 not 17

E. Guidelines

(Developed by the Evidence Based Informatics Project at McMaster University)

1 guideline.pt.
2 practice guideline.pt.
3 exp guidelines/
4 health planning guidelines/
5 or/1-4

F. Outcomes

(Based on a strategy developed by Brettle, A. and Grant, M.J. at UK Clearing House on Health Outcomes, Nuffield Institute for Health, University of Leeds)

1 health status indicators/
2 outcome and process assessment (health care)/
3 outcome assessment (health care)/
4 quality of life/
5 (outcome and measure$).tw.
6 (health and outcome$).tw.
7 (qaly or quality adjusted life year$).tw
8 or/1-7

G. Economic evaluations

(Developed by NHS Centre for Reviews and Dissemination at the University of York)

1. economics.sh.
2. exp "costs and cost analysis"/
3. economic value of life.sh.
4. exp "economics, dental"/
5. exp "economics, hospital"/
6. exp "economics, medical"/
7. exp "economics, nursing"/
8. economics, pharmaceutical.sh.
9. exp "fees and charges"/
10. exp "budgets"/
11. (cost or costs or costed or costly or costing).ab,ti.
12. (economic$ or pharmacoeconomic$ or price$ or pricing).ab,ti.
13. or/1-12
14. letter.pt.
15. editorial.pt.
16. historical article.pt.
17. 14 or 15 or 16
18. 13 not 17
19. "animal"/
20. "human"/
21. 19 not (19 and 20)
22. 18 not 21

APPENDIX 4. Quality checklist for randomised controlled trials

Reviewer's Initials:……

Paper:

A. Randomisation procedure

A1	Was the trial described as "randomised"?	N	Y
A2	Was allocation truly random? (random numbers, coin toss etc),or		A
	Was allocation quasi-random (patient number, date of birth), or		B
	Was allocation systematic (alternate), or		C
	Was the method of randomisation not stated or unclear		D

B. Allocation concealment

B1	Was concealment adequate? (central allocation at trials office or pharmacy, sequentially numbered or coded vials, other methods where the trialist allocating treatment could not be aware of the treatment), or	A
	Was concealment inadequate? (allocation was alternate (by patient, day of the week, admission ward, etc.) or based on information, such as date of birth, already known to the trialist), or	B
	Was concealment unclear? (inadequate information given)	C

C. Methods of blinding

C1	Was the trial described as "double-blind"?		N	Y
C2	Was the treatment allocation masked from the participants? (either stated explicitly, or an identical placebo is used)	U	N	Y
C3	Was the treatment allocation masked from the investigators?	U	N	Y
C4	Was the treatment allocation masked at the outcome assessments?	U	N	Y

D. Completeness of the trial

D1 Were the number of withdrawals in each group stated? U N Y

D2 Was an intention-to-treat analysis (analysis according to allocation) performed? U N Y

D3 What were the drop-out rates in each group of the trial for each of the main outcomes?

(write unclear or not stated as appropriate)

Group	Outcome 1	Outcome 2	Outcome 3
1			
2			
3			
4			
5			

JADAD Scale Circle when point awarded or removed

Score 1 point if the answer to A1 is YES ***+1***

Score 1 point if the answer to C1 is YES ***+1***

Score 1 point if the answer to D1 is YES ***+1***

Score 1 point if the answer to A2 is A

and the answer to B1 is A ***+1***

Deduct 1 point if the answer to A1 is Y

and the answer to A2 is B or C ***or*** the answer to B1 is B ***-1***

Score 1 point if the answer to C2 is YES,

and the answer to C4 is YES ***+1***

Deduct 1 point if the answer to C1 is YES

and the answer to C2 is NO ***or*** the answer to C4 is NO ***-1***

Total score (between 0 and 5)

======

APPENDIX 5. Quality checklist for economic evaluations

Based on [26]

	Yes	No	Not clear	NA
1. Was a well-defined question posed in answerable form				
2. Was a comprehensive description of the competing alternatives given?				
3. Was the effectiveness of the programmes or services esablished?				
4. Were all the important and relevant costs and consequences for each alternative identified?				
5. Were costs and consequences measured accurately in appropriate physical units?				

6. Were the costs and consequences valued credibly?				
7. Were the costs and consequences adjusted for differential timing?				
8. Was an incremental analysis of costs and consequences of alternatives performed?				
9. Was allowance made for uncertainty in the estimates of costs and consequences?				
10. Did the presentation and discussion of study results include all issues of concern to users?				

APPENDIX 6. References excluded in preliminary screen

Rosiglitazone maleate. Ketotifen fumarate. *American journal of health-system pharmacy* 1999;**56**:1924-6.
Notes: Not clinical study.

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Notes: Not comparative study of rosiglitazone.

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Notes: In vitro.

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Notes: Animal.

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Notes: RCT evaluating effect of troglitazone compared to placebo in patients with impaired glucose tolerance.

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Notes: In vitro and animal.

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Notes: Review of treatments for diabetic neuropathy.

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Notes: In vitro, animal.

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Notes: In vitro.

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Notes: Uncontrolled study of effect of troglitazone on brachial artery vasoactivity.

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Notes: RCT evaluating effect of troglitazone in preventing incidence of diabetes in women with previous gestational diabetes.

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Notes: Non-English language review.

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Notes: In vitro.

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Notes: RCT of troglitazone combination therapy vs placebo and alpha-glucosidase inhibitor alone.

Barroso I, Gurnell M, Crowley VE, Agostini M, Schwabe JW, Soos MA *et al*. Dominant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes mellitus and hypertension [see comments]. *Nature* 1999;**402**:880-3.
Notes: Not comparative study of rosiglitazone.

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Notes: Not clinical trial.

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Notes: Animal study.

Berkowitz K, Peters R, Kjos SL, Goico J, Marroquin A, Dunn ME *et al*. Effect of troglitazone on insulin sensitivity and pancreatic beta-cell function in women at high risk for NIDDM. *Diabetes* 1996;**45**:1572-9.
Notes: RCT of effect of troglitazone (2 dosages) vs placebo on development of NIDDM in women with impaired glucose tolerance and previous gestational diabetes.

Bolton GC, Keogh JP, East PD, Hollis FJ, Shore AD. The fate of a thiazolidinedione antidiabetic agent in rat and dog. *Xenobiotica* 1996;**26**:627-36.
Notes: Animal study.

Brockman JA, Gupta RA, Dubois RN. Activation of PPARgamma leads to inhibition of anchorage-independent growth of human colorectal cancer cells [see comments]. *Gastroenterology* 1998;**115**:1049-55.
Notes: In vitro study.

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protein-3 gene expression at birth. *Diabetes* 1999;**48**:1217-22.
Notes: Animal.

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Notes: Animal study.

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Ref Type: Abstract
Notes: Animal study

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Notes: Pharmacokinetic study

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Notes: Not clinical trial.

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Notes: Review of pioglitazone

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Notes: Not clinical trial

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Notes: Animal study

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Notes: Controlled comparison (randomised?) of effects of troglitazone vs placebo on carbohydrate metabolism.

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Notes: Review of mechanisms of action.

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Notes: In vitro study.

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Notes: Dose-ranging study in which 303 patients with type 2 diabetes were randomised to placebo or rosiglitazone (2mg, 4mg or 6mg). Results showed significant improvement in glucose control (FPG and PPG)

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Notes: In vitro.

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Notes: Animal study

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Notes: Not clinical trial.

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Notes: In vitro.

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Notes: RCT of epalrestat for NIDDM (+ health controls).

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Notes: Review of troglitazone.

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Notes: Non-English language review

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Notes: Review of pioglitazone

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Notes: In vitro study.

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Notes: RCT of troglitazone (2 dosages) or placebo in combination with insulin for type 2 diabetes.

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Notes: Not relevant.

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Notes: Not relevant.

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Notes: Report of animal and in vitro studies to investigate effect of free fatty acids on insulin resistance.

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APPENDIX 7. Data used in SB economic model

[This information has been removed due to confidentiality.]